Assessment report

for

Bydureon

International nonproprietary name: exenatide

Procedure No. EMEA/H/C/002020

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted
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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 4 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bydureon, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 October 2009. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

BYDUREON is indicated for treatment of type 2 diabetes mellitus in combination with
• Metformin
• Sulphonylurea
• Thiazolidinedione
• Metformin and sulphonylurea
• Metformin and thiazolidinedione
in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/12/2010 for the following conditions:

- type 2 diabetes mellitus
  on the agreement of a paediatric investigation plan (PIP) including a deferral.

The PIP is not yet completed.

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.
**Scientific Advice**

The applicant received Scientific Advice from the CHMP on 19 July 2007 and 17 December 2009. The Scientific Advice pertained to quality and clinical aspects of the dossier.

**Licensing status**

A new application was filed in the following countries: USA. The product was not licensed in any country at the time of submission of the application.

**1.2. Steps taken for the assessment of the product**

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Kristina Dunder Co-Rapporteur: Pieter de Graeff

- The application was received by the EMA on 4 March 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2010. The Co-Rapporteur’s first Assessment Report was circulated to all CHMP members on 11 June 2010.
- During the meeting on 19-22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 November 2010.
- During the CHMP meeting on 15-18 November 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 September 2010. An updated version of the responses was submitted on 19 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 31 January 2011.
- During the CHMP meeting on 14-17 February 2010, the CHMP agreed on the Second List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP Second List of Outstanding Issues on 14 March 2011. Additional information was provided on 6 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the Second List of Outstanding Issues to all CHMP members on 29 March 2011. An updated assessment reports were circulated on 7 April 2011.
- During the meeting in April 2011, 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 to Bydureon on 14 April 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 11 April 2011.
2. Scientific discussion

2.1. Introduction

Type 2 diabetes has a complex pathophysiology characterized by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of these abnormalities.

The condition is a chronic widespread disease in the western world with an expected increased incidence worldwide. Type 2 diabetes accounts for approximately 90% of individuals with diabetes, has a usual onset in adults but is seen in growing numbers of children, and is typically associated with excess body weight and physical inactivity. It is well known that patients with type 2 diabetes are at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality. A major purpose of using antidiabetic agents is to reduce these risks. Since all treatment alternatives are associated with different adverse events profiles and may not be tolerated by certain patients, it is of importance that clinicians have access to different options when treating patients with type 2 diabetes.

According to current guidelines for the treatment of type 2 diabetes, the treatment target should be HbA1c <7 %. Diet modification and exercise typically form the first line of treatment, but eventually most patients need at least two different antidiabetic compounds during the course of pharmacological intervention to reach treatment goals. The EASD/ADA treatment algorithm from 2006 recommends metformin and life style changes as first line treatment. In the case of therapy failure (HbA1c ≥ 7%), insulin, sulfonylurea or thiazolidinediones should be added.

This application concerns Bydureon (exenatide QW). Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist with an amino acid sequence that partially overlaps that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor in vitro, its mechanism of action mediated by cyclic AMP and/or other intracellular signaling pathways. Currently, exenatide is authorised as Byetta 5μg and 10μg (EU/1/06/362/001-004). Byetta is a solution for injection which is injected twice a day (BID) while Bydureon is a 2 mg suspension formulation which allows once weekly (QW) administration of exenatide. Exenatide QW consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable poly(D,L-lactide—co-glycolide (PLG) microspheres that are designed to release exenatide over an extended period of time. Bydureon thereby represents the first long acting GLP-1 analogue submitted for marketing authorisation. As a different invented name has been assigned to clearly differentiate the two formulations, a separate marketing authorisation under art.8(3) of Directive (EC) 2001/83/EC was submitted.

The indication for Bydureon claimed for by the Applicant is treatment of type 2 diabetes mellitus in combination with metformin, sulphonylurea, thiazolidinedione, metformin and sulphonylurea, metformin and thiazolidinedione in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. The indication is the same as for exenatide BID and is also considered acceptable for Bydureon by the CHMP.

The Applicant has received two CHMP scientific advices during the development programme:

- **CHMP Follow-up Scientific Advice for exenatide once weekly clinical program (July 2007)**
  Advice was given on comparability issues (quality), dose-finding, drug interactions, the need for a QT study, the size of the safety data base, the appropriate background OADs and a possible monotherapy indication. In principal, the advice has been followed.

- **CHMP Follow-up Scientific Advice for exenatide once weekly clinical program (December 2009)**
  This advice concerned the design of the planned cardiovascular outcome study H80-MC-GWDQ.

Throughout this report, the prolonged release formulation (Bydureon) is named “exenatide QW” while the twice daily formulation (Byetta) is named “exenatide” or “exenatide BID”.
2.2. **Quality aspects**

2.2.1. **Introduction**

Bydureon powder and solvent for prolonged release suspension for injection is a parenteral drug product for weekly, subcutaneous administration of the known active substance exenatide. The product is supplied in a single-dose kit that contains a vial with 2.0 mg exenatide, a pre-filled syringe with solvent, a vial connector and needles. Before administration the solvent (0.65 ml) should be added to the powder for suspension for injection and after suspending the suspension it is withdrawn from the vial into the syringe.

The drug substance Exenatide is a 39-amino-acid peptide amid. Exenatide once weekly consists of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres that are designed to release exenatide over an extended period of time. Other excipients include sucrose, carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate and water for injections.

The immediate packaging materials are commonly used for this type of formulation and consist in a Type I glass vial sealed with a rubber stopper and an aluminium seal with a plastic flip-off cap. The solvent is packaged in a Type 1 glass syringe sealed with a rubber tip cap and a rubber plunger.

2.2.2. **Active Substance**

Exenatide is a chemically synthesized peptide obtained from two manufacturers. Scientific data can be found in their respective Active Substance Master Files (ASMF) consisting of Open part, Closed part, Quality Overall Summaries and letter of access, as appropriate.

Figure 1

Exenatide - molecular structure
**Manufacture**

Exenatide is a 39-amino acid single-chain peptide containing 37 chiral carbon atoms obtained by solid-phase peptide synthesis. There are theoretically $2^{37}$ potential optical isomers. However, the drug substance is synthesized from protected L-amino acids and protected glycine, and the coupling and cleavage methods have been selected to minimize isomerisation of both starting materials and the growing peptide chain. Exenatide is freely soluble in water (>100 mg/ml). Exenatide is reversibly hygroscopic. The relative molecular mass is 4186.6 Daltons and the molecular formula is $C_{184}H_{282}N_{50}O_{60}S$.

The exenatide peptide is synthesized using 9-fluorenyl-methoxycarbonyl (Fmoc) solid-phase peptide chemistry. A satisfactory description of the manufacturing processes is provided.

The proof of chemical structure was achieved by Edman degradation, tryptic mapping and sequence/mass spectrometric, NMR spectrometry, studies on the solution state structure, circular dichroism and SE-HPLC.

**Specification**

Satisfactory specification has been set for exenatide; this includes parameters such as appearance, identification and assay of the peptide content, assay of product-related impurities, residual solvents, acetate content, and microbial limit. Impurity limits have been adequately justified by batch analysis, stability studies, toxicological and clinical studies.

Analytical Methods to control the active substance including methods such as Strong Cation-exchange chromatography (SCX-HPLC), Tryptic Peptide Map, Mass Spectrometry, Peptide Content, Reversed-Phase Chromatography (RP-HPLC), Ion Chromatography (for acetate and amino acid analysis), Gas Chromatography (for residual solvents), and Size-exclusion HPLC (for oligomer content) have been suitably described and validated according to ICH guidelines.

Batch analyses of exenatide manufactured at the two manufacturing sites have been provided. Results comply with the specification and are consistent with batch results used in the toxicological and clinical studies.

**Stability**

Stability studies were conducted on a satisfactory number of batches and batch sizes of active substance supplied by both manufacturers. The batches were evaluated at -20°C ± 5°C, accelerated conditions of 5°C ± 3°C, and stress conditions of 25°C ± 2°C/60 % RH. Results are given after 2 – 3 years at -20°C, 1 year at 5°C, and 6 months at 25°C. No significant change in appearance, peptide content, water content, or purity (by RP-HPLC and SCX-HPLC) was observed over the time points evaluated for the storage condition of -20°C.

Photo stability studies were carried out on exenatide. Results indicated that significant degradation of the drug substance occurred as a result of light exposure. The drug substance is therefore light-sensitive and should be packaged to protect it from excessive light exposure.

The proposed retest period of 2 or 4 years, according to which supplier, when stored at $\leq$ - 15°C protected from light is justified by stability data.

In accordance with EU GMP guidelines$^1$, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

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$^1$ 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union
2.2.3. Finished Medicinal Product

**Pharmaceutical Development**

**Powder**

The pharmaceutical development involves seven clinical formulations differing mainly in polymer type, exenatide content, concentration and identity of the sugar, and presence or absence of ammonium sulfate. The final formulation was chosen because it exhibited an acceptable pharmacokinetic profile with a lower $\frac{C_{\text{max}}}{C_{\text{ave}}}$ (maximum plasma concentration/average plasma concentration) ratio and overall lower variability in plasma exenatide concentration. The release mechanism has been characterised by in vitro release methods and is described as 3 phases: Initial release, Release and Extended release phase. Whereas the first phase has a rapid release of exenatide loosely bound to the surface of the microspheres, phase 2 shows slow release and consists of hydrolysisation and gradual shortening of the polymer resulting in erosion of the polymer matrix. Phase 3 takes place when the degraded polymers reached a molecular weight target which results in a controlled release of exenatide until the remaining active substance is released. The release mechanism has been characterised by separate methods for initial release and complete release of exenatide, respectively.

The product vial contains overfill based on a factor needed to compensate for hold up of the suspension in the delivery system. The feasibility of this was demonstrated in dose accuracy experiments. An in vitro/in vivo correlation has been demonstrated for the initial release method. To demonstrate compatibility of the exenatide with the various component of the drug product, including the solvent, the company has performed a reconstitution stability study along with other stability data.

The manufacturing process has been gradually developed mainly by an increase in scale and transferring to the commercial manufacturer plant. Three different scales, including commercial scale, have been used during clinical trials. For these reasons the company has provided data to support comparability between all manufacturing processes.

**Solvent**

The solvent is used to suspend the exenatide microspheres prior to administration by subcutaneous injection. Clinical and preclinical studies used a microsphere solvent. The solvent was optimised for the intend purpose. It is a pH 6.5, phosphate buffered solution containing carmellose sodium to modify the viscosity, sodium chloride to adjust the osmolality, and polysorbate 20 to facilitate wetting of the exenatide microspheres.

**Adventitious agents**

None of the manufacturing process used by the active substance manufacturers involves recombinant DNA technology, fermentation, or extraction of biological matrices.

Exenatide is obtained by solid phase peptide chemistry from chemically protected amino acids which are the only potential sources of transmittable spongiform encephalitis (TSE), since none of the other raw materials is of human/animal origin.

However, the amino acid derivatives are sourced from non-human/non-ruminant animal materials. Certificates of origin for the protected amino acids used in the manufacture of exenatide were provided. No TSE risk is anticipated.
**Manufacture of the product**

**Powder**

The manufacturing process involves three distinct steps: bulk microsphere production, sieving, and filling. Since the powder is not suitable for terminal sterilisation the process involves aseptic procedures to assure a sterile product. For these reasons a closed manufacturing system is employed with double 0.2 filtration of incoming solutions and the final steps (sieving and filling) are performed under grade A conditions. Regarding the validation of manufacturing process, the company has provided information which along with the positive outcome of the GMP inspection report supports an aseptic manufacturing process of the drug product.

**Solvent**

The solvent in syringe is terminally sterilized and is a single use unit. The compatibility of the solvent with exenatide powder for injection and with the entire delivery system for periods of time sufficient for dose preparation and administration by the patient was evaluated.

The manufacturing process involves solvent solution preparation, filtration, filling, terminal sterilization, and bulk packaging processes. The amount of carmellose sodium may vary in order to achieve the desired viscosity of the solvent. The process, including sterilization by autoclave has been suitably validated.

**Product Specification**

**Powder**

The control of the drug powder includes methods to test identity, assay, purity, two methods for in vitro release, polymer molecular weight, particle size, water content, residual solvents, bacterial endotoxins and sterility. The safety and suitability of release and shelf life limits for the wide variety of product related impurities has been justified in toxicological studies. The analytical methods used were adequately described and validated.

Batch analysis data were provided for six commercial scale batches. The results are satisfactory and support the proposed indications.

**Solvent**

A separate specification is applied for the solvent. Validation has been performed for the only in house method. Compendial methods have been validated taken the solvent itself into account. Batch analysis data include also testing of the plunger force. Potential impurities formed during sterilization of carmellose sodium have been studied.

**Stability of the product**

The established stability, based on supportive data, is two years stored in a refrigerator (2ºC - 8ºC) in the original package in order to protect from light. The kit may be kept for up to 4 weeks below 30 ºC prior to use.

**Powder**

Stability studies include up to 30 months long term data. Data to support the intermediate holding step of bulk microspheres include 12 months storage at -20ºC, temperature cycling studies and data to support that microspheres are suitable for downstream processing. In use stability include a 4 week period of storage at 30ºC. This includes a validated 15 minute incubation period prior to test of delivery from the solution in the syringe.

**Solvent**

Stability data include 6 month data from commercial scale and data (24 month) from pilot scale.
In accordance with EU GMP guidelines\(^2\), any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

**Comparability Exercise for Finished Medicinal Drug Product**

No compatibility studies were provided. This medicinal product must not be mixed with other medicinal products.

**GMO**

Not applicable.

**2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

The active substance and the medicinal product have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that both can be reproducibly manufactured.

**2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of the active substance and finished product are satisfactory. At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

**2.3. Non-clinical aspects**

**2.3.1. Introduction**

Exenatide has been previously authorised by the European Commission as Byetta 5 μg and Byetta 10 μg. Byetta is a solution for injection which is injected twice a day. The company developed a new formulation of exenatide QW which allows once weekly administration of exenatide.

The primary pharmacologic, pharmacokinetic, and toxicologic properties of the exenatide peptide were well characterized during the development of Exenatide BID. Therefore, most of the nonclinical pharmacology information presented stems directly from the nonclinical program for Exenatide BID. The primary aim of the nonclinical studies conducted specifically for exenatide QW focused on determining the impact of the extended-release formulation on the pharmacologic, pharmacokinetic, and toxicologic profile of exenatide. In addition, these studies assessed the local tolerance (i.e. injection site reaction) of the exenatide QW formulation and also monitored for the emergence of anti-exenatide antibodies.

Pivotal nonclinical studies were performed in compliance with GLP.

**2.3.2. Pharmacology**

The pharmacology of exenatide was studied in the development program for Exenatide BID and reference is made to the Byetta EPAR for further details. In summary:

Exenatide is a 39-amino acid peptide amide. Exenatide binds to and activates the GLP-1 receptor. GLP-1, the endogenous mammalian incretin is secreted in response to a meal by intestinal L-cells. Exenatide and GLP-1 exert multiple anti-hyperglycaemic actions. Exenatide is not degraded by the protease dipeptidyl peptidase (DPP-IV) known to rapidly inactivate GLP-1. In animal models for type 2 diabetes, as well as in humans with type 2 diabetes, exenatide has been shown to:

- increase insulin secretion
- suppress basal and postprandial glucagon secretion

\(^2\) 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union
- slow gastric emptying
- reduce food intake and body weight
- improve insulin sensitivity
- stimulate islet neogenesis

Exenatide QW consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable poly(D,L-lactide—co-glycolide (PLG) microspheres that are designed to release exenatide over an extended period of time. Following SC administration, the polymer biodegrades over time, providing extended release of exenatide into the circulation.

**Primary pharmacodynamic studies**

*In vitro* studies have demonstrated binding of exenatide to the GLP-1 receptor with similar binding affinity and functional potency as GLP-1. In vitro tissue studies showed that exenatide enhanced glucose-mediated insulin secretion and inhibited glucagon secretion in isolated rat islets and perfused rat pancreas. The glucose-lowering activity of exenatide was shown in vivo in a variety of animal models. Additional effects shown in animal models were suppression of glucagon secretion, slowing of gastric emptying and preservation of pancreatic β-cell mass.

A study was performed with exenatide QW in the Zucker Diabetic Fatty (ZDF) rat. Exenatide QW administered as a single injection (at doses of 1000, 3000, or 9000 μg in experiment 1 and doses of 1, 10 and 100 μg in experiment 2) evoked dose-dependent reductions in HbA1c and fasting glucose concentrations in measurements up to 28 days post-dose. There was a significant (p<0.05) difference in HbA1c between placebo treated rats and those administered higher doses of exenatide QW (100, 1000, 3000, or 9000 μg/rat). Mean plasma concentrations of exenatide averaged from samples taken on Days 1, 3, 10, 20, and 28 post-dose were 252, 2677, 6454, and 30,871 pg/ml for the 100, 1000, 3000, or 9000 μg doses, respectively. For comparison, in the Clinical Study 2993LAR-105, the geometric mean concentration for pharmacokinetic analysis population at steady state (between Week 29 and 30 of weekly dosing with 2 mg exenatide once weekly) was 300.2 pg/mL. In the ZDF rat model, exenatide QW also significantly (p<0.05) increased insulin sensitivity and enhanced β-cell function. This study demonstrates a long duration of exenatide exposure and pharmacological activity, as measured by reduction of fasting blood glucose and HbA1c.

**Secondary pharmacodynamic studies**

The effects of exenatide on gastric acid secretion, pancreatic enzyme secretion and other hormonal systems were examined in rodent species. An additional nonclinical study was conducted in a rodent model of hypertension. The subchronic administration of exenatide (7 days) normalized glucocorticoid-induced hypertension and lowered blood pressure in normotensive rats, with no effect on body weight at the dose tested.

**Safety pharmacology programme**

A battery of safety pharmacology studies were conducted in mice, rats and monkeys to evaluate the effects of exenatide on central nervous (mice only), cardiovascular (including in vitro hERG assay), and renal (rats only) systems to support the Exenatide BID submission. In addition, assessment of the potential effects of exenatide on the cardiovascular (ECGs, histopathology), respiratory (clinical signs, histopathology) and central nervous (clinical signs, histopathology) systems were incorporated into the design of the single dose and repeated dose toxicology studies with exenatide and exenatide QW. There were no safety pharmacology findings in the repeat-dose toxicity studies with exenatide QW. No ECG measurements were included in these studies. This is acceptable since safety pharmacology deals with acute pharmacological effects on major organ systems, and these are sufficiently addressed in the studies with exenatide.

**Pharmacodynamic drug interactions**

Pharmacodynamic drug interaction studies have not been conducted, which was found to be acceptable by the CHMP.
2.3.3. Pharmacokinetics

The pharmacokinetic characteristics of exenatide were previously evaluated in the Exenatide BID nonclinical program. Studies with exenatide QW were performed to compare PK profiles between the two formulations. The program consists of two single dose GLP PK rat studies and a pilot (non-GLP) single dose monkey PK study. Repeat dose PK was evaluated in the toxicokinetic assessments, which were part of the repeat-dose toxicity studies in rats and monkeys. The PK studies in rats and monkeys confirm the extended release profile. After a SC injection of exenatide QW, absorption occurs over an extended period of time (weeks). While the release kinetics differs between rats and monkeys, in both cases repeated weekly dosing result in drug accumulation finally reaching a steady state with a constant exposure with small variations over time.

The absolute bioavailability and relative bioavailability of exenatide QW were not determined in a specific study, but were estimated retrospectively relative to immediate release SC and IV data from previous studies. The absolute bioavailability of the immediate release formulation of exenatide is higher than that of the estimated absolute bioavailability for exenatide QW in both rat and monkey, which results in a relative bioavailability for exenatide QW of approximately 63% in rat and 23% in monkey.

The EPAR for Byetta states that "Whole-animal distribution studies were not done, since exenatide is composed of natural amino acids. Exenatide was shown to be transported across the placenta only to a low degree with a maximal foetal to maternal ratio of 0.035 in mice and rabbits." There were no novel studies on distribution with exenatide QW.

No metabolism evaluation was conducted for exenatide QW. Previous studies with exenatide show no major metabolite in the plasma of rats. In renally ligated rats, metabolites detected at trace concentrations in the plasma had no biological activity when tested in an in vitro activity assay.

No specific excretion study was conducted with exenatide QW. Previous studies with exenatide suggest that the kidney may be a site for the proteolytic degradation of exenatide and also the major contributor to exenatide clearance. Exenatide was present in the milk of lactating mice at a level of approximately 2.5% of the plasma concentration. Similar as for exenatide BID the transport to milk has not been adequately studied. Bydureon should therefore not be used during breast-feeding, as mentioned in the SPC, section 4.6.

No non-clinical drug interaction studies were performed with exenatide or exenatide QW.

2.3.4. Toxicology

A complete nonclinical safety program was previously conducted with exenatide to support the development of exenatide BID. Additional studies for exenatide QW were subchronic, chronic, genotoxicity and carcinogenicity studies.

Single dose toxicity

Single dose toxicity of exenatide was assessed in mice, rats and monkeys. No lethality or serious toxicity was observed.

Repeat dose toxicity

Repeat dose toxicity studies with exenatide QW were performed in rats (8 weeks and 18 weeks) and monkeys (3 months and 9 months). Toxicokinetic data show the expected accumulation over time. The only toxicity findings were injection site reactions which showed partial or complete recovery. Injection site reactions have also been observed in the clinical program. The multiple to human exposure at the highest dose (=NOAEL for both rats and monkeys) was 27 in the rat 4 month study and 14 in the monkey 9 month study. Repeat-dose toxicity studies in rats and monkeys were performed with exenatide QW. These studies are summarized in the following table:
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Species/Sex/Number/Group</th>
<th>Dose (mg/kg SC)</th>
<th>Duration</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>REST060307</td>
<td>Rat / 15M, 15F</td>
<td>0, 0.3, 3, 9 + microsphere control, every other week</td>
<td>8 weeks + 12 weeks recovery</td>
<td>Dose-related decreases in body weight and food consumption were noted at ≥0.3 mg/kg. Injection site findings, noted microscopically as granulomatous inflammation, were observed in the microsphere control and exenatide QW-treated groups. Partial to complete recovery was observed by week 20.</td>
</tr>
<tr>
<td>REST080043</td>
<td>Rat / 15M, 15F</td>
<td>0, 0.3, 3, 9 + microsphere control, every other week</td>
<td>8 weeks + 12 weeks recovery</td>
<td>Decreases in body weight gain and food consumption, expected pharmacological effects of exenatide, were noted at ≥0.3 mg/kg exenatide. Injection site findings, noted microscopically as foreign body granulomas and chronic inflammation, were observed in the microsphere control and exenatide QW-treated groups. Partial recovery was observed by Week 18.</td>
</tr>
<tr>
<td>REST050369</td>
<td>Rat / 15M, 15F</td>
<td>0, 1, 3, 9 + microsphere control, every other week</td>
<td>18 weeks + 13 weeks recovery</td>
<td>Dose-related in body weight and food consumption were noted at ≥3 mg/kg. Microsphere-related injection site findings, noted microscopically as granulamotous inflammation, were observed in the microsphere control and exenatide QW treated groups. Partial to complete recovery was observed following a 3-month recovery period.</td>
</tr>
<tr>
<td>REST04289R</td>
<td>Cynomolgus / 4M, 4F</td>
<td>0, 0.11, 0.44, 1.1 + microsphere control, once weekly</td>
<td>13 weeks</td>
<td>Macroscopic and microscopic changes were observed at the injection sites, were typical of a foreign body reaction or expected form the SC administration of microspheres, and were partially or completely reversible. A challenge dose of microspheres during the recovery period did not elicit a local reaction.</td>
</tr>
<tr>
<td>REST050370</td>
<td>Cynomolgus / 6M, 6F</td>
<td>0, 0.11, 0.42, 1.1 + microsphere control, once weekly</td>
<td>39 weeks + 13 weeks recovery</td>
<td>Reversible, dose-related injection site reactions (erythema, swelling, inflammation, thickening, and granulomas associated with presence of microspheres) were observed in microsphere- and exenatide QW-treated groups.</td>
</tr>
</tbody>
</table>

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.

**Genotoxicity**

A complete standard battery of genotoxicity studies were completed with exenatide to support the Byetta application. Exenatide was negative in all assays. Additional genotoxicity studies were conducted with exenatide and exenatide QW during the exenatide QW program. Exenatide and exenatide QW from different manufacture sites were tested for induction of gene mutations in bacteria and chromosomal aberrations in CHO cells. All assays were negative.

**Carcinogenicity**

Two year carcinogenicity studies were previously performed in rats and mice with exenatide (daily SC injections) to support the Exenatide BID. There was no increase in neoplastic lesions in mice. In rats there was an increase in benign thyroid C-cell adenomas in female animals. The numerical increase in tumours was not statistically significant when adjusting for survival.

A 2-year carcinogenicity study in rats with exenatide QW was conducted to support the current application. Exenatide QW was given every other week at doses of 0.3, 1.0 and 3.0 mg/kg.

There was a statistically significant increase in C-cell adenomas at all doses in females and at 1.0 and 3.0 mg/kg in males. At 0.3 mg/kg in males, the incidence of adenomas (29%) was above historical control data (5-15.4%) from the laboratory. There was a statistically significant increase in C-cell carcinomas in females at 3.0 mg/kg (6%). The incidence in male rats (3%, 7% and 4% at low, mid and high dose respectively) were all above the historical control data range (1.5-1.7%) but were not statistically significant.

For calculation of human exposure multiples, AUC values in antibody-negative animals at day 183 were compared to steady-state AUC in humans. The exposure multiples were (M/F):

- 0.3 mg/kg : 2.1/1.4
- 1 mg/kg : 10/8
- 3 mg/kg : 26/25

Since no NOAEL was established, there is no safety margin. For comparison, in the highest dose group in the rat carcinogenicity study with exenatide (250 μg/kg/day), the exposure multiple to clinical exposure was 37.

The applicant has not performed any mechanistic studies to explore the mode of action behind the development of thyroid C-cell tumours in rats, but refers to the conclusions drawn by regulatory agencies regarding similar findings for liraglutide.

New data submitted to the EMA in November 2010 for exenatide BID from an epidemiological study using an i3 Aperio tool raises serious concerns. A re-analysis of the i3 Aperio assessment of pancreatic and thyroid neoplasms in patients using exenatide compared to those using metformin and glyburide, provides results (RR 1.7, 1.2-2.3) that are in conflict with the previously submitted study report submitted in December 2009 to the EMA with respect to thyroid cancer. However, although the clinical relevance of the rodent thyroid C-cell tumours cannot be fully excluded, the clinical findings on thyroid tumours should not be taken as support for a clinical relevance of the non-clinical findings, given that the observed tumours were not of C-cell origin.

The concern of thyroid cancer was identified as a major objection by CHMP in the second List of outstanding Issues. This issue is further discussed under the clinical section. The findings of C-cell adenomas and/or carcinomas in the rat carcinogenicity study have been reflected in section 5.3 of the SmPC.

Additional findings in the carcinogenicity study were parathyroid gland adenoma in mid-dose and high-dose males. The Applicant argued that the occurrence of the parathyroid gland tumours might be spontaneous. It is not likely that parathyroid adenomas might be due to an elevated PTH secretion. In addition there is up till now no evidence for a GLP-1 receptor expression in parathyroid gland.
**Reproduction Toxicity**

No studies on reproductive and developmental toxicity were performed with exenatide QW. The applicant argued that the studies performed with exenatide to support the Exenatide BID application were sufficient to characterize the developmental and reproductive toxicity potential.

The following text, derived from the Byetta EPAR, summarizes the findings from these studies:

"Exenatide showed no effect on fertility and early embryonic development in mice. In the embryo-foetal toxicity studies in mice and rabbits, maternal food consumption and body weights were reduced. In both species, developmental toxicity occurred in conjunction with maternal toxicity. Pregnant rabbits exhibited a particularly high sensitivity to the anorexogenic activity of exenatide. It was not clear to what extent this high sensitivity was specific for pregnant animals. In mice, foetal growth was slowed, and there were skeletal variations associated with slowed foetal growth, including changes in number of ribs pairs or vertebral ossification site and wavy ribs. The NOEL for developmental toxicity in mice was 6 μg/kg/day (3 times the human exposure). In rabbits, developmental toxicity was manifested as morphologic markers of foetal growth retardation (umbilical hernias and skeletal variations). In a second rabbit study, additional groups were pair-fed (fed the same average daily amount of food) to match the three exenatide-dosed groups. In the pair-fed animals, skeletal variations occurred at similar incidences in exenatide and pair-fed animals. Umbilical hernias were not observed in pair-fed animals. However, the pair-fed animals did not demonstrate maternal toxicity to the same extent as exenatide-dosed animals. In exenatide-treated animals but not in pair-fed animals, water consumption and body weights were decreased. The NOEL for developmental toxicity in rabbits was 2 μg/kg/day (12 times human exposure).

In the perinatal and postnatal developmental toxicity study in mice, developmental effects occurred in the F1 offspring in conjunction with maternal toxicity. Developmental toxicity was indicated by increased perinatal and neonatal mortality in the F1 offspring of the high-dose group (760 μg/kg/day), and by reduced growth in the F1 offspring of the mid-dose group (668 μg/kg/day). The NOEL for developmental toxicity was 6 μg/kg/day (3 times human exposure).

It thus has been concluded, that exenatide is not considered teratogenic. The control of blood glucose is of great importance during pregnancy and this is best achieved by insulin treatment. Exenatide should therefore not be used during pregnancy, which is reflected in the SPC section 4.6.

In the view of the CHMP the studies on reproductive and developmental toxicity with immediate release exenatide were not considered sufficient to evaluate the reproductive and developmental toxicity potential of exenatide QW. The exenatide BID studies did not sufficiently take into account the potential effects of continuous pharmacological activity.

In patients treated with exenatide QW, exenatide will remain in plasma at levels above LLOQ (10 pg/ml) for 10 weeks after treatment interruption. Therefore, in case of an unplanned pregnancy, exposure throughout a large part of the organogenesis period cannot be avoided. It is critical that a thorough non-clinical investigation of the developmental toxicity of exenatide QW is performed. The CHMP considered this as a major objection in the List of Questions and 1st List of outstanding issues. In response to the CHMP’s concern, the applicant has demonstrated that the embryofetal toxicity study in the rabbit using immediate release exenatide twice daily was associated with continuous pharmacological activity at the two highest doses. At these doses, there were findings on maternal and foetal toxicity (growth retardation/developmental delay). There was no evidence for teratogenicity.

Moreover, the applicant has performed an embryofetal toxicity study with exenatide QW in the rat. No final report for the study is available yet (will be submitted as post-approval commitment), but the data demonstrate foetal toxicity, characterized by a decreased foetal weight, in association with maternal effects (decreased food intake and body weight increase). There is no evidence for a teratogenic activity.

In conclusion, exenatide extended release shows similar effects as immediate release exenatide in the developmental toxicity studies. With the immediate release formulation there was a small exposure margin for foetal effects at the NOAEL; this is not the case for the extended release formulation. The foetal effects (lower weight, skeletal findings suggestive of growth retardation/delay in the rats) are likely a direct consequence of the lower food intake in the dams, and should therefore be possible to avoid in the clinical setting.

It is clear that treatment with exenatide should be avoided in pregnancy. A recommendation not to use Bydureon during pregnancy has been included in section 4.6 of the SmPC. However, due to the long washout period for Bydureon, a cautious recommendation for use in women of childbearing potential is warranted. Therefore the SmPC, section 4.6 states that women of childbearing potential should use contraception during treatment with Bydureon.
**Local Tolerance**

Separate local tolerance studies were not conducted with exenatide QW as local tolerance assessment was integrated into the design of the repeated dose toxicity studies. Injection site reactions were observed. Injection site reactions were also observed in the clinical programme, which to some degree, seems to be associated with the development of treatment-emergent antibodies, but also to the delivery system as such. Most reactions were mild to moderate in severity and resolved spontaneously without need for medical intervention. However as they could constitute a problem for the patient, advice on how to handle these reactions have been included in the SmPC, section 4.8. (see further under clinical discussion)

**Other toxicity studies**

- **Antigenicity**

  Antibody formation against exenatide occurred to a considerable extent. Immunogenicity was higher for exenatide QW than for exenatide BID. Antibodies to exenatide were observed in 25 – 46% of rats and 58 – 75% of monkeys. This extended duration of exposure and a potential adjuvant effect of microspheres could contribute to the increased antibody response. While these treatment-emergent antibodies altered exposures to variable degrees, the nonclinical species were exposed to exenatide over the course of the studies in a predictable manner. As such, these antibodies do not appear to have compromised the safety evaluation of exenatide QW as relevant pharmacodynamic effects (e.g. decreased food consumption) were observed in the toxicity studies. Also, there is no evidence from the repeat-dose toxicity studies that the anti-exenatide antibodies resulted in immune-mediated disease. It is concluded that exenatide QW appears to be more immunogenic than exenatide BID, as expected by the particulate nature of the formulation which is expected to lead to a more efficient antigen presentation. The nonclinical data do not reveal any important consequences of the immune response to exenatide. The clinical importance of exenatide antibodies must be judged from clinical data. (see clinical discussion).

- **Immunotoxicity**

  No data on immunotoxicity are presented. In the 9 month repeat-dose toxicity in monkeys supporting the exenatide BID application, the immune response to keyhole limpet hemocyanin (KLH) was evaluated. There was no exenatide-related effect on the anti-KLH antibody response. There were no findings in the toxicity studies with exenatide QW suggesting an immunotoxic potential.

- **Studies on impurities**

  No studies were performed with specific exenatide-related impurities. Drug substances and drug products from different sources and different manufacture scale were studied for genetic toxicity and repeat dose toxicity in mice or rats. No differences between the different sources of drug substance / drug product were observed.

- **Other studies**

  The applicant refers to published data on the safety of biodegradable poly(D,L-lactide-co-glycolide) (PLG) microspheres. PLG polymers are used in medical devices and in a number of medicinal products to allow sustained delivery of proteins and peptides. PLG polymers have been shown to exhibit low systemic toxicity, not to cause any reproductive and developmental effects, and have been negative in studies for genotoxicity and carcinogenicity. The observed injection site reactions seem to be mostly caused by PLG polymers.

**2.3.5. Ecotoxicity/environmental risk assessment**

No environmental risk assessment has been performed, which is in line with the CHMP guideline which states that peptides are exempted from such assessment.
2.3.6. Discussion on non-clinical aspects

Endogenous GLP-1 is released mainly by intestinal L cells in response to food intake. GLP-1 is rapidly inactivated by the enzyme DPP-4. Thus, under physiological conditions, the activity of GLP-1 is limited in time. Exenatide and other analogues of GLP-1 can be used for pharmacological treatment of diabetes, since they are more stable than GLP-1. Still, exenatide has a half-life of a few hours, with a twice daily treatment (the approved dosing for Exenatide BID) is associated with a transient period of GLP-1 receptor activation followed by a period of drug holiday and no receptor activation. Exenatide QW is developed to exhibit a constant exposure at a pharmacological active level. While this may allow stronger beneficial effects in terms of glucose control, there are uncertainties what this will mean for safety as discussed below. While no other differences have been observed in toxicity studies, which would imply a different toxicity profile with exenatide QW, the unphysiological constant activation of GLP-1 receptors is a concern that has been considered in the overall benefit-risk assessment.

Repeat dose toxicity studies with exenatide QW in rats and monkeys did not identify any novel toxicity associated with the extended release formulation. However, the carcinogenicity study in rats showed a clear difference to the previous study with immediate release exenatide. Exenatide QW caused C-cell tumours in both sexes, with no safety margin to clinical exposure. The applicant refers to the findings on thyroid tumours in the carcinogenicity study show that this difference may result in potential. Bydureon has been developed to result in a constant exposure, which in contrast to what is the case with the immediate release formulation leads to a continuous activation of the GLP-1 receptor. The findings on thyroid tumours in the carcinogenicity study show that this difference may result in dramatic differences in vivo. It cannot be excluded that GLP-1 receptors are involved in metabolic events occurring in the maternal-fetal interface, and that the continuous receptor activation may lead to events not predicted from studies with the immediate release formulation. In the List of Questions and 1st List of outstanding issues the absence of such studies was considered a major objection and a request for studies addressing the embryofetal toxicity of exenatide QW was included.

Additional findings in the carcinogenicity study were parathyroid gland adenoma in mid-dose and high-dose males. CHMP agreed that these findings are likely to be spontaneous and that there is no rational for a mechanism similar or related to the one proposed for the occurrence of thyroid tumours (activation of GLP-1R on thyroid c-cells and up-regulation of calcitonin production).

Antibody formation against exenatide occurred to a considerable extent. Immunogenicity was higher for Bydureon than for Exenatide BID. Antibodies to exenatide were observed in 23 – 46% of rats and 58 – 75% of monkeys. This extended duration of exposure and a potential adjuvant effect of microspheres could contribute to the increased antibody response. There were no indications for immune-mediated disease.

In the original application there were no studies on reproductive and developmental toxicity with exenatide QW. The applicant argued that the studies performed with exenatide to support the Exenatide BID application were sufficient to characterize the developmental and reproductive toxicity potential. Bydureon has been developed to result in a constant exposure, which in contrast to what is the case with the immediate release formulation leads to a continuous activation of the GLP-1 receptor. The findings on thyroid tumours in the carcinogenicity study show that this difference may result in dramatic differences in vivo. It cannot be excluded that GLP-1 receptors are involved in metabolic events occurring in the maternal-fetal interface, and that the continuous receptor activation may lead to events not predicted from studies with the immediate release formulation. In the List of Questions and 1st List of outstanding issues the absence of such studies was considered a major objection and a request for studies addressing the embryofetal toxicity of exenatide QW was included.

Analysis of PK data from the rabbit developmental study with immediate release exenatide showed that at the two highest doses, plasma exposure was continuously above a level associated with pharmacological activity. This study is therefore considered acceptable for assessing the effects of exenatide QW. In the response to the CHMP question, the company has submitted data from a developmental study in rats with exenatide QW. In the dams treated with exenatide, food intake and body weight gain was decreased. As a consequence of this fetal weights were decreased at all doses. There was no evidence for teratogenic activity. No full report is yet available for this study. The study report should be submitted when available (Follow-up measure).

In conclusion, exenatide extended release shows similar effects as immediate release exenatide in the developmental toxicity studies. With the immediate release formulation there was a small exposure margin for foetal effects at the NOAEL; this is not the case for the extended release formulation. The foetal effects (lower weight, skeletal findings suggestive of growth retardation/delay in the rats) are
likely a direct consequence of the lower food intake in the dams, and should therefore be possible to avoid in the clinical setting.

It is clear that treatment with exenatide should be avoided in pregnancy. A recommendation not to use Bydureon during pregnancy has been included in section 4.6 of the SmPC. Due to the long washout period for Bydureon, section 4.6 of the SmPC also includes a recommendation that women of childbearing potential should use contraception during treatment with Bydureon.

2.3.7. Conclusion on the non-clinical aspects

The unknown risks associated with the continuous unphysiological activation of GLP-1 receptors have been considered in the overall benefit-risk assessment. The necessary information and recommendations have been included in the SmPC. Although the Applicant already presented data from the rat embryofoetal toxicity study with exenatide QW, the full study report should be submitted as a Follow-up measure.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Bydureon (exenatide) according to Article 8 (3) (full application) for the treatment of patients with type 2 diabetes mellitus. Currently, exenatide is authorised as Byetta 5μg and 10μg (EU/1/06/362/001-004). Byetta is a solution for injection which is injected twice a day while Bydureon is a 2 mg suspension formulation which allows QW administration of exenatide. Bydureon thereby represents the first long acting GLP-1 analogue being submitted for marketing authorisation. As a different invented name has been assigned to clearly differentiate the two formulations, a separate marketing authorisation application is being submitted.

The proposed indication for Bydureon is identical to the indication of Byetta and is proposed to be for the treatment of type 2 diabetes mellitus in combination with metformin, sulphonylurea, thiazolidinedione, metformin and sulphonylurea, metformin and thiazolidinedione in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

The recommended Bydureon dose is 2 mg exenatide once weekly, administered at any time of day, with or without meals. The dose should be administered in the abdomen, thigh, or upper arm as a subcutaneous injection immediately after suspension of the powder in the solvent. The exenatide once weekly formulation consists of exenatide (5%) and sucrose (2%) encapsulated within biodegradable poly(D,L-lactide-co-glycolide) (PLG) microspheres that are designed to release exenatide over an extended period of time. Following subcutaneous administration, the polymer biodegrades over time (Riley et al. 1997), providing extended release of exenatide into the circulation. PLG has a history of safe use in human sutures, bone plates and extended release pharmaceuticals. The slow absorption, steady-state concentration profile, and weekly dosing regimen of exenatide once weekly is suggested to provide several therapeutic advantages over exenatide twice daily. Specifically, exenatide twice daily is administered within the 60-minute period before the morning and evening meals and, given a half-life (t1/2) of approximately 2.4 hours, exerts its pharmacodynamic effects predominantly on glucose concentrations during the postprandial period of those meals. In contrast, exenatide once weekly provides continuous exenatide exposure, with a potentially improved glycemic control throughout the day. The gradual increase in exenatide exposure to target therapeutic steady-state concentrations appears to result in improved tolerability of exenatide once weekly compared with exenatide twice daily. Furthermore, the weekly administration frequency may be more convenient than twice daily administration and therefore may improve patient adherence to therapy.
The Applicant has received two CHMP advices during the development programme:

- **CHMP Follow-up Scientific Advice for exenatide once weekly clinical program (July 2007)**
  Advice was given on comparability issues (quality), dose-finding, drug interactions, the need for a QT study, the size of the safety data base, the appropriate background OADs and a possible monotherapy indication. In principal, the advice has been followed.

- **CHMP Follow-up Scientific Advice for exenatide once weekly clinical program (December 2009)**
  This advice concerned the design of the planned cardiovascular outcome study H80-MC-GWDQ.

**GCP**

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

The applicant 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.

The following should however be noted. One study site involved in Studies 2993LAR-105 and BCB106 was closed following the discovery of suspected GCP violations (US FDA notified in Investigational New Drug [IND] 67,092, Serial 0130, 17 December 2008). These violations were identified after completion of the 52-week clinical study report for Study 2993LAR-105. Only 3 subjects from this site participated in Study 2993LAR-105 and analyses indicated that removal of the data from these 3 subjects would have no impact on the primary endpoint. Six subjects enrolled in Study BCB106 were excluded from the 26-week evaluable population. These 6 subjects were included and analyzed in the intent-to-treat (ITT) population. Additionally, a sensitivity analysis was performed for the analysis of the primary endpoint by excluding these subjects from the ITT population demonstrating no impact. Otherwise, all clinical trials were conducted in adherence to the principles of GCPs.

- **Tabular overview of clinical studies**

  Exenatide once weekly has been evaluated in 10 controlled, completed or ongoing clinical studies (2993LAR-102, 2993LAR-103, 2993LAR-104, 2993LAR-105, BCB106, BCB107, BCB108, H80-JE-GWBW [GWBW], GWBR, and GWDC). Three single-dose studies (ALK23-001, 2993LAR-101, and 2993LAR-102) were performed to evaluate the safety and pharmacokinetics of different formulations of exenatide once weekly, resulting in selection of the AC2993-F17 (F17) formulation for further clinical development.
Table 2. Completed Studies and Number of Subjects (Intent to Treat) in the Exenatide QW Clinical Program

<table>
<thead>
<tr>
<th>Study Group - Completed Study</th>
<th>Length of Study (weeks)</th>
<th>Number of Subjects Exposed to Exenatide QW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Pharmacology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK23-001</td>
<td>[1]</td>
<td>--</td>
</tr>
<tr>
<td>2993LAR-101</td>
<td>[1]</td>
<td>--</td>
</tr>
<tr>
<td>2993LAR-102</td>
<td>[1]</td>
<td>10</td>
</tr>
<tr>
<td>2993LAR-103</td>
<td>[1]</td>
<td>47</td>
</tr>
<tr>
<td>BCB107</td>
<td>[1]</td>
<td>60</td>
</tr>
<tr>
<td><strong>Total Clinical Pharmacology</strong></td>
<td></td>
<td><strong>117</strong></td>
</tr>
<tr>
<td><strong>Efficacy and Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo-Controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-104</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>H8O-JE-GWBW</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td><strong>51</strong></td>
</tr>
<tr>
<td>Comparator-Controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCB106</td>
<td>26</td>
<td>160</td>
</tr>
<tr>
<td>H8O-MC-GWBR</td>
<td>26</td>
<td>233</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td><strong>670</strong></td>
</tr>
<tr>
<td>Uncontrolled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-105 Extension [4, 5]</td>
<td>74</td>
<td>130</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td><strong>264</strong></td>
</tr>
<tr>
<td><strong>Total Efficacy and Safety</strong></td>
<td></td>
<td><strong>985</strong></td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td></td>
<td><strong>1102</strong></td>
</tr>
</tbody>
</table>

[1] Single-dose studies; only the subjects exposed to AC2993-F17, the proposed commercial formulation, are presented.
[2] Subjects may have been exposed to exenatide QW for up to 104 consecutive weeks; 30 weeks during the comparator-controlled period and up to 74 weeks in the open-label extension of Study 2993LAR-105.
[4] The open-label extension of Study 2993LAR-105 consisted of 130 unique subjects exposed to exenatide QW; these subjects were previously treated with exenatide BID during the comparator-controlled, 30-week period of the study.
[5] Safety data for the open-label extension of Study 2993LAR-105 are analyzed for 74 weeks. Efficacy data from this extension are analyzed for 52 weeks: the 30-week comparator-controlled period and the 30-week data combined with 22 weeks of the open-label extension.

2.4.2. Pharmacokinetics

The clinical pharmacology of exenatide QW has been evaluated in 8 completed studies (Table 2) using the intended commercial formulation, F17. In these studies, 735 subjects were exposed to exenatide once weekly (70 subjects without diabetes, 665 subjects with type 2 diabetes). The main pharmacokinetic characterization of exenatide QW has been based on analyses of Studies 2993-103, -104 and -105.
Exenatide plasma concentrations were determined using an immunoenzymatic (IEMA) method.
Table 3. Studies Providing Clinical Pharmacology Data Regarding the Exenatide Once Weekly F17 Formulation [1]

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Exenatide Once Weekly Dosing/Duration</th>
<th>Study Sample</th>
<th>Intent-to-Treat</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Pharmacology (Single-Dose) Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-102</td>
<td>Single SC injection: 2.5 mg/8-week observation period</td>
<td>Healthy subjects</td>
<td>21</td>
<td>10 [3], [8]</td>
</tr>
<tr>
<td>2993LAR-103</td>
<td>Single SC injection: 2.5, 5, 7, or 10 mg/12-week observation period</td>
<td>Type 2 diabetes</td>
<td>62</td>
<td>47</td>
</tr>
<tr>
<td>BCB107</td>
<td>Single SC injection: 8 or 10 mg/101-day observation period</td>
<td>Healthy subjects</td>
<td>120</td>
<td>60 [3]</td>
</tr>
<tr>
<td><strong>Placebo-Controlled Efficacy and Safety Studies with Pharmacokinetics and Pharmacodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-104</td>
<td>Weekly SC injections: 0.8 mg or 2 mg/15-week treatment period and 12-week follow-up period</td>
<td>Type 2 diabetes</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>H8O-JE-GWBW</td>
<td>Weekly SC injections: 0.8 mg or 2 mg/10-week treatment period and 11-week follow-up period</td>
<td>Japanese subjects, Type 2 diabetes</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td><strong>Comparator-Controlled Efficacy and Safety Studies with Pharmacokinetics and Pharmacodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-105</td>
<td>Weekly SC injections: 2 mg/30-week treatment period and open-ended treatment period</td>
<td>Type 2 diabetes</td>
<td>295</td>
<td>278 [5]</td>
</tr>
<tr>
<td>BCB106</td>
<td>Weekly SC injections: 2 mg/26-week treatment period and open-ended treatment period</td>
<td>Type 2 diabetes</td>
<td>491</td>
<td>160</td>
</tr>
<tr>
<td>BCB108</td>
<td>Weekly SC injections: 2 mg/24-week treatment period</td>
<td>Type 2 diabetes</td>
<td>252</td>
<td>129</td>
</tr>
</tbody>
</table>

Abbreviation: BID = twice daily; SC = subcutaneous.

[1] Not included in this table are 2 clinical pharmacology studies (ALK23-001 and 2993LAR-101) that were performed with formulations other than the intended commercial formulation (F17) of exenatide once weekly.

[2] The clinical study report designated Study 2993LAR-103 as double blind. In this document, this extent of study blinding is referred to as single blind (i.e., the subjects, investigator, and study-site personnel were blinded [except study-site staff dispensing study medication]).

[3] Subjects in these studies received more than one formulation of exenatide once weekly. These numbers represent subjects who received the F17 formulation.

[4] Comparator was exenatide twice daily 5 mcg dosed BID for 4 weeks followed by exenatide twice daily 10 mcg dosed BID for 26 weeks.
[5] Includes 148 subjects exposed to exenatide once weekly during the 30-week assessment period and an additional 130 subjects newly exposed to exenatide once weekly during the open-ended assessment period.

[6] Comparators were sitagliptin 100 mg once daily in the morning, and pioglitazone 45 mg once daily in the morning.

[7] Comparator was exenatide twice daily 5 mcg dosed BID for 4 weeks followed by exenatide twice daily 10 mcg dosed BID for 20 weeks.

[8] N does not include one subject who withdrew after receiving lead-in therapy (exenatide BID) and before receiving exenatide once weekly.


**Absorption**

After a subcutaneous single-dose of the exenatide once weekly formulation the concentration-time curve is characterized by an initial rise in plasma exenatide concentrations during the first few hours after injection, followed by a gradual increase reaching peak plasma concentrations after 6-8 weeks. After continued weekly administration steady-state concentrations are reached after about 7-8 weeks. After once weekly administration of Bydureon a large accumulation was observed. Geometric mean steady-state concentration during a weekly interval of dosing with exenatide once weekly 2 mg were estimated to be approximately 8.6-fold higher than those observed after the first dose. Due to the large accumulation, the applicant has provided simulations and a discussion regarding the possibility of using a longer dosage interval (administration every 2 or 3 weeks). Doubling the dosage interval would probably result in steady-state levels within the desired therapeutic range. However, as inter-individual variability is high, a larger part of the patients would risk not reaching therapeutic levels. Hence, using a longer dosage interval may not be as therapeutically effective, which is consistent with the lower efficacy of the 0.8 mg exenatide once weekly dose used in Study 2993LAR-104. After discontinuation of treatment, plasma concentrations slowly decrease to reach non-quantifiable limits after about 10 weeks. This could be compared to exenatide twice daily where peak plasma concentrations are achieved in approximately 2 h and drug concentrations reach non-quantifiable limits in approximately 8 h after single-dose administration. There is also an indication of higher overall systemic exposure of exenatide following once weekly administration compared to the exenatide twice daily formulation.

The relative bioavailability compared to the exenatide twice daily formulation was approximately 22-25%. The final formulation has been used in all clinical studies with the exception of two early formulation screening studies. In the clinical studies, Bydureon has been manufactured at pilot scales and at commercial scale. PK-data indicate slight differences in exposure between the different manufacturing scales. However, the assessment of comparability has to rely on quality and clinical data.

Figure 2 presents the mean (SD) plasma exenatide concentration over time for repeated dosing of exenatide once weekly 2 mg.
Figure 2. Mean (SD) plasma exenatide concentration over time for exenatide once weekly 2 mg (Study 2993LAR-104; evaluable subjects [N = 15]).

Abbreviations: LLOQ = lower limit of quantification; SD = standard deviation.

Notes: The dotted vertical line indicates the beginning of the follow-up period after last injection at Week 14.
- Plasma exenatide concentrations less than the LLOQ (10 pg/mL) were included using an imputed value of LLOQ divided by 2 (5 pg/mL) and missing values were not included.

**Distribution**

No studies have been conducted with Bydureon. For exenatide BID, the mean apparent volume of distribution (Vz/F) was 28.3 L. Protein binding of exenatide to serum albumin has not been determined. *In vitro* 82% of exenatide has been shown to be associated with the plasma fraction and 18% with erythrocytes.

**Elimination**

No studies have been conducted with Bydureon. In previous studies with the exenatide twice daily formulation (Exenatide BID) the mean apparent volume of distribution (Vz/F) was determined to 28.3 L and the apparent clearance (CL/F) was 9.1 L. Exenatide is primarily renally cleared (by degradation and reabsorption in the renal tubules). The excretion of exenatide has not been evaluated. This is acceptable given that exenatide is a polypeptide. The *in vivo* metabolism of exenatide has not been evaluated. The lack of in vivo metabolism data is acceptable, given that exenatide is a polypeptide.

**Dose proportionality and time dependencies**

The dose proportionality of exenatide QW was assessed in Study 2993LAR-103 following single doses of 2.5-10 mg. Exenatide, administered as the once weekly formulation, displays roughly dose proportional pharmacokinetics up to 5 mg. At higher doses the increase in exposure was slightly less than dose-proportional. Geometric mean AUC (CV%) was 43777 (48), 94942 (37), 111827 (60) and 128048 (41) pg*h/ml in the 2.5, 5.0, 7.0 and 10.0 mg groups respectively. Consistent with the results of lower doses in study 2993LAR-103, weekly dosing of 0.8 mg and 2 mg resulted in proportional increases in steady-state plasma exenatide concentrations in Study 2993LAR-104. The mean (SD) Css,ave for subjects with quantifiable exenatide concentrations from Weeks 14 to 15 was 117.9 (59.1) pg/mL and 288.8 (134.0) pg/mL for the 0.8- and 2-mg doses, respectively.

Exenatide has time independent pharmacokinetics.
Inter-individual variability was relatively high and higher than reported for exenatide BID (70% variability in AUC and Css,av for Bydureon compared to about 50% for AUC and 55% for Cmax for exenatide BID).

Occurrence of antibodies towards exenatide results in increased systemic exposure, since total exenatide levels are measured and the larger complex cannot be excreted renally.

**Special populations**

No specific studies were performed to study the systemic exposure in various sub-populations following treatment with Bydureon. The main part of the information was obtained from the population PK analysis based on data from studies 2993LAR-104 and 2993LAR-105.

The population PK analysis was a simplified modelling approach where Css,av was modelled as an effect of dose and other covariates. Due to identified deficiencies in the modelling procedures the quantitative interpretation of the estimated effect of renal impairment should be made with caution and this was taken into account in the outcome with respect to dosing in renal impairment.

The influence of reduced hepatic function on exenatide pharmacokinetics has not been evaluated and no dosage adjustments for exenatide once weekly are recommended. Lack of data in hepatic impairment is acceptable given that exenatide is eliminated renally.

A statistically significant effect of renal impairment was estimated in the population PK analysis and it was indicated that the systemic exposure may increase up to approximately 74% and 23% in a typical individual with moderate and mild renal impairment, respectively, compared with a typical subject with normal renal function. This effect appears greater than the effect estimated for exenatide BID. Considering the limited experience in this specific population and the long wash out phase for exenatide QW, Bydureon should not be used in patients with moderate renal impairment until more data is available. This recommendation has been reflected in section 4.2 of the SmPC.

The population PK analysis did not identify any effects of sex, body weight or age in addition to the effect of renal function. Cross-study comparisons suggest similar pharmacokinetics in Japanese and Caucasian subjects. However, the number of Japanese subjects was limited. The population PK analysis cannot yield useful information with respect to race, since 82% of the subjects were Caucasian in the data set used.

There are no PK data in children or adolescents.

**Pharmacokinetic interaction studies**

- **In vitro**
  The potential for inhibition of CYP450 isoenzymes has not been evaluated. The lack of evaluation of the inhibitory potential of CYP450 isoenzymes is acceptable given that exenatide is a polypeptide.

- **In vivo**
  From studies with exenatide BID it is known that exenatide delays gastric emptying, which could delay absorption, decrease the absorption rate and to some extent decrease the extent of absorption of concomitantly administered drugs. Interaction studies with digoxin, warfarin, lisinopril, lovastatin and oral contraceptives have previously been conducted with the exenatide twice daily formulation.

  For Bydureon the effect of exenatide on gastric emptying was evaluated at steady state using paracetamol as a marker substrate. In Study 2993LAR-105, the effect of exenatide once weekly on paracetamol absorption was evaluated in a cohort of subjects. When 1,000 mg paracetamol tablets were administered, either with or without a meal, following 14 weeks of Bydureon therapy, no significant changes in paracetamol AUC were observed compared to the control period. Paracetamol Cmax decreased by 16 % (fasting) and 5 % (fed) and tmax was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed). The results indicate only a minor effect of Bydureon on gastric emptying which is not considered to be of clinical relevance. No specific instructions regarding concomitant administration of drugs sensitive to gastric delay is therefore considered necessary.

  No additional interaction studies have been performed with the exenatide once weekly formulation; the same interaction profile as exenatide twice daily is expected.
2.4.3. Pharmacodynamics

Mechanism of action

The original Byetta MAA included data from clinical studies to demonstrate that exenatide improves glycemic control in patients with type 2 diabetes by reducing fasting and postprandial glucose concentrations through the following actions:

- enhancement of glucose-dependent insulin secretion,
- restoration of first-phase insulin secretion,
- glucose-dependent suppression of glucagon secretion, and
- slowing of gastric emptying, resulting in slowed absorption of meal-derived glucose.

In addition, reductions in food intake have been observed, which may partly explain observed reductions in body weight.

The mechanism of action of exenatide QW is expected to be in general the same as for the BID formulation. However, the PK profile of exenatide QW is to some extent different compared to the BID formulation. A low bioavailability of slow-release exenatide compared to immediate-release exenatide has been shown both experimentally and clinically (approximately 20%). It could be questioned if long-acting exenatide could remain somewhere in a depot-like situation in subcutaneous tissue as well as the possible relationship of this potential situation with the higher immunogenicity compared to immediate-release exenatide. However, although long term follow-up data are not available, it is unlikely that exenatide once weekly does accumulate subcutaneously. It is more likely that a large amount of exenatide is hydrolysed due to the acids that develop after polymer hydrolyses. There is no difference in observed time-to peak response in terms of antibody formation, but, the adverse events profile for subjects with antibodies to exenatide QW differs to some extent from that of subjects receiving exenatide twice daily. However, most of the reactions were localised events and were mild in intensity.

Primary and Secondary pharmacology

The pharmacodynamics of exenatide QW was assessed in 5 efficacy and safety studies (2993LAR-104, H8O-JE-GWBW, 2993LAR-105, BCB106 and BCB108). See table 1 for summary on studies.

For Studies 2993LAR-105 and BCB108, both treatments resulted in decreases in fasting plasma glucose concentrations, but treatment with exenatide QW resulted in significantly greater reductions than those seen with exenatide BID therapy throughout the study possibly due to a more profound suppression of glucagon secretion.

On the other hand, the effect on postprandial glucose concentrations may be less pronounced. Postprandial plasma glucose profiles were assessed in a subset of subjects in the Evaluable Gastric-Emptying Cohort (Study 2993LAR-105). The LS mean (SE) change in 2-hour postprandial plasma glucose concentration at Week 14 compared with baseline was -5.33 (0.47) mmol/L with exenatide QW and -7 (0.46) mmol/L with exenatide BID.

Fasting insulin data were compared in study 2993LAR-105. Despite reductions in fasting plasma glucose concentrations of 1.39 mmol/L (25 mg/dL) with exenatide BID treatment and 2.3 mmol/L (42 mg/dL) with exenatide QW treatment, fasting insulin concentrations tended to increase slightly or remain unchanged over the course of treatment with exenatide QW, and remained largely unchanged with exenatide BID treatment.

In the MAA for Byetta, there were no preclinical or clinical indications of an effect of exenatide on QT interval. However, the Applicant has since then conducted a thorough QT study (Study H8O-EW-GWCI) examining a single 10-mcg dose of exenatide BID. Study H8O-EW-GWCI with the BID formulation showed a modest increase of the QTc interval (see table 3 below). However, several findings could be interpreted as reassuring:
- the QT interval did not exceed 500 msec
- exenatide BID has so far not been associated with proarrhythmic effects
- the results from the clinical trials do not indicate additional risks
- plasma concentrations of exenatide QW were not related to the QTc interval, indicating that the relationship between exenatide QW and QTc interval is weak.

CHMP however does not agree that this study shows that plasma concentrations of exenatide QW are similar to BID, since the Applicant compares maximum concentrations of exenatide twice daily with steady state concentrations of exenatide once weekly and plasma concentrations following the QW administration may exceed the plasma concentrations following bid administration, albeit in a minority
of patients. The CHMP is therefore of the opinion that a thorough QTc study should also be performed for the QW administration. However, due to the reasons mentioned above, this study is agreed to be performed post-approval.

Table 4. Statistical Comparison of Mean Changes from Predose in QTc Intervals Between 10 μg Exenatide and Placebo

<table>
<thead>
<tr>
<th>Parameter (msec)</th>
<th>Time (h)</th>
<th>10 μg Exenatide (N=62)</th>
<th>Placebo (N=62)</th>
<th>Least Squares Mean Difference (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF (^a)</td>
<td>1</td>
<td>3.58</td>
<td>-0.36</td>
<td>3.93 (1.74, 6.13)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.32</td>
<td>-0.49</td>
<td>5.81 (3.62, 8.00)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.46</td>
<td>0.44</td>
<td>4.02 (1.82, 6.22)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2.65</td>
<td>0.95</td>
<td>1.70 (-0.49, 3.90)</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>0.55</td>
<td>-0.70</td>
<td>1.25 (-0.94, 3.45)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-3.18</td>
<td>-4.45</td>
<td>1.27 (-0.92, 3.47)</td>
</tr>
<tr>
<td>QTcF (^b)</td>
<td>1</td>
<td>0.73</td>
<td>-0.32</td>
<td>1.06 (-0.98, 3.09)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.41</td>
<td>-0.03</td>
<td>2.44 (0.40, 4.47)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.42</td>
<td>0.99</td>
<td>0.43 (-1.61, 2.47)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-0.23</td>
<td>1.21</td>
<td>-1.44 (-3.48, 0.59)</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>-3.34</td>
<td>-2.72</td>
<td>-0.62 (-2.65, 1.41)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-4.26</td>
<td>-4.85</td>
<td>0.59 (-1.44, 2.63)</td>
</tr>
<tr>
<td>QTcF((^c))</td>
<td>1</td>
<td>3.99</td>
<td>-0.55</td>
<td>4.34 (2.12, 6.56)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.80</td>
<td>-0.54</td>
<td>6.34 (4.12, 8.56)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.93</td>
<td>0.39</td>
<td>4.53 (2.31, 6.76)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.09</td>
<td>0.94</td>
<td>2.15 (-0.07, 4.37)</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>1.23</td>
<td>-0.17</td>
<td>1.40 (-0.82, 3.62)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-2.87</td>
<td>-4.23</td>
<td>1.37 (-0.85, 3.59)</td>
</tr>
<tr>
<td>Model based</td>
<td>1</td>
<td>0.67</td>
<td>-0.46</td>
<td>1.14 (-1.12, 3.39)</td>
</tr>
<tr>
<td>QTc (^d)</td>
<td>2</td>
<td>1.82</td>
<td>-0.27</td>
<td>2.09 (-0.24, 4.33)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.08</td>
<td>0.70</td>
<td>0.38 (1.95, 2.71)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-0.30</td>
<td>1.16</td>
<td>-1.46 (-3.74, 0.82)</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>-4.70</td>
<td>-4.84</td>
<td>0.14 (-2.00, 2.29)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-5.10</td>
<td>-5.97</td>
<td>0.87 (-1.27, 3.01)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; N = number of subjects studied; QTcF = Fridericia QT correction; QTcI = individual QT correction; QTcP = population QT correction.

\(^a\) ANOVA model: Change in QTc = TIME + TREATMENT + TREATMENT*TIME with random effects for SUBJECT, SUBJECT*TREATMENT.

\(^b\) ANOVA model: Change in QTc = SEQUENCE + TIME + TREATMENT + TREATMENT*TIME with random effects for SUBJECT, SUBJECT*TREATMENT.

\(^c\) ANCOVA model: Change in QT = Change in RR + TIME + TREATMENT + TREATMENT*TIME with random effects for SUBJECT, SUBJECT*TREATMENT.

\(^d\) Least squares means estimated at change in RR=0 at each timepoint for model based correction.

2.4.4. Discussion and conclusion on clinical pharmacology

The systemic exposure following once weekly administration of Bydureon has been characterised following single doses and multiple dosing in type 2 diabetic patients. Treatment with Bydureon results in a constant exposure to exenatide, in contrast to the daily fluctuating concentrations levels following twice daily treatment with exenatide BID. In comparison with exenatide BID, overall systemic exposure is higher following treatment with Bydureon and the washout period is long, which can have potential implications for clinical safety. A statistically significant effect of renal impairment was estimated in the population PK analysis and it was indicated that the systemic exposure may increase up to approximately 74% and 23% in a typical individual with moderate and mild renal impairment, respectively, compared with a typical subject with normal renal function. For Bydureon, the effect of exenatide QW on gastric emptying was evaluated at steady state using paracetamol as a marker substrate. The results indicate only minor effect of Bydureon on gastric emptying which is not considered to be of clinical relevance.

The mechanism of action of exenatide QW is in general the same as for the BID formulation with indications of a more pronounced effect on fasting plasma glucose.

Possible effects on QT intervals need to be further assessed post-approval in a QTc study.
2.5. **Clinical efficacy**

2.5.1. **Dose response studies**

Nonparametric simulations based on exenatide QW single-dose data from the PK study 2993LAR-103 suggested that weekly doses of 0.8 and 2 mg would bracket the lower end and optimal range of efficacious concentrations, and therefore, would be suitable doses for further testing.

The exenatide BID program showed that an exenatide plasma concentration of approximately 50 pg/mL is required to provide a measurable glucose reduction. Accordingly, the Cmax achieved with a 10-mcg exenatide BID dose (geometric mean [10th, 90th percentile]: 211 pg/mL [100, 385 pg/mL]) was considered a desirable therapeutic target for the exenatide QW clinical development program.

Subsequently, the weekly doses of 0.8 and 2 mg were used in the placebo-controlled studies phase 1/2 studies 2993LAR-104 and H80-JE-GWBW. (Study GWBW was a Phase 1 study conducted in Japanese subjects with type 2 diabetes. The efficacy results from this study have not been presented in support of this submission). Additional support for the dose-selection strategy was provided by retrospective analyses of data from Studies 2993LAR-104 and 2993LAR-105 using the exposure-response model.

**Study 2993LAR-104**

This was a Phase 2, randomized, double-blind, placebo-controlled, multicenter study with the primary objective to examine safety and pharmacokinetics of exenatide QW 0.8 or 2 mg for 15 weeks in 45 subjects with type 2 diabetes. At Week 15, the mean changes in HbA1c compared to baseline (approximately 8.5%) were -1.4 (0.3)% and -1.7 (0.3)% for the 0.8 and 2 mg exenatide QW treatment groups, respectively. HbA1c increased by 0.4 (0.3) % for the placebo group.

Subjects in the exenatide QW 2 mg treatment group lost body weight, with a mean (SE) reduction of 3.8 (1.4) kg at Week 15 compared to baseline; body weight remained relatively unchanged in the exenatide QW 0.8 mg and placebo treatment groups.

At Week 15, mean plasma exenatide concentrations for the 0.8 mg and 2 mg exenatide QW groups were 104.4 (55.4) pg/mL and 233.5 (193.0) pg/mL, respectively. Thereafter, plasma exenatide concentrations gradually declined throughout the 12-week follow-up period. Seven weeks after the last injection of exenatide, mean plasma exenatide concentrations were below the anticipated therapeutic threshold (< 50 pg/mL).

Even though the 0.8 mg dose resulted in a clinically relevant reduction of HbA1c, no weight reduction was seen and the mean plasma exenatide concentration was lower compared to the 10-mcg exenatide BID dose. Thus, the 2 mg dose was chosen for the phase III studies.

2.5.2. **Main studies**

Demonstration of safety and efficacy of exenatide QW largely relies on 4 comparator-controlled studies. Study 2993LAR-105 and BCB108 compared the effect on glucose control of exenatide QW to exenatide BID in subjects with type 2 diabetes treated with OAD therapy or diet and exercise alone. Study BCB106 compared exenatide QW to sitagliptin and pioglitazone in subjects with type 2 diabetes on metformin treatment, and Study H80-MC-GWBR compared exenatide QW to insulin glargine in subjects with type 2 diabetes treated with metformin alone or metformin plus a sulfonylurea.

Patients eligible for add-on treatment with exenatide QW should be failures on maximally tolerated dose of the background therapy. Furthermore, comparators in clinical trials should be optimally dosed. The Applicant has provided additional information showing that the number of patients at baseline on TZD, SU and Met as well as mean doses of these treatments reflected inclusion criteria in the studies and did not differ substantially between exenatide QW groups and comparator groups.

Dose adjustments during the studies were primarily done for SU in line with study protocols. The mean doses of the comparators in the comparator-controlled studies were in line with treatment recommendations.
Study 2993LAR-105
This is a Phase 3, ongoing, open-label, randomized, comparator controlled trial comparing the long-term effects of exenatide QW and BID in terms of safety, tolerability, and glucose control in subjects treated with diet and exercise alone or with OADs. Study 2993LAR-105 further assessed the long-term safety and efficacy of exenatide QW and examined the switch from exenatide BID to QW in an open-ended assessment period. Results are reported through the 52-week assessment period of which has been completed; the open-label assessment period is ongoing.

Two hundred ninety-five ITT subjects were included, treated with diet modification and exercise and/or a stable regimen of metformin, SU, TZD, a combination of metformin and SU, a combination of metformin and TZD, or a combination of SU and TZD for a minimum of 2 months prior to screening. Additional eligibility criteria included screening HbA1c of 7.1% to 11.0% and body mass index (BMI) of 25 kg/m2 to 45 kg/m2. Patients with a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator, including hepatic, renal, cardiovascular and gastrointestinal conditions, were excluded.

Randomization was stratified by HbA1c (< 9.0% and ≥ 9.0%) at screening and by whether or not a subject was taking a concomitant SU agent at screening.

Treatment started with a 3-day exenatide BID 5 mcg lead-in period for both groups followed by 30-week assessment period of exenatide QW 2 mg or exenatide BID 5 mcg for 4 weeks followed by exenatide BID 10 mcg therapy and an open-ended assessment period of exenatide QW therapy. Subjects in both treatment groups that were treated with an SU were required to decrease their SU dose to the minimum recommended dose on Day –3 to minimize the risk of hypoglycemia. Subjects randomized to exenatide BID were required to decrease their SU dose again at Week 30, preceding the switch to exenatide QW.

**Figure 3. Study 2993LAR-105**

**Primary objectives**
- To compare the effect on glucose control, as measured by HbA1c, of exenatide QW administered by subcutaneous injection to that achieved by exenatide BID for 30 weeks in subjects with type 2 diabetes
- To examine the safety and tolerability of exenatide QW administered subcutaneously for 30 weeks in subjects with type 2 diabetes
- To examine glucose control during the transition from treatment with exenatide BID to exenatide QW administered subcutaneously in subjects with type 2 diabetes

**Secondary objectives**
- To examine the effects of exenatide QW administered subcutaneously for 30 weeks in subjects with type 2 diabetes on the following: body weight, fasting and postprandial glucose and insulin, fasting glucagon, proinsulin and lipids, rate of gastric emptying,
- Exenatide pharmacokinetics, homeostatic model assessment (HOMA), and patient reported outcomes (PROs) in terms of the change in satisfaction and the impact of weight change on quality of life
- To examine the incidence and rate of hypoglycemic events associated with SU management (reducing the SU dose upon initiation of treatment) for subjects using a concomitant SU
To examine the long-term (at least 52 weeks of treatment) effect on glucose control (HbA1c) of exenatide QW administered subcutaneously in subjects with type 2 diabetes

To assess the long-term (at least 52 weeks of treatment) safety and tolerability of exenatide QW administered subcutaneously in subjects with type 2 diabetes

Statistics

**Efficacy:** The primary study endpoint was change in HbA1c from baseline to Week 30. Noninferiority of the change in HbA1c with exenatide QW versus that with exenatide BID was demonstrated if the upper limit of a two-sided 95% confidence interval (CI) for the difference between exenatide QW and exenatide BID fell beneath 0.4%; superiority of exenatide QW was demonstrated if the CI fell below zero. The least squares (LS) mean change in HbA1c from baseline to Week 30 was estimated for each treatment using an analysis of variance model (ANOVA). Proportions of subjects achieving HbA1c target values of ≤6.0%, ≤6.5%, and ≤7.0% were compared between treatments. The LOCF approach was applied to estimate missing values at Day 1 through Week 30.

**Anthropometric Measures:** An analysis of covariance model (ANCOVA) was used to compare treatment groups with respect to change in body weight. Waist and hip circumferences were summarized.

**Pharmacokinetics:** Pharmacokinetic parameters were determined using the non-compartmental method.

**Pharmacodynamic Variables:** An ANCOVA model was used to compare treatment groups with respect to change in the analyte. Seven-point SMBG profiles were summarized descriptively by treatment. Pharmacodynamic parameters for postprandial glucose and insulin were determined using the non-compartmental method and an ANOVA model used to compare treatment groups.

**Patient Reported Outcomes:** A 2-sided 95% CI was calculated for differences in PRO scores between treatments.

**Safety:** Treatment-emergent adverse events, including events leading to withdrawal and serious events, were summarized by treatment. Treatment-emergent hypoglycemic events were summarized separately by treatment and concomitant SU use at screening. Clinical hematology, chemistry, and urinalysis results.

**Study BCB 108**

This was a Phase 3, randomized, open-label, comparator-controlled, 2-arm study with a 24-week treatment period of subcutaneously administered exenatide QW 2 mg and exenatide BID 5 mcg for 4 weeks followed by exenatide BID 10 mcg for 20 weeks. Patients were 252 ITT subjects (204 evaluable subjects) treated with diet and exercise alone or in combination with a stable regimen of metformin, an SU, a TZD, a combination of metformin and an SU, a combination of metformin and a TZD, or a combination of an SU and a TZD for a minimum of 2 months prior to screening. Additional eligibility criteria included screening HbA1c of 7.1% to 11.0% and body mass index (BMI) of 25 kg/m2 to 45 kg/m2.

No exenatide BID lead-in period prior to the first dose of exenatide QW was included in Study BCB108. Similarly, no required dose adjustment of concomitant SU agents was required, although, at the discretion of the investigator, dose reductions in concomitant SU agents were allowed in the event of hypoglycemia.

**Figure 4. Study BCB 108**

Abbreviation: SC, subcutaneous.

[1] Visit 2 (Day 1) occurred within 14 days following Visit 1 (Screening). Subsequent visits occurred at the indicated interval (±2 days) relative to Visit 2.
Primary objectives
To compare the effect on glucose control, as measured by HbA1c, of exenatide QW to that of exenatide BID in subjects with type 2 diabetes

Secondary objectives
- To examine the effects of exenatide QW in subjects with type 2 diabetes on fasting plasma glucose concentration and body weight
- To examine the pharmacokinetics of exenatide QW in subjects with type 2 diabetes
- To examine the safety and tolerability of exenatide QW in subjects with type 2 diabetes

Statistics
Efficacy: The change in HbA1c between exenatide QW and exenatide BID from baseline to Week 24 (primary study endpoint) was compared using a general linear model (GLM), including factors for treatment group, baseline HbA1c stratum (<9.0% or ≥9.0%), and concomitant SU use at screening (with SU or without SU). Noninferiority of the change in HbA1c with exenatide QW versus that with EXENATIDE BID was demonstrated if the upper limit of a two-sided 95% confidence interval (CI) for the difference between exenatide QW and EXENATIDE BID fell beneath 0.4%; superiority of exenatide QW was demonstrated if the CI fell below zero. Proportions of subjects achieving HbA1c <7.0% at Week 24 were compared between treatments using a Cochran-Mantel-Haenszel (CMH) test adjusting for baseline HbA1c stratum and concomitant SU use at screening. The proportion of subjects achieving the HbA1c ≤6.5% at Week 24 was summarized. In the ITT Population, missing postbaseline efficacy, anthropometric, and pharmacodynamic data up to Week 24 were imputed using the last observation carried forward (LOCF) approach for subjects who had data for at least one scheduled visit (including Early Termination) subsequent to the baseline measurement.

Safety Endpoints: Treatment-emergent adverse events, including events leading to withdrawal and serious events, were summarized by treatment. Treatment-emergent hypoglycemic events were summarized separately by treatment and concomitant SU use at screening. Clinical hematology, chemistry, and urinalysis results, vital signs, and the change in antibody to exenatide status over time were summarized. Data from physical examinations were listed.

Study BCB 106
This was a Phase 3b, randomized, double-blind, comparator-controlled, 3-arm study with a 26-week treatment period of exenatide QW (exenatide QW 2 mg subcutaneously plus placebo by mouth every morning), sitagliptin (sitagliptin 100 mg by mouth every morning plus placebo subcutaneously QW), or pioglitazone (pioglitazone 45 mg by mouth every morning plus placebo subcutaneously QW). A single arm, open-ended assessment period with exenatide QW 2 mg administered subcutaneously is currently ongoing.

Included patients were 491 ITT subjects (387 evaluable subjects) treated with a stable regimen of metformin for a minimum of 2 months prior to screening. Additional eligibility criteria included screening HbA1c of 7.1% to 11.0% and body mass index (BMI) of 25 kg/m2 to 45 kg/m2.
Primary objectives
To compare the effect of exenatide QW to those of sitagliptin and pioglitazone on glucose control, as measured by HbA1c, in subjects with type 2 diabetes

Secondary objectives
• To examine the safety and tolerability of exenatide QW compared to sitagliptin and pioglitazone in subjects with type 2 diabetes
• To compare the effects of exenatide QW to those achieved by sitagliptin and pioglitazone in subjects with type 2 diabetes on the following:
  o body weight
  o parameters related to glycemic control, including fasting and postprandial plasma glucose and insulin, 6-point SMBG profiles, and 1,5-anhydroglucitol (1,5-AG)
  o parameters related to cardiovascular health, including fasting lipids, cardiovascular risk markers, postprandial triglycerides, and blood pressure

Statistics
Efficacy: The primary study endpoint was change in HbA1c from baseline to Week 26. Superiority of exenatide QW to sitagliptin or pioglitazone was demonstrated if the Hochberg adjusted p-value for the pairwise comparison (exenatide QW vs. sitagliptin or exenatide QW vs. pioglitazone) was less than 0.05 based on a general linear model which included factors for treatment group, country, and baseline HbA1c stratum (<9.0% or ≥9.0%). The least squares (LS) mean change in HbA1c from baseline to Week 26 for each treatment and the difference in LS means between exenatide QW and sitagliptin or pioglitazone were estimated using this model. The primary analysis was based on the ITT Population using imputed data. Proportions of subjects achieving HbA1c target values of ≤6.5% and ≤7.0% were compared between treatments using the Cochran-Mantel-Haenszel procedure.

Anthropometric Measures and Blood Pressure: A general linear model was used to compare treatment groups with respect to change in body weight, waist and hip circumferences, and systolic and diastolic blood pressure.

Pharmacokinetics: Plasma exenatide concentrations were summarized descriptively.

Pharmacodynamic Variables: A general linear model was used to compare treatment groups with respect to change in the analyte. HOMA-B and HOMA-S were computed from a computerized HOMA model and a general linear model was used for comparison in HOMA-B and HOMA-S between treatment groups.

Patient Reported Outcomes: A general linear model was used to compare the change in PRO scores across treatments.

Safety: Treatment-emergent adverse events, including events leading to withdrawal, serious events, and hypoglycemic events were summarized by treatment. Clinical hematology, chemistry, and urinalysis results, vital signs, and the change in antibody to exenatide status over time were summarized.
**Study H8O-MC-GWBR**

This was a phase 3, open-label, randomized, comparator-controlled, 2-arm study with a 26-week treatment period of exenatide QW 2 mg administered subcutaneously and insulin glargine once daily. Patients were instructed to adjust insulin doses to achieve a target fasting blood glucose (FBG) of 4.0 to 5.5 mmol/L by increasing insulin doses 2 to 4 IU when FBG was >5.5 mmol/L for 3 consecutive days. If FBG was <4.0 mmol/L or the patient experienced symptoms of hypoglycemia without a reasonable explanation (e.g., exercise or illness), the patient was asked to decrease the insulin dose by 2 IU/day. Insulin glargine was to be injected at approximately the same time each day, preferably at bedtime.

Four hundred and fifty-six ITT subjects were included. Patients were at least 18 years old, had been treated with Met therapy alone or Met therapy in combination with SU for at least 3 months and a stable dose for at least 8 weeks prior to screening, had an HbA1c between 7.1% and 11.0% (inclusive), a body mass index (BMI) of 25 kg/m² to 45 kg/m² (inclusive), and a stable weight for at least 3 months. Patients with a clinically significant history of cardiac disease, liver disease, renal disease, oncolytic disease, or proliferative retinopathy were excluded.

An open-label, 2-arm, comparator-controlled, open-ended extension period is currently ongoing with exenatide QW 2 mg administered subcutaneously and insulin glargine once daily expected to continue at least 130 weeks.

**Figure 6. Study GWBR**

**Primary objectives**

To compare the effect of exenatide QW to that of insulin glargine once daily on glucose control, as measured by HbA1c, in subjects with type 2 diabetes and inadequate glycemic control using metformin alone or in combination with SU

**Secondary objectives**

To compare the effect of exenatide QW to that of insulin glargine with respect to:
- proportion of subjects achieving HbA1c < 7% and < 6.5%
- fasting serum glucose
- change in body weight
- 1,5-AG
- 8-point SMBG profile (blood glucose measurements before and 2 hours after the start of the morning, midday, and evening meals; at bedtime; and at the 0300 hour)
- serum lipids (total cholesterol, HDL-C, fasting triglycerides, and calculated LDL-C)
- frequency and rate of hypoglycemic events (overall, daytime, and nocturnal) in the set of subjects using metformin alone or in combination with SU
- safety and tolerability
- PROs
- long-term maintenance of glycemic control, safety, and tolerability

**Statistics**

No adjustments for missing data were performed, with the exception of LOCF. All tests of treatment effects were conducted at a two-sided alpha level of 0.05.

The primary efficacy analysis of the change in HbA1c from baseline (Week 0) was based on the ITT
analysis set. Superiority of exenatide QW to insulin glargine was concluded if the upper limit of the 95% CI for the treatment difference was less than zero. Noninferiority was concluded if this upper limit was \(< -0.3\%\), but \(\geq -0.0\%\). If superiority of exenatide QW to insulin glargine was demonstrated in the ITT analysis set, then superiority was to be tested in the non-SU ITT analysis set. Analysis of HbA1c based on the per-protocol and core-completer analysis sets were conducted to support conclusions of the ITT analysis set. The CI was based on analyses using a mixed-effects model repeated measures (MMRM) analysis of covariance (ANCOVA) with change in HbA1c as the dependent variable; treatment, baseline HbA1c, country, background OAD stratum, week of visit, and treatment-by-week interaction as fixed effects; and patient and error as random effects. Change in HbA1c from baseline to Week 26 endpoint was further analyzed using LOCF ANCOVA with the ITT, non-SU ITT, and perprotocol analysis sets. The explanatory variables in the ANCOVA model included treatment, baseline HbA1c, country, and background OAD stratum. Secondary efficacy measures were analyzed using MMRM ANCOVA model similar to that of the primary analysis with baseline value of the dependent variable as a covariate. Exploratory efficacy measures were analyzed using LOCF ANCOVA model similar to that for HbA1c with the baseline value of the dependent variable as a covariate. Both efficacy and safety categorical variables (for example, incidence of treatment-emergent adverse events [TEAEs]) were summarized as frequencies and percentages. Between-treatment differences were compared using Fisher’s exact test if computationally feasible; otherwise, a Pearson’s chi-square test was used. If other variables needed to be adjusted for the comparison, a Cochran-Mantel-Haenszel test was used. Health outcomes and exploratory measures were compared between treatments using LOCF ANCOVA model similar to that for HbA1c with baseline value of the dependent variable as a covariate.

**Results**

**Subject Disposition**

**Table 5. Disposition in Studies 105 and 108 (studies comparing exenatide QW and BID)**

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide QW 2 mg n=148</td>
<td>Exenatide QW 2 mg n=128</td>
</tr>
<tr>
<td></td>
<td>Exenatide BID 10 mcg n=147</td>
<td>Exenatide BID 10 mcg n=130</td>
</tr>
<tr>
<td>Completed (%)</td>
<td>128 (86.5)</td>
<td>122 (82.4)</td>
</tr>
<tr>
<td>Withdrew (%)</td>
<td>20 (13.5)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Reason for Discontinuation n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>9 (6.1)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Loss of glucose control</td>
<td>-</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (3.4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
<td>5 (3.4)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Exenatide QW 2 mg n=129</th>
<th>Exenatide BID 10 mcg n=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed (%)</td>
<td>109 (84.5)</td>
<td>95 (77.0)</td>
</tr>
<tr>
<td>Withdrew (%)</td>
<td>20 (15.5)</td>
<td>28 (23.0)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>6 (4.7)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Entry Criteria not met</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>-</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Loss of glucose control</td>
<td>3 (2.3)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>-</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (3.9)</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>Subject decision</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
<td>6 (4.7)</td>
<td>10 (8.1)</td>
</tr>
</tbody>
</table>

In Study 105 more than 80% of the patients in both groups completed the 52-week assessment period. In Study 108 the proportions of patients completing the studies were 84.5 and 77% in the exenatide QW and BID groups, respectively. The proportions of patients completing the studies were rather high without any major differences between the groups except for a larger proportion withdrawing consent in the BID group of study 108.
Table 6. Subject Disposition in Studies 106 and GWBR (studies comparing QW with other comparators)

<table>
<thead>
<tr>
<th></th>
<th>BCB106 N=491</th>
<th>H8O-MC-GWBR N=456</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide QW 2 mg n=160</td>
<td>Sitagliptin 100 mg n=166</td>
</tr>
<tr>
<td>Completed (%)</td>
<td>127 (79.4) 144 (86.7) 131 (79.4)</td>
<td></td>
</tr>
<tr>
<td>Withdrew (%)</td>
<td>33 (20.6) 22 (13.3) 34 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Reason for Discontinuation n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrative</td>
<td>2 (1.3)</td>
<td>-</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>11 (6.9)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Entry Criteria not met</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>-</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Loss of glucose control</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>1 (0.6)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (3.1)</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Sponsor decision</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject decision</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
<td>13 (8.1)</td>
<td>4 (2.4)</td>
</tr>
</tbody>
</table>

In Study 106 the proportions of patients completing the studies were 79.4, 86.7 and 79.4 % in the exenatide QW, sitagliptin and pioglitazone groups, respectively. In Study GWBR the proportions of patients completing the studies were 89.7 and 93.7 % in the exenatide QW and insulin glargine groups, respectively.

In study 106, the withdrawal rate due to adverse events was twice as large in the exenatide group compared to comparators. The difference was even larger in study GWBR. The Applicant was requested
to perform sensitivity analyses for the proportion of patients achieving HbA1c below 6.0, 6.5 and 7.0% for all main studies in which all withdrawn patients, independent on reason for withdrawal, are considered as failures and discuss the selection of LOCF to handle missing data. It can be concluded that the difference in favour of exenatide QW is overestimated due to the differential withdrawal pattern, especially in study 106. Furthermore, the consistent results in the LOCF and MMRM analyses are not indicative of robustness since these analyses are based on more or less similar assumption about the missing values. However, the degree of overestimation does not question the overall efficacy conclusion for exenatide QW.

Baseline data

Studies 105 and 108
In Study 105 patients in the ITT population had a mean duration of diabetes of 6.7 years and a mean baseline HbA1c of 8.3%. In Study 108 patients in the ITT population had a mean duration of diabetes of 7.0 years and a mean baseline HbA1c of 8.4%.

Baseline characteristics are typical for what is usually seen in populations with diabetes duration of about 7 years. There were no major differences between treatment groups. The only difference between the studies were a higher proportion of Hispanic patients in study 108 compared to study 105.

Baseline OAD treatment
In study 105, 44 (14.9%) subjects were treated with diet and exercise alone, 131 (44.4%) subjects were treated with a single oral antidiabetic agent, and 120 (40.7%) subjects were treated with a combination of oral antidiabetic medications. In study 108, 47 (18.7%) subjects were treated with diet and exercise alone, 118 (46.8%) subjects were treated with a single oral antidiabetic agent, and 87 (34.5%) subjects were treated with a combination of oral antidiabetic medications.

The doses of oral antidiabetes therapies used in the studies represent the typical scenario of patients with type 2 diabetes mellitus no longer achieving good glucose control on optimally effective or maximally tolerated doses of their oral antidiabetes therapy. Study participants maintained their oral antidiabetes drug doses for at least 2 months prior to and throughout the studies unless dose changes were medically required. To prevent hypoglycemia, subjects treated with SU had to reduce the SU dose either proactively before starting exenatide once weekly (Study 2993LAR-105) or reactively in case of hypoglycemia (Studies BCB108 and GWBR).

Studies 106 and GWBR
In Study 106 patients in the ITT population had a mean duration of diabetes of 5.7 years and a mean baseline HbA1c of 8.5%. In Study GWBR patients in the ITT population had a mean duration of diabetes of 7.9 years and a mean baseline HbA1c of 8.3%.

There were no major differences in baseline demographic characteristics in treatment groups in either of the studies.

Baseline OAD treatment
In study 106, mean Met dose was 1523 mg with no major difference between treatment groups. In study GWBR, all patients were taking Met therapy (N = 456). At baseline, both groups took similar mean doses of Met (1989.7 mg Met in exenatide once-weekly treatment group 2046.1 mg Met in the insulin glargine treatment group). The 2 most frequently used SUs were glimepiride (43.7%) and glibenclamide (34.8%). Similar numbers of patients in each treatment group reported using different OAs. At baseline, the exenatide once-weekly treatment group reported a mean dose for glimepiride of 4.4 mg/day and a mean dose of glibenclamide of 12.3 mg/day. Similarly, at baseline the insulin glargine treatment group reported a similar dose for glimepiride of 4.9 mg/day and glibenclamide of 14.3 mg/day.

Outcomes and estimation

Change in HbA1c was the primary endpoint in all main studies. Changes in fasting glucose and body weight were important secondary endpoints. The reduction in HbA1c was more pronounced in the QW groups compared to all comparators. These differences were statistically significant. The same was true for fasting glucose except for study GWBR in which the reduction with insulin glargine was more pronounced. Furthermore, the difference in fasting glucose compared to pioglitazone was not statistically significant.

The body weight reductions recorded with exenatide QW was similar to the BID formulation in study 105, but more pronounced in study 108. The effects on body weight by other comparators were as expected based on previous knowledge.
The comparability test in study 105 indicated that the Bydureon formulation manufactured at commercial scale may have a somewhat less pronounced glucose lowering effect compared to the formulation manufactured at pilot scale. However, the results from study 108 using the commercial scale product were clearly of clinical significance.

Table 7. Change from Baseline to Endpoint (LS Mean [SE]) in HbA1c (%), Fasting Glucose (mmol/L), and Body Weight (kg) by Treatment for Studies 2993LAR-105, BCB106, GWBR, and BCB108; ITT Analyses Sets

<table>
<thead>
<tr>
<th>Intent-to-Treat Analysis Set (N)</th>
<th>HbA1c (%)</th>
<th>Fasting Glucose (mmol/L) [1]</th>
<th>Body Weight (kg)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2993LAR-105 (N=295); Week 30</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW 2 mg (n=148)</td>
<td>-1.9 (0.1)*#</td>
<td>-2.3 (0.2)**#</td>
<td>-3.7 (0.5)#</td>
<td>-3.5 (0.5)#</td>
</tr>
<tr>
<td>Exenatide BID 10 mcg (n=147)</td>
<td>-1.5 (0.1) #</td>
<td>-1.4 (0.2)#</td>
<td>-3.6 (0.5)#</td>
<td>-3.4 (0.5)#</td>
</tr>
<tr>
<td><strong>BCB106 (N=491); Week 26</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW 2 mg (n=160)</td>
<td>-1.6 (0.1)*#</td>
<td>-1.8 (0.2)#</td>
<td>-2.3 (0.3) ^#</td>
<td>-2.1 (0.3) ^#</td>
</tr>
<tr>
<td>Sitagliptin 100 mg (n=166)</td>
<td>-0.9 (0.1)#</td>
<td>-0.9 (0.2)#</td>
<td>-0.8 (0.3)#</td>
<td>-0.7 (0.3)#</td>
</tr>
<tr>
<td>Pioglitazone 45 mg (n=165)</td>
<td>-1.2 (0.1)#</td>
<td>-1.5 (0.2)#</td>
<td>2.8 (0.3)#</td>
<td>2.7 (0.3)#</td>
</tr>
<tr>
<td><strong>H8O-MC-GWBR (N=456); Week 26</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW 2 mg (n=233)</td>
<td>-1.5 (0.05)*#</td>
<td>-2.1 (0.2)*#</td>
<td>-2.6 (0.2)*#</td>
<td>-2.5 (0.2)*#</td>
</tr>
<tr>
<td>Glargine QD (n=223)</td>
<td>-1.3 (0.06)#</td>
<td>-2.8 (0.2)#</td>
<td>1.4 (0.2)#</td>
<td>1.3 (0.2)#</td>
</tr>
<tr>
<td><strong>BCB108 (N=252); Week 24</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW 2 mg (n=129)</td>
<td>-1.6 (0.1)*#</td>
<td>-1.4 (0.2)*#</td>
<td>-2.3 (0.4)#</td>
<td>-2.2 (0.4)#</td>
</tr>
<tr>
<td>Exenatide BID 10 mcg (n=123)</td>
<td>-0.9 (0.1)#</td>
<td>-0.3 (0.3)</td>
<td>-1.4 (0.4)#</td>
<td>-1.3 (0.4)#</td>
</tr>
</tbody>
</table>

*p <.05, exenatide QW versus placebo or comparator
**p <.0001, exenatide QW versus placebo or comparator
#p <.05, for the difference within treatment
^p <.05, exenatide QW versus sitagliptin (Hochberg adjustment).
◊ p <.0001, exenatide QW versus sitagliptin (Hochberg adjustment).
† p <.05, exenatide QW versus pioglitazone (Hochberg adjustment).
‡ p <.0001, Exenatide QW versus pioglitazone (Hochberg adjustment).

The proportions of subjects reaching HbA1c targets were generally higher in exenatide QW treated groups compared to comparators. However, in study 106, the withdrawal rate due to adverse events was twice as large in the exenatide QW group compared to comparators. The difference was even larger in study GWBR. The Applicant has performed sensitivity analyses for the proportion of patients achieving HbA1c below 6.0, 6.5 and 7.0% for all main studies in which all withdrawn patients are considered as failures. It can be concluded that the difference in favour of exenatide QW is somewhat overestimated due to the differential withdrawal pattern, especially in study 106. Furthermore, the consistent results in the LOCF and MMRM analyses are not indicative of robustness since these analyses are based on more or less similar assumption about the missing values. However, the degree of overestimation does not question the overall efficacy conclusion for exenatide QW.

In studies 105 and 108, the reduction in HbA1c was largely similar independent on background OAD.
Table 8. Change from Baseline to Endpoint (Mean [SE]) in HbA1c for Exenatide QW by Diabetes Management Methods’ Status (Studies 105, 108)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Study 2993LAR-105 Week 30</th>
<th>Study BCB108 Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide QW 2 mg (N=148)</td>
<td>Exenatide BID 10 mcg (N=147)</td>
</tr>
<tr>
<td>Diet and Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet Exercise</td>
<td>21</td>
<td>8.2 (0.2)</td>
</tr>
<tr>
<td>Met Only</td>
<td>56</td>
<td>8.3 (0.1)</td>
</tr>
<tr>
<td>Met + SU</td>
<td>43</td>
<td>8.4 (0.1)</td>
</tr>
<tr>
<td>Met All [3]</td>
<td>114</td>
<td>8.3 (0.1)</td>
</tr>
<tr>
<td>SU All [4]</td>
<td>55</td>
<td>8.3 (0.1)</td>
</tr>
<tr>
<td>TZD All [5]</td>
<td>22</td>
<td>8.1 (0.2)</td>
</tr>
</tbody>
</table>

Study 105 also examined the switch from exenatide BID to QW as well as the maintenance of efficacy over 52 weeks of treatment. After 30 weeks of exenatide twice-daily treatment, exenatide BID-treated subjects switched to exenatide QW for the remainder of the open-ended assessment period. Patients switching experienced a transient rise in mean fasting plasma glucose concentration. By 3 to 4 weeks following initiation of once-weekly treatment, the mean fasting plasma glucose in this group had returned to concentrations observed prior to switching. There was no clinically significant adverse effect on overall glycemic control following the switch to exenatide QW; the rise in mean HbA1c was approximately +0.1%.

At Week 52, the LS mean change in HbA1c from baseline was -2.0% in both the group that had switched from exenatide BID to QW and in the group of subjects who were treated with exenatide QW for 52 weeks. The body weight beyond Week 30 was maintained, with a mean change in body weight from baseline of -4.5 kg at Week 52.

In the response to the day 120 LOQ, the Applicant submitted results for patients continuing treatment for 2 years in the studies with long-term extensions, showing that HbA1c reductions remained relatively constant (figure 7).
Figure 7. LS Mean (SE) change in HbA1c (%) from baseline to Week 52 by treatment; Study 2993LAR-105, 52-Week Evaluable Analysis Set (N=241)

- Exenatide Once Weekly 2 mg (N = 120)
- BYETTA 10 mcg BID → Exenatide Once Weekly 2 mg (N = 121)

Figure 8. Time course of mean (SEM) change in hemoglobin A1c(%) from baseline to final week of response data cutoff period (Studies 2993LAR-105, H8O-MC-GWBR, H8O-MC-GWDC, BCB106; ITT subjects).
Ancillary analyses

The effect of exenatide on lipid parameters was largely neutral with only minor reductions of LDL cholesterol not considered to be of clinical relevance. A reduction of systolic blood pressure of 3-4 mm in the exenatide QW groups was seen in all main studies. There were also indications of improved beta cell function and insulin sensitivity. The clinical relevance of these findings is not established. Several PRO (Patient Related Outcomes) questionnaires were administered during the studies, but in general, no differences were seen between treatment groups.

Summary of main studies

The following tables summarise the efficacy results from the 4 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 9. Summary of Efficacy for trial 2993LAR-105

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>2993LAR-105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, open-label, comparator controlled, multiple-dose study</td>
</tr>
<tr>
<td>Duration of main phase:</td>
<td>30 weeks</td>
</tr>
<tr>
<td>Duration of Run-in phase:</td>
<td>3 days</td>
</tr>
<tr>
<td>Duration of Extension phase:</td>
<td>open ended extension</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>The primary study endpoint was change in HbA1c from baseline to Week 30. Tested for non-inferiority and superiority between treatment groups.</td>
</tr>
<tr>
<td>Treatments groups</td>
<td></td>
</tr>
<tr>
<td>Controlled study</td>
<td>exenatide once weekly (QW) 2mg, weekly, subcutaneous (SC) injection, 30 weeks</td>
</tr>
<tr>
<td>303 subjects randomised</td>
<td>exenatide twice daily (BID) 5mcg BID 4 weeks /10mcg BID 26 weeks SC injection</td>
</tr>
<tr>
<td>Treatments group</td>
<td>exenatide once weekly (QW) Following 30 weeks of treatment, all subjects received exenatide 2 mg SC QW Study ongoing</td>
</tr>
<tr>
<td>Open label extension</td>
<td></td>
</tr>
<tr>
<td>Background therapy</td>
<td>Diet and exercise alone or with a stable regimen of metformin, sulphonylurea (SU), thiazolidinedione (TZD), or a combination of up to 2 of these oral medicinal products. To minimize hypoglycemia risk, subjects treated with an SU were required to decrease their SU dose and then optimized to reach a fasting blood glucose concentration of ≤110 mg/dL.</td>
</tr>
<tr>
<td>Endpoints and definitions</td>
<td>Primary Efficacy Efficacy during the transition of treatment Change in HbA1c from baseline with exenatide QW compared to exenatide BID at 30 weeks Glucose control during the transition from treatment with exenatide BID to exenatide QW</td>
</tr>
<tr>
<td>Analysis description</td>
<td>Primary Analysis</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Analysis population and time point description</td>
<td>Intent to treat at 30 weeks from baseline</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability</td>
<td>Treatment group</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>148</td>
</tr>
<tr>
<td>Mean HbA1c (%) change from baseline</td>
<td>-1.9 (8.3)</td>
</tr>
<tr>
<td>± standard error, p-value</td>
<td>±0.1, p&lt;0.05</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c ≤7%</td>
<td>73</td>
</tr>
<tr>
<td>Change in fasting plasma glucose (mmol/l)</td>
<td>-2.3</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.2</td>
</tr>
<tr>
<td>Mean body weight (kg) change from baseline</td>
<td>-3.7 (102)</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.5</td>
</tr>
<tr>
<td>Effect estimate per comparison</td>
<td>Primary endpoint</td>
</tr>
<tr>
<td>HbA1c (%): mean difference change from baseline between treatments</td>
<td>-0.33</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(-0.54, -0.12)</td>
</tr>
<tr>
<td>P-value</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Secondary</td>
<td>Comparison groups</td>
</tr>
<tr>
<td>Body weight (kg): Mean difference change from baseline</td>
<td>-0.08</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(-1.29, 1.12)</td>
</tr>
</tbody>
</table>

3 Only major secondary endpoints are listed in table
**Notes**

<table>
<thead>
<tr>
<th>Analysis description</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy: Change in HbA1c</td>
<td>A total of 86.5% of exenatide QW subjects and 88.4% of exenatide BID subjects completed the 30-week period. Exenatide QW achieved noninferiority and statistical superiority to exenatide BID. Statistically significantly more subjects on exenatide QW compared to exenatide BID patients achieved an HbA1c reduction to ≤ 7% (p &lt; 0.05). The change in HbA1c was durable through 52 weeks of exenatide QW therapy. The evaluable patients who switched from exenatide BID daily to exenatide QW(n= 121) achieved the same improvement in HbA1c of - 2.0 % , at the end of the 22 week extension compared to the initial baseline, as the patients treated with exenatide QW for 52 weeks.</td>
</tr>
</tbody>
</table>

**Secondary analysis**

<table>
<thead>
<tr>
<th>Change in Body Weight</th>
<th>Both exenatide QW and exenatide BID patients achieved a reduction in weight compared to baseline, although the difference between the two treatment arms was not significant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic: Change in Fasting Plasma Glucose:</td>
<td>The change in fasting plasma glucose concentration was durable through 52 weeks of exenatide QW therapy, with an additional reduction in mean fasting plasma glucose concentration in the exenatide BID group following the switch from exenatide BID to exenatide QW.</td>
</tr>
</tbody>
</table>

**Table 10. Summary of Efficacy for trial BCB108**

**Title:** A randomized, open-label, parallel-group, comparator-controlled, multicenter study to evaluate the glycaemic effects, safety, and tolerability of exenatide once weekly in subjects with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>BCB108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, open-label, comparator controlled, multiple-dose study</td>
</tr>
<tr>
<td></td>
<td>Duration of main phase: 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Duration of Run-in phase: not applicable</td>
</tr>
<tr>
<td></td>
<td>Duration of Extension phase: not applicable</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>The primary study endpoint was change in HbA1c from baseline to week 24. Tested for non-inferiority and superiority between treatment groups.</td>
</tr>
<tr>
<td>Treatments groups</td>
<td>exenatide once weekly (QW) 2mg, weekly, subcutaneous (SC) injection, 24 weeks</td>
</tr>
<tr>
<td>Controlled study</td>
<td>exenatide twice daily (BID) 5mcg BID 4 weeks /10mcg BID 20 weeks SC injection</td>
</tr>
<tr>
<td>252 subjects</td>
<td>randomised</td>
</tr>
<tr>
<td>Background therapy</td>
<td>Diet and exercise alone or with a stable regimen of metformin, sulphonylurea (SU), thiazolidinedione (TZD), or a combination of up to 2 of these oral medicinal products.</td>
</tr>
<tr>
<td>Endpoints and definitions</td>
<td>Primary Efficacy Change in HbA1c from baseline with exenatide QW compared to exenatide BID at 24 weeks</td>
</tr>
<tr>
<td>Analysis population and time point description</td>
<td>Intent to treat at 24 weeks from baseline</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability</td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>exenatide once weekly (QW)</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>129</td>
</tr>
<tr>
<td>Mean HbA1c (%) change from baseline</td>
<td>-1.6</td>
</tr>
<tr>
<td>± standard error, p-value</td>
<td>±0.1, p&lt;0.0001</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c &lt;7%</td>
<td>58</td>
</tr>
<tr>
<td>Change in fasting plasma glucose (mmol/l)</td>
<td>-1.4</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.2</td>
</tr>
<tr>
<td>Mean body weight (kg) change from baseline</td>
<td>-2.3</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.4</td>
</tr>
</tbody>
</table>

Effect estimate per comparison

Primary endpoint

HbA1c (%): mean difference change from baseline between treatments

95% confidence interval (-0.94, -0.39)

P-value

P<0.0001

Secondary

Body weight (kg): Mean difference change from baseline

95% confidence interval (-1.91, 0.01)

Notes

Only major secondary endpoints are listed in table
**Analysis description**

**Primary Analysis**

**Efficacy: Change in HbA1c**

A total of 84.5% of exenatide QW subjects and 76% of exenatide BID subjects completed the 24-week period.

Exenatide QW achieved noninferiority and statistical superiority to exenatide BID.

Statistically significantly more subjects on exenatide QW compared to exenatide BID patients achieved an HbA1c reduction to < 7% (p < 0.0001).

---

**Secondary analysis**

**Change in Body Weight**

Both exenatide QW and exenatide BID patients achieved a reduction in weight compared to baseline, although the difference between the two treatment arms was not significant.

**Change in Fasting Plasma Glucose:**

The change in fasting plasma glucose concentration was statistically greater for exenatide QW than the exenatide BID group.

---

**Table 11. Summary of Efficacy for trial BCB106**

**Title:** A randomized, double-blind, parallel-group, multicenter study to compare the glycaemic effects, safety, and tolerability of exenatide once weekly to those of sitagliptin and pioglitazone in subjects with type 2 diabetes mellitus treated with metformin.

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>BCB106</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, double blind, comparator controlled, three arm study</td>
</tr>
<tr>
<td><strong>Hypothesis</strong></td>
<td>The primary study endpoint was change in HbA1c from baseline to Week 26 comparing the effect of exenatide once weekly to those of sitagliptin and pioglitazone. The change in effect was tested for superiority between sitagliptin and exenatide QW and pioglitazone and exenatide QW.</td>
</tr>
<tr>
<td><strong>Treatments groups</strong></td>
<td><strong>Controlled study</strong> exenatide once weekly (QW) + oral placebo 2mg, weekly, subcutaneous (SC) injection, 26 weeks</td>
</tr>
<tr>
<td><strong>514 subjects randomised</strong></td>
<td>sitagliptin + placebo injection 100mg, once a day, oral, 26 weeks</td>
</tr>
<tr>
<td></td>
<td>pioglitazone + placebo injection 45mg, once a day, oral, 26 weeks</td>
</tr>
<tr>
<td><strong>Uncontrolled study</strong></td>
<td>exenatide once weekly (QW) 2mg, weekly, subcutaneous (SC) injection</td>
</tr>
<tr>
<td><strong>Background therapy</strong></td>
<td>Patients with a stable regimen of metformin for two months before screening</td>
</tr>
<tr>
<td><strong>Endpoints and definitions</strong></td>
<td><strong>Primary</strong> Efficacy Change in HbA1c from baseline</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary endpoints</strong>5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

5 Only major secondary endpoints are listed in table
### Results and Analysis

#### Analysis description

**Primary Analysis**

- **Analysis population and time point description**: Intent to treat at 26 weeks from baseline

#### Descriptive statistics and estimate variability

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>exenatide once weekly (QW)</th>
<th>Sitagliptin 100mg</th>
<th>Pioglitazone 45mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subject</td>
<td>160</td>
<td>166</td>
<td>165</td>
</tr>
<tr>
<td>Mean HbA1c (%) change from baseline</td>
<td>-1.6 (8.6)</td>
<td>-0.9 (8.5)</td>
<td>-1.2 (8.5)</td>
</tr>
<tr>
<td>± standard error, p-value</td>
<td>± 0.1, p&lt;0.05</td>
<td>± 0.1, p&lt;0.05</td>
<td>± 0.1, p&lt;0.05</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c ≤7%</td>
<td>62</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>Change in fasting serum glucose (mmol/l)</td>
<td>-1.8</td>
<td>-0.9</td>
<td>-1.5</td>
</tr>
<tr>
<td>± standard error</td>
<td>± 0.2</td>
<td>± 0.2</td>
<td>± 0.2</td>
</tr>
<tr>
<td>Mean body weight (kg) change from baseline</td>
<td>-2.3 (89)</td>
<td>-0.8 (87)</td>
<td>+2.8 (88)</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

#### Effect estimate per comparison

**Primary endpoint Comparison groups**

- **HbA1c (%): mean difference change from baseline between treatments**
  - exenatide QW sitagliptin: -0.63
  - 95% confidence interval: (-0.89, -0.37)
  - P-value: p<0.0001

**Comparison groups**

- **HbA1c (%): mean difference change from baseline between treatments**
  - exenatide QW pioglitazone: -0.32
  - 95% confidence interval: (-0.57, -0.06)
  - P-value: P<0.05

**Secondary**

- **Body weight (kg): Mean difference change from baseline**
  - exenatide QW sitagliptin: -1.54
  - 95% confidence interval: (-2.35, -0.72)
  - P-value: p<0.05
Body weight (kg): Mean difference change from baseline: -5.10
95% confidence interval (-5.91 , -4.28) P-value p< 0.0001

Notes

Analysis description
Primary Analysis

Efficacy: Change in HbA1c
A total of 79% of exenatide QW, 87% of sitagliptin, and 79% of pioglitazone subjects completed the 26-week period.

Exenatide QW demonstrated superiority to both sitagliptin and pioglitazone with respect to change in HbA1c from baseline.

Statistically significantly more subjects on exenatide QW compared to sitagliptin and pioglitazone patients achieved an HbA1c reduction to ≤ 7% (p < 0.001 and p < 0.05 respectively).

Secondary analysis

Body Weight
In the exenatide once weekly group, significantly greater reductions in body weight were observed as early as Week 4 and maintained through Week 26, compared to a smaller reduction with sitagliptin and continued increases in body weight with pioglitazone treatment.

Fasting Plasma Glucose
significantly greater reductions in fasting glucose with exenatide QW compared to sitagliptin as early as Week 4 and compared to pioglitazone at Week 6 were observed.

Table 12. Summary of Efficacy for trial H8O-MC-GWBR

Title: Efficacy of once-weekly exenatide long-acting release and once-daily insulin glargine in patients with type 2 diabetes treated with metformin alone or in combination with sulphonylurea.

Study identifier H8O-MC-GWBR

Design
Randomized, open-label, two-arm, parallel, comparator controlled, multiple-dose study

Duration of main phase: 26 weeks
Duration of Run-in phase: Not applicable
Duration of Extension phase: open ended extension

Hypothesis
The primary study endpoint was change in HbA1c from baseline to Week 26. Tested for non-inferiority and superiority between treatment groups.

Treatments groups

Controlled study
exenatide once weekly (QW) 2mg, weekly, subcutaneous (SC) injection, 26 weeks, open ended extension

Insulin glargine once daily, variable dose titrated to achieve a target blood glucose of 4.0 to 5.5. mmol/l. 26 weeks, open ended extension

456 subjects randomised

Background therapy
Metformin therapy alone or metformin therapy in combination with a sulphonylurea(SU) for at least 3 months and a stable dose for at least 8 weeks prior to screening.

Endpoints and definitions
Primary Efficacy Change in HbA1c from baseline with exenatide QW compared to insulin glargine at 26 weeks

Secondary endpoints
Body Weight Change in body weight
Fasting Serum glucose Change in serum glucose

Database lock 1 July 2009 (26 week data)

6 Only major secondary endpoints are listed in table
## Results and Analysis

<table>
<thead>
<tr>
<th>Analysis description</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis population and time point description</td>
<td>Intent to treat at 26 weeks from baseline</td>
</tr>
<tr>
<td>Descriptive statistics and estimate variability</td>
<td>Treatment group</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>233</td>
</tr>
<tr>
<td>Mean HbA1c (%) change from baseline</td>
<td>-1.5 (8.3)</td>
</tr>
<tr>
<td>± standard error, p-value</td>
<td>±0.1, p&lt;0.05</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c ≤7%</td>
<td>62</td>
</tr>
<tr>
<td>Change in fasting serum glucose (mmol/l)</td>
<td>-2.1</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.2</td>
</tr>
<tr>
<td>Mean body weight (kg) change from baseline</td>
<td>-2.6 (91)</td>
</tr>
<tr>
<td>± standard error</td>
<td>±0.2</td>
</tr>
</tbody>
</table>

| Effect estimate per comparison | Primary endpoint | Comparison groups | exenatide QW | Insulin glargine |
|---------------------------------|------------------|------------------|
| HbA1c (%): mean difference change from baseline between treatments | -0.16 |
| 95% confidence interval | (-0.29, -0.03) |
| P-value | P<0.05 |

<table>
<thead>
<tr>
<th>Secondary</th>
<th>Comparison groups</th>
<th>exenatide QW</th>
<th>Insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg): Mean difference change from baseline</td>
<td>-4.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(-4.57, -3.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>P&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: By the end of the study, the mean dose of insulin glargine had nearly tripled from 10.10 IU/day at the beginning of treatment to 31.10 IU/day for insulin glargine-treated patients. Approximately 25% of patients in the exenatide QW treatment group and 23% in the insulin glargine treatment group reduced their SU dose anytime during the study.
**Analysis description**

<table>
<thead>
<tr>
<th>Efficacy: Change in HbA1c</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A total of 89% of exenatide QW subjects and 94% of insulin glargine subjects completed the 26-week period.</td>
<td></td>
</tr>
<tr>
<td>Exenatide QW treatment significantly improved glycaemic control, as measured by decrease in HbA1c. This treatment effect was statistically superior to that of insulin glargine.</td>
<td></td>
</tr>
<tr>
<td>A similar percentage of patients in each treatment group had an endpoint HbA1c ≤7%.</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary analysis**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Exenatide QW significantly reduced patient body weight, whereas insulin glargine was associated with progressive weight gain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose:</td>
<td>Both treatment groups had a significant decrease in FSG with insulin glargine treatment having a significantly greater decrease in FSG compared with exenatide QW treatment.</td>
</tr>
</tbody>
</table>

**Clinical studies in special populations**

There were no major difference in effect between men and women, patients with BMI <or> 30 or between patients below or above 65 years of age in the submitted studies. The number of patients older than 75 years was very limited which is reflected in the SmPC.

A reduction in body weight was seen in subjects treated with exenatide once weekly irrespective of the occurrence of nausea, although the mean reduction was larger in the group with nausea (range -5.2 kg to -2.9 kg) compared to the group without nausea (-2.9 kg to -2.2 kg).

Nearly all subjects in the exenatide QW treatment group in Studies 2993LAR-105 and GWBR had normal or mild impairment of renal function at baseline; 24 subjects had moderate impairment. Subjects with mild renal impairment treated with exenatide QW had similar reductions in HbA1c as those with normal renal function. The use of exenatide QW in renal impaired patients is further discussed in the safety section.

Overall, there was a higher incidence of treatment-emergent antibody positivity among exenatide QW-treated subjects (range 49% to 64%) than typically among exenatide BID-treated subjects (36.3%). Likewise, the incidence of subjects with higher (≥625) treatment-emergent titers across studies was greater for exenatide QW (range 6.1% to 22.8%) than for exenatide BID (4.6%) in Studies 2993LAR-105 and BCB108. The incidence of antibody positivity seemed to decline over time (see figure 9 from study 105).
As previously seen for the BID formulation, the mean effect in patients with high titers is considerably attenuated compared to patients with low titers or no antibodies. However, there is a large variability in the glycaemic response in subjects with high titers (see figure 10); some patients who develop high titers have an attenuated response, while others have a satisfactory response. This is very similar to what has previously been seen with exenatide BID. Section 4.8 of the SmPC reflects this information.
2.5.3. Discussion on clinical efficacy

Treatment with exenatide 2mg QW added to ongoing OAD treatment resulted in clinically relevant reductions in HbA1c, body weight and fasting plasma glucose. The reductions were sustained at 52 weeks of treatment. HbA1c reductions remained relatively constant in patients continuing treatment for 2 years. In the presented studies at 30 weeks, the reductions in HbA1c were more pronounced compared to the BID formulation. The study examining a switch from the BID to the QW formulation of exenatide also indicates that the QW dosing could result in additional glucose lowering effect. The glucose lowering effect was also more pronounced compared to sitagliptin and pioglitazone. There is no comparison to SU which is often considered as the first choice for patients who fail on metformin and lifestyle interventions. However, considering that the absolute reduction of HbA1c associated with the use of exenatide QW is clearly of clinical relevance in the available studies, a comparison to SU is not considered as mandatory for approval. The reduction in HbA1c was largely similar independent on background OAD. Thus, these results show that exenatide QW added to ongoing OAD can provide clinically relevant further reductions of glucose parameters and body weight in patients with inadequate glycaemic control with ongoing treatment. As for exenatide BID, some of the patients with high titers of treatment-emergent antibody have an attenuated response to the treatment. Long term studies are ongoing, and the Applicant has committed to submit results from these studies post-approval (FUM).

2.5.4. Conclusions on the clinical efficacy

Based on the results from the studies it is concluded that exenatide QW added to ongoing OAD can provide clinically relevant further reductions of glucose parameters and body weight in patients with inadequate glycaemic control with ongoing treatment.

2.6. Clinical safety

Patient exposure

The exenatide QW clinical development program consisted of 13 completed and 8 ongoing studies. For a study to have been considered completed and incorporated into the Integrated Completed Studies Database used for the analyses of safety, a study report and/or database lock must have occurred by the 31 July 2009 cut-off date. Two completed studies (H8O-MC-GWDC [GWDC] and BCB108) have not been integrated into the Integrated Completed Studies database. The data from these studies have been discussed separately, where applicable.

At the time of the original MAA, in total, 779 subjects had been exposed to exenatide QW in the Integrated Completed Studies out of which 274 and 112 subjects have an exposure of ≥ 26 and ≥ 52 weeks, respectively. The table below shows the exposure based on background OAD treatment.
Table 13. Summary of Exenatide QW Subjects by Baseline Oral Antidiabetes Drug Stratum-All Completed Efficacy and Safety Studies (ITT Subjects)

<table>
<thead>
<tr>
<th>Oral Antidiabetes Drug(s)</th>
<th>Efficacy and Safety Studies</th>
<th>Met Alone</th>
<th>SU Alone</th>
<th>TZD Alone</th>
<th>Met + SU</th>
<th>Met + TZD</th>
<th>SU + T ZD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Integrated Completed Efficacy and Safety Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2993LAR-104 (N=31)</td>
<td>Duration: 15 weeks</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>H8O-JE-GWBR (N=20)</td>
<td>Duration: 10 weeks</td>
<td>2</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>2993LAR-105 (N=148)</td>
<td>Duration: 30 weeks</td>
<td>56</td>
<td>6</td>
<td>2</td>
<td>43</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>BCB106 (N=160);</td>
<td>Duration: 26 weeks</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>H8O-MC-GWBR; N=233</td>
<td>Duration: 26 weeks</td>
<td>162</td>
<td>-</td>
<td>71</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Integrated Completed Efficacy and Safety Studies</td>
<td>398</td>
<td>13</td>
<td>2</td>
<td>114</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>BCB108; N=129</td>
<td>Duration: 24 weeks</td>
<td>51</td>
<td>1</td>
<td>4</td>
<td>34</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>H8O-MC-GWDC; N=134</td>
<td>Duration: 26 week cut</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>-</td>
<td>118</td>
<td>-</td>
</tr>
<tr>
<td>Grand Total Efficacy and Safety Studies</td>
<td>449</td>
<td>14</td>
<td>22</td>
<td>148</td>
<td>145</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Due to differences in pharmacokinetic and pharmacodynamic profile between the once weekly and the twice daily formulation of exenatide, more long term safety data (at least an adequate number of patients exposed for at least 18-24 months) were requested by CHMP before approval. This was reflected as a major objection in the D120 LOQ. In the context of long term safety, the following issues were considered of particular importance by CHMP (which are further discussed under the relevant safety sections): - The influence of the relatively high incidence of treatment-emergent antibody positivity on long term efficacy and safety; - A potentially increased risk of rare, but serious adverse events such as thyroid and pancreatic malignancies and pancreatitis possibly related to the continuous exenatide exposure; - The limited data in populations sensitive to adverse events, such as the elderly and patients using SU (increased risk of hypoglycaemia), considering the long period of time for washout in case therapy is stopped due to adverse events; - The depot-like situation in subcutaneous tissue (with each administered dose residing an average of 6 weeks in subcutaneous tissue and the excessive accumulation of 8-9 doses in subcutaneous tissue at any one time) that could eventually result in a higher immunogenicity both locally and systemically.

In the response to the day 120 LOQ, the Applicant has submitted additional data from the open-label extension periods of the phase 3 studies (2993LAR-105, GWBR, GWDC, and BCB106) contributing additional subjects for a total of 1050 subjects exposed to exenatide once weekly for ≥6 months (1085 subject-years of exposure). Of these subjects, 110 received exenatide once weekly ≥2 years, while 279 subjects received exenatide once weekly for ≥1.5 years and 221 subjects for ≥1 year. Of these studies, GWBR is controlled also during the extension phase (insulin glargine as comparator), while the others are uncontrolled.

Adverse events in exenatide QW clinical dataset

Table 14 summarizes treatment-emergent adverse events from the 7 core safety studies with an incidence of ≥5% (excluding hypoglycemia) in exenatide once weekly- compared to twice daily-treated subjects. Treatment-emergent adverse events that are ≥5% and are biologically plausible are included in the summary of safety profile in the SmPC; therefore, the events of nasopharyngitis and urinary tract infection are not in the SmPC. Those terms ≥1% and biologically plausible are also listed by system organ class and frequency in the SmPC. The events of vomiting and constipation are presented below in the very common category of the SmPC from the frequency observed in a previous analysis (Table 14).
Specific adverse events from the exenatide QW clinical dataset are discussed in detail below.

**Gastrointestinal Adverse Events**

The system organ class with the greatest percentage of exenatide-treated subjects reporting adverse events was gastrointestinal disorders. Exenatide QW-treated subjects in the efficacy- and safety-controlled studies reported similar percentages of gastrointestinal disorders (41%) compared with exenatide BID-treated subjects (52%). In the Integrated Completed Studies Database, more exenatide BID-treated subjects (34%) experienced nausea as compared to exenatide QW-treated subjects (20%) while similar percentages of subjects in both treatment groups experienced diarrhoea (13%). More exenatide BID-treated subjects experienced vomiting (19%) compared to exenatide QW-treated subjects (8%).

Figure 10 illustrates the incidence of new events or worsening of treatment-emergent nausea per 2-week interval during the 30-week assessment period for Study 2993LAR-105. In the first 4 weeks of therapy, the frequency of nausea was similar in both treatment groups. At Week 4, the number of subjects experiencing new nausea in the exenatide BID group increased compared with the exenatide QW group, coinciding with the timing of the dose escalation of exenatide BID from 5 mcg to 10 mcg. New events of nausea peaked at the Week 6 to Week 8 interval, and then generally decreased over time for both groups, with the incidence of nausea remaining lower in the exenatide QW group in each 2-week time interval.

In the extension phase of study 105, no increase in the incidence of new onset gastrointestinal adverse events was observed upon the switch from BID to exenatide QW therapy.
In studies 106, 108 and GWBR, no run in on exenatide BID was included. In study 106, the incidence of nausea slightly increased from Day 1 to Week 2 (6.9%) through Weeks 8 to 10 (15.3%) but subsequently declined with continued exposure (5.4% at Weeks 24 to 26). The duration of most nausea events was short, with the majority of events in all treatment groups (68%, 64% and 67%, for exenatide QW, sitagliptin and pioglitazone, respectively) resolving within a week. The majority (97.4%) of gastrointestinal adverse events were mild or moderate in intensity.

**Hypoglycaemia**

In the Integrated Completed Studies Database, 18.9% of exenatide BID-treated subjects experienced minor hypoglycemia as compared to 15.9% of exenatide QW-treated subjects in the efficacy- and safety-controlled studies. Symptoms of hypoglycemia were reported in 26.8% of exenatide QW-treated subjects, and 30.2% of subjects in the exenatide BID-treated subjects. The incidence of hypoglycaemia was largely dependent on presence or absence of concomitant SU use with an increased incidence of minor and symptomatic hypos compared to patients not taking SU. However, since this could be solved by reducing the SU dose, the continuous exposure of exenatide may be of less importance. However, in patients with mild renal impairment and SU use, the incidence of minor and symptomatic hypos was increased compared to patients with normal renal function. This is included in the SmPC, and a reduction in SU dose should be considered.

**Table 15. Treatment–Emergent Hypoglycemia by Treatment and Concomitant Sulfonylurea Use - Integrated Efficacy and Safety Studies (ITT Subjects)**

<table>
<thead>
<tr>
<th>Safety Summary</th>
<th>Exen-QW (N=592)</th>
<th>Placebo (N = 23)</th>
<th>Exen-BIDPioglitazone (N = 145)</th>
<th>Sitagliptin (N = 166)</th>
<th>Insulin (N = 223)</th>
<th>Exen-QW only (N= 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonyurea</td>
<td>138</td>
<td>7</td>
<td>53</td>
<td>0</td>
<td>67</td>
<td>108</td>
</tr>
<tr>
<td>Major Hypoglycemia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Minor Hypoglycemia</td>
<td>22 (15.9)</td>
<td>0 (0.0)</td>
<td>10 (18.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>28 (41.8)</td>
</tr>
<tr>
<td>Symptomatic Hypoglycemia</td>
<td>37 (26.8)</td>
<td>0 (0.0)</td>
<td>16 (30.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>32 (47.8)</td>
</tr>
<tr>
<td>Non Sulfonyurea</td>
<td>454</td>
<td>16</td>
<td>92</td>
<td>165</td>
<td>166</td>
<td>156</td>
</tr>
<tr>
<td>Major Hypoglycemia</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Minor Hypoglycemia</td>
<td>9 (2.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>1 (0.6)</td>
<td>5 (3.0)</td>
<td>30 (19.2)</td>
</tr>
<tr>
<td>Symptomatic Hypoglycemia</td>
<td>35 (7.7)</td>
<td>0 (0.0)</td>
<td>8 (8.7)</td>
<td>9 (5.5)</td>
<td>11 (6.6)</td>
<td>38 (24.4)</td>
</tr>
</tbody>
</table>
**Weight reduction**

The numbers of exenatide-treated subjects experiencing weight loss was as follows: ≥5% weight loss, n=254; ≥10% weight loss, n=58; ≥20% weight loss, n=3. No obvious differences in adverse events were observed in these strata. Exenatide once weekly-treated subjects with baseline BMI <30 kg/m² reported a similar incidence of adverse events relative to subjects with higher baseline BMI. The SmPC includes information in sections 4.4 and 4.8 that rapid weight loss has been reported and can be harmful.

**Cardiac Events**

In the Integrated Completed Studies Database, 20 (3.0%) exenatide QW-treated subjects in the efficacy- and safety-controlled studies experienced treatment-emergent adverse events in the system organ class cardiac disorders. Of these, 10 (1%) experienced a serious adverse event and 1 event (myocardial infarction) was fatal and led to subject discontinuation. The percentage and type of cardiac events experienced by exenatide BID-treated subjects was similar to that observed in the exenatide QW-treated subjects. In Study BCB108, 3 subjects (1 exenatide once weekly, 2 exenatide BID) experienced cardiac events, all of which were assessed as being unrelated to study drug. Three of the events were assessed as serious adverse events. In Study GWDC, 2 subjects experienced 2 cardiac events (angina pectoris and palpitations). Only angina pectoris was considered a serious adverse event and neither event was considered related to study drug.

**Table 16. Number (%) of Subjects with Treatment-Emergent Adverse Events in the System Organ Class “Cardiac Disorders” by Preferred Term- All Completed Efficacy and Safety Studies (ITT Subjects)**

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Integrated Studies Database</th>
<th>Study BCB108</th>
<th>Study GWDC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide BID (n=145)</td>
<td>Exenatide QW (n=592)</td>
<td>Exenatide BID (N=123)</td>
</tr>
<tr>
<td>Treatment-Emergent Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>3(2)</td>
<td>20(3)</td>
<td>2(1.6)</td>
</tr>
<tr>
<td>Serious Treatment-Emergent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Cardiac Disorders</td>
<td>1(1)</td>
<td>5(1)</td>
<td>2</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>0</td>
<td>1(1)</td>
<td>0</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>0</td>
<td>1(1)</td>
<td>0</td>
</tr>
<tr>
<td>Arteriosclerosis Coronary Artery</td>
<td>1(1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrioventricular Block</td>
<td>0</td>
<td>1(1)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1(1)</td>
<td>1(1)</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>0</td>
<td>0</td>
<td>1(0.8)</td>
</tr>
<tr>
<td>Coronary Artery Occlusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>1(1)</td>
<td>1(0.8)</td>
</tr>
<tr>
<td>Myocardial Ischemia</td>
<td>0</td>
<td>1(1)</td>
<td>1(0.8)</td>
</tr>
</tbody>
</table>

Overall, there appeared to be no pattern of abnormalities suggested by serial ECG testing for exenatide QW. However as discussed under the section "Primary and Secondary Pharmacology" the Applicant undertook a QT study with exenatide BID which showed a modest increase of the QTc interval. As discussed before several findings could be interpreted as reassuring. However the CHMP was of the opinion that a QT study with exenatide QW should be performed post-approval. The Applicant committed to perform such study.

**Thyroid neoplasms**

In the nonclinical program with exenatide QW, the detection of thyroid c-cell hyperplasia and neoplasia at all exenatide QW dose levels in a rat carcinogenicity study was observed. In contrast to the marginal effect on thyroid C-cells in the exenatide BID rat carcinogenicity study, exenatide QW resulted in a prominent increase in thyroid C-cell hyperplasia and neoplasia in the rat (see non-clinical section).
No events of thyroid cancer were reported in exenatide-treated subjects in the Integrated Completed Studies Database. There was however 1 event of thyroid papillary cancer reported in the sitagliptin group. One subject in the exenatide QW treatment group experienced a thyroid mass. This subject of Study 2993LAR-105 was diagnosed with a thyroid mass 2 days after the first dose of exenatide QW. During the 4 open-label extensions, 1 subject reported an event of concern (thyroid nodules) after the subject had received exenatide once weekly for approximately 9 months. It was mild in severity and did not lead to discontinuation of treatment. Even though no conclusion on increased risk can be drawn from the available neoplasm, these events need to be carefully followed. Thyroid events will be captured in the planned CV safety study GWDQ. Furthermore, the Applicant commits to conduct an epidemiological study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly. (see further under discussion on clinical safety)

**Injection Site Reactions**

In the efficacy- and safety- controlled studies, 16% of exenatide QW subjects experienced an injection site reaction, compared to a range of 2% to 7% in the comparator groups including exenatide BID. The most common injection site-related events in the exenatide QW group in the efficacy- and safety-controlled studies were injection site pruritus (8%); injection site erythema (4%); injection site induration (4%); and injection site nodule (3%). Furthermore, there was a high incidence of asymptomatic nodule formation (up to 77%) at the injection site. Most reactions were mild to moderate in severity and resolved spontaneously without medical intervention. Approximately 73% of the first incidence of treatment-emergent injection site reactions reported by exenatide once weekly-treated patients had resolved within 60 days. Health care providers are not recommended to discontinue treatment of exenatide once weekly in the occurrence of an injection site reaction, unless clinical severity or professional expertise dictates otherwise. Patients should be instructed to use a different site of injection each week and to seek symptomatic treatments, if desired, to relieve itching or discomfort. This recommendation has been incorporated into the SmPC and Package Leaflet.

**Pancreatitis**

Pancreatitis has been previously identified as a potential safety issue for the GLP-1 receptor agonist class, based on spontaneous post-marketing reports of pancreatitis received for exenatide BID. These reports have included some cases that were severe with complications of hemorrhage, necrosis, or with outcome of death. The exenatide BID SmPC has included pancreatitis since the license was issued and has been updated to include the fact that hemorrhagic and necrotizing cases had been reported. The Exenatide QW product labelling includes this information.

In the Integrated Completed Studies Database supporting the exenatide QW submission, there were 3 cases of acute pancreatitis (1 subject receiving exenatide QW and 2 subjects receiving pioglitazone). The event in the exenatide QW group was serious, rated moderate in severity and considered related to drug. The subject did not receive additional study drug following this event. There was 1 additional event of pancreatitis reported in an exenatide QW-treated subject in Study BCB108. The event was considered to be a serious adverse event, related to the study drug and the subject was withdrawn from the study for this reason. With up to 2 years of exenatide once weekly exposure, no additional events were reported. Cases of pancreatitis will be further assessed and captured in the planned CV safety study GWDQ. Furthermore, the Applicant commits to undertake a Modified Prescription Event Monitoring Study in the United Kingdom to identify possible cases of pancreatitis.

**Acute Renal Failure**

In the Integrated Completed Studies Database for exenatide QW there were 7 cases of altered renal function (3 subjects receiving exenatide QW and 4 subjects receiving comparator therapy). None of the exenatide QW subjects experienced acute renal failure, while 2 comparator subjects (1 pioglitazone, 1 exenatide BID) did experience acute renal failure. Both events were considered to be serious adverse events. Information on events of altered renal function (including acute renal failure) has been included in the SmPC.

**Immunological events**

There was a higher incidence of treatment-emergent antibody positivity among exenatide QW-treated subjects (range 49% to 64%) than among exenatide BID-treated subjects (36.3%). The incidence of subjects with higher (≥625) treatment-emergent titers across studies was greater for exenatide QW (range 6.1% to 22.8%) than for exenatide BID (4.6%) in Studies 2993LAR-105 and BCB108.
The incidence of treatment-emergent adverse events for exenatide BID- and exenatide QW-treated subjects by their antibody status (positive or negative) at endpoint has been evaluated in Studies 2993LAR-105, BCB106, and GWBR. No overall increase in the incidence of treatment-emergent adverse events was observed in antibody-positive compared to antibody-negative subjects in these studies. However, those who were antibody positive had a higher overall incidence (24%) of potentially immune-related adverse events than those who were antibody negative (15%). The higher incidence was primarily accounted for by injection site-related events. More exenatide QW-treated subjects with high (34%) than low (22%) titers to exenatide reported potentially immune-related events. The most frequently reported events among higher titer subjects were also injection site related. In comparison, the incidence of potentially immune-related adverse events in Study 2993LAR-105 was lower overall for exenatide BID subjects (8% antibody-positive and 12% antibody-negative).

An increase in the incidence of mild to moderate injection site pruritus was observed upon the switch at Week 30 from exenatide BID (2 subjects [1.4%] during the 30-week assessment period) to exenatide QW therapy (6 subjects [4.6%] during the first 22 weeks of the open-ended assessment period). Five of the 6 subjects experiencing injection site pruritus after the switch to exenatide QW were antibody positive with low titers of antibodies to exenatide. No subjects reported potentially immune-related adverse events that were serious in nature. No cases of anaphylaxis were reported. Seven subjects reported events with the MedDRA preferred term hypersensitivity. Of these 5 were treated with exenatide QW and 4 were antibody positive.

In the updated safety data set, with 2 years of exposure, more antibody-positive (59%) than antibody-negative subjects (31%) had experienced a potentially immune-related treatment-emergent adverse event with the most frequently occurring events being injection site-related, particularly injection site pruritus and injection site erythema. These numbers are considerably higher compared to what was reported in the MAA. The incidence of injection site related events was generally higher in antibody-positive subjects with approximately one-third of antibody-positive subjects experiencing injection site pruritus. The majority of the events were mild/moderate, but may nevertheless constitute a relevant problem for the patients. Therefore the SmPC includes information on the incidence of antibodies in the clinical trials and injection site reactions. As discussed above also information on how to handle injection site reactions have been included in the SmPC and Package Leaflet.

The consequences of immunogenicity will be further assessed in the ongoing exenatide BID study GWBE (randomized, Phase 3, multicenter, open-label, two-arm, parallel, active comparator controlled study in 1021 overweight patients) in which storage of identifiable serum samples for optional future safety assessments, such as anti-exenatide antibody testing, is a mandatory part of this study.

**Serious adverse event/deaths/other significant events**

Overall, 6% of all exenatide QW-treated subjects experienced at least 1 treatment-emergent serious adverse event. Within the efficacy- and safety-controlled studies, 4% of exenatide QW-treated subjects experienced at least 1 treatment-emergent serious adverse event compared with 3% of exenatide BID-treated subjects. The incidences for pioglitazone, sitagliptin and insulin glargine were 6, 3 and 4 %, respectively.

Similar percentages (~1%) of exenatide QW- and exenatide BID-treated subjects in the efficacy- and safety-controlled studies experienced a serious cardiac disorder or infection and infestation, while all other system organ classes were <1%. Other system organ classes with approximately 1% treatment-emergent serious adverse events in all exenatide QW-treated subjects included: gastrointestinal disorders (5 of 779), injury, poisoning and procedural complications (5 of 779), neoplasms benign specific and unspecified (5 of 779), general disorders and administration site conditions (4 of 779), and hepatobiliary disorders (4 of 779).

Four deaths have been reported during the exenatide QW clinical development program, all considered as unrelated to the treatment.

**Laboratory findings**

Overall, the percentage of subjects with potentially clinically important laboratory abnormalities was low and generally similar for subjects treated with exenatide QW, placebo QW, or exenatide BID. No clinically meaningful changes from baseline to last visit were noted in hematology, chemistry, or urinalysis assessments for subjects treated with exenatide QW or exenatide BID.
Safety in special populations

In general, in the dataset submitted in the original MAA, the percentage and type of adverse events experienced by subjects within the ≥18 - <65 years and ≥65 - <75 years age groups (n=113 on exenatide QW) were comparable. The number of patients ≥75 years was very limited (n=12).
In the 4 studies with open-label extensions, a total of 165 subjects were ≥65 years with 22 subjects ≥75 years.
Since elderly patients have a higher incidence of, as well as an increased risk of developing, renal impairment these patients may have an increased risk of increased exenatide exposure and possible adverse events. In the responses to the day 180 LoOI, the Applicant proposed to not recommend exenatide once weekly for use in patients with moderate renal impairment and included this recommendation in the SmPC. The CHMP considered that this potential safety issue has been adequately addressed.

In the long term clinical studies, 54 % of the patients were men and 46 % were women. The most notable differences between the genders treated with exenatide (males vs. females) were in the following adverse events: nausea (12% vs. 26%); vomiting (4% vs. 13%), hypoglycemia (14% vs. 21%), and urinary tract infections (3% vs. 10%). Similar differences were recorded in the exenatide BID groups.

As mentioned above, in patients with mild renal impairment and SU use, the incidence of minor and symptomatic hypoglycaemia was increased compared to patients with normal renal function. The experience in patients with moderate renal impairment is very limited, but population pharmacokinetic analysis indicate that there may be 74% increase in exposure in moderately impaired patients. The SmPC includes a recommendation that exenatide once weekly should not be used in patients with moderate renal impairment.

In relation to the proposed indication, the exposure of exenatide QW in combination with Met alone, Met+SU and Met+ TZD could be considered as acceptable. Overall, the recorded adverse event profiles do not seem to differ from the experience with exenatide BID. The number of patients treated with TZD monotherapy was limited and it can be questioned whether results can be extrapolated from the triple combination with Met, considering the restricted monotherapy indication for TZD. The target population for dual therapy with TZD + exenatide (patients inadequately controlled by diet and exercise for which metformin is inappropriate because of contraindications or intolerance) is not the same as for triple therapy. Patients treated with TZD monotherapy due to intolerance to Met is not likely to differ from the population treated with dual therapy, Met+TZD, and for these patients efficacy and safety data could be extrapolated between populations.
The patients with contraindications to Met may on the other hand be a more vulnerable population including patients with renal/hepatic impairment and cardiac disease. However, considering the warnings and contraindications for TZD, only patients with renal impairment would be eligible for TZD monotherapy. Considering that exenatide QW is not recommended in patients with moderate/severe renal impairment, the target population in Europe for the TZD+exenatide QW combination is likely to be small. Concerning alternative add-on treatments for patients on TZD monotherapy, SU as an alternative treatment to exenatide can lead to hypoglycaemia and weight increase, although the long term experience of SU speaks in its favour. Insulin, on the other hand, should in general be avoided in combination with TZD due to the risk of fluid retention. Considering the small target population for the TZD+exenatide QW combination, the very limited safety data presented could be considered as acceptable. The data supporting the dual therapy indication is therefore considered as acceptable.

Discontinuation due to adverse events

Of the subjects assigned to the exenatide QW treatment arm in the Integrated Completed Studies Database, 85.8% of subjects in the efficacy- and safety-controlled studies and 83.7% of subjects in the uncontrolled extension study completed the protocols as planned. In the efficacy- and safety-controlled studies, adverse events (5.4%), withdrawal of consent (4.1%), and lost to follow-up (2.0%) were the most frequently observed reasons for discontinuation in exenatide QW-treated subjects. Similar percentages of exenatide BID-treated subjects discontinued due to an adverse event (4.8%). Gastrointestinal disorders was the system organ class from which most exenatide-treated subject discontinuations were observed [exenatide BID: 4%; exenatide QW 2%]. In this context, when discontinuing the product, the long time for elimination could pose additional problems in association with the occurrence of serious adverse events, e.g. pancreatitis and injection site reactions. Even
though there are currently no data supporting a problem in the case of a serious adverse events, this remains a potential issue that could cause a problem, e.g. in the case of severe GI adverse events or pancreatitis. This warrants for a careful use in patients with the highest risk of increased exposure for exenatide, e.g. the elderly and patients with moderate renal impairment. Bydureon is therefore not recommended in patients with moderate renal impairment. Furthermore, there is information in the SmPC that after discontinuation, the effect of Bydureon may continue as plasma levels of exenatide decline over 10 weeks. Choice of other medicinal products and dose selection should be considered accordingly, as adverse reactions may continue and efficacy may, at least partly, persist until exenatide levels decline.

2.6.1. Discussion on clinical safety

For exenatide BID, the most common short-term safety issue is gastrointestinal side effects and the labelling includes a recommendation concerning a gradual uptitration of the dose to reduce these symptoms. Also for the exenatide QW formulation, GI adverse events are common, but the incidence seems to be somewhat lower compared to the BID dosing. Therefore no recommendation of uptitration is included in the Bydureon labelling. Based on the results from the submitted studies this is acceptable. Furthermore, there does not seem to be an increase in GI adverse events when switching from BID to QW dosing.

Another identified common adverse event is injection site reactions, which, to some degree, seems to be associated with the development of treatment-emergent antibodies, but also to the delivery system as such. The incidence of treatment-emergent antibody positivity among exenatide QW-treated subjects was higher than among exenatide BID-treated subjects. In the QW groups, subjects who were antibody positive had a higher overall incidence of potentially immune-related adverse events (primarily injection site-related events) than those who were antibody negative. This is reflected in the SmPC.

As for exenatide BID, hypoglycaemia is mainly seen in the combination with SU. The product information states that when Bydureon is added to SU therapy, a reduction in the dose of SU should be considered, to reduce the risk of hypoglycaemia.

There is no preclinical or mechanistic rationale to suspect that exenatide would increase the risk of cardiovascular events. A meta-analysis of exenatide twice-daily studies has shown a trend to lower relative risk for CV events versus placebo of 0.70 (95% confidence interval 0.38-1.31). However, the events were few. The available study data for the QW formulation do not indicate any adverse cardiac effects, but the duration of the studies are much too short to draw any firm conclusions. Furthermore, patients with CV disease and risk factors were to a large degree excluded from the clinical studies. The draft diabetes guideline states that high risk patients are strongly recommended to be included either in the phase II and phase III studies or in a specific study. The Applicant is planning a long term cardiovascular outcome study (H80-MC-GWDQ) which will include patients at a higher CV risk, but the study results are only expected to be submitted in 2018. However, considering that there is no mechanistic rationale for an increased CV risk and the lack of observed increased risk associated with exenatide BID, the CHMP considers it acceptable to submit CV safety data post approval. The Applicant also committed to perform a QT study with exenatide QW.

The thyroid C-cell data from the exenatide QW program is generally consistent with that reported for another long-acting GLP-1 agonist, liraglutide. Collectively, the data suggest that the thyroid C-cell effects in rats result from continuous stimulation of C-cells with long-acting agonists in contrast to the intermittent stimulation of the short-acting exenatide. Considering the continuous exposure of exenatide with the QW dosing, it could be hypothesised that this could increase the risk of thyroid c-cell hyperplasia/cancer. The MAH for Exenatide BID has recently performed an assessment of the risk of pancreatic malignancy and thyroid neoplasm in association with exenatide BID based on data from i3 Aperio® in which it was concluded that no signal of elevated risk of any of the cancer outcomes associated with initiation of exenatide could be detected. However, in an ongoing FUM for Exenatide BID, the MAH has reported results based on new methodology from the investigators of the i3 Aperio® study which is in conflict with the submitted study report with respect to thyroid cancer (RR 1.7, 1.2-2.3 compared to comparators). These updated i3 Aperio results became available during the review of the MAA for Bydureon and this issue was considered a major objection in the 2nd List of Outstanding Issues. In response to the CHMP concerns, the applicant has provided further information from this study. In the updated manuscript from the i3 investigators, the RR for thyroid cancer ranged from 0.9 to 1.6 depending on the inclusion/exclusion of pre-existing cases, the duration of follow up and in-or out-patient claims, most likely not including any cases of medullary thyroid cancer. Considering all
limitations, this cannot be considered as a strong safety signal. However, considering the preclinical findings, the commitment of the Applicant to conduct a robust pharmacoepidemiology study for Exenatide BID is welcomed. However, considering that the preclinical signal for thyroid c-cell cancer is stronger for Bydureon compared to Exenatide BID, a potential finding of an absence of increased risk for thyroid malignancies with Exenatide BID cannot automatically be extrapolated to patients treated with Bydureon. The Applicant should also perform a study for exenatide QW.

The CHMP’s Pharmacovigilance Working party, at its April 2011 plenary meeting, discussed the matter and its position is in line with the CHMP’s view. The PhVWP concluded that the data on increased risk of thyroid malignancies cannot be considered as a strong safety signal but need to be further investigated. Regarding the epidemiological study using one or more European databases, further contacts with European third-party operators are needed to find a design that will make it possible to include enough patients exposed to exenatide once weekly. The Applicant should communicate the progress of these plans to the CHMP on a regular basis including in the PSURs. The details of the study proposal, should be discussed at a later stage post marketing in the Risk Management Plan.

The Applicant committed to perform an epidemiological study to identify possible cases of thyroid neoplasms among patients who initiate exenatide QW. The study is part of the Risk Management Plan. A study proposal has been submitted to the CHMP. But further contacts with European third party operators will be needed to find a design that will make it possible to include enough patients exposed to exenatide once weekly. A study protocol will be provided by July 2011 with an update on projected timelines.

The progress of the study will be communicated through annual updates in the RMP after 2 years post-approval.

The association of GLP-1 analogues and acute pancreatitis is based on post-marketing cases in patients treated with exenatide, and the product label for Exenatide BID was updated in October 2006 and 2007 to include this information as well as precautionary measures. An FDA alert was issued in August 2008 regarding several serious cases of necrotizing or hemorrhagic pancreatitis and a small number of deaths. In a recent FUM for Exenatide BID, study reports from 2 retrospective database studies aimed to monitor pancreatitis in patients receiving exenatide BID and to compare these pancreatitis rates with those seen with other anti-diabetic agents were assessed. In these studies there were no risk differences for acute pancreatitis between current or recent use of exenatide and of other oral anti diabetic agents. However, it was considered that the results should be interpreted with caution due to a low absolute risk and the possibility for residual confounding. Thus, even if the risk of pancreatitis in patients treated with GLP-1 analogues may be rather low, it is most likely related to the mechanism of action of these drugs and it could be questioned whether the continuous exposure with the QW formulation could increase this risk. This is not confirmed in the submitted studies (with up to 2 years of exenatide once weekly exposure, no additional events were reported), but this needs to be followed postmarketing. Cases of pancreatitis will be further assessed and captured in the planned CV safety study GWDQ. Furthermore, the Applicant commits to undertake a Modified Prescription Event Monitoring Study in the United Kingdom to identify possible cases of pancreatitis.

There have been rare, spontaneously reported events of reduced renal function with exenatide BID. Some of these events occurred in patients experiencing events that may affect hydration, including nausea, vomiting, and/or diarrhoea and/or receiving pharmacological agents known to affect renal function/hydration status. This information is included in the SmPC for Exenatide BID but also for Bydureon. It is plausible that the mechanism is dehydration due to gastrointestinal side effects, and as there are indications that these are less common for the QW formulation, it is not expected that the risk will be increased compared to exenatide BID. However, these events should be monitored post marketing.

2.6.2. Conclusions on the clinical safety

Except for an increased incidence of injection site reactions and development of anti exenatide antibodies, the short term safety profile of exenatide QW seem to be largely similar to the BID formulation. However, potential long term effects of the QW dosing are more difficult to evaluate considering the differences in pharmacokinetic profile between the once weekly and the twice daily formulation of exenatide. Currently 221 and 110 patients have been exposed for 1 and 2 years respectively. The updated dataset supports the increased incidence of injection site reactions in particular in patients with antibodies compared to comparators including exenatide BID. However, these reactions were not classified as severe. Therefore, with adequate SmPC wording and the proposed PhV activities, this issue is not considered to preclude an approval. Concerning pancreatitis, no additional cases have been identified. However, there is still a potential issue as how the continuous exposure may affect this risk as well as the risk of thyroid malignancies. These events will be captured in the planned CV safety study GWDQ. Furthermore, the Applicant commits to conduct an
epidemiological study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly and undertake a Modified Prescription Event Monitoring Study in the United Kingdom.

There are currently no data supporting a problem in the case of a serious adverse event in the context of the long washout phase. However, this remains a potential issue that could cause a problem, e.g. in the case of severe GI adverse events or pancreatitis. This warrant for a careful use in patients with the highest risk of increased exposure for exenatide, e.g. the elderly and patients with renal impairment. Bydureon should not be used in patients with moderate renal impairment.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan including both exenatide BID (Byetta) and exenatide QW (Bydureon).

Table 17 Summary of the risk management plan
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities (Routine and Additional)</th>
<th>Proposed Risk Minimization Activities (Routine and Additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>• Routine pharmacovigilance</td>
<td>• SmPC 4.4 and 4.8, includes an appropriate description of the observed events of pancreatitis.</td>
</tr>
<tr>
<td></td>
<td>• Targeted surveillance of pancreatitis events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Additional information from ongoing clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A mechanistic study to evaluate potential change in gallbladder emptying following exenatide administration as a surrogate measure of increased tone of the sphincter of Oddi is ongoing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A post-marketing study to monitor for pancreatitis events will be conducted.</td>
<td></td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>• Routine pharmacovigilance</td>
<td>• SmPC 4.4 and 4.8, includes an appropriate description of the observed events of acute renal failure.</td>
</tr>
<tr>
<td></td>
<td>• Additional information from ongoing clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Targeted surveillance of acute renal failure/insufficiency, dehydration, and hypovolaemia events.</td>
<td></td>
</tr>
<tr>
<td>Rapid Weight Loss</td>
<td>• Routine pharmacovigilance</td>
<td>• SmPC 4.4 and 4.8 includes an appropriate description of the observed event of rapid weight loss.</td>
</tr>
<tr>
<td>Risks Associated with Anti-exenatide Antibodies (focus on anaphylactic-type reactions)</td>
<td>• Routine pharmacovigilance</td>
<td>• In general no association has been identified between anti-exenatide antibodies and SAEs. An association has been identified for nonserious injections-site reactions.</td>
</tr>
<tr>
<td></td>
<td>• Targeted surveillance of allergic/immunologic events (anaphylaxis, angiooedema, laryngeal oedema).</td>
<td>• SmPC 4.8 includes language on anti-exenatide antibodies and injection site reactions.</td>
</tr>
<tr>
<td></td>
<td>• Additional information from ongoing clinical trials</td>
<td>• SmPC 4.3 includes contraindication for use in individuals with known hypersensitivity to exenatide or formulation excipients</td>
</tr>
<tr>
<td>Cardiac Events</td>
<td>• Routine pharmacovigilance</td>
<td>• No association identified between exenatide and cardiac events to date.</td>
</tr>
<tr>
<td></td>
<td>• Conduct a prospective, long-term study to assess cardiovascular outcomes in subjects with type 2 diabetes randomized to standard of care diabetes regimens with or without exenatide once weekly.</td>
<td></td>
</tr>
<tr>
<td>Malignant Neoplasms (focus on pancreatic cancer and thyroid neoplasms)</td>
<td>• Routine pharmacovigilance</td>
<td>• No association identified between exenatide and malignant neoplasms to date.</td>
</tr>
<tr>
<td></td>
<td>• Additional information from ongoing clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Targeted surveillance for treatment-emergent malignancies and neoplasms with focus on pancreatic cancer and thyroid</td>
<td></td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Proposed Pharmacovigilance Activities (Routine and Additional)</td>
<td>Proposed Risk Minimization Activities (Routine and Additional)</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
</tbody>
</table>
|                | neoplasms.  
• The MAH commits to conduct an epidemiologic study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly |                                                                 |
<p>| Adolescents    | • Conduct a double blind, placebo controlled study to assess safety and efficacy of exenatide once weekly (as monotherapy and adjunctive therapy to oral antidiabetic agents) in children and adolescents with type 2 diabetes. | • SmPC 4.2 states with respect to children and adolescents, “The safety and effectiveness of exenatide have not been established in patients under 18 years of age.” |
| Pregnant Women | • Implemented a pregnancy registry beginning in December 2007 to determine whether exenatide poses a risk to pregnant women or their developing foetuses. | • SmPC 4.6 states with respect to pregnancy and lactation, That there are no adequate data from the use of BYDUREON in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 [of the SmPC]). The potential risk for humans is unknown. BYDUREON should not be used during pregnancy and the use of insulin is recommended. Due to the long washout period of BYDUREON, women of childbearing potential should use contraception during treatment with BYDUREON. BYDUREON should be discontinued at least 3 months before a planned pregnancy. |
| Very Elderly (≥75 years of age) | • Routine pharmacovigilance | • SmPC 4.2 states with respect to the elderly, “as renal function generally declines with age, consideration should be given to the patient’s renal function (see patients with renal impairment). The clinical experience in patients ≥75 years is very limited.” |</p>
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities (Routine and Additional)</th>
<th>Proposed Risk Minimization Activities (Routine and Additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Exenatide in Combination with TZDs</td>
<td>• Routine pharmacovigilance</td>
<td>• No differential adverse event profile has been found for patients taking exenatide in combination with TZDs.</td>
</tr>
<tr>
<td>Severe Gastrointestinal Disease</td>
<td>Not applicable</td>
<td>• SmPC 4.4 states with respect to patients with severe gastrointestinal disease, “BYDUREON has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of BYDUREON is not recommended in patients with severe gastrointestinal disease. “</td>
</tr>
<tr>
<td>Various Degrees of Impaired Renal Function</td>
<td>• Routine pharmacovigilance</td>
<td>• SmPC 4.2 states with respect to patients with varying degrees of renal function impairment, “No dosage adjustment is necessary for patients with mild renal impairment (creatinine clearance 50 – 80 ml/min). Clinical experience in patients with moderate renal impairment (creatinine clearance:30-50 ml/min), is very limited. BYDUREON is not recommended in these patients. BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance &lt;30 ml/min). “</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>• Routine pharmacovigilance</td>
<td>• SmPC 5.2 states with respect to patients with hepatic impairment, “No pharmacokinetic study has been performed in patients with hepatic insufficiency. Exenatide is cleared primarily</td>
</tr>
</tbody>
</table>
The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

As summarised in above RMP table pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to further investigate some of the safety concerns. In particular a Randomised, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide Once weekly in Patients with type 2 Diabetes Mellitus (study GWDQ/BCB109) will be conducted to provide information concerning cardiac events. Also important are the Modified Prescription-Event Monitoring (Modified PEM) to identify possible cases of pancreatitis to be conducted in the UK, enrolling primary care patients with type 2 diabetes who receive prescription for exenatide once weekly and the epidemiological study using one or more European databases to identify possible cases of thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide once weekly which will be conducted post-authorisation. (details on timelines are discussed under section 2.7 Follow-up measures following marketing authorisation)

**User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

**2.8. Benefit-Risk Balance**

**Benefits**

- **Beneficial effects**

  It is well known that patients with type 2 diabetes are at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality. A major purpose of using antidiabetic agents is to reduce these risks. HbA1c is generally accepted as surrogate marker for treatment effect and was included as the primary endpoint in all main studies of exenatide 2mg QW. Other important endpoints in studies of patients with type 2 diabetes are changes in body weight, fasting glucose as well as the possible effect on other cardiovascular risk factors.

  In the 4 main studies, treatment with exenatide 2mg QW added to ongoing OAD treatment for 24-30 weeks resulted in clinically relevant reductions in HbA1c (mean reductions 1.5-1.9%), body weight (mean reductions 2.3-3.7 kg) and fasting plasma glucose (mean reduction 1.4-2.3 mmol/l). The reductions were sustained at 52 weeks of treatment in one of the studies. In the presented studies, the reductions in HbA1c were more pronounced compared to the exenatide BID formulation. The study examining a switch from the BID to the QW formulation of exenatide also indicates that the QW dosing could result in additional glucose lowering effect. The glucose lowering effect as well as the effect on body weight was more pronounced compared to sitagliptin and pioglitazone. The reduction in HbA1c was largely similar independent on background OAD. There was a largely neutral effect on lipid parameters while a small, but consistent mean reduction of systolic blood pressure compared to baseline was seen in patients treated with exenatide QW.
There were no major difference in effect between men and women, patients with BMI < or > 30 or between patients below or above 65 years of age in the submitted studies.

- **Uncertainty in the knowledge about the beneficial effects.**

A potential benefit of the once weekly dosing as compared to the BID dosing could be increased patient compliance. Several PRO questionnaires were administered in the studies, but in general, no differences were seen between treatment groups. It could have been expected that the once weekly dosing would have increased patient satisfaction, but apparently, this was not reflected in the results of the questionnaires.

For patients who do not reach treatment goals despite of maximally tolerated doses of metformin, the gold standard is still addition of SU and not pioglitazone or sitagliptin which were chosen as comparators in study 106. Thus, the effect of exenatide QW in comparison to SU is unknown. However, considering that the absolute reduction of HbA1c associated with the use of exenatide QW is clearly of clinical relevance in the presented studies, a comparison to SU is not considered as mandatory for approval.

The number of patients older than 75 years was very limited, and the effect in these patients is not known. The limited clinical experience in patients older than 75 years is reflected in the SmPC. Overall, there was a higher incidence of treatment-emergent antibody positivity among exenatide QW-treated subjects and also a higher proportion of patients with high antibody titers compared to exenatide BID. The mean effect in patients with high titers is considerably attenuated compared to patients with low titers or no antibodies. However, there is a large variability in the glycaemic response in subjects with high titers. This is very similar to what has previously been seen with Exenatide BID.

**Risks**

- **Unfavourable effects**

For exenatide BID, the most common short-term safety issue is gastrointestinal side effects. Also for the QW formulation, GI adverse events are common, but the incidence seems to be somewhat lower compared to the BID dosing. In the Integrated Completed Studies Database, more exenatide BID-treated subjects (34%) experienced nausea as compared to exenatide QW-treated subjects (20%) while similar percentages of subjects in both treatment groups experienced diarrhoea (13%). More exenatide BID-treated subjects experienced vomiting (19%) compared to exenatide QW-treated subjects (8%). New events of nausea peaked at the Week 6 to Week 8 interval of the treatment, and then generally decreased over time.

Injection site reactions were observed more frequently in patients treated with exenatide QW versus comparator treated patients (16 % versus range of 2-7 %) during the 6 month controlled phase of studies. These injection site reactions were generally mild and usually did not lead to withdrawal from studies. Patients may be treated to relieve symptoms, while continuing treatment. Subsequent injections should use a different site of injection each week. Information is included in the SmPC.

There was a relatively high incidence of treatment-emergent antibody positivity seen in the clinical trials compared to the BID formulation. Subjects who were antibody positive had a higher overall incidence of potentially immune-related adverse events (primarilyinjection site-related events) than those who were antibody negative. This was not seen for exenatide BID. Overall, 15 % of exenatide QW-treated subjects experienced an injection site-related event in the original MAA. The updated dataset supports the increased incidence of injection site reactions in particular in patients with antibodies compared to comparators including exenatide BID. However, these reactions were not classified as severe. Therefore, with adequate SmPC wording and the proposed PhV activities, this issue does not preclude an approval.

Hypoglycaemia is mainly seen in the combination with SU. The product information states that when exenatide QW is added to SU therapy, a reduction in the dose of SU should be considered, to reduce the risk of hypoglycaemia. This is of particular importance in patients with impaired renal function.

- **Uncertainty in the knowledge about the unfavourable effects**

The differences in pharmacokinetics between the once weekly and the twice daily formulation of exenatide may potentially have an impact on the safety profile of the QW formulation, particularly considering the findings of the thyroid C cell tumours in rats. In a 2-year carcinogenicity study in rats, exenatide QW caused thyroid C-cell adenomas in both male and female rats at all doses, and C-cell carcinomas in male rats at all doses and female rats at the high dose. In previous studies with exenatide BID, there was an increase in benign thyroid C-cell adenomas in female animals. The
Numerical increase in tumours was not statistically significant when adjusting for survival. These
tumours have also been seen for liraglutide and have been considered to represent a class effect to
GLP-1 receptor agonists.

Even though no specific concerns have arisen from the presented studies, new data recently reported
for Exenatide BID from an epidemiological study using an i3 Aperio tool have raised some concerns.
Even though a re-analysis of the i3 Aperio assessment of thyroid neoplasms in patients using
exenatide BID indicated an increased risk compared to other OADs (RR 1.4, CI 0.8-2.4), the results are
associated with several limitations and cannot be considered as conclusive. Considering all limitations
of the available data, this cannot be considered a strong safety signal. However, considering the
preclinical signal for exenatide QW, an epidemiological study to identify possible cases of thyroid
neoplasms among patients who initiate exenatide once weekly should be performed post-approval. The
Applicant already submitted a study proposal and will be further assessed post-approval. A formal
study protocol will be submitted by the Applicant in July 2011. Furthermore, thyroid events will be
captured in the planned CV safety study GWDQ.

There are currently no data supporting a problem in the case of a serious adverse event in the context
of the long washout phase. However, this remains a potential issue that could cause a problem, e.g. in
the case of severe GI adverse events or pancreatitis. This warrants for a careful use in patients with
the highest risk of increased exposure for exenatide e.g. the elderly and patients with renal impairment.
Bydureon should not be used in patients with moderate renal impairment. Information on the long
washout time is included in the SmPC.

A recently performed QT study (H80-EW-GWCI) with the BID formulation showed a modest increase of
the QTc interval. However, several findings could be interpreted as reassuring. First, the QT interval
did not exceed 500 msec. Second, exenatide twice daily has so far not been associated with
proarrhythmic effects. Third, the results from the clinical trials do not indicate additional risks. Fourth,
plasma concentrations of exenatide once weekly were not related to the QTc interval, indicating that
the relationship between exenatide once weekly and QTc interval is weak. The CHMP is of the opinion
that a QTc study with exenatide should be performed. However, due to the reasons mentioned above,
this study could be performed post-approval.

**Benefit-Risk Balance**

- **Importance of favourable and unfavourable effects**

  The treatment effect seen with exenatide QW is of clear clinical relevance based on the association of
  reduction of HbA1c and reduction of the risk of microvascular complications. The absolute mean
  reductions are considered as rather large in the context of a moderately high mean baseline HbA1c and
  are also more pronounced compared to the comparators in the studies. Even though other treatment
  alternatives are available, it is well known that since all treatment alternatives are associated with
different adverse events profiles and may not be tolerated by certain patients, it is of importance that
clinicians have access to different options when treating patients with type 2 diabetes.
The reduction in body weight is of clinical importance considering that many of the patients are obese
and that some of the treatment alternatives (e.g. glitazones, SU, insulin) are associated with weight
increase.

  The observed side effects such as gastrointestinal adverse events, injection site reactions,
hypoglycaemia is considered to be manageable, and the information in the SmPC is considered as
acceptable. Concerning the potential issue of long lasting adverse events due to the long wash out
phase, exenatide QW should not be used in patients with moderate renal impairment. It should also be
noted that the experience in patients older than 75 years is very limited. Potential long term safety
issues, e.g. pancreatitis and thyroid cancers, will be followed post marketing.

- **Benefit-risk balance**

  The benefits of the effects on glucose parameters and body weight, that were more pronounced
  compared to the comparators in the studies, are considered to exceed the increased risk of non-serious
  adverse events such as injection site reaction and GI adverse events as well as the consequences of
  increased incidence of anti-exenatide antibodies. Potential, serious adverse events, such as
  pancreatitis and thyroid cancers will be further assessed post-marketing. The overall benefit-risk
  balance of Bydureon is positive.
2.8.1. Discussion on the benefit-risk balance

The benefits of the effects on glucose parameters and body weight, that were more pronounced compared to the comparators in the studies, are considered to exceed the increased risk of non-serious adverse events such as injection site reaction and GI adverse events as well as the consequences of increased incidence of anti-exenatide antibodies. Potential, serious adverse events, such as pancreatitis and thyroid cancers will be further assessed post-marketing. The Applicant has committed to perform several studies post-approval.

The indication for Bydureon claimed for by the Applicant is treatment of type 2 diabetes mellitus in combination with metformin, sulphonylurea, thiazolidinedione, metformin and sulphonylurea, metformin and thiazolidinedione in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. The indication is the same as for exenatide BID and is also considered acceptable for Bydureon by the CHMP. The CHMP concluded that the overall benefit-risk balance of Bydureon is positive in the claimed indication.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and that no additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Bydureon in the treatment of type 2 diabetes mellitus in combination with

- Metformin
- Sulphonylurea
- Thiazolidinedione
- Metformin and sulphonylurea
- Metformin and thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies, was favourable and therefore recommended the granting of the marketing authorisation.