Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Exenatide

Proprietary Product Name: Byetta and Bydureon

Sponsor: Eli Lilly Australia Pty Ltd

February 2013

TGA Health Safety Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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I. Introduction to product submission

Submission details

Type of Submission	Extension of Indication and New Dosage Form
Initial Decision:	Rejected
Final Decision:	Extension of Indication: Rejected; New Dosage Form: Approved
Date of Initial Decision:	13 February 2012
Date of Final Decision:	5 July 2012 (Byetta) and 6 December 2012 (Bydureon)
Active ingredient(s):	Exenatide
Product Name(s):	Byetta and Bydureon
Dose form(s):	Byetta: Solution for Injection
	Bydureon: Powder for modified release injection
Strength(s):	Byetta 5 (5 µg/20 µL), 1.2 mL solution for injection multidose cartridge;
	Byetta 10 (10 µg/40 µL), 2.4 mL solution for injection multidose cartridge;
	Bydureon 2 mg, powder for injection vial with diluent syringe.
Container(s):	The product consists of a single dose kit containing a vial of powder, a prefilled syringe of diluent, a vial connector and two needles (one spare)
Pack size(s):	1's
Route(s) of administration:	Byetta: Subcutaneous (SC) injection in the abdomen, thigh or arm
	Bydureon: Subcutaneous injection in the abdomen
Dosage:	Byetta: 5 or 10 µg twice daily; Bydureon: 2 mg/week
ARTG number(s):	

Product background

Exenatide is a synthetic 39 amino acid version of the peptide exendin-4 that belongs to a class of agents known as glucogon-like peptide-1 (GLP-1) receptor agonists. It has also been classified as an incretin mimetic. It displays biological properties similar to human GLP-1, a regulator of glucose metabolism and insulin secretion.

Exenatide is currently registered for twice daily SC administration as Byetta 5 (5 µg dose) and Byetta 10 (10 µg dose) to improve glycaemic control in patients with Type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.

This AusPAR describes the application by the sponsor to extend the indications for exenatide to include combination with thiazolidinediones (TZDs). In addition, the sponsor proposes to register a new 2 mg extended release microsphere formulation of exenatide (Bydureon) for once weekly administration.

The sponsor proposes the same indications for Bydureon as for Byetta. Byetta requires twice daily dosing prior to meals and has relatively short duration of action, primarily after those meals. Bydureon is intended to prolong the duration of action of exenatide and to reduce the dosing frequency to once weekly.

The long active formulation is referred to as exenatide-LAR and Byetta is referred to as exenatide-IR in this report.

Regulatory status

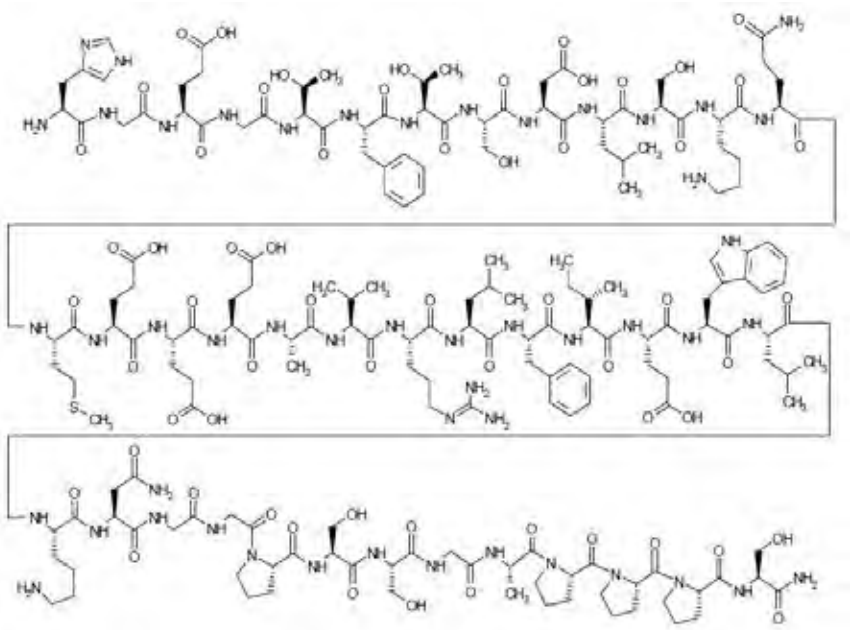
Exenatide was first approved on 28 April 2005 in the USA. As of 31 March 2011 it has been granted marketing authorisation in approximately 87 countries. Exenatide is currently marketed in 72 countries.

II. Quality findings

Drug substance (active ingredient)

Exenatide is a white to off white powder. It is freely soluble in de-ionised water as well as in buffered aqueous solutions twixt pH 3.0 and 8.0. Exenatide is reversibly hygroscopic. The exenatide structure is shown in Figure 1 below.

Figure 1. Exenatide structure.



The manufacture quality control and stability of the drug substance produced at two manufacturing sites have each been assessed and found acceptable.

Drug product

The proposed Bydureon product comprises two components:

- The 2 mg exenatide powder for injection, which consists of exenatide (5% weight/weight (w/w)) and sucrose (2% w/w) encapsulated within biodegradable lactide-glycolide polymer microspheres that are designed to release therapeutic concentrations of exenatide over an extended period of time.
- The exenatide solvent, which is a pH 6.5 phosphate buffer solution containing carmellose sodium to modify the viscosity, sodium chloride to adjust the osmolality and polysorbate to facilitate wetting of the exenatide microspheres.

The product is supplied in a drug product kit consisting of the microsphere powder in a glass vial, the exenatide solvent in a pre-filled glass syringe, needles and a vial connector for ease of solvent and suspension transfer. Addition of exenatide solvent in the syringe to the powder in the vial provides a suspension, which is administered subcutaneously using the solvent syringe.

Powder batches produced to support this application were produced at a developmental production site as well as at the proposed commercial production site. The manufacturing process uses a co-acervation process to encapsulate the drug substance and sucrose (used as a stabiliser) in the lactide-glycolide polymer. The process is performed aseptically in a closed sterile system. The diluent used to suspend the powder is manufactured and sterilised using standard processes.

The quality of the product is controlled by separate specifications for the microspheres powder and diluent. The key features of the product's quality as controlled by the powder specification are the impurities, drug substance release and water content.

Impurities in the exenatide containing microspheres are specified within regions of the high performance liquid chromatography (HPLC) chromatogram. This approach is also used for the approved Byetta product and is necessary because of the complex nature of the drug substance's impurity profile. However, while many of the impurities in the proposed Bydureon product are common to the Byetta product, others are unique to Bydureon and arise from reaction of the drug substance with the lactide-glycolide polymer. Toxicological qualification was supplied for the proposed impurity limits in the Bydureon product and this qualification has been found to be acceptable.

Drug substance release from the microspheres is controlled by two separate *in vitro* test methods; an Initial and a Complete release test. The Initial release test is conducted in pH 7.4 buffer at 37ºC and measures exenatide release after incubation of the microspheres for 1 h. The Complete release test quantifies exenatide release after incubation of the microsphere product in pH 9.4 buffer at 37ºC. The sponsor had originally proposed a Complete release test which was conducted at 45ºC in pH 9.4 buffer, which had the advantage that the drug substance release could be measured over a shorter time period. However, the method has been abandoned because of unexplained out of specification results. It should be noted that the *in vitro* test is conducted under unusually alkaline conditions and spans 52 days, which is much longer than the proposed dosing interval.

Water content is another key determinant of the product's quality. Increasing moisture content in the stability trials correlated with increasing degradation products. The sponsor's limits at both release and expiry are considered sufficient to control the impurities.

The proposed shelf life for the exenatide powder is 24 months at 2-8ºC, which includes a patient in use (unsuspended) duration of up to 4 weeks at 30ºC. The stability data support the proposed shelf life and storage conditions.

Biopharmaceutics

The immediate release pharmacokinetic properties of exenatide are known. After subcutaneous administration to patients with Type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 hours and the mean apparent volume of distribution is 28.3 L. After a dose of 10 mg exenatide, the mean peak exenatide concentration was 211pg/mL and the overall mean area under the curve (AUC) was 1036 pg.hour/mL. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 to 10 mg, while the maximum plasma concentration (C_{max}) values increased less than proportionally.

To characterise the pharmacokinetic profiles of exenatide in the delayed release Bydureon product, the following studies were provided:

- BCB107. An open label parallel group study to evaluate the pharmacokinetics of multiple exenatide long acting release formulations in healthy volunteers to establish an in vitro/in vivo correlation;

- 2993LAR-105 Comparability Assessment. A randomised, open label, multicenter, comparator controlled study. The main aim of this study was to examine the effects of exenatide once weekly from different manufacturing sites/scales on glycaemic control;
- BCB108 (comparison of Byetta and Bydureon). A randomised, open label, multicenter, comparator controlled, two-arm study that compared the effects on exenatide once weekly (manufactured at final 15 kg commercial scale) with those of exenatide twice daily over a 24 week treatment period.
- BCB106 Site of injection study. A study designed to assess the effects of the proposed exenatide once weekly administered subcutaneously in the upper arm, thigh and abdomen on glycaemic control and exenatide pharmacokinetics.

Because analytical problems the plasma samples for Studies BCB108 and BCB106 needed to be re-analysed and this data was supplied after the initial submission.

Study BCB107 was the only single dose study conducted with the proposed delayed release formulation and the immediate release Byetta product. In it the single dose pharmacokinetic characteristics of the proposed formulation were examined and compared with specially prepared fast and slow release drug product formulations. From these studies an attempt was made to develop an *in vitro – in vivo* correlation.

The average plasma concentration profiles in this study indicate that a single dose of the proposed delayed release formulation exhibits multiphasic release over an approximately 10 week period. This was interpreted by the sponsor as an initial period with release of surface-bound exenatide (Phase 1) followed by 2 subsequent peaks representing the hydration (Phase 2) and erosion (Phase 3) of the microspheres. The mean plasma concentration profile (shown in Figure 2A below, where S426-2377CA and S426-2507AA represent the proposed formulation profiles) broadly supports these statements, however their value is questionable given the large inherent individual variability of the product's release (shown in Figure 2B, below).

Figure 2-A. Mean plasma concentration profiles (Top)

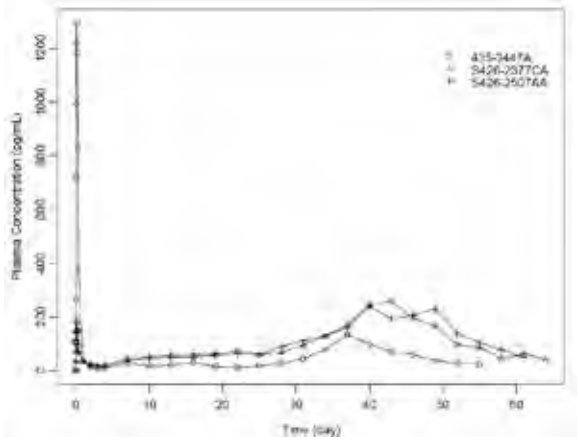
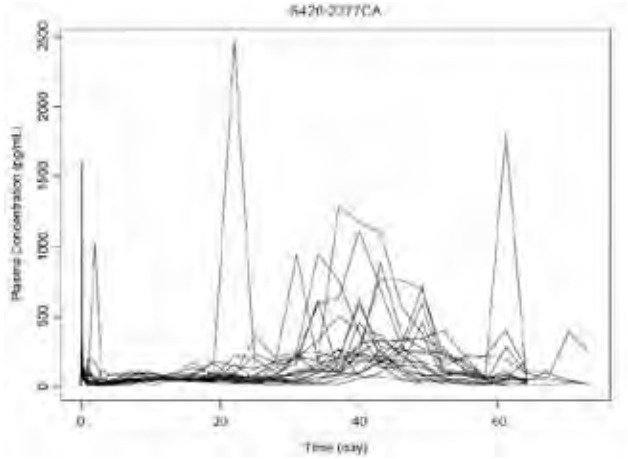


Figure 2-B. Individual profiles for the proposed formulations (Bottom)



Results from this study also indicated that the initial 'burst' release of exenatide gives a C_{max} of about 200 pg/mL and accounts for less than 1% of the overall AUC. The bioavailability of the delayed release formulation was approximately 22% compared with the immediate release formulation. The reason for the low relative bioavailability of the proposed modified release formulation is not understood.

The other studies all examined the steady state pharmacokinetics of the proposed delayed release formulation. Overall, the studies revealed that continued once weekly 2 mg exenatide doses led to a gradual increase in mean plasma exenatide concentrations over approximately 6 to 7 weeks; subsequently, exenatide concentrations achieved a steady state at approximately 248 pg/mL; with minimal peak-to-trough fluctuations over the weekly dosing interval.

Geometric mean steady-state concentrations 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. About 10 weeks after the last injection of exenatide once weekly treatment, mean plasma exenatide concentrations approached the lower limit of quantitation (10pg/mL).

Study 2993 LAR-105. Comparability assessment compared drug product produced at the commercial site with that produced at a site used to manufacture development drug product batches. Results from this study confirmed the product's high degree of pharmacokinetic variability and also showed that (on the basis of steady state AUC (AUCss) and maximum plasma concentration at steady state (Css)) the drug products produced at the respective sites were not **equivalent**. The sponsor argues that this result is not significant, based on the equivalence of pharmacodynamic (glycaemic) endpoints in drug product produced between the two sites.

The proposed delayed release product was also compared with the approved immediate release Byetta formulation is Study BCB108, however no meaningful comparisons between the formulations could be made from the steady data described in this report.

Finally, an attempt was made to demonstrate that subcutaneous injection of the proposed delayed release product in the abdomen thigh or upper arm produces equivalent exenatide plasma concentration profiles (Study BCB106 Site of injection study). However, it was found that the 90% confidence intervals for the mean ratios of plasma exenatide concentrations between the upper arm-abdomen and the thigh-abdomen were outside the

normally accepted limits (0.8-1.25) for demonstration of bioequivalence. The PI recommends injection in any of these sites.

In summary, the biopharmaceutic data presented in the current submission were largely inconclusive and the acceptability of formulations from the proposed manufacturing site must rely on clinical rather than biopharmaceutic data.

Quality summary and conclusions

Details of the submission were considered at the 141st meeting of the Pharmaceutical Subcommittee (PSC) (2011/6). The chemistry and quality control issues raised have been resolved; however the committee also concluded that the submission is not acceptable on biopharmaceutical grounds. The pharmacokinetic data were so variable that no useful correlation can be made between the proposed delayed release Bydureon product and the immediate release Byetta product.

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

The nonclinical data submission included previously evaluated studies provided in the original Byetta application, and new studies on pharmacology, pharmacokinetics, repeat dose toxicity, genotoxicity and carcinogenicity, mostly conducted with the new exenatide long acting release (LAR) formulation (Bydureon). No nonclinical data regarding use in combination with TZDs to support the proposed new indication for exenatide were provided in this application (nor previously). All of the definitive safety related studies were Good Laboratory Practice (GLP) compliant, and the few studies that were non GLP were conducted in established laboratories and adequately documented.

Pharmacology

Primary pharmacodynamics

The pharmacological effects of exenatide have been previously characterised. GLP-1 receptor agonist activity was demonstrated for the drug *in vitro* and *in vivo*. In animal models of diabetes and obesity, sub chronic administration of the immediate release (IR) formulation of exenatide resulted in decreased plasma glucose and HbA1c, increased insulin sensitivity and decreased body weight.

Because the pharmacologic effects of exenatide (IR) have already been characterised in animals and humans, only a single nonclinical efficacy study was conducted with exenatide-LAR, examining its glucose and HbA1c lowering actions in the Zucker Diabetic Fatty rat model. There was no remarkable effect on weight gain at any dose (≤9000 µg SC; single administration), however dose related reductions in food consumption were seen at ≥1000 µg SC. Dose dependent reductions in glycaemic (HbA1c, fasting glucose, fructosamine) and lipidemic indices (fasting cholesterol and triglyceride) were observed at ≥100 or ≥1000 µg

SC at 28 days post injection. Exenatide-LAR also increased insulin sensitivity and enhanced β cell function. Mean plasma exenatide concentration at the lowest efficacious dose, averaged over Days 1–28 (252pg/mL at 100 μg), was comparable to the mean concentration at steady state in clinical trial participants receiving exenatide-LAR 2 mg once weekly as proposed.

Secondary pharmacodynamics and safety pharmacology

No secondary or safety pharmacology studies were conducted with exenatide-LAR. This is considered acceptable given the existence of adequate prior studies with exenatide-IR to assess potential effects on the central nervous system, cardiovascular function, renal function, gastrointestinal secretion, and secretion of some hormones in mice, rats and monkeys. Significant adverse effects were not observed in these studies in which exposure to the drug was in excess of that expected with the proposed clinical use based on expected C_{max}. In addition, cardiovascular (heart rate, clinical signs), respiratory (respiration rate, clinical signs) and/or central nervous (body temperature, clinical signs) effects were examined, albeit in a more limited fashion, in repeat dose toxicity studies of exenatide-LAR in rats and/or monkeys, with no treatment-related effects seen.

In a newly submitted study, the activity of exenatide-IR was studied in a rat model of hypertension and metabolic syndrome. Low continuous infusion of exenatide (1 μg/kg/day for 7 days) normalised glucocorticoid-induced hypertension and lowered blood pressure in normotensive rats, with no effect on heart rate, apparent cardiac contractility, body weight, caloric intake, fasting glucose, insulin or HOMA (homeostasis model assessment [of insulin resistance]) at the dose tested. These results suggest that the anti hypertensive effect of exenatide observed in this study is likely mediated via a mechanism that is independent from any effect on energy balance or glucose control.

Pharmacokinetics

The pharmacokinetic characteristics of exenatide have been previously examined in the original Byetta nonclinical submission. Exenatide-LAR is composed of the same peptide (exenatide) as Byetta, but formulated to prolong absorption by encapsulation in poly(D,L-lactide-co-glycolide) (PLG) microspheres. Once exenatide is absorbed systemically, the distribution, metabolism, and excretion of the peptide itself are not expected to be different from that of exenatide in the IR formulation. As such, the absence of further studies of the peptide's biological fate is considered acceptable. Appropriately though, additional pharmacokinetic assessments were conducted in rats and monkeys given a single SC exenatide-LAR injection to characterise the drug's modified absorption profile in the extended release form. Toxicokinetics were also examined in the repeat dose SC toxicity studies in rats and monkeys.

In rats and monkeys given exenatide-LAR by SC injection, absorption was shown to continue over an extended period of time (weeks). Relative bioavailability of exenatide-LAR compared to exenatide-IR was estimated to be approximately 63% in rats and 23% in monkeys. There were no consistent sex differences in exposure in either animal species. Exposure after a single dose was dose proportional in monkeys and less than dose-proportional in rats. Following the administration of multiple doses of exenatide-LAR, there was significant accumulation, as expected given the long duration of exposure. Steady state was reached after the fifth fortnightly dose in rats and the fifth to ninth weekly dose in monkeys. As well, antibodies to exenatide were observed at high frequency and impacted

the measured plasma concentrations in both species with continued dosing, generally increasing exposure with increasing antibody titre (consistent with an effect to reduce clearance).

Comparison of toxicokinetic data for the two exenatide formulations show that the peak and overall exposure (C_{max} and AUC) achieved in the toxicology studies with the immediate release formulation was greater than that achieved with exenatide-LAR. Animals administered exenatide-IR were exposed daily to higher concentrations of exenatide for a short period of time followed by a period of diminished exposure, compared to continuous but lower exposure to the drug over the entire 24 h interval with exenatide-LAR. In the rat, daily exenatide exposure (AUC) at the high dose in the pivotal 3 month exenatide-IR (250 µg/kg/day SC) and 4 month exenatide-LAR (9 mg/kg/fortnight SC) toxicity studies was only modestly lower at 233 ng·h/mL and 177 ng·h/mL, respectively. In the monkey, daily exenatide exposure at the high dose in the pivotal 9 month exenatide-IR study (150 µg/kg/day SC) was 6.5 fold greater than in the 9 month exenatide-LAR study (1.1 mg/kg/week SC) at 1000 ng·h/mL and 153 ng·h/mL, respectively. As expected, C_{max} values at the high dose in the 3 month rat (162 ng/mL) and 9 month monkey (212ng/mL) exenatide-IR studies were greater (6–8 fold) than in the 4 month rat (19.8 ng/mL) and 9 month monkey (36.5ng/mL) exenatide-LAR studies.

Relative exposure

Exposure ratios for exenatide achieved in the key toxicology studies with the extended release form of the drug have been calculated based on animal:human mg/kg dose, C_{max} and weekly AUC (see Table 1 below). Toxicokinetic data are for all animals combined (both sexes; antibody negative and positive). Human reference values are derived from a clinical study (2993LAR-105 comparability) using exenatide-LAR manufactured at the commercial site and scale.

Table 1. Animal: Human Exposure ratios

Species	Dosing		Dose (mg/kg); SC	C_{max} (pg/mL)	AUC_{0-7d} (pg·h/mL)	Exposure ratio		
	Frequency	Duration				mg /kg	C_{max}	AUC
Rat (SD)	once fortnightly*	18 weeks	1	35793	1005168	25	143	41
			3	20035	997421	75	80	40
			9	19833	1237326	225	79	50
		26 weeks#	0.3	2897	85473	8	12	3.4
			1	23362	811192	25	93	33

Species	Dosing		Dose (mg/kg); SC	C_{max} (pg/mL)	$AUC_{0-7\,d}$ (pg·h/mL)	Exposure ratio		
	Frequency	Duration				mg /kg	C_{max}	AUC
			3	23896	2663489	75	95	107
Monkey (Cynomolgus)	once weekly	13 weeks	0.11	2895	114397	2.8	12	4.6
			0.44	5434	283977	11	22	11
			1.1	19939	973761	28	79	39
		39 weeks	0.11	9099	227674	2.8	36	9
			0.42	20873	1115646	11	83	45
			1.1	36538	1073952	28	146	43
Human [2993LAR-105 comparability]	once weekly	20 weeks / steady state	0.04[a] [2 mg]	251	24789	–	–	–

* = Rat AUC values (0–14 days) are corrected for weekly exposure; # = toxicokinetic data for carcinogenicity study;
Human data are for the commercial exenatide-LAR scale/manufacturer; a = assuming 50 kg body weight.

In humans receiving the immediate-release form of exenatide (Byetta) twice daily at 10 µg, the C_{max} is 211 pg/mL and AUC from time 0 to 24 h (AUC_{0-24h}) is 2072 pg·h/mL (yielding a weekly AUC of 14504 pg·h/mL). Thus, peak and weekly exposure to exenatide with Bydureon is 19% and 71% higher, respectively, than with treatment at the maximum recommended dose of Byetta.

Toxicology

Acute toxicity

No acute toxicity studies were conducted with exenatide-LAR. This is considered acceptable given adequate single SC dose toxicity studies in rats and monkeys conducted with exenatide-IR provided exposures estimated to be several hundred times the expected clinical exposure on an AUC or C_{max} basis and did not reveal significant acute toxicity.

Repeat-dose toxicity

GLP compliant repeat-dose toxicity studies were conducted with exenatide-LAR in rats and cynomolgus monkeys for up to 4 months and 9 months, respectively. The studies were conducted in appropriate species (identical to those employed for exenatide-IR), at adequate dose levels (based on the large exposure margins over the anticipated clinical AUC; refer to the table above) using the clinical route and appropriate group sizes, and were of sufficient duration (the same or longer length as exenatide-IR studies) to allow an assessment of the safety of the extended release formulation as well as a comparison of the toxicological profiles of the two exenatide formulations. Dosing with exenatide-LAR was once weekly in monkeys (as proposed clinically) but fortnightly in rats. Nevertheless, given the sustained drug exposure, the studies in rats are considered valid. The studies with exenatide-LAR included both vehicle control and microsphere control groups.

Despite the difference in exposure profiles, no remarkable differences in the systemic toxicological profiles were observed between the two formulations in either species. Exenatide-LAR was well tolerated in the laboratory animal species with no toxicologically significant effects on systemic tissues observed in rats at doses up to 9 mg/kg/fortnight SC for 4 months (relative exposure based on AUC, 50) or in monkeys at up to 1.1 mg/kg/week for 9 months (relative exposure, 43).

In the pivotal studies, treatment was associated with reduced body weight gain (and initial loss) and decreased food consumption in rats (at all doses) and decreased thymus weight (all doses) and thymic lymphocyte depletion (at the high dose) in monkeys. The reductions in body weight and food consumption are likely related to the pharmacological action of the drug, as previously seen with exenatide-IR. Similarly, reductions in thymus weights were also previously observed with exenatide-IR and are consistent with non specific toxicity/stress. The thymic lymphocyte depletion was minimal and there was no accompanying effect on haematological parameters. None of these findings are considered to indicate a significant safety risk to patients using exenatide.

Local injection site changes were noted consistently following the subcutaneous injection of exenatide-LAR at all doses. These also occurred in the microsphere control groups, and comprised inflammatory and foreign body reactions (erythema, swelling, thickening and granulomas). These are expected from the injection of a biodegradable PLG microsphere product, and showed partial to complete reversibility over time. The doses administered to the animals are significant multiples of the clinical dose on a mg/kg basis. According to the sponsor, injection site reactions were noted during the clinical development program and are described in the proposed product labelling.

Genotoxicity

In the current submission, exenatide-IR (manufactured by a new synthetic method) and exenatide-LAR were tested for potential genotoxic effects *in vitro* (assays for bacterial reverse mutation and for chromosomal aberration in Chinese hamster ovary cells). All studies were performed in compliance with GLP using adequate concentrations and validated by positive controls. An adequate battery of *in vitro* (bacterial reverse mutation and chromosomal aberration assays) and *in vivo* (mouse micronucleus test) genotoxicity studies with exenatide-IR was also evaluated previously for Byetta. As expected for a peptide, exenatide was devoid of mutagenic or clastogenic potential in all assays.

Carcinogenicity

In previously evaluated rodent carcinogenicity studies with the exenatide-IR formulation, the most notable observation was an increased incidence of thyroid C-cell adenomas among female rats which received 250 µg/kg/day SC (the high-dose level) compared to concurrent and historical controls. This was statistically significant by pairwise comparison. Although no statistically significant increase in these tumours was observed when adjusted for survival (which was substantially increased among exenatide-treated rats), a relationship to treatment was considered probable. Exenatide was negative in the mouse carcinogenicity study (≤250 µg/kg/day SC) and no treatment related increase in the incidence of thyroid C-cell carcinomas or other non C-cell tumours of the thyroid were observed in any species. In addition, no positive signals for proliferative tissue changes were noted in the general repeat dose toxicity studies conducted in mice, rats and monkeys with exenatide-IR.

In the current submission, a GLP-compliant rat carcinogenicity study was conducted with exenatide-LAR to ascertain whether the extended period of exposure to exenatide would affect its carcinogenicity profile. The rat was selected as the single species for evaluation based on technical feasibility of chronic SC dosing and its prior identification as the most relevant and sensitive species for the thyroid C-cell lesions. The use of a single rodent species is considered acceptable and the selection of the rat is endorsed. The dose levels employed in this study (0.3, 1, and 3 mg/kg/fortnight SC) were appropriate, and selected based on exaggerated pharmacodynamic effects (decreased body weight gain). The exposure multiple at the high dose level (107, based on animal:human AUC from Day 0 to Day 7 (AUC_{0-7d}) easily surpassed the minimum multiple recommended under TGA-adopted European Union (EU) guideline[1] without adversely affecting survival. Group size was appropriate, and as in the repeat dose toxicity studies, there were both vehicle and microsphere control groups.

Treatment with exenatide-LAR produced clear increases in the incidence of thyroid C-cell tumours in rats. The incidence of C-cell adenomas exceeded concurrent and historical controls in both sexes at all doses (≥0.3 mg/kg/fortnight; relative exposure, ≥3.4), with the increase statistically significant by Peto trend analysis at all dose levels in females and at ≥1 mg/kg/fortnight in males. The incidence of C-cell carcinomas was increased beyond the historical control range at all doses in males and at 3 mg/kg/fortnight in females (statistically significant in the high-dose female group only). The increase in C-cell neoplasia occurred in the context of an increase in the incidence and severity of C-cell focal hyperplasia, modest in the male drug treated groups and marked in females. A No Observed Effect Level (NOEL) could not be established for exenatide-LAR-induced thyroid carcinogenicity in the rat.

Thyroid C-cell carcinogenicity by exenatide in the rat was far more prominent with exenatide-LAR compared with exenatide-IR. This is in terms of the exposure levels associated with carcinogenicity (19 times lower for exenatide-LAR compared with the IR form), the nature of the tumours (with malignant tumours additionally found only for exenatide-LAR) and the sex distribution (both sexes compared with females only with exenatide-IR). These data indicate that it is the change in the pattern of exposure

[1] ICH Topic S1C(R2). Dose Selection for Carcinogenicity Studies of Pharmaceuticals. Step 4. Note For Guidance On Dose Selection For Carcinogenicity Studies Of Pharmaceuticals (EMEA/CHMP/ICH/383/1995). http://www.tga.gov.au/pdf/euguide/ich038395final.pdf

(continuous compared to pulsatile) rather than a change in the overall level of exposure that is associated with the increased thyroid C-cell tumours in rats.

Similar thyroid C-cell findings as seen here with exenatide-LAR have been observed with liraglutide, another long acting GLP-1 receptor agonist (Australian Public Assessment Report [AusPAR] for Liraglutide (rys) [Victoza®][2]). Liraglutide caused thyroid C-cell focal hyperplasia, adenomas and carcinomas in 2 year studies in mice and rats. C-cell neoplasia was observed in mice at SC doses ≥1 mg/kg/day (relative exposure based on plasma AUC, ≥7.7) and in rats at all doses tested (≥0.075 mg/kg/day SC; relative exposure, ≥0.5). As in the 9 month monkey study with exenatide-LAR (≤1.1 mg/kg/week SC; relative exposure, ≤45), no tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day SC; relative exposure, ≤64).

Available data suggest that the thyroid C-cell tumours induced in rodents by GLP-1 receptor agonists occur via a non genotoxic, receptor mediated mechanism. Key data supporting this mechanism (described in detail in the evaluation report for liraglutide) have demonstrated significant species differences in GLP-1 receptor expression in the thyroid, with strong expression in rats and mice compared to low or undetectable expression in monkeys and humans. The chronic toxicity studies conducted with the class have demonstrated proliferative effects on thyroid C-cells by GLP-1 receptor agonists in rodents only and not in primates.

The finding of thyroid C-cell tumours in rats with exenatide-LAR is considered unlikely to be predictive of similar effects in patients treated with Bydureon. However, the relevance of the tumours cannot be completely excluded and the sponsor's nomination of thyroid cancer as a particular focus for pharmacovigilance activities in the Risk Management Plan is warranted.

Reproductive toxicity

No reproductive toxicity studies were conducted with exenatide-LAR. This is considered acceptable given that an adequate battery of reproductive toxicology studies has been previously conducted in mice and rabbits with exenatide-IR, and that no change in the systemic toxicity profile has been noted with the LAR formulation (including effects on the reproductive organs) in the general toxicity studies. Furthermore, placental transfer of exenatide is very limited and effects on embryofetal development observed previously were considered to be secondary to maternal effects. Levels of exenatide excreted in milk are also low.

Use in children

Studies in juvenile animals were not conducted with exenatide-IR or exenatide-LAR.

Local tolerance

No specific local tolerance studies were performed with exenatide-IR or exenatide-LAR. However, clinical observations and pathological examinations were made in the general repeat dose toxicity studies in rats and monkeys to assess the local tissue reactions to

[2] http://www.tga.gov.au/pdf/auspar/auspar-victoza.pdf

exenatide and the PLG microspheres and injection sites were also examined (in-life) as part of a pharmacokinetic study in monkeys.

Nonclinical summary and conclusions

- The pharmacological and toxicological profile of exenatide has been previously characterised in the nonclinical submission for the original registration of the immediate release (IR) form (Byetta). Additional pharmacology, pharmacokinetic (absorption) and toxicology studies were provided in the current submission to evaluate alterations in the efficacy and safety profile of the new long acting release (LAR) formulation of exenatide (Bydureon).
- Anti-diabetic activity was demonstrated for exenatide-LAR in a relevant rat model, with decreases in glycaemic and lipidemic indices and increased insulin sensitivity and enhanced β-cell function observed 28 days after a single SC dose.
- No secondary or safety pharmacology studies were conducted with exenatide-LAR. This is considered acceptable based on previous data.
- Pharmacokinetic studies with exenatide-LAR demonstrated absorption over an extended period of time (weeks) following SC injection. Relative bioavailability of exenatide-LAR compared to exenatide-IR was estimated to be 63% in rats and 23% in monkeys. Following multiple doses of exenatide-LAR to rats and monkeys, antibodies to exenatide were observed at high frequency and impacted the measured plasma concentrations in both species (generally increasing exposure).
- No acute toxicity studies were conducted with exenatide-LAR. This was considered acceptable.
- Repeat dose toxicity studies in rats and monkeys with exenatide-LAR for up to 4 months and 9 months respectively, did not reveal any novel systemic toxicities at exposure levels up to 45–50 times higher than that anticipated clinically (based on AUC). Local injection site reactions consisting of inflammatory and foreign body reactions were observed in both exenatide treated and microsphere control groups. These were expected from the injection of a poly(D,L-lactide-co-glycolide) (PLG) microsphere product, and showed partial to complete reversibility over time.
- Exenatide-LAR (like exenatide-IR) was not genotoxic in bacterial reverse mutation or chromosome aberration assays in vitro.
- In a 2 year carcinogenicity study in rats, an increased incidence of thyroid C-cell neoplasia was observed at all doses of exenatide-LAR (relative exposure based on AUC ≥3.4). The prominent increase in thyroid C-cell hyperplasia and neoplasia observed in rats with exenatide-LAR stands in contrast to the more marginal effects on thyroid C-cell proliferation observed previously with exenatide-IR.
- No reproductive toxicity studies were conducted with exenatide-LAR. This was considered acceptable.

Conclusions and recommendations

- Nonclinical efficacy data, demonstrating long lasting antidiabetic activity for exenatide-LAR in a rat model following a single SC dose, support the use of the once weekly dosage form.
- No novel safety concerns were identified in the general repeat dose toxicity studies conducted with the new extended release formulation over a relevant range of doses and exposures.
- The primary safety concern identified from the nonclinical data is the risk of thyroid C-cell neoplasia, as observed in the rat carcinogenicity study. This was much more prominent with exenatide-LAR compared with exenatide-IR, consistent with the involvement of continuous activation of the GLP-1 receptor. Potential clinical relevance is diminished based on the absence of proliferative effects on the thyroid in monkeys treated with exenatide-LAR for 9 months at doses yielding high margins of the clinical exposure (≤45) and species differences in the level of GLP-1 receptor expression. While these rodent thyroid C-cell tumours are not considered to be predictive of similar effects in patients, the relevance of these findings cannot be completely excluded. Appropriately, the risk management plan for Bydureon has included pharmacovigilance monitoring, targeted surveillance and database analysis of neoplasm events for thyroid tumours in its action plan for specific safety concerns.
- There are no nonclinical objections to the registration of Bydureon (exenatide-LAR) for the treatment of Type 2 diabetes mellitus as currently indicated for Byetta. However, in the absence of nonclinical data pertaining to use in combination with thiazolidinediones (TZDs), the acceptability of the proposed extension of indications for exenatide (Byetta and Bydureon) has to be assessed from the clinical data only.

IV. Clinical findings

Introduction

Exenatide is a GLP-1 receptor agonist currently approved for the treatment of type-2 diabetes mellitus. Byetta is a formulation of exenatide that requires twice daily dosing prior to meals and has relatively short duration of action, primarily after those meals. Bydureon is an extended release formulation that is intended to prolong the duration of action of exenatide and reduce the dosing frequency to once weekly.

The studies submitted in this application were stated to have been conducted according to Good Clinical Practice (GCP).

Pharmacokinetics

Introduction

Study 2993LAR-102 was a single centre, randomised, single arm, open label trial to assess the safety and tolerability, and PK of two formulations of exenatide once weekly. The study was sponsored by Amylin Pharmaceuticals. The study included healthy male and female volunteers, aged 18 to 65 years of age, inclusive. Females were surgically sterile,

postmenopausal, or, if of childbearing potential, using appropriate contraceptive methods. Eligible subjects had a body mass index (BMI) in the range of 23 kg/m^2 to 35 kg/m^2, inclusive.

The study treatments were:

1. During the 14 day lead in period exenatide 5 μg, three times daily administered subcutaneously.

Followed by either:

   a. Exenatide-LAR-F16: 3% exenatide (2.5 mg), 2% sucrose, and 95% Medisorb in 50:50 PLGA.

   b. Exenatide-LAR-F17: 5% exenatide (2.5 mg), 2% sucrose, and 93% Medisorb in 50:50 PLGA.

The study treatments were administered as a single dose, subcutaneously into the anterior abdominal wall. Plasma samples and observations were performed for a 56 day period after dosing. The study duration was 70 days in total.

A total of 21 subjects were randomised, ten to LAR-F16 and eleven to LAR-F17. One subject in the LAR-F17 group withdrew from the study because of a motor vehicle accident. Hence, 20 subjects completed and were included in the analysis. The two treatment groups had similar demographic characteristics. There were twelve (57.1%) male subjects and nine (42.9%) female subjects. The age range was 28 to 64 years. The PK parameters for the two formulations were similar. Average (standard deviation (SD)) plasma concentration of exenatide was 17.7 (13.02) pg/mL for LAR-F16 and 24.4 (9.44) pg/mL for LAR-F17. Average (SD) C_{max} was 87.9 (20.73) pg/mL for LAR-F16 and 61.1 (5.18) pg/mL for LAR-F17. The average time to maximum plasma concentration (T_{max}) (SD) was 3.2 (1.04) hours for LAR-F16 and 588.6 (458.53) hours for LAR-F17. The formulation LAR-F17 had a more favourable PK profile as a sustained release formulation.

Study 2993LAR-103 was a multicenter, randomised, double blind, placebo controlled study to assess the PK of a single injection of exenatide once weekly, to the assess safety and tolerability of a single injection of exenatide once weekly; and to examine the effect of a single injection of exenatide once weekly on HbA1c; fasting and postprandial (PP) plasma glucose; body weight (BW); and fasting insulin and proinsulin. The study was sponsored by Amylin Pharmaceuticals.

The inclusion criteria included:

- Aged 30 to 65 years, inclusive
- Clinical diagnosis of Type 2 diabetes mellitus and otherwise healthy
- HbA1c of 7.0% to 10.0%, inclusive
- Either treated with a stable regimen of metformin for a minimum of 3 months and/or treated with diet modification and exercise for a minimum of 3 months
- If female, negative pregnancy test and agreement to continue using birth control throughout the study to prevent pregnancy.
- BMI of 25 kg/m^2 to 40 kg/ m^2, inclusive
- Clinical laboratory test values (clinical chemistry, hematology, urinalysis) either within normal range or abnormal but consistent with Type 2 diabetes mellitus and/or judged

not clinically significant by the investigator. An exception was for liver function tests, which should be within three times the upper limit of normal and serum creatinine, which should be <1.5 mg/dL for males and <1.4 mg/dL for females

- No clinically significant blood pressure readings as judged by the investigator at the screening period.
- Electrocardiogram (ECG) at entry to run-in phase with no clinically significant abnormality

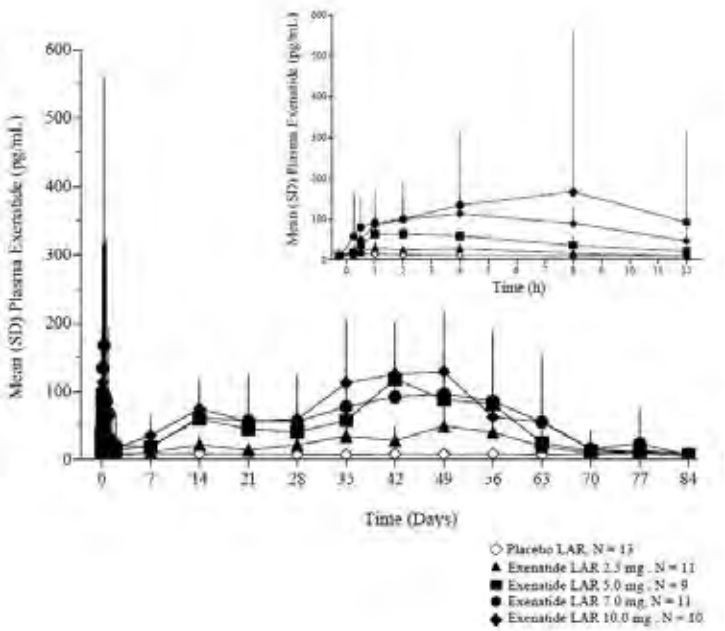
The study treatments were:

1. 2.5 mg exenatide once weekly (formulation LAR-F17)
2. 5 mg exenatide once weekly (formulation LAR-F17)
3. 7 mg exenatide once weekly (formulation LAR-F17)
4. 10 mg exenatide once weekly (formulation LAR-F17) or
5. placebo

There was a 14 day run-in phase of exenatide 5 mg three times daily SC followed by a single SC injection of study treatment. The study duration was 98 days in total.

A total of 62 subjects were randomised and included in the Intent to Treat (ITT) group. There were 58 evaluable subjects: 13 in the 2.5 mg group, ten in the 5 mg, twelve in the 7 mg, ten in the 10 mg and 13 in the placebo. The age range was 30 to 66 years and 32 (51.6%) subjects were female and 30 (48.4%) were male. Other than in gender distribution, the treatment groups were similar in demographic characteristics. AUC, C_{max} and average maximum plasma concentration (C_{ave}) were not dose proportional above the 5 mg dose level (Figure 3). Above the 5 mg dose there was less than expected increase in AUC, C_{max} and $C_{ave.}$

Figure 3. Mean (SD) Plasma Exenatide Concentration-Time Curve by Treatment Following Exenatide-LAR Administration (Population: Evaluable Subjects in Study 2993LAR-103 Excluding Subjects 04409, 04413, 03304, and 04424 [N = 54])



Study BCB107 was an open label, parallel group, study to evaluate single dose PK profiles, safety and tolerability of exenatide once weekly formulations. The study was sponsored by Amylin Pharmaceuticals. The study included healthy males and non pregnant females 19 to 65 years of age, inclusive, with BMI of 23 kg/m^2 to 35 kg/m^2 at screening.

The study treatments were:

1. F17 (Lot No. S426-2377CA), 10 mg
2. F17 (Lot No. S426-2507AA), 10 mg
3. F28, up to 8 mg, or
4. F30, 10 mg

The study treatments were administered as single SC injections. All study subjects received exenatide 10 mg SC on the day prior to exenatide once weekly dosing. This was followed by a 101 day assessment period.

A total of 120 subjects were enrolled and 119 received exenatide once weekly. Eleven patients withdrew during the follow-up period. The treatment groups were similar in demographic characteristics. The F17 formulations had the most favourable PK profiles (Table 2). The F17 formulations had similar PK profiles to each other.

Table 2. Pharmacokinetic Parameters for Exenatide Once Weekly by Treatment (Study BCB107; Pharmacokinetic Evaluable Population [N = 77])

Parameter Statistic	Treatment [1] Exenatide Once Weekly Formulation A (F17) (N = 21)	Exenatide Once Weekly Formulation B (F17) (N = 17)	Exenatide Once Weekly Formulation A and B (F17) (N = 38)	Exenatide Once Weekly Formulation C (F28) (N = 19)	Exenatide Once Weekly Formulation D (F30) (N = 20)
$AUC_{(0\text{-}tlast)}$ (pg·h/mL)					
Geometric Mean (SE) [2]	197,008 (19,975)	212,874 (25,518)	203,954 (15,654)	78,102 (6,987)	99,018 (9,881)
$C_{max(0\text{-}5h)}$ (pg/mL)					
Geometric Mean (SE) [2]	213.6 (33.4)	185.0 (14.6)	200.3 (18.6)	1392.4 (87.8)	128.5 (8.4)
$C_{max(0\text{-}tlast)}$ (pg/mL)					
Geometric Mean (SE) [2]	567.6 (91.9)	746.3 (175.3)	641.5 (88.5)	1392.4 (87.8)	203.3 (29.3)
$T_{max(0\text{-}5h)}$ (h)					
Median	2.0	3.0	3.0	3.0	3.0
Min, Max	1.5, 3.0	1.5, 4.0	1.5, 4.0	1.4, 4.1	1.5, 4.0
$T_{max(0\text{-}tlast)}$ (h)					
Median	961.0	960.0	960.7	3.0	780.1
Min, Max	2.0, 1680.9	3.0, 1320.0	2.0, 1680.9	1.4, 4.1	1.5, 1392.0
T_{last} (h)					
Median	1537.0	1535.9	1536.4	1391.9	1536.0
Min, Max	1177.0, 1753.0	1104.1, 1824.0	1104.1, 1824.0	1104.0, 1680.4	1152.2, 1896.0
Relative Bioavailability (%) [3]					
Mean (SD)	21 (7.5)	25 (13.3)	22 (10.5)	14 (8.5)	11 (5.2)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, peak concentration determined as the maximum observed concentration during the sampling interval; Max, maximum; Min, minimum; QW, once weekly; SC, subcutaneous; T_{last}, time of last point with quantifiable concentration; T_{max}, time of peak concentration.

[1] Formulation A: single dose of exenatide once weekly AC2993-F17 Lot S426-2377CA 10 mg SC; Formulation B: single dose of exenatide once weekly AC2993-F17 Lot S426-2507AA 10 mg SC; Formulation C: single dose of exenatide once weekly AC2993-F28 8 mg SC; Formulation D: single dose of exenatide once weekly AC2993-F30 10 mg SC. Exenatide once weekly doses are nominal doses.

[2] Geometric Mean = exp(mean(log(X))); SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

[3] Relative bioavailability (%) = 100 * ($AUC_{(0\text{-}tlast)QW}$ / $Dose_{QW}$) / ($AUC_{(0\text{-}inf)BYETTA}$ / $Dose_{BYETTA}$). The overall geometric mean of $AUC_{(0\text{-}inf)}$ BYETTA obtained from all available subjects was used for Subjects 101080, 101094, and 101095 who had exenatide once weekly data and no BYETTA data.

Study 2993LAR-104 was a multicentre, randomised, double blind, placebo controlled study to assess PK, safety and tolerability, and the effect on glucose control (HbA1c), BW, and fasting and PP plasma glucose of exenatide once weekly for 15 weeks. The study was sponsored by Amlyn Pharmaceuticals and conducted at seven study sites.

The inclusion criteria included subjects with:

- Type 2 diabetes mellitus managed with a stable regimen of metformin and/or diet modification and exercise for a minimum of three months prior to screening
- Age 18 to 75 years, inclusive
- HbA1c of 7.1% to 11.0%, inclusive
- BMI of 25 kg/m^2 to 45 kg/m^2, inclusive
- fasting glucose measurement of <14.4 mmol/L
- Male or if female, have a negative pregnancy test and if not postmenopausal (no menses for a minimum of 1 year) agreement to continue using two forms of birth control throughout the study to prevent pregnancy
- No evidence of poorly controlled hypertension within the last 3 months.

The study treatments were:

1. Exenatide once weekly 0.8 mg
2. Exenatide once weekly 2.0 mg
3. Placebo

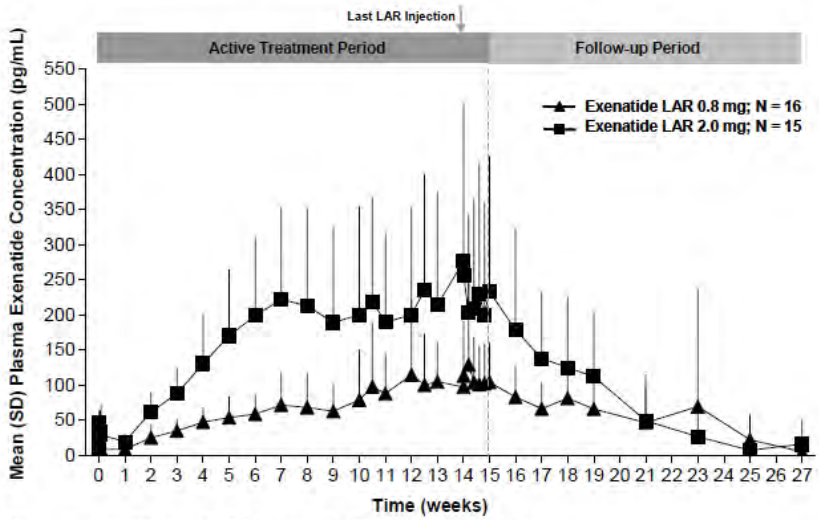
The treatments were given SC once weekly for 15 weeks. This was followed by an additional 12 week follow-up period. There was a three day exenatide or placebo twice daily lead-in. The total study duration was 28 weeks.

A total of 47 subjects were enrolled in the study and two withdrew prior to run-in. Forty five subjects were randomised: 16 to 0.8 mg, 15 to 2.0 mg and 14 to placebo. Two subjects in the placebo group did not complete the study. There were 27 (60%) males, 18 (40%) females and the age range was 31 to 72 years. The treatment groups were similar demographic characteristics and in concomitant antidiabetic medication.

Plasma exenatide concentrations were 2.5 times higher in the 2.0 mg group than the 0.8 mg group (Figure 4). AUC and C_{max} were also 2.5 times higher in the 2.0 mg group than in the 0.8 mg group.

During the follow-on phase for Study 2993LAR-105, some PK assessments were performed to compare two manufacturing batches of exenatide formulation LAR-F17. Study 2993LAR-105 was a multicentre, randomised, open label, comparator controlled study to examine the effects of exenatide long acting release on glucose control (HbA1c) and safety in subjects with Type 2 diabetes mellitus managed with diet modification and exercise and/or OAD. The pharmacokinetic parameters are summarised in Table 3. Exenatide formulation LAR-F17 from the two manufacturing sites was not bioequivalent. The ratio (90% CI) for AUC was 0.77 (0.70 to 0.85) and the ratio (90% CI) for C_{max} was 0.77 (0.70 to 0.85). The initial release characteristics were similar but still not bioequivalent: ratio (90% CI) for AUC 0.85 (0.76 to 0.94) and for C_{max} 0.94 (0.80 to 1.11).

Figure 4. Mean (SD) Plasma Exenatide Concentrations by Time and Treatment (Study 2993LAR-104; Evaluable Population [N = 31])



Abbreviations: SD, standard deviation; LAR, long-acting release.

Table 3. Summary of Key Pharmacokinetic Parameters Following Administration of Exenatide-LAR 2 mg on Day 1 and Week 29 to Week 30 (Study 2993LAR-105; Pharmacokinetics Population [N = 129]

Time Point Parameter	Units	n	Geometric Mean (SE) [1]	CV % [2]	10^{th}, 90^{th} Percentile
Pharmacokinetics Population					
Day 1 (0-6 h)					
C_{max}	pg/mL	127	44.5 (2.4)	76.1	23.4, 84.3
T_{max}	h	127	4.0		1.5, 6.0
Week 29 to Week 30 Dosing Interval (0-168 h)					
$C_{ss,ave}$	pg/mL	114	300.2 (23.4)	69.8	145.1, 702.2
$C_{ss,max}$	pg/mL	114	432.7 (35.7)	86.3	213.9, 1186.1
$T_{ss,max}$	h	114	22.8		1.2, 167.8
AUC_{ss}	pg·h/mL	114	50484 (3932)	69.7	24274, 117796
Subjects in Pharmacokinetics Population Negative for Anti-Exenatide Antibodies Through Week 30					
Day 1 (0-6 h)					
C_{max}	pg/mL	25	41.4 (3.8)	48.1	24.3, 76.9
T_{max}	h	25	2.0		1.5, 6.0
Week 29 to Week 30 Dosing Interval (0-168 h)					
$C_{ss,ave}$	pg/mL	23	312.7 (30.2)	53.3	193.5, 602.4
$C_{ss,max}$	pg/mL	23	436.5 (42.1)	48.1	288.1, 684.4
$T_{ss,max}$	h	23	6.0		1.0, 167.7
AUC_{ss}	pg·h/mL	23	52640 (5087)	53.4	32515, 100948

Abbreviations: AUC_{ss}, steady-state area under the concentration-time curve; $C_{ss,ave}$, steady-state average concentration; C_{max}, maximum concentration; $C_{ss,max}$, steady-state maximum concentration; CV, coefficient of variation; SD, standard deviation; SE, standard error; T_{max}, time to maximum concentration; $T_{ss,max}$, time to steady-state maximum concentration.

[1] Geometric Mean = exp(mean(log(X))); SE of Geometric Mean = Geometric Mean x SE of Mean(log(X)). For T_{max} and $T_{ss,max}$, median is displayed instead of geometric mean and both median and percentiles are based on the raw values.

[2] CV% = 100 x SD / Mean.

Study H8O-JE-GWBW was a multicentre, randomised, double blind, placebo controlled, parallel design, multiple dose, Phase I study to evaluate exenatide-LAR when given at weekly doses of 0.8 and 2.0 mg to Japanese patients with Type 2 diabetes mellitus for 10

weeks. The study included males or females with Type 2 diabetes; aged 20 to 75 years inclusive; body weight ≥50 kg; suboptimal diabetes control (defined as HbA1c 6.5% to 10% inclusive, 6.5% to 9.5% if treated with alpha glucosidase inhibitor or meglitinide derivative; and treated with diet modification alone or in combination with a stable regimen of oral antidiabetic drug (OAD)).

The study treatments were:

1. Exenatide-LAR-F17 0.8 mg once weekly
2. Exenatide-LAR-F17 2 mg once weekly
3. Placebo once weekly

The treatment duration was 10 weeks and it was followed by an additional 10 week follow-up phase.

The study outcome measures were: PK profile, HbA1c, FPG, AEs, weight anti-exenatide antibodies and laboratory tests.

The study included 30 subjects: ten in the exenatide 0.8 mg, ten in the exenatide 2 mg and ten in the placebo. There were 17 (58.6%) males, 12 (41.4%) females, and the age range was 37 to 72 years. One subject in the exenatide 2 mg group was excluded from analysis because they received the wrong study dose. Steady state appeared to be achieved around Week 8 of treatment for both the 0.8 mg and the 2 mg dose (Figure 5). AUC and C_{max} were not dose proportional and there was relatively greater exposure at the higher dose (Table 4).

Figure 5. Arithmetic mean (+SD) trough concentrations-time profiles following subcutaneous injections of 0.8 mg and 2.0 mg Exenatide QW to Japanese patients with Type 2 diabetes mellitus

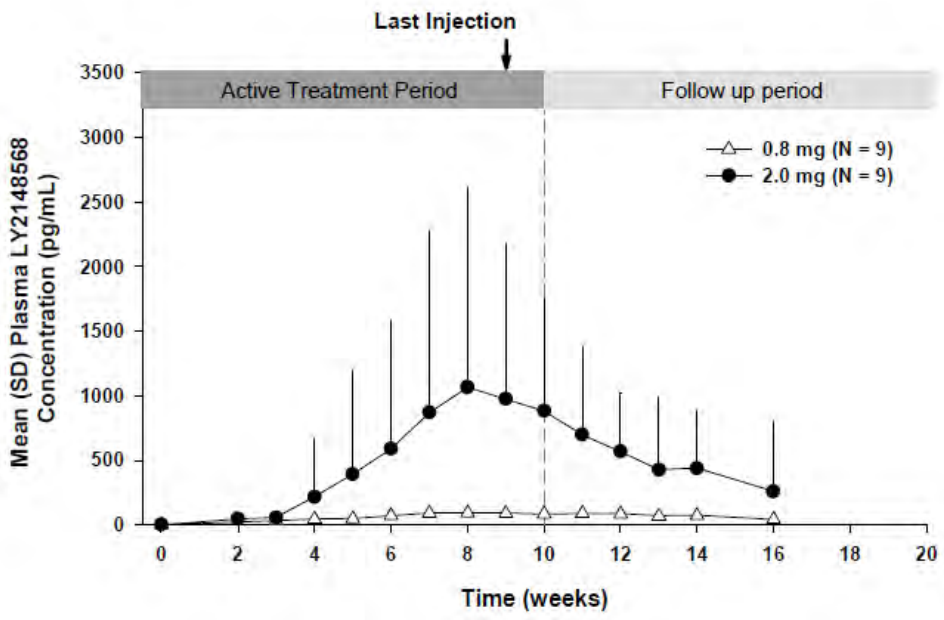


Table 4. Summary of Non-compartmental Pharmacokinetic Parameters during Once-Weekly Dosing of Exenatide QW to Japanese Patients with Type 2 Diabetes Mellitus (all evaluable patients)

	Geometric Mean (CV%)	
	0.8 mg QW	2.0 mg QW
Day 1		
N	9	9
Cmax (pg/mL)	55.2 (104)	101 (89.1)
tmax (h)[a]	2.00 (0.980 - 8.00)	2.00 (0.500 - 8.00)
Week 9 to 10		
N	9	9
Cmax,ss (pg/mL)	149 (26.0)	1130 (123)
Cav,ss (pg/mL)	84.4 (27.3)	645 (112)
tmax,ss (h)[a]	2.08 (1.88 - 72.0)	23.9 (0.00 - 216)
AUCweek 9 to 10 (pg•h/mL)	14600 (28.9)	111000 (108)

[a] Median (range)

Evaluator's overall conclusions on pharmacokinetics

The sponsor has conducted development studies for prolonged release injectable formulations of exenatide. Study 2993LAR-102 and Study BCB107 indicated that the extended release formulation with the most favourable PK profile appeared to be exenatide-LAR-F17. Study H8O-JE-GWBW indicated steady state appeared to be achieved around Week 8 of treatment for both the 0.8 mg and the 2 mg dose.

Study 2993LAR-103 indicated that the pharmacokinetics of exenatide-LAR were not dose proportional; above a 5 mg dose level there was less than expected increase in AUC, C_{max} and C_{ave}. Study 2993LAR-104 indicated dose proportional PK between the 0.8 mg and 2.0 mg dose levels. However Study H8O-JE-GWBW indicated that AUC and C_{max} were not dose proportional between the 0.8 mg and 2 mg dose levels and there was relatively greater exposure at the higher dose.[3]

Study 2993LAR-105 indicated that exenatide formulation LAR-F17 produced at two different manufacturing sites were not bioequivalent. The sponsor will need to indicate whether any issues with manufacturing have been resolved and also which manufacturing site will be used to supply the formulation intended for marketing in Australia as Bydureon.

The PK data did not give any indication of dose-dumping, as indicated by the relatively small values of SD for C_{max}.

[3] The sponsor added the following comment: "Study 104 confirmed that repeat dosing of the 2 mg dose yielded continuous exposure to therapeutic levels of exenatide."

Pharmacodynamics

Introduction

The sponsor provided data in support of the pharmacodynamic (PD) characteristics of the new dose form of exenatide (BYDUREON®).

In Study 2993LAR-103 there was no clinically or statistically significant difference between the four doses of exenatide once weekly in the change in HbA1c (Figure 6). At Week 6, the mean (SD) change from baseline in HbA1c% was -0.1 (0.95)% for placebo, -0.4 (1.16)% for 2.5 mg, -0.8 (0.66)% for 5 mg, -0.7 (0.81)% for 7 mg and -0.4 (0.50)% for 10 mg. Similarly there was little difference between the active treatment groups in blood glucose concentrations. There was a clear inverse relationship between plasma exenatide concentrations and fasting plasma glucose (Figure 7). There were no significant changes in body weight during the study. There were no consistent, statistically significant or clinically significant changes in plasma insulin or proinsulin concentrations.

In Study 2993LAR-104, FPG decreased over time in both the 0.8 mg and 2.0 mg groups, and this decrease was greater in the 2.0 mg group. At Week 15, FPG the mean (SE) reduction in the 0.8 mg group was 2.37 (0.87) mmol/L and in the 2.0 mg group was 2.16 (0.52) mmol/L. The decreases were also observed across the 7-point SMPG.

In Study H8O-JE-GWBW, maximum reduction in HbA1c was achieved at Week 10 for both the 0.8 mg and 2 mg doses (Figure 8). There was a significant decrease in HbA1c in both exenatide treatment groups but no statistically significant difference between the two treatment groups: the mean (95% CI) change from baseline was -0.99 (-1.5 to -0.5) % for the 0.8 mg dose and -1.48 (-2.8 to -0.9) % for the 2 mg dose. FPG decreased to Week 3 then stabilised. There did not appear to be any statistically significant differences from baseline to Week 10 in preprandial PG, postprandial PG, insulin or glucagon concentrations.

Figure 6. Mean (SE) HbA1c Values by Study Day and Treatment (Population: Evaluable Subjects in Study 2993LAR-103 [N = 58])

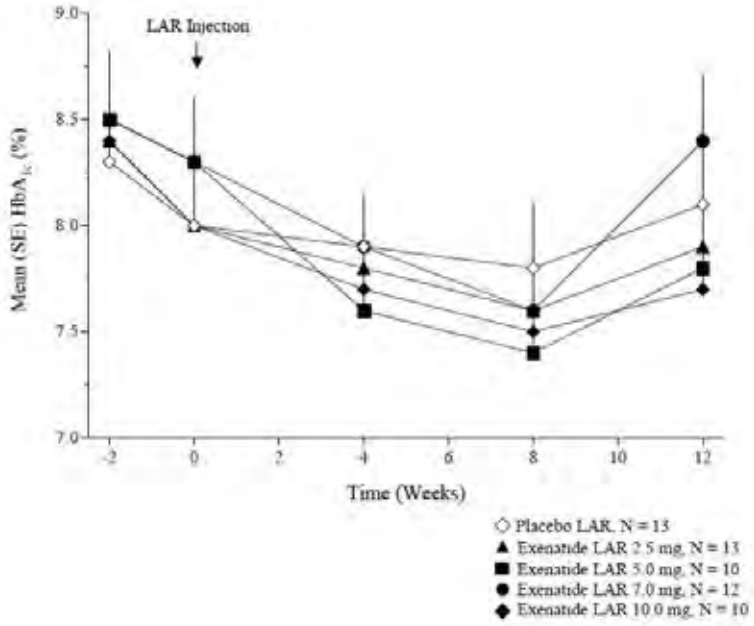


Figure 7. Mean (SE) Fasting Plasma Glucose Versus Mean (SD) Plasma Exenatide Concentrations by Week (Population: Evaluable Exenatide-LAR Subjects in Study 2993LAR-103 [N = 45])

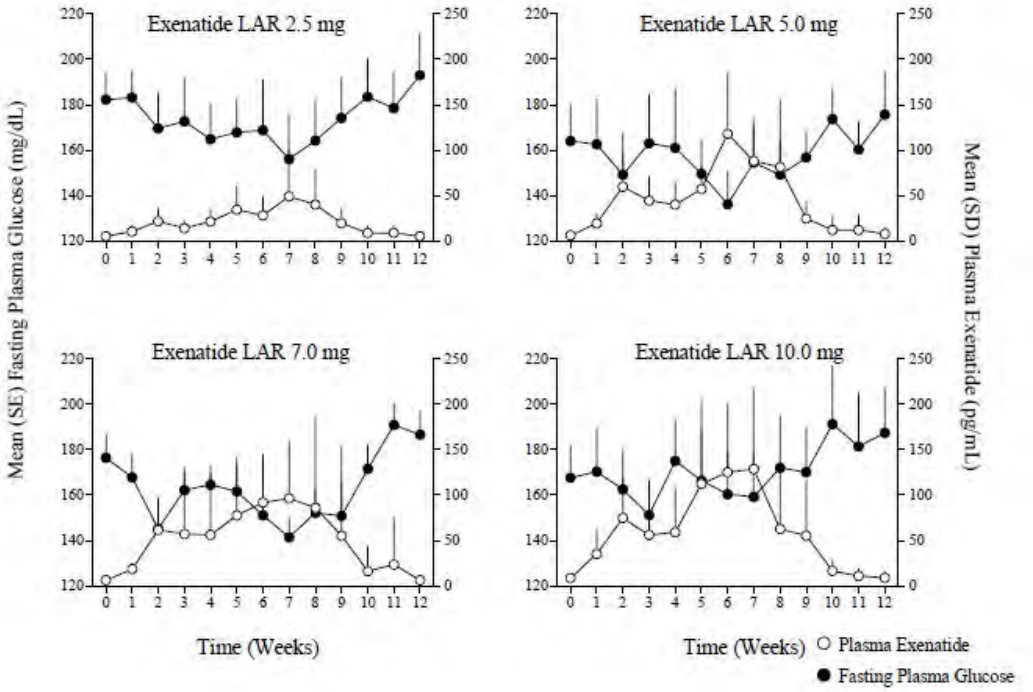
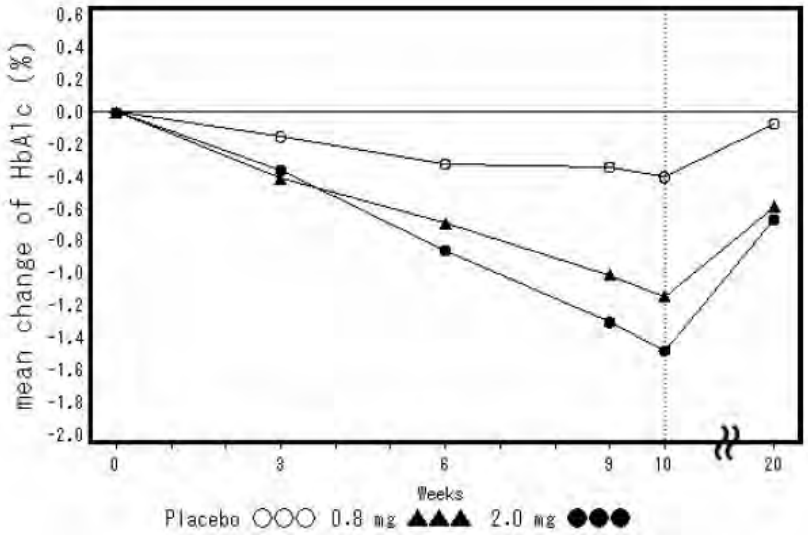


Figure 8. Time-courses of mean change in HbA1c from baseline at each intermediate time Full Analysis Set



Evaluator's overall conclusions on pharmacodynamics

The PD data are supportive of the choice of the 2 mg dose form for exenatide-LAR. Study 2993LAR-103 indicated a plateau in effect above the 2.5 mg dose form. Study 2993LAR-104 and Study H8O-JE-GWBW indicated greater effect with the 2 mg dose form than the 0.8 mg. Maximum reduction in HbA1c was achieved at Week 10 of treatment.

Efficacy

Introduction

The sponsor submitted data in support of the new dosage form of exenatide (Bydureon) and in support of the efficacy of exenatide in combination with TZD.

Efficacy data for once weekly exenatide

Dose finding studies for exenatide-LAR

Study 2993LAR-104

In Study 2993LAR-104, HbA1c decreased from baseline to a greater extent in the 2 mg group than the 0.8 mg group: mean (SD) change from baseline 0.43 (0.956) % for placebo, -1.35 (1.182) % for 0.8 mg and -1.73 (1.226) % for 2.0 mg. HbA1c ≤7% was achieved at Week 15 for 12 (85.7%) subjects in the 2.0 mg group, five (35.7%) in the 0.8 mg group and none in the placebo group. Mean body weight decreased by 4 kg in the 2.0 mg group by Week 15, but there was no change for either the 0.8 mg group or the placebo group.

Efficacy of exenatide-LAR in comparison with twice daily

Study 2993LAR-105

Methods

Study 2993LAR-105 was a multicentre, randomised, open label, comparator controlled study to examine the effects of exenatide long acting release on glucose control (HbA1c) and safety in subjects with Type 2 diabetes mellitus managed with diet modification and exercise and/or OAD. The study was sponsored by Amlyn Pharmaceuticals and conducted at 29 sites.

The inclusion criteria included:

- Age 16 to 75 years of age, inclusive.
- Type 2 diabetes mellitus treated with diet modification and exercise alone or in combination with 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.
- HbA1c of 7.1% to 11.0%, inclusive.
- Fasting glucose concentration of <15.5 mmol/L.
- BMI 25 kg/m^2 to 45 kg/m^2, inclusive.
- Stable body weight, that is, not varying by >10% for at least 6 months prior to Visit 1.
- Male or female. Females require negative pregnancy test and if of childbearing potential must practice appropriate birth control during the entire duration of the study.
- Physical examination and electrocardiogram (ECG) judged to be not clinically significant
- Clinical laboratory test values (chemistry, hematology, or urinalysis) judged to be not clinically significant

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations within three times the upper limit of the normal reference range
- Serum creatinine ≤ 1.6 mg/dL (males) or ≤ 1.4 mg/dL (females)

The study treatments were:

1. Exenatide-LAR (formulation AC2993-F17), 2 mg once weekly by SC injection
2. Exenatide (BYETTA), 5 mg twice daily for 4 weeks followed by 10 mg twice daily, by SC injection

At Week 30, the subjects in the twice daily group were switched to exenatide once weekly. Total study duration was 52 weeks. Subjects were randomised to treatment group but were not blinded to treatment.

The primary efficacy outcome measure was the change in HbA1c from baseline to Week 30. Secondary efficacy outcome measures were:

- Change in HbA1c from baseline to Week 52 and other applicable visits during the study
- Change in body weight from baseline to Weeks 30 and 52 and other applicable visits during the study
- Change in fasting glucose concentrations from baseline to Weeks 30 and 52.
- PD parameters from the postprandial glucose and insulin concentrations at baseline and Week 14 for the subjects in the Gastric-Emptying Cohort who participated in the standard meal tolerance test.

Additional efficacy outcome measures were:

- Change in HbA1c from Week 30 to Week 52 and other applicable visits during the open ended assessment period for subjects receiving exenatide 10 mcg twice a week during the 30 week assessment period
- Change in fasting glucagon, proinsulin, insulin, proinsulin to insulin ratio and lipid concentrations from baseline to Week 30 and Week 52.
- Gastric emptying as assessed by the appearance of acetaminophen in circulation at baseline and Week 14.
- Exenatide pharmacokinetic characteristics: AUC and C_{ave}.
- Homeostatic model assessment (HOMA), including HOMA-B and HOMA-S, at Week 30
- Change in summary measures derived from PRO instruments, including the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Impact of Weight on Quality Of Life (IWQOL-Lite), from baseline to Weeks 14, 30 and 52.

The safety outcome measures were: adverse events (AEs), clinical laboratory tests, physical examination findings, 12-lead ECGs, vital signs and anti-exenatide antibodies.

Statistical considerations

The study was designed as a non inferiority comparison and the sample size calculation was based on the primary efficacy outcome measure. The margin for non inferiority was a difference in HbA1c between treatments of not greater than 0.4 %. A sample size of 123 subjects in each treatment group provided 90% power to show the change in HbA1c from baseline and assumed a greater reduction (0.1%) in HbA1c from baseline to Week 30 for

exenatide-LAR versus BYETTA, a common standard deviation of 1.2% and a withdrawal rate of 20%. Hypothesis tests were performed using 95% CI. Least squares (LS) mean change and 95% CI in HbA1c from baseline to Week 30 were estimated from an analysis of variance (ANOVA) model. Hypotheses for secondary outcome measures were tested using either analysis of co variance (ANCOVA) or ANOVA models.

Results

A total of 470 subjects were screened, 303 were randomised and 295 received study treatment and were included in the ITT analysis. In the ITT population, there were 157 (53.2%) males, 138 (46.8%) females and the age range was 19 to 80 years. The treatment groups were similar in baseline demographics but FPG was higher at baseline in the once weekly group: mean (SD) 173 (44.4) mg/dL compared with 165 (41.0) mg/dL in the twice weekly. Concomitant use of antidiabetic drugs was similar for the two treatment groups except that there was a higher proportion of the once weekly group treated with biguanides: 113 (76.4%) subjects compared with 102 (69.4%) in the twice weekly. Overall, 14.9% subjects were treated with TZD and 38.3% with sulfonamides. A total of 258 subjects completed the 30 week treatment phase and were entered into the open ended treatment period. Twenty (13.5%) subjects in the once weekly group and fifteen (10.2%) subjects in the twice daily group withdrew during the 30 week treatment phase. Sixteen withdrew because of AEs: nine (6.1%) in the once weekly group, and seven (4.8%) subjects in the twice daily group. In the per protocol (PP) population for the primary efficacy outcome analysis there were 129 (84.9%) subjects in the once weekly group and 130 (86.1%) in the twice daily.

The PP analysis indicated non inferiority according to the predefined criteria. The LS mean (SE) change in HbA1c from baseline to Week 30 was -2.0 (0.08) % in the exenatide-LAR group and -1.6 (0.08) % in the twice daily; (95% CI) for the difference (-0.59 to -0.18) p = 0.0003. The ITT analysis confirmed the PP analysis and also indicated superiority for exenatide-LAR compare with twice daily exenatide: LS mean (standard error (SE)) change in HbA1c -1.9 (0.08) % compared with -1.5 (0.08) % for twice daily, ; p = 0.0023 (Table 5). The effects on HbA1c over time are displayed in Figure 9. At Week 52 the change in HbA1c from baseline was -2 % for both treatment groups. This indicated the benefit was preserved over the 52 week treatment period. There was no interaction effect from concomitant medications.

Table 5. Parametric Analysis [1] of Change in HbA1c (%) from Baseline to Week 30 (Study 2993LAR-105; Intent-to-Treat Population [N = 295])

Time Point Statistic	Treatment BYETTA 10 mcg BID (N = 147)	Treatment Exenatide LAR 2 mg QW (N = 148)
Day -3 (Baseline)		
Mean (SE) (%)	8.3 (0.08)	8.3 (0.08)
Change from Baseline to Week 30 (%)		
Mean (SE)	-1.3 (0.08)	-1.6 (0.09)
LS Mean (SE)	-1.5 (0.08)	-1.9 (0.08)
95% Confidence Interval	-1.7, -1.4	-2.0, -1.7
LS Mean Difference (SE) [2]		-0.33 (0.11)
95% Confidence Interval Difference [2]		-0.54, -0.12
p-value [2]		0.0023

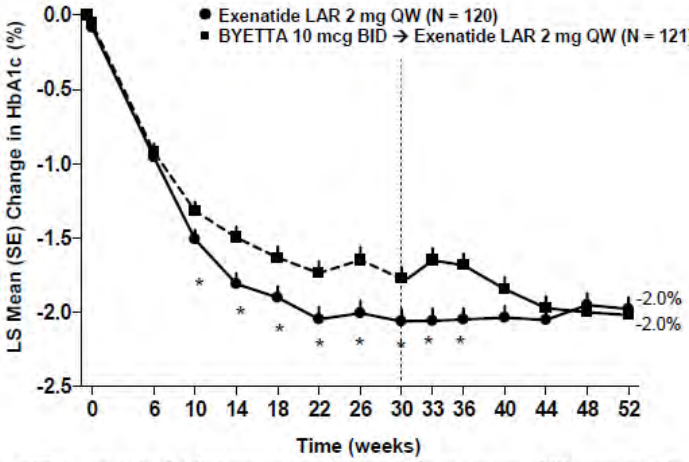
Abbreviations: BID, twice daily; LAR, long-acting release; LOCF, last observation carried forward; LS, least squares; QW, once weekly; SE, standard error.

Notes: The LOCF approach was applied to estimate missing values at Day 1 through Week 30.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

[1] Based on a general linear model including treatment, baseline HbA1c stratum, and concomitant SU use at screening. Baseline = Day -3; if unavailable, a value from an earlier visit (the last measurement prior to the first lead-in injection) was used.

[2] BYETTA was used as the reference group.

Figure 9. LS Mean (SE) Change in HbA1c (%) from Baseline to Week 52 b



Abbreviations: BID, twice daily; LAR, long-acting release; LS, least squares; QW, once weekly; SE, standard error.

Notes: Mean baseline HbA1c was 8.2% and 8.3% for the BYETTA and exenatide LAR groups, respectively.
- Vertical dashed line indicates the timing of the switch from BYETTA to exenatide LAR.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

*p <0.05, exenatide LAR versus BYETTA→exenatide LAR.

Weight loss was similar for the two treatment groups at Week 30: LS mean (SE) changes in body weight from baseline -3.7 (0.47) kg for exenatide-LAR and -3.6 (0.47) kg for twice daily. The weight loss was maintained through to Week 52. Changes in waist and hip circumferences were also similar for the two treatment groups. At Week 30, the mean (SE) change in waist circumference from baseline was -3.24 (0.52) cm for exenatide-LAR and -3.13 (0.57) cm for twice daily. At Week 30, the mean (SE) change in hip circumference from baseline was -2.55 (0.48) cm for exenatide-LAR and -2.16 (0.52) cm for twice daily subjects.

There was a greater decrease in FPG in the exenatide-LAR group: mean (SE) change -45 (3.6) mg/dL compared with -23 (3.3) mg/dL in the twice daily group. There were similar

decreases in the 7-point SMPG profiles for both treatment groups. There was no significant change in insulin concentrations, proinsulin concentrations or insulin/proinsulin ratio in either treatment group. At baseline, mean (SE) fasting plasma glucagon concentrations were 103 (3.1) pg/mL and 99 (3.0) pg/mL in the exenatide-LAR and twice daily groups, respectively. The LS mean (SE) change at Week 30 in fasting plasma glucagon concentration was -18 (2.9) pg/mL in the exenatide-LAR group and -6 (2.9) pg/mL in the twice daily; p = 0.0023. HOMA-B improved to a greater extent in the exenatide-LAR group compared with the twice daily: Geometric LS Mean Ratio (95% CI) 1.31 (1.18 to 1.46) p<.0001. However, there was no significant change or difference between groups in HOMA-S: Geometric LS Mean Ratio (95% CI) 0.97 (0.84 to 1.10) p=0.6050. There were decreases in total cholesterol and Low Density Lipoprotein (LDL) cholesterol in the exenatide-LAR group relative to the twice daily group: LS Mean Difference (95% CI) in cholesterol -8.2 (-14.1 to -2.2) mg/dL, and in LDL cholesterol -6.1 (-11.2 to -1.0). Gastric emptying was not altered in the fed state but was delayed by 20 minutes in the fasted state by exenatide-LAR. There were improvements in DTSQs from baseline in both treatment groups but no differences between the treatment groups. IWQOL-Lite scores increased from baseline in both treatment groups, with LS mean changes (95% CI) in IWQOL-Lite scores of 10.2 (8.5 to 12.0) for exenatide-LAR and 8.6 (6.9, 10.3) for twice daily; but there was no statistically significant difference between treatment groups (p=0.1619).

Study BCB108

Methods

BCB108 was a multicentre, randomised, open label, comparator controlled, parallel group, two-arm study comparing exenatide-LAR with exenatide (BYETTA) twice daily. The study was sponsored by Amylin Pharmaceuticals and conducted at 43 study sites.

The study included male and non pregnant female subjects, at least 18 years of age, with Type 2 diabetes mellitus but otherwise healthy and treated with diet modification and exercise alone or in combination with 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 inclusion criteria included screening HbA1c of 7.1% to 11.0% and BMI of 25 kg/m^2 to 45 kg/m^2.

The study treatments were:

1. Exenatide-LAR 2 mg by SC injection once weekly, formulation AC2993-F17.
2. Exenatide (Byetta) 5 µg for 4 weeks followed by 10 µg, both administered by SC injection twice daily.

Treatment duration was 24 weeks. Study subjects were randomised to treatment but not blinded. Subjects continued with their prior diabetes treatment regimens during the study.

The primary efficacy outcome measure was the change in HbA1c from baseline to Week 24/Study Termination. The secondary efficacy outcome measures were:

- Proportion of subjects achieving HbA1c target value of <7% at Week 24/Study Termination.
- Change in fasting glucose concentration from baseline to Week 24/Study Termination.
- Proportion of subjects achieving fasting plasma glucose concentration target value of ≤126 mg/dL at Week 24/Study Termination.

- Proportion of subjects achieving HbA1c target value of ≤6.5% at Week 24/Study Termination).
- Change in body weight from baseline to Week 24/Study Termination.
- Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to Week 24/Study Termination.
- Change in fasting lipid concentrations from baseline to Week 24/Study Termination.

Additional efficacy outcome measures were:

- Change in HbA1c from baseline to intermediate visits during the study.
- Change in fasting plasma glucose concentration from baseline to intermediate visits during the study.
- Change in body weight from baseline to intermediate visits during the study.
- Change in SBP and DBP from baseline to intermediate visits during the study.
- Plasma exenatide concentration profiles.

The safety outcome measures were AEs, clinical laboratory tests, physical examination findings, vital signs, and antibodies to exenatide.

Statistical issues

Hypothesis tests were performed using a general linear model. Multiplicity was corrected for by the Hochberg procedure. The study was designed as a non inferiority test based on the primary efficacy outcome measure. The sample size was determined for a margin in HbA1c of 0.4 % for a one-sided test at a significance level of 0.025. The sample size calculation used a power of 90%, a common SD of 1.1%, randomisation to treatment in the ratio of 1:1 and assumed a drop-out rate of 15%. The calculation determined a sample size of 206 subjects (103 in each treatment group).

Results

A total of 391 subjects were screened and 254 subjects were randomised: 129 to exenatide-LAR and 125 to twice daily. Of these subjects, 252 received at least one dose of study medication and were included in the ITT analysis: 123 in the twice daily and 129 in the exenatide-LAR. A total of 109 (84.5%) subjects in the exenatide-LAR and 95 (76.0%) subjects in the twice weekly completed treatment. There were 145 (57.5%) males, 107 (42.5%) females and the age range was 23 to 83 years. The treatment groups were similar in demographic and baseline characteristics. A higher proportion of subjects in the exenatide-LAR group were treated with thiazolidinediones during the study: 20 (15.5%) subjects compared with 10 (8.1%) in the twice daily. Lipid lowering agents were taken by 67 (51.9%) subjects in the exenatide-LAR group and 56 (45.5%) subjects in the twice daily group.

For the primary efficacy outcome measure the PP evaluation indicated non inferiority and the ITT evaluation indicated superiority for exenatide-LAR exenatide (Table 6). For the ITT population, the LS mean (95% CI) change in HbA1c from baseline to Week 24 was -1.6 (-1.8 to -1.4) % for exenatide-LAR and -0.9 (-1.1 to -0.7) % for twice daily, LS mean (95% CI) difference -0.7 (-0.9 to -0.4), $p<0.0001$. The relative improvement in HbA1c with exenatide-LAR exenatide was significant from Week 8 through to Week 24 (Figure 10). In the exenatide-LAR group, 75 (58.1%) subjects achieved an HbA1c of <7% at Week 24 compared

with 37 (30.1%) subjects in the twice daily group (p<0.0001). In the exenatide-LAR group, 48 (43.6%) subjects achieved an HbA1c of <6.5% at Week 24 compared with 18 (19.6%) subjects in the twice daily group (p=0.0002). Efficacy was not influenced by baseline severity or concomitant diabetes medication.

Table 6. Parametric Analysis [1] of Change in HbA1c (%) from Baseline to Week 24 (Study BCB108; Intent-to-Treat Population [N = 252] and Evaluable Population [N = 204])

	Treatment			
	ITT Population (N = 252)		Evaluable Population (N = 204)	
Time Point Statistic	BYETTA (N = 123)	Exenatide Once Weekly (N = 129)	BYETTA (N = 93)	Exenatide Once Weekly (N = 111)
Day 1 (Baseline)				
n	122	128	92	110
Mean (SE) (%)	8.4 (0.1)	8.5 (0.1)	8.3 (0.1)	8.5 (0.1)
Change from Baseline to Week 24 (%)				
n	116	126	92	110
Mean (SE)	-0.7 (0.1)	-1.4 (0.1)	-0.8 (0.1)	-1.4 (0.1)
LS Mean (SE)	-0.9 (0.1)	-1.6 (0.1)	-0.9 (0.1)	-1.6 (0.1)
95% Confidence Interval	-1.1, -0.7	-1.8, -1.4	-1.2, -0.7	-1.8, -1.4
LS Mean Difference (SE) [2]		-0.7 (0.1)		-0.7 (0.2)
95% Confidence Interval Difference [2]		-0.9, -0.4		-1.0, -0.3
p-value [2]		<0.0001		<0.0001

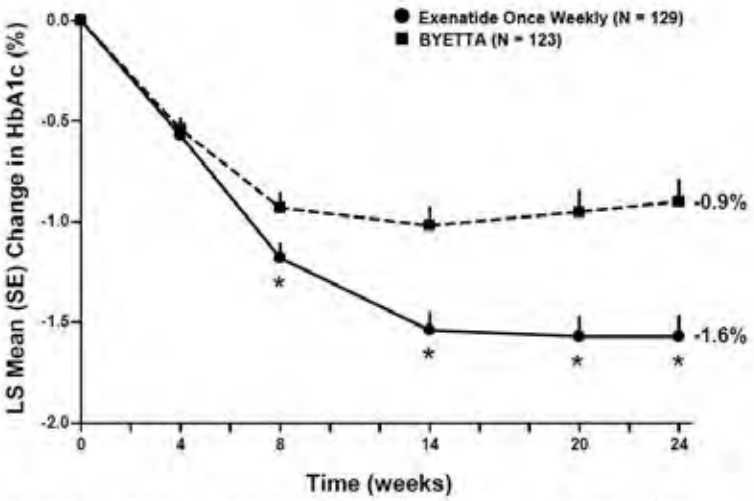
Abbreviations: ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error.

Notes: For the ITT Population, the LOCF approach was applied to estimate missing values at postbaseline time points through Week 24. For the Evaluable Population, missing values at Week 24 were imputed using data from Early Termination visits occurring between Week 20 and Week 24 (if applicable).
- Subjects randomized to BYETTA received BYETTA 5 mcg SC BID for 4 weeks followed by BYETTA 10 mcg SC BID for 20 weeks. Subjects randomized to exenatide once weekly received exenatide once weekly 2 mg SC for 24 weeks.
- The HbA1c values from 2 intent-to-treat subjects are not reported, as screening, baseline, and postbaseline HbA1c values were subsequently deleted due to invalid chromatograms. Mean HbA1c values were calculated using only reported HbA1c values.

[1] Based on a general linear model including treatment, baseline HbA1c stratum, and concomitant SU use at screening. Baseline = Day 1; if unavailable, a value from an earlier visit (the last measurement prior to the first injection) was used.

[2] BYETTA was used as the reference group.

Figure 10. LS Mean (SE) Change in HbA1c (%) from Baseline to Week 24 by Treatment (Study BCB108; Intent-to-Treat Population [N = 252])



Abbreviations: LOCF, last observation carried forward; LS, least squares; SE, standard error.

Notes: Based on a general linear model including treatment, baseline HbA1c stratum, and concomitant SU use at screening. Baseline = Day 1; if unavailable, a value from an earlier visit (the last measurement prior to the first injection) was used.

-Mean baseline HbA1c was 8.4% and 8.5% in the BYETTA and exenatide once weekly groups, respectively.

- The LOCF approach was applied to estimate missing values at postbaseline time points.
- Subjects randomized to BYETTA received BYETTA 5 mcg SC BID for 4 weeks followed by BYETTA 10 mcg SC BID for 20 weeks. Subjects randomized to exenatide once weekly received exenatide once weekly 2 mg SC for 24 weeks.
- The HbA1c values from 2 intent-to-treat subjects are not reported, as screening, baseline, and postbaseline HbA1c values were subsequently deleted due to invalid chromatograms. Mean HbA1c values were calculated using only reported HbA1c values.

*p <0.01, exenatide once weekly versus BYETTA.

There was a statistically significant decrease in weight from baseline to Week 24 in both treatment groups but no significant difference between treatments. The LS mean (95%) change from baseline to Week 24 in body weight was -2.3 (-3.1 to -1.6) kg in the exenatide-LAR group and -1.4 (-2.1 to -0.6) kg in the twice daily; LS mean (95% CI) difference between treatments -1.0 (-1.9 to 0.01) kg. The mean (SE) change in waist circumference from baseline to Week 24 was -2.9 (0.4) cm in the exenatide-LAR group and -1.7 (0.4) cm in the twice daily. The mean (SE) change in waist circumference from baseline to Week 24 was -2.0 (0.4) cm in the exenatide-LAR group and -1.6 (0.5) cm in the twice daily.

There was a statistically significant decrease from baseline in FPG in the exenatide-LAR group but not in the twice daily group. The LS mean (95% CI) change from baseline to Week 26 was -25 (-34 to -17) mg/dL in the exenatide-LAR group and -5 (-14 to 4) mg/dL in the twice daily. The LS mean (95% CI) difference between treatments was -20 (-31 to -10) mg/dL, p=0.0006. The difference between treatments in FPG was apparent from Week 4 through to Week 24.

SBP decreased in both treatment groups during the study but there was no significant difference between treatment groups. The LS mean change (95% CI) in SBP from baseline to Week 24 was -2.9 (-5.2 to -0.7) mmHg in the exenatide-LAR group and -1.2 (-3.5 to 1.2) mmHg in the twice daily. There was no significant change in DBP during the study.

Total cholesterol and LDL decreased significantly in the exenatide-LAR group but not in the twice daily group. In the exenatide-LAR group, the LS mean (95% CI) change from baseline

to Week 24 in total cholesterol was -15.4 (-20.5 to -10.2) mg/dL and for LDL was -6.4 (-10.7 to -2.2) mg/dL.

Efficacy data for exenatide-LAR from comparator controlled studies

Study BCB106

Methods

Study BCB106 was a multicentre, randomised, double blind, comparator controlled, parallel group, three arm study, with an open label, open ended extension of exenatide once weekly compared to sitagliptin and pioglitazone in subjects with Type 2 diabetes mellitus treated with metformin. The study was sponsored by Amylin Pharmaceuticals and conducted at 72 sites: 57 in the US, eight in India and seven in Mexico.

The inclusion criteria included:

- ≥18 years old.
- Diagnosed with Type 2 diabetes mellitus.
- HbA1c of 6.5% to 10.5%, inclusive.
- BMI of 25 kg/m^2 to 45 kg/m^2, inclusive.
- Stable body weight, that is, not varying by >3% for at least 3 months.
- FPG concentration <15.5 mmol/L.
- Stable treatment regimen of metformin for a minimum of 2 months.
- Either is not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 2 months;
  - Hormone replacement therapy (female subjects).
  - Oral contraceptives (female subjects).
  - Antihypertensive agents.
  - Lipid lowering agents.
  - Thyroid replacement therapy.
  - Antidepressant agents.
  - Drugs known to affect body weight, including prescription medications (such as orlistat [Xenical®], sibutramine [Meridia®], topiramate [Topamax®]) and over-the-counter antiobesity agents
- Is male or female and meets all the following criteria:
  - Nonlactating.
  - Negative pregnancy test result.
  - If of childbearing potential must practice and be willing to continue to practice appropriate birth control measures.
- Clinical laboratory test values (clinical chemistry, hematology, and urinalysis) judged as not clinically significant by the investigator.

The exclusion criteria included:

- Clinically significant medical condition that could potentially affect study participation and/or personal well being, as judged by the investigator, including but not limited to the following conditions:
  - Hepatic disease or ALT or AST value of >3 times the upper limit of normal
  - Renal disease (corresponding to serum creatinine levels of >1.5 mg/dL in men and >1.4 mg/dL in women)
  - Cardiovascular disease, including significant edema, congestive heart failure, or New York Heart Association Class III or Class IV cardiac status
  - Gastroparesis
  - Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years
  - Macular edema
  - Evidence of known or suspected chronic infections (such as human immunodeficiency virus or tuberculosis)
- Currently abuses drugs or alcohol or has a history of abuse.
- Fasting triglyceride concentration ≥600 mg/dL at Visit 1.
- Has been previously exposed to exenatide (Byetta®), exenatide-LAR, or any GLP-1 analog.
- Currently being treated, or is expected to require or undergo treatment with any of the following treatment excluded medications:
  - Any DPP-4 inhibitor, SU, or TZD within 3 months prior to Visit 1 (Screening).
  - Alpha-glucosidase inhibitor, meglitinide, nateglinide, or pramlintide (Symlin®) within 30 days.
  - Insulin within 2 weeks or for more than 1 week within 3 months.
  - Systemic corticosteroids by oral, intravenous (IV), or intramuscular (IM) route; or potent, inhaled, or intrapulmonary (including Advair®) steroids known to have a high rate of systemic absorption
  - Drugs interacting with the cytochrome P450 (CYP)2C8 enzyme system, including gemfibrozil (Lopid®) and rifampin
- Has previously shown a lack of tolerability or a lack of responsiveness to TZD therapy.

The study treatments were:

1. Exenatide once weekly, 2 mg F17 subcutaneously, formulation AC2993-F17.
2. Sitagliptin 100 mg, once daily oral.
3. Pioglitazone 45 mg, once daily oral.

There were placebo SC and oral treatments. Randomisation was in the 1:1:1 ratio. After Week 26, all subjects were treated with exenatide (sitagliptin and pioglitazone were discontinued. Subjects continued on their baseline dose of metformin.

The primary efficacy outcome measure was the change in HbA1c from Baseline to Week 26/Study Termination. The secondary efficacy outcome measures were:

- Change in HbA1c from baseline to intermediate visits.
- Change in body weight from baseline to Week 26/Study Termination) and to intermediate visits.
- Change in waist and hip circumferences from baseline to Week 26/Study Termination).
- Change in fasting and postprandial glucose and insulin concentrations from baseline to Week 26/Study Termination.
- Change in fasting lipid concentrations (total cholesterol, High Density Lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides) and postprandial triglyceride concentration from baseline to Week 26/Study Termination.
- Change in C-reactive Protein (CRP), adiponectin, and urinary albumin concentrations from baseline to Week 26/Study Termination.

The safety outcome measures were AEs, clinical laboratory tests, physical examination findings, vital signs, and anti-exenatide antibodies.

Statistical issues

The hypothesis test for the primary efficacy outcome measure was performed using a general linear model. The linear model included treatment and baseline HbA1c stratum (<9.0% or ≥9.0%). Multiplicity from the comparisons of exenatide-LAR to sitagliptin and rosiglitazone was adjusted using Hochberg's multiple test procedure. All tests of treatment effects used a two-sided significance level of 0.05.

The sample size calculation used a 90% power, an alpha of 0.05, randomisation in a ratio of 1:1:1, a 0.5 % difference in HbA1c, a common SD of 1.3%, and a drop-out rate of 10%. The calculation resulted in a sample size of 534 subjects.

Results

A total of 514 subjects were randomised to treatment group: 170 to exenatide, 172 to sitagliptin and 172 to pioglitazone. A total of 160 (94.1%) subjects in the exenatide group, 166 (96.5%) subjects in the sitagliptin group and 165 (95.9%) subjects in the pioglitazone group received at least one dose of study medication and were included in the ITT analysis. A total of 127 (79.4%) subjects in the exenatide group, 144 (86.7%) subjects in the sitagliptin group and 131 (79.4%) subjects in the pioglitazone group completed the study. Eleven (6.9%) subjects in the exenatide group, five (3.0%) subjects in the sitagliptin group and six (3.6%) subjects in the pioglitazone group withdrew from the study because of AEs. The study included 251 (51.7%) males, 237 (48.3%) females and the age range was 24 to 85 years. The treatment groups were similar in demographic and baseline characteristics. Few subjects were taking antidiabetic drugs other than biguanides at baseline. Sixty five (40.6%) subjects in the exenatide group, 66 (39.8%) in the sitagliptin and 67 (40.6%) in the pioglitazone were taking lipid lowering agents at baseline. Eleven (6.9%) subjects in the exenatide group, nine (5.4%) subjects in the sitagliptin group and eleven (6.7%) subjects in the pioglitazone group commenced lipid modifying agents during the study.

There was a statistically significant greater improvement in HbA1c from baseline to Week 26 in the exenatide group compared with either sitagliptin or pioglitazone (Table 7). The LS Mean (95% CI) change from baseline in HbA1c was -1.55 (-1.74 to -1.35) % for exenatide, -

0.92 (-1.11 to -0.72) % for sitagliptin and -1.23 (-1.43 to -1.04) % for pioglitazone. The LS mean (95% CI) difference between treatments was 0.63 (0.37 to 0.89), p<0.001, for sitagliptin-exenatide and 0.32 (0.06 to 0.57), p= 0.0165, for pioglitazone – exenatide. The treatment effect was not influenced by country or HbA1c stratum at baseline.

Table 7. Parametric Analysis [1] of Change in HbA1c (%) from Baseline to Week 26 (Study BCB106; Intent-to-Treat [N = 491] and 26-Week Evaluable [N = 387] Populations)

	Treatment [2]		
HbA1c (%)	Exenatide QW 2 mg	Sitagliptin 100 mg	Pioglitazone 45 mg
ITT Population (N = 491)	**N = 160**	**N = 166**	**N = 165**
Baseline			
Mean (SE)	8.57 (0.09)	8.49 (0.09)	8.47 (0.08)
Change from Baseline to Week 26			
Mean (SE)	-1.42 (0.11)	-0.79 (0.09)	-1.09 (0.09)
LS Mean (SE)	-1.55 (0.10)	-0.92 (0.10)	-1.23 (0.10)
95% Confidence Interval	-1.74, -1.35	-1.11, -0.72	-1.43, -1.04
LS Mean Difference (SE) [3]		0.63 (0.13)	0.32 (0.13)
95% Confidence Interval Difference [3]		0.37, 0.89	0.06, 0.57
p-value [3]		<.0001	0.0165
Adjusted p-value [4]		<.0001	0.0165
26-Week Evaluable Population (N = 387)	**N = 122**	**N = 137**	**N = 128**
Baseline			
Mean (SE)	8.62 (0.11)	8.45 (0.10)	8.41 (0.09)
Change from Baseline to Week 26			
Mean (SE)	-1.60 (0.12)	-0.87 (0.10)	-1.27 (0.09)
LS Mean (SE)	-1.70 (0.10)	-0.98 (0.10)	-1.42 (0.10)
95% Confidence Interval	-1.90 -1.50	-1.17, -0.79	-1.62, -1.22
LS Mean Difference (SE) [3]		0.72 (0.13)	0.28 (0.13)
95% Confidence Interval Difference [3]		0.46, 0.98	0.02, 0.54
p-value [3]		<.0001	0.0373
Adjusted p-value [4]		<.0001	0.0373

LOCF = last observation carried forward; LS = least squares; PO = per oral; QAM = once daily, in the morning; QW = once weekly; SC = subcutaneous; SE = standard error.

Notes: For the ITT Population, the LOCF approach was applied to estimate post-baseline missing values through Week 26. For the 26-Week Evaluable Population, missing values at Week 26 were imputed using data from the early termination visit occurring between Week 22 and Week 26.

[1] Based on a general linear model including treatment, country and baseline HbA1c stratum.

[2] Treatment: Exenatide QW 2 mg = Exenatide QW 2 mg SC weekly plus placebo PO QAM; Sitagliptin 100 mg = Sitagliptin 100 mg PO QAM plus placebo QW SC weekly; Pioglitazone 45 mg = Pioglitazone 45 mg PO QAM plus placebo QW SC weekly.

[3] Based on pairwise comparison using exenatide QW as the reference group.

[4] Based on the Hochberg procedure.

Relative to the sitagliptin group there was weight loss in the exenatide group and weight gain in the pioglitazone group. The LS Mean (95% CI) change from baseline in weight was -2.3 (-2.9 to -1.7) kg for exenatide, -0.8 (-1.4 to -0.1) kg for sitagliptin (p=0.0002) and 2.8 (2.26 to 3.4) kg for pioglitazone p<0.0001. Similarly, there were decreases in mean hip and waist circumference in the exenatide group but no change in the sitagliptin and increases in the pioglitazone.

The LS Mean (95% CI) change from baseline to Week 26 in fasting plasma glucose was -32 (-39 to -24) mg/dL for exenatide, -16 (-24 to -9) mg/dL for sitagliptin (p=0.0019) and -27 (-35 to -20) mg/dL for pioglitazone (p=0.3729). At each time point for the 6-point SMPG profile exenatide resulted in a lower plasma glucose concentration than sitagliptin but no significant difference with pioglitazone. Total cholesterol increased from baseline in the pioglitazone group but remained stable in the exenatide group. Exenatide once weekly treatment resulted in an increase in LS mean (95% CI) fasting insulin concentrations from

baseline to Week 26: 3.6 [1.6, 5.6] µIU/mL) compared with sitagliptin 0.4 (-1.6 to 2.3) µIU/mL (p = 0.0161) and pioglitazone -3.9 (-5.9 to -2.0) µIU/mL (p <0.0001).

HOMA-B and HOMA-S improved in all treatment groups but to a greater extent in the exenatide group. The geometric LS mean (95% CI) ratios (Week 26/baseline) of HOMA-B were 1.79 (1.63 to 1.97) for exenatide, 1.21 (1.10 to 1.32) for sitagliptin and 1.23 (1.13 to 1.35) for pioglitazone. The geometric LS mean (95% CI) ratios (Week 26/baseline) of HOMA-S were 0.86 (0.79 to 0.94) for exenatide, 0.99 (0.90 to 1.07) for sitagliptin and 1.39 (1.27 to 1.51) for pioglitazone.

SBP and DBP both decreased in the exenatide group compared with the other two treatments. However, this only reached statistical significance for SBP. There was no significant difference between the treatment groups in hsCRP, urinary albumin or urinary creatinine. Adiponectin was higher in the pioglitazone group than in the other two treatment groups.

There was a significantly greater improvement in DTSQc in the exenatide group compared with the sitagliptin group. There was a significant difference between exenatide and pioglitazone groups in IWQOL-Lite total scores (p = 0.0038). There was no difference between the treatment groups in DTSQs, Psychological General Well-Being Index (PGWB) or EuroQol (EQ-5D)[4].

Study H8O-MC-GWBR

Methods

Study H8O-MC-GWBR was a multicentre, open label, randomised, comparator controlled, two arm, parallel group of exenatide-LAR in comparison with glargine. The study was sponsored by Eli Lilly and Company and was conducted at 72 sites.

The study included males or females with:

- Type 2 diabetes based on the WHO diagnostic criteria.
- At least 18 years of age at screening.
- Suboptimal glycaemic control as evidenced by an HbA1c between 7.1% and 11.0%, inclusive.
- BMI of 25 kg/m^2 to 45 kg/m^2, inclusive.
- Stable body weight (not varying by >5% for at least 3 months prior to screening).
- Treated with metformin for at least 3 months and have been taking a stable dose of ≥1500 mg/day immediate-release metformin or extended-release metformin alone for at least 8 weeks prior to screening, unless lower doses are required due to tolerability concerns. Or
- Have been treated with metformin for at least 3 months and have been taking a stable dose of ≥1500 mg/day immediate-release metformin or extended-release metformin

[4] EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. EQ-5D is primarily designed for self-completion by respondents.

alone for at least 8 weeks prior to screening, unless lower doses are required due to tolerability concerns and have been treated with SU for at least 3 months and have been taking a stable dose of at least an optimally effective dose of brand of SU for 8 weeks prior to screening

- Females of child-bearing potential that are not breastfeeding, are not pregnant and agree to continue to use a reliable method of birth control during the study.

The study treatments were:

1. Exenatide-LAR, 2 mg once weekly by SC injection.
2. Insulin glargine, adjusted according to the following algorithm: dose initially 10 IU/day and adjusted by morning FBG to achieve a target of 4.0 to 5.5 mmol/L by increasing insulin doses 2 to 4 IU when FBG was >5.5 mmol/L for three consecutive days. If FBG was <4.0 mmol/L or the patient experienced symptoms of hypoglycaemia without a reasonable explanation (such as exercise or illness), the dose was decreased by 2 IU/day. Insulin glargine was to be injected at approximately the same time each day, preferably at bedtime.

Subjects were randomised to treatment group but were not blinded to their treatment. Subjects continued their usual therapy of metformin only or metformin plus SU but the SU dose could be decreased based on the incidence of hypoglycemic episodes.

The primary efficacy outcome measure was the change in HbA1c from baseline to Week 26.

The secondary efficacy outcome measures were:

- The proportion of patients achieving HbA1c ≤7% and ≤6.5%.
- Fasting serum glucose.
- Change in body weight.
- 1,5-AG.
- 8-point SMBG profile.
- Serum lipids (TC, HDL-C, fasting triglycerides, calculated LDL-C).

The exploratory efficacy outcome measures were:

- The proportion of patients achieving HbA1c ≤6.0%.
- hsCRP.
- Urinary albumin/creatinine ratio (based on a single, random urine collection).
- HOMA-B and HOMA-S.
- Waist and hip circumference, including waist-hip circumference ratio.

Health outcome measures were:

- Impact of Weight on Quality of Life-Lite (IWQOL-Lite).
- The EuroQol instrument (EQ-5D).
- The Binge Eating Scale (BES).
- Diabetes Treatment Satisfaction Questionnaire: DTSQs and DTSQc.

The safety outcome measures were: AEs, frequency and rate of hypoglycemic events (overall, daytime, and nocturnal), clinical chemistry and hematology, anti-exenatide antibodies, ECGs and vital signs.

Statistical issues

Hypothesis tests were performed using a maximum likelihood based mixed model repeated measures (MMRM) analysis of covariance with change in HbA1c as the dependent variable and treatment, baseline HbA1c, country, OAD stratum, week of visit, and treatment-by-week interaction as fixed effects and patient and error as random effects. All post baseline measurements of the change in HbA1c were included in the analysis with no imputation of missing data other than that inherent in the MMRM model. Using SAS® PROC MIXED, least-squares (LS) estimates of the treatment difference (exenatide-LAR minus insulin glargine) and standard errors were obtained from the MMRM model to compute the two-sided 95% confidence intervals at each visit week. The primary analysis was based on the estimate of the treatment difference at Week 26 but still used the data from all the post baseline measures in order to determine the LS mean difference and SE.

The sample size calculations were designed to enable a non inferiority comparison for the complete study population and also for the population only co medicated with metformin (and not SU). For the complete study population 228 subjects in each treatment group, assuming a dropout rate of 10% would provide 92% power to detect a difference between treatments of 0.3% (changed from 0.4% as a protocol amendment, based on regulatory feedback from the Committee on Medicinal Products for Human Use (CMPH)) in change in HbA1c from baseline with a two-sided *t* test at a significance level of 0.05, assuming a common standard deviation of 1.2%. For the population of subjects treated with metformin alone, 159 subjects in each treatment group assuming a 10% dropout rate, would provide 80% power to detect a difference between treatments of 0.4% in change in HbA1c from baseline with a two-sided *t* test at a significance level of 0.05, assuming a common standard deviation of 1.2%. Superiority of exenatide-LAR to insulin glargine with regard to change in HbA1c would be concluded if the upper limit of the 95% confidence interval for the treatment difference (exenatide-LAR minus glargine) was less than zero. Non inferiority would be concluded if this upper limit is less than 0.3%, but greater than or equal to 0.0%.

Results

A total of 659 subjects were screened and 467 were randomised to treatment: 233 to exenatide-LAR and 234 to glargine. Eleven subjects in the glargine group discontinued before receiving the first dose of study medication, so in the ITT population there were 233 subjects in the exenatide-LAR group and 223 in the glargine. A total of 209 subjects in each treatment group completed the study. Eleven subjects in the exenatide-LAR group and two in the glargine discontinued because of AEs. The treatment groups were similar in demographic and baseline characteristics and in OAD treatment at baseline. There were 243 (53.3%) males, 213 (46.7%) females and the age range was 26 to 84 years. No subjects were commenced on additional OAD during the treatment phase.

Exenatide-LAR was superior to glargine at all time points as demonstrated by the 95% CI for the difference in HbA1c between treatments (exenatide-LAR – glargine) being less than 0 (Table 8). At Week 26 the treatment difference (95% CI) was -0.16 (-0.29 to -0.03) %, p=0.017. Superiority was also demonstrated in the subgroup of subjects not treated with SU: treatment difference (95% CI) at Week 26 -0.18 (-0.34 to -0.02) %, p=0.031. The PP analysis demonstrated non inferiority but this analysis was made redundant by the superiority analysis based on the ITT population: treatment difference (95% CI) -0.15 (-

0.28 to -0.02), p=0.027. There was no difference between the treatment groups in the proportion of subjects achieving HbA1c ≤7 % at Week 26: 123 (63.7%) subjects in the exenatide-LAR group and 111 (57.2%) in the glargine, p=0.214. A higher proportion of subjects in the exenatide-LAR group achieved HbA1c ≤6.5% at Week 26: 92 (44.0%) subjects in the exenatide-LAR group and 60 (29.6%) in the glargine, p=0.004. There was no difference between the treatment groups in the proportion of subjects achieving HbA1c ≤6 % at Week 26: 30 (14.3%) subjects in the exenatide-LAR group and 18 (8.8%) in the glargine, p=0.214.

Table 8. Hemoglobin A1c (%) – Analysis of Treatment Difference in Change from Baseline Using Repeated Measures – Intent-to-Treat Patients (N=456)

Variable Analyzed: Hemoglobin A1c (%) Change from Baseline

Week	Treatment	N	LS Mean	SE	Within-group p-value*a	LS Mean Difference ((1)-(2))	SE	p-value*b	95% CI (Lower, Upper)
8	(1) Exenatide 2 mg QW	222	-1.06	0.05	<.001	-0.24	0.07	<.001	(-0.37,-0.11)
	(2) Glargine QD	214	-0.82	0.05	<.001				
14	(1) Exenatide 2 mg QW	215	-1.48	0.05	<.001	-0.32	0.07	<.001	(-0.45,-0.18)
	(2) Glargine QD	210	-1.17	0.05	<.001				
18	(1) Exenatide 2 mg QW	213	-1.52	0.05	<.001	-0.29	0.07	<.001	(-0.42,-0.16)
	(2) Glargine QD	208	-1.22	0.05	<.001				
22	(1) Exenatide 2 mg QW	206	-1.53	0.05	<.001	-0.25	0.07	<.001	(-0.38,-0.12)
	(2) Glargine QD	209	-1.28	0.05	<.001				
26	(1) Exenatide 2 mg QW	205	-1.47	0.05	<.001	-0.16	0.07	.017	(-0.29,-0.03)
	(2) Glargine QD	206	-1.31	0.06	<.001				

Abbreviations: CI = confidence interval; LS Mean = least-squares mean; N = total number of patients; OAD = oral antidiabetic agent; QD = once daily; QW = once weekly; SE = standard error.

Note: Only patients with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
*a - Within group p-values are from t-tests on LS Mean change.
*b - Analysis of covariance (ANCOVA) model: Post-baseline Response Variable = Treatment + Baseline HbA1c + Country + Background OAD Stratum + Week + Treatment*Week (Type III sums of squares), covariance structure = Autoregressive(1);
Analysis of variance (ANOVA) model: Baseline Response Variable = Treatment (Type III sums of squares).

In both treatment groups there was a statistically significant decrease in FSG from baseline to Week 26: LS mean (SE) change: -2.1 (0.16) mmol/L, p<.001, for exenatide-LAR and -2.8 (0.16) mmol/L, p<.001, for glargine. However, there was a greater decrease in the exenatide-LAR group: LS mean (95% CI) difference (exenatide-glargine) 0.63 (0.25 to 1.00) mmol/L p=0.001. Weight decreased from baseline in the exenatide-LAR group but increased in the glargine group. The LS mean (SE) change from baseline was -2.63 (0.20) kg p<.001 for exenatide-LAR and 1.42 (0.20) kg p<0.001 for glargine; LS mean (95% CI) difference -4.05 (-4.57 to -3.52) kg, p<0.001. In both treatment groups 1,5-AG increased from baseline to Week 26, with a greater increase in the exenatide-LAR group: 6.0 mg/mL for exenatide-LAR and 4.2 mg/mL for glargine, LS mean (95% CI) difference between treatments (exenatide-glargine) 1.8 (0.97 to 2.59) mg/mL (p<.001). The 8-point SMPG profile was more favourable for exenatide-LAR than glargine, with higher 03:00 and morning preprandial glucose concentrations, and lower evening postprandial concentrations. There was no difference between treatment groups in fasting serum lipids. There were no consistent differences between treatments in IWQOL-lite, EQ-5D, BES, DTSQc and DTSQs. There were no differences between treatments in hsCRP and urine albumin/creatinine ratio. HOMA-S (insulin sensitivity) improved in the glargine group and HOMA-B (beta cell function) improved in the exenatide-LAR. Waist circumference decreased in the exenatide-LAR group relative to glargine: LS mean (95% CI) difference -2.58 (-3.52 to -1.64). Hip circumference decreased in the exenatide group relative to glargine: for exenatide minus insulin glargine in hip circumference: LS mean (95% CI) difference -2.39 (-3.22 to -1.57) cm.

Supportive efficacy data for exenatide-LAR

Study H8O-MC-GWDC was a multicentre, single arm (no control group), open label study of the safety of exenatide 2 mg once weekly in combination with thiazolidinediones alone or thiazolidinediones in combination with metformin. The inclusion criteria included:

- Type 2 diabetes based on the WHO diagnostic criteria.
- At least 18 years of age.
- Treated with commercial exenatide-IR for at least 3 months at the time of screening, or who had completed a clinical study examining safety/efficacy of exenatide-IR within 3 months.
- HbA1c ≤10.0%; or if not previously treated with exenatide-IR must have had HbA1c of 7.1% to 10.0%, inclusive.
- BMI of 25 kg/m^2 to 45 kg/m^2, inclusive.
- History of stable body weight (not varying by >10% for at least 3 months prior to screening).
- Treated with a stable dose of TZD (≥4 mg/day rosiglitazone or ≥30 mg/day pioglitazone), for at least 120 days prior to Visit 1; or, with or without metformin for at least 90 days.

The study treatment was: exenatide-LAR once weekly (formulation AC2993-F17) 2 mg by SC injection. Treatment duration was planned to be 52 weeks but the report provided data for the first 26 weeks only. There was no control group.

The study outcome measures were: AEs, change in HbA1c, change in FBG, change in body weight, fasting lipids, frequency and rate of hypoglycaemic events, vital signs and occurrence of anti-exenatide antibodies.

A total of 157 subjects entered the study but 23 did not meet entry criteria and were excluded. A total of 134 subjects were enrolled and included in the ITT dataset. Of the ITT subjects, 44 were exenatide naïve, 90 were previously exposed to exenatide twice daily, 74 (55.2%) were male, 60 (44.8%) were female and the age range was 54 to 78 years. A total of 123 subjects completed 26 weeks of treatment: four (3%) discontinued because of AEs.

In the complete subject group, the mean (95% CI) change from baseline in HbA1c was -0.83 (-0.99 to -0.67) %, p<0.001. In the exenatide naïve subjects the change from baseline was -1.25 (-1.57 to -0.92) %, p<0.001. In those previously exposed to exenatide the change from baseline was -0.63 (-0.80 to -0.45), p<0.001. There was a mean reduction from baseline in FSG of 1.89 mmol/L but hypothesis tests were not provided. There was a mean decrease from baseline in body weight of 2.41 kg in the total population, 3.47 kg in the exenatide naïve and 1.90 kg in those with prior exenatide exposure but hypothesis tests were not provided for these variables.

Efficacy data for exenatide in combination with TZD

The sponsor has conducted an extension of the development program to include studies of co-medication with thiazolidinediones. This is to enable registration of exenatide products to include adjunctive use in combination with thiazolidinediones.

Study H8O-MC-GWAP

Methods

Study H8O-MC-GWAP was a multicentre, double blind, randomised, two parallel arm, placebo controlled superiority study in subjects taking TZDs alone or in combination with metformin.

The inclusion criteria included:

- Males and females with Type 2 diabetes between 21 and 75 years of age.
- Stable dose of TZD (rosiglitazone ≥4 mg/day; pioglitazone ≥30 mg/day) for at least 120 days alone or in combination with metformin for at least 30 days.
- Had suboptimal glycaemic control (HbA1c between 7.1% and 10.0% inclusive).
- BMI >25 kg/m^2 and <45 kg/m^2.
- History of stable body weight, not varying by >10% for at least 3 months.

The study treatments were:

1. Exenatide 5 µg twice daily for 4 weeks, then 10 µg twice daily within 15 minutes before morning and evening meals.
2. Placebo.

Treatments were administered by SC injection. Subjects were block randomised by consecutive study number. Subjects continued their current TZD ± metformin during the study.

The primary efficacy outcome measure was change in HbA1c from baseline to endpoint (Week 16 or last visit). The secondary efficacy outcome measures were:

- Proportion of patients achieving HbA1c ≤7%
- FSG
- 7-point self-monitored blood glucose (SMBG) profile (glucose level before and 2 hours after the start of the morning, midday and evening meals, and at bedtime)
- Beta-cell function and insulin sensitivity as assessed by HOMA analyses and the proinsulin/insulin ratio
- Body weight
- Serum lipids (TC, HDL-C, fasting triglycerides, calculated LDL-C).

Safety outcome measures were AEs, laboratory tests, vital signs and ECG.

Statistical issues

Hypothesis tests were performed using ANCOVA models. There were no adjustments for multiplicity. The sample size calculation assumed a 25% dropout rate, a difference in treatments of 0.5% in HbA1c, a two-sided level of significance of 0.05, a common SD of 1.1% and a power of 90%. The sample size was 280 subjects, but a protocol modification decreased the sample size to 220 subjects based on a dropout rate of 20%.

Results

A total of 435 subjects entered the study but 202 discontinued prior to randomisation. A total of 233 subjects were randomised to treatment and received at least one dose of study drug: 121 in the exenatide group and 112 in the placebo group. A total of 86 (71.1%) subjects in the exenatide group and 96 (85.7%) in the placebo completed the study. Nineteen (15.7%) subjects in the exenatide group and two (1.8%) subjects in the placebo group discontinued due to AEs. A total of 129 (55.4%) subjects were male, 104 (44.6%) were female and the age range was 21 to 75 years. The treatment groups were similar in demographic and baseline characteristics. Twenty eight (23.1%) subjects in the exenatide group and 22 (19.6%) subjects in the placebo group were treated with TZD alone and 93 (76.9%) subjects in the exenatide group and 90 (80.4%) subjects in the placebo group were treated with TZD and metformin.

There was a significant improvement in HbA1c from baseline in the exenatide group compared with placebo: mean (95% CI) -0.88 (-1.100 to -0.654) % p<0.0001. HbA1c ≤7% was achieved by 49 (62.0%) subjects in the exenatide group and 13 (16.2%) placebo subjects, p<.0001. HbA1c ≤6.5% was achieved by 25 (29.8%) subjects in the exenatide group and seven (8.0%) placebo subjects, p=0.0002. There was a significant improvement in FSG from baseline in the exenatide group compared with placebo: mean (95% CI) -1.36 (-1.843 to -0.873) mmol/L, p<0.0001. FSG <7 mmol/L at Endpoint was achieved by 22 (29.7%) subjects in the exenatide group and eleven (13.8%) placebo subjects, p=0.0126. In the exenatide group there was a significant decrease in body weight from baseline to Week 16: mean (SE) change -1.75 (0.25) kg, p<0.0001, but there was no significant change in the placebo group: -0.24 (0.26) kg p=0.3560; mean (95% CI) difference (exenatide-placebo) -1.51 (-2.15 to -0.88) kg p<0.0001. There were no statistically significant changes from baseline in fasting serum lipids but relative to placebo, there was a decrease in HDL in the exenatide group: mean (SE) difference -0.042 (0.017) mmol/L p=0.0159. There was a significant decrease in 7-point SMPG at all time points in the exenatide group. There was no

significant difference between treatments in insulin/proinsulin ratio or HOMA-S. There was an improvement in HOMA-B from baseline in the exenatide group relative to placebo of 25%: LS mean (95% CI) ratio 1.26 (1.08 to 1.46) p=0.0032 (Table 9).

Table 9. Analysis of Treatment Differences in Change from Baseline to Endpoint (LOCF) in HOMA-B (Log-Transformed)* – Intent-to-Treat Patients

HOMA - B (Log-Transformed)*		
Week	Exenatide (N=121)	Placebo (N=112)
Baseline		
Geometric Mean (SEM)	37.85 (2.46)	35.91 (2.50)
Ratio of Week 16 to Baseline		
Geometric Mean (SEM)	1.19 (0.08)	0.93 (0.05)
Geometric Mean LS Mean (SEM)	1.14 (0.08)	0.91 (0.07)
Geometric 95% CL	(0.99,1.32)	(0.79,1.05)
Geometric LS Mean Ratio (SEM)		1.25 (0.10)
Geometric 95% CL Ratio		(1.06,1.47)
Treatment Comparison p-value**		0.0071
Ratio of Endpoint (LOCF) to Baseline		
Geometric Mean (SEM)	1.14 (0.07)	0.92 (0.05)
Geometric Mean LS Mean (SEM)	1.15 (0.07)	0.92 (0.06)
Geometric 95% CL	(1.02,1.30)	(0.81,1.05)
Geometric LS Mean Ratio (SEM)		1.26 (0.10)
Geometric 95% CL Ratio		(1.08,1.46)
Treatment Comparison p-value**		0.0032

Abbreviations: CL = confidence limit; LOCF = last post-baseline measurement carried forward; LS= least squares; MET = metformin; N = number of patients; SEM = standard error of mean; TZD = thiazolidinediones.

Note: Stratum = TZD or TZD + MET.

*The dependent variable and its baseline value have been logarithmically transformed.
**Analysis of covariance (ANCOVA) model: Log (Variable) = Treatment + Pooled Investigator + Stratum + Log(Baseline)(Type III sums of squares).

Study H8O-BP-GWBG

Study H8O-BP-GWBG was a multicentre, open label, randomised, parallel group, comparator controlled trial comparing exenatide with glargine. The study included subjects with Type 2 diabetes mellitus, aged ≥30 years, on a stable dose combination of dual or triple oral therapy for at least 3 months; HbA1c between 7.5% and 10.0%, with a cardiovascular risk factor. Women of childbearing potential had to have a negative pregnancy test and practice a reliable method of birth control. The study was primarily a comparison of exenatide with glargine and only limited analyses with regard to TZD were performed. The formulations of exenatide used in the study were designed for twice daily administration. The study was not designed or powered to demonstrate efficacy in the subgroup treated with TZD and exenatide.

A total of 235 subjects were randomised to treatment: 118 to exenatide and 117 to glargine. A total of 99 (83.9%) subjects in the exenatide group and 104 (89.7%) subjects in the glargine group completed the study. There were 160 (68.4%) males, 74 (31.6%) females, and the age range was 30 to 75 years. A total of 133 (56.8%) subjects were co medicated with TZD: 67 (56.8%) subjects in the exenatide group and 66 (56.9%) in the glargine. The

multivariate analysis of the primary outcome variable (HbA1c) indicated that presence of TZDs did not affect efficacy (p=0.725).

Study H8O-US-GWAY

Study H8O-US-GWAY was a multicentre, open label, randomised, comparator controlled, three parallel group study of exenatide in combination with and in comparison with rosiglitazone in subjects with Type 2 diabetes mellitus treated with metformin. The study included adult patients, age 18 to 75 years inclusive, with Type 2 diabetes as defined by World Health Organization (WHO) criteria[5], who were inadequately controlled with a stable dose of metformin and had HbA1c ≥6.8% and ≤10.0%. Only a summary report of the study was provided and there were limited patient data and data tabulations.

The study treatments were:

1. Exenatide 5 µg twice daily for 4 weeks followed by 10 µg twice daily, subcutaneous
2. Rosiglitazone 4 mg twice daily oral, and Exenatide 5 µg twice daily for 4 weeks followed by 10 µg twice daily, subcutaneous
3. Rosiglitazone 4 mg twice daily, oral

Treatment duration was for 20 weeks.

The outcome measures were:

- Beta-cell function, as measured by the arginine-stimulated incremental insulin AUC (ASI-iAUC).
- AUC for glucose during a meal challenge test.
- The insulin sensitivity index as measured by M-value during the hyperinsulinemic euglycemic clamp test for a subset of subjects.
- The insulin AUC and the incremental AUC (iAUC) during the first 10 minutes after reaching a steady state during the hyperglycemic clamp test for a subset of subjects.
- AUC for insulin and C-peptide during a meal challenge test.
- Glucose, insulin, and C-peptide during a meal challenge test.
- Glycaemic measurements including:
  - Hemoglobin A1c (HbA1c)
  - Fasting serum glucose
  - Fasting C-peptide, insulin and proinsulin
- Body weight.
- Fasting lipids (total cholesterol, high-density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides).

[5] The World Health Organization definition of diabetes Type 2 is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either: fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

- Body composition (percent fat, fat mass, and fat free mass) assessed using bioimpedance.
- Waist circumference, hip circumference and waist-to-hip ratio.
- Safety and tolerability.
- Incidence and rate of hypoglycemic events.

Hypothesis tests were performed using ANCOVA models with no adjustment for multiplicity. The sample size was calculated for a test of superiority for the primary outcome measure: ASI-iAUC ratio. To detect a difference between treatments of 1.37, given a SD of 1.48, a power of 80%, and a two-sided level of significance of 0.05, 60 completers (20 per group) would be required. For the glucose AUC test, 105 completers (35 per group) would be required.

A total of 141 subjects were randomised to treatment arms and 138 subjects received one or more doses: 45 exenatide, 47 exenatide + rosiglitazone, and 46 rosiglitazone. There were 33 exenatide, 34 exenatide + rosiglitazone, and 34 rosiglitazone subjects who completed the study. Mean (SD) age was 56 (10) years and 49% subjects were female. There was no significant difference between exenatide + rosiglitazone and rosiglitazone in ASI-iAUC. HbA1c decreased to a greater extent in the exenatide + rosiglitazone group than the rosiglitazone. Weight decreased in the exenatide + rosiglitazone but increased in the rosiglitazone group. Glucose AUC was lower in the exenatide + rosiglitazone group than the rosiglitazone.

Study H8O-MC-GWCG

Methods

Study H8O-MC-GWCG was a multicentre, randomised, double blind, two-arm parallel group, placebo controlled trial in subjects with Type 2 diabetes treated with TZD.

- The inclusion criteria included:
- Males or females with Type 2 diabetes at least 18 years of age.
- Treated with rosiglitazone (≥4 mg/day) or pioglitazone (≥30 mg/day) alone or in combination with metformin; TZD dose stable for at least 120 days; and the metformin dose stable for at least 90 days.
- Suboptimal glycaemic control as evidenced by an HbA1c between 7.1% and 10.0%, inclusive.
- BMI between 25 kg/m^2 and 45 kg/m^2.
- Stable body weight (not varying by >10%) for at least 3 months.

The study treatments were:

1. Exenatide 5 μg twice daily for 4 weeks, then 10 μg twice daily.
2. Placebo.

The treatments were administered by SC injection. All subjects continued with their current regimen of TZD ± metformin during the study. Randomisation was stratified by centre and current treatment. Treatment duration was for 26 weeks, followed by an open label extension.

The primary efficacy outcome measure was the change in HbA1c from baseline to endpoint. Secondary efficacy outcome measures were:

- Proportion of patients achieving HbA1c ≤7% and ≤6.5%.
- Fasting serum glucose (FSG).
- Body weight.
- Waist circumference.
- Beta cell function and insulin sensitivity as assessed by homeostasis model assessment (HOMA) analyses.
- Health outcome measures, including (1) IWQOL-Lite, (2) EQ-5D.
- Incidence and rate of hypoglycemic events

Fasting serum lipids were performed as exploratory outcome measures. Safety outcome measures were: AEs, laboratory data, vital signs and ECGs.

Statistical issues

Hypothesis tests were performed using ANCOVA models with no adjustment for multiplicity. The sample size was determined to be 171 subjects at a 2:1 (exenatide:placebo) ratio in order to provide greater than 99% power to detect a difference between treatments of 0.88% in change in HbA1c from baseline with a two-sided t test at a significance level of 0.05, assuming a common standard deviation of 0.9% (based on results from Study H8O-MC-GWAP).

Results

A total of 302 subjects entered the study and 165 were randomised and received at least one dose of study drug: 111 in the exenatide group and 54 in the placebo group. In the exenatide group 96 (86.5%) subjects completed the study compared to 50 (92.6%) subjects in the placebo group. Four (3.6%) subjects in the exenatide group and one (1.9%) subject in the placebo group discontinued because of AEs. Seventeen subjects (ten exenatide and seven placebo subjects) were enrolled in the open label extension phase and were treated with exenatide for at least 12 weeks. There were 98 (59.4%) males, 67 (40.6%) females and the age range was 32 to 74 years. The study groups were similar in demographic and baseline characteristics.

There was a significant decrease in HbA1c from baseline and compared to placebo in the exenatide group: LS mean (SE) change from baseline -0.84 (0.20) % p<0.001 for exenatide and -0.10 (0.23) % for placebo: LS Mean Difference (95% CI) (exenatide-placebo) -0.74 (-1.06 to -0.41) %, p<0.001. There was no significant difference between the treatment groups in the proportion of subjects with HbA1c ≤7 % at endpoint: 51 (49.0%) subjects in the exenatide group and 19 (36.5%) in the placebo, p=0.113. A higher proportion of subjects in the exenatide group had HbA1c ≤6.5 % at endpoint: 37 (33.6%) subjects compared to seven (13.0%), p=0.004. There was no significant change from baseline in FSG for either group but FSG was lower in the exenatide group at endpoint: LS mean (SE) change from baseline -0.65 (0.46) mmol/l, (p=0.158) for exenatide compared to 0.37 (0.52) mmol/L for placebo: LS Mean Difference (95% CI) (exenatide-placebo) -1.02 (-1.78 to -0.28) mmol/L, p=0.009. There was no significant difference between the treatment groups in HOMA-S. There was a significant improvement in HOMA-B from baseline in the exenatide group but not in the placebo group: LS mean (SE) ratio baseline to endpoint 1.08 (0.12) for

exenatide and 0.84 (0.11) for placebo: LS mean (95% CI) ratio exenatide to placebo 1.28 (1.07 to 1.54), p=0.009. There was a significant decrease in body weight in the exenatide group but not in the placebo group: LS mean (SE) change from baseline -1.43 (0.61) kg, p=0.02, for exenatide and -0.75 (0.70) kg for placebo. There was no significant difference between the treatment groups in weight loss to endpoint: LS mean (95% CI) difference exenatide-placebo -0.69 (-1.69 to 0.31) kg, p=0.176. There was a mean decrease in waist circumference of 2.26 cm in the exenatide group and 1.85 cm in the placebo group. There were no significant changes in fasting lipids from baseline to endpoint for either treatment group and there were no between group differences. There were no significant changes in health outcomes/ quality of life evaluation from baseline to endpoint for either treatment group and no between group differences.

Evaluator's overall conclusions on clinical efficacy

Efficacy conclusions with regard to exenatide-LAR

Study 2993LAR-104 was supportive of greater efficacy, as measured by HbA1c and weight, of the 2 mg dose level of exenatide-LAR than the 0.8 mg dose level. It appears that the minimum effective dose is the 2 mg dose level.

Study 2993LAR-105 indicated superiority for exenatide-LAR in comparison with twice daily exenatide with regard to the decrease from baseline in HbA1c and the fact that treatment effect was preserved over a 52 week period. There were similar effects for the two dosage forms on FPG, SMPG profile and weight loss. During Study 2993LAR-105 subjects received concurrent treatment with metformin, SU, TZD, a combination of metformin and SU, a combination of metformin and TZD or a combination of SU and TZD. It is not clear from the data why exenatide-LAR should have greater efficacy than twice daily exenatide but it might be related to the effects of twice daily exenatide wearing off between doses with resultant increases in plasma glucose. [6]

Study BCB108 also indicated superiority for exenatide-LAR in comparison with exenatide twice daily by the primary efficacy outcome measure of HbA1c. There were similar effects on weight and waist circumference. Subjects were concurrently treated with metformin, SU, TZD, a combination of metformin and SU, a combination of metformin and TZD or a combination of SU and TZD. Efficacy was not influenced by concomitant antidiabetic medication.

Data were presented that supported the efficacy of exenatide when in combination with metformin, as dual therapy. Study BCB106 demonstrated superiority for exenatide compared with sitagliptin or pioglitazone when used in combination with metformin for the outcome measure of HbA1c. There was also better weight control in the exenatide group than in either of the comparator groups. Exenatide also gave better control of FSG and SMPG profile than sitagliptin. The doses of sitagliptin and pioglitazone used in the study were consistent with clinical practice and the manufacturer's recommendations as pioglitazone dose can be increased to 45 mg/day if there is inadequate response.

In Study H8O-MC-GWBR exenatide was superior to glargine with respect to HbA1c in subjects concurrently medicated with metformin or metformin plus SU. Superiority was also demonstrated in the subgroup of subjects co medicated with metformin alone. Weight

[6] The sponsor added the comment that in their opinion this is due to continuous exposure to exenatide with QW versus intermittent exposure with Byetta.

control was better in the exenatide group. FSG was also lower in the exenatide group. The 8-point SMPG profile was more favourable for exenatide-LAR than glargine, with higher 03:00 and morning preprandial glucose concentrations and lower evening postprandial concentrations. In this study glargine was used as basal insulin therapy and the timing and dose were in accordance with usual clinical practice and the manufacturer's recommendations in Type 2 diabetes. However, glargine might have been more effective if used in a basal-bolus regimen in combination with short acting insulins.

At the time of submission of the present application the comparator drugs used in the studies were registered in Australia for use in Type 2 diabetes, and for the populations included in the studies.

Efficacy conclusions for exenatide in combination with TZD

Study H8O-MC-GWAP demonstrated efficacy for exenatide in comparison with placebo in subjects treated with TZD or TZD and metformin as assessed by HbA1c. There was also superior weight control and 7-point SMPG with exenatide.

Study H8O-MC-GWCG also demonstrated efficacy for exenatide in comparison with placebo in subjects treated with TZD or TZD and metformin as assessed by HbA1c. There was also weight loss in the exenatide group which did not occur in the placebo group.

Study H8O-US-GWAY was supportive of the efficacy of exenatide in combination with rosiglitazone, in comparison with both exenatide and rosiglitazone alone. Study H8O-MC-GWDC was supportive of the efficacy of exenatide-LAR in subjects treated with TZD or TZD and metformin.

Study H8O-BP-GWBG was an open label study that did not contribute data that could be evaluated for efficacy. This study did not appear to have been designed to support the current application.

Hence the data submitted in support of the use of exenatide in combination with TZD are from 279 subjects treated with the combination in three studies (Study H8O-MC-GWAP, Study H8O-MC-GWCG and Study H8O-US-GWAY).

The treatment effect was clinically significant and sustained for the duration of the studies (up to 26 weeks). The patients included in the studies were typical of those who would be considered for combination antidiabetic therapies in Australia. However, the use of glargine was only as basal insulin whereas it would more typically be used in basal bolus regimens in combination with short acting insulin. In addition, the studies did not examine the duration of effect prior to the need to introduce insulin and did not determine the optimal sequence of treatments, or treatment combinations.

Safety

Introduction

Safety data were provided in support of both parts of the application: exenatide-LAR; and exenatide in combination with TZD.

Patient exposure

Exenatide-LAR

In Study ID: 2993LAR-102, 20 subjects were exposed to a single dose of once weekly exenatide.

Study ID: 2993LAR-103, there were 45 subjects exposed to a single dose of once weekly exenatide: 13 in the 2.5 mg group, ten in the 5 mg group, twelve in the 7 mg group, and ten in the 10 mg group.

In Study BCB107, 119 subjects were exposed to up to 10 mg of once weekly exenatide as a single SC injection.

In Study 2993LAR-104, 16 subjects were exposed to 0.8 mg exenatide once weekly for 15 weeks and 15 subjects were exposed to 2.0 mg exenatide once weekly for 15 weeks.

In Study 2993LAR-105, 148 subjects were treated with once weekly exenatide 2 mg for a median duration of 364 days and a further 130 subjects were treated for a median duration of 155 days.

In Study H8O-JE-GWBW, ten subjects were exposed to exenatide-LAR 0.8 mg once weekly for a median (range) of 64 (1 to 65) days and to exenatide-LAR 2 mg once weekly for a median (range) of 64 (63 to 64) days.

In Study BCB108, 168 subjects were treated with once weekly exenatide for a median (range) of 168 (1 to 191) days.

In Study BCB106, 160 subjects were exposed to once weekly exenatide for a median (range duration) of 176 (1 to 200) days.

In Study H8O-MC-GWBR, 233 subjects were treated with exenatide-LAR for a median (range) of 183 (1 to 220) days.

In Study H8O-MC-GWDC, 124 subjects were exposed to exenatide-LAR 2mg once weekly for more than 114 days. The median (range) duration of treatment was 176 (1 to 211) days.

Exposure to exenatide in combination with TZD

In Study H8O-MC-GWAP, 121 subjects were exposed to twice daily exenatide in combination with TZD for a median (range) of 112 (4 to 134) days; and 91 subjects were exposed to this combination for more than 85 days.

Study H8O-BP-GWBG, 67 subjects were treated with TZD in combination with exenatide.

In Study H8O-US-GWAY, 47 subjects were treated with a combination of exenatide, rosiglitazone and metformin for up to 20 weeks.

In Study H8O-MC-GWCG, a total of 111 subjects were treated with twice daily exenatide in combination with TZD ± metformin for a median (range) of 182 (2 to 201) days and 99 of these subjects were treated for more than 114 days.

Adverse events

Adverse events reported with exenatide-LAR

In Study ID: 2993LAR-102, 35 treatment-emergent (TE) AEs were reported in 15 (71.4%) subjects. The most commonly reported TEAEs were: nausea (9), dizziness (3) contusion (3)

and headache (2). No hypoglycaemia was reported. Four (40%) subjects had palpable injection site nodules at end of study.

In Study ID: 2993LAR-103, a total of 33 TEAEs were reported in14 (93.3%) subjects in the placebo group, 16 TEAEs were reported in seven (50.0%) subjects in the 2.5 mg group, seven TEAEs in five (50.0%) subjects in the 5 mg group, 33 TEAEs in ten (83.3%) subjects in the 7 mg and 24 TEAEs in eight (72.7%) subjects in the 10 mg group. There was a dose related increase in gastrointestinal TEAEs. Eight (17.0%) subjects in the once weekly exenatide group and seven (46.7%) subjects in the placebo group reported one or more adverse events related to an injection site reaction. The events were injection site erythema (two [4.3%] subjects in the exenatide-LAR group and seven [46.7%] in the placebo group) injection site bruising (three [6.4%] in the exenatide group, none in the placebo group), injection site pain (two [4.3%] exenatide subjects, one [6.7%] placebo subject), injection site pruritis (three [6.4%] exenatide subjects, no placebo subjects), and injection site swelling (none in exenatide group, one [6.7%] placebo subject).

In Study BCB107, 214 TEAEs were reported in 110 (92.4%) subjects (Table 10). The most commonly reported TEAEs were nausea, 58 (48.7%) subjects; vomiting, 42 (35.3%); and headache, 42 (35.3%). Injection site reactions were common: pruritis reported by 38 (31.9%); pain by 30 (25.2%) and erythema by 27 (22.7%).

In Study 2993LAR-104, 22 TEAEs were observed in 11 (84.6%) subjects in the placebo group, 48 TEAEs in 14 (87.5%) subjects in the 0.8 mg group and 42 TEAEs in eight (53.3%) subjects in the 2.0 mg group (Table 11). Nausea occurred in two (15.4%) subjects in the placebo group, three (18.8%) in the 0.8 mg and four (26.7%) in the 2.0 mg. Four (25%) subjects in the 0.8 mg group were reported with hypoglycaemia.

In Study 2993LAR-105, 691 TEAEs were reported during the 30 week treatment period in 129 (87.2%) subjects in the once weekly group and 543 TEAEs in 118 (81.4%) subjects in the twice daily group. During the 22 week follow-on phase there were 554 TEAEs reported in 183 (70.9%) subjects. Injection site pruritis was common in the once weekly group, occurring in 27 (18.2%) subjects compared with two (1.4%) subjects in the twice daily group (Table 12). Nausea was the most frequently reported treatment emergent adverse event (TEAE), occurring in 39 (26.4%) subjects in the once weekly group and 50 (34.5%) in the twice daily. In the 22 week follow-on phase the incidence of nausea was lower: 19 (7.4%) subjects (Table 13). Other than those subjects also treated with SU medication, hypoglycaemia was only recorded in one subject in the twice daily group. Symptoms of hypoglycaemia were reported in 12 (12.9%) subjects in the once weekly group (27 occasions) and in eight (8.6%) subjects in the twice daily group (11 occasions). Injection site related AEs were reported in 11% of injections in the once weekly group. These reactions were pruritis/urticaria in 5.5% injections, haemorrhage in 1.9% of injections, erythema in 1.6% of injections and irritation/burning/pain/stinging in 1.4% of the injections. The LS mean (SE) change from baseline to Week 30 in SBP was -4.7 (1.10) mmHg in the once weekly group and -3.4 (1.09) mmHg in the twice weekly group. The LS mean (SE) change from baseline to Week 30 in DBP was -1.7 (0.72) mmHg in the once weekly group and -1.7 (0.71) mmHg in the twice weekly group. The LS mean (SE) change from baseline to Week 30 in pulse rate was 4.5 (0.92) beats per minute (BPM) in the once weekly group and 2.1 (0.91) BPM in the twice weekly group. There were no clinically significant changes in ECG parameters.

Table 10. Frequent Adverse Events (With Incidence ≥10% in Any Treatment Group) During the Exenatide Once Weekly Assessment Period by Preferred Term and Treatment (Study BCB107; Intent-to-Treat Subjects Participating in the Exenatide Once Weekly Assessment [N = 119])

	Treatment [1]									
	Exenatide Once Weekly Formulation A (F17) (N = 30)		Exenatide Once Weekly Formulation B (F17) (N = 30)		Exenatide Once Weekly Formulation C (F28) (N = 29)		Exenatide Once Weekly Formulation D (F30) (N = 30)		All Subjects (N = 119)	
	Subject [2]	Events	Subject [2]	Events	Subject [2]	Events	Subject [2]	Events	Subject [2]	Events
Preferred Term [3]	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Nausea	17 (56.7)	38	13 (43.3)	23	18 (62.1)	22	10 (33.3)	22	58 (48.7)	105
Vomiting	14 (46.7)	33	9 (30.0)	29	12 (41.4)	30	7 (23.3)	15	42 (35.3)	107
Headache	12 (40.0)	21	10 (33.3)	15	9 (31.0)	15	11 (36.7)	16	42 (35.3)	67
Injection Site Pruritus	10 (33.3)	20	8 (26.7)	18	11 (37.9)	23	9 (30.0)	18	38 (31.9)	79
Injection Site Pain	12 (40.0)	15	10 (33.3)	17	1 (3.4)	2	7 (23.3)	10	30 (25.2)	44
Injection Site Erythema	9 (30.0)	15	6 (20.0)	13	8 (27.6)	17	4 (13.3)	8	27 (22.7)	53
Pharyngolaryngeal Pain	10 (33.3)	14	6 (20.0)	9	8 (27.6)	10	3 (10.0)	4	27 (22.7)	37
Injection Site Bruising	8 (26.7)	9	7 (23.3)	11	5 (17.2)	6	4 (13.3)	8	24 (20.2)	34
Dizziness	9 (30.0)	12	7 (23.3)	11	3 (10.3)	5	2 (6.7)	2	21 (17.6)	30
Decreased Appetite	11 (36.7)	15	4 (13.3)	5	3 (10.3)	3	3 (10.0)	3	21 (17.6)	26
Cough	9 (30.0)	11	2 (6.7)	3	6 (20.7)	7	3 (10.0)	3	20 (16.8)	24
Injection Site Swelling	2 (6.7)	3	10 (33.3)	19	0 (0.0)	0	5 (16.7)	10	17 (14.3)	32
Rhinorrhoea	3 (10.0)	3	5 (16.7)	6	4 (13.8)	5	5 (16.7)	5	17 (14.3)	19
Back Pain	5 (16.7)	5	4 (13.3)	7	3 (10.3)	3	4 (13.3)	5	16 (13.4)	20
Diarrhoea	3 (10.0)	8	3 (10.0)	8	3 (10.3)	9	4 (13.3)	14	13 (10.9)	39
Constipation	2 (6.7)	2	0 (0.0)	0	5 (17.2)	5	6 (20.0)	6	13 (10.9)	13
Abdominal Pain Upper	5 (16.7)	8	2 (6.7)	2	4 (13.8)	8	1 (3.3)	1	12 (10.1)	19
Sinus Congestion	3 (10.0)	5	6 (20.0)	9	1 (3.4)	1	2 (6.7)	2	12 (10.1)	17
Fatigue	6 (20.0)	6	3 (10.0)	6	2 (6.9)	2	1 (3.3)	1	12 (10.1)	15
Dyspepsia	3 (10.0)	3	2 (6.7)	4	2 (6.9)	5	2 (6.7)	3	9 (7.6)	15
Eructation	5 (16.7)	8	0 (0.0)	0	2 (6.9)	3	1 (3.3)	1	8 (6.7)	12
Nasal Congestion	5 (16.7)	6	1 (3.3)	2	1 (3.4)	1	1 (3.3)	1	8 (6.7)	10
Pain	2 (6.7)	3	1 (3.3)	1	1 (3.4)	1	4 (13.3)	4	8 (6.7)	9
Dysmenorrhoea	0 (0.0)	0	4 (13.3)	7	1 (3.4)	4	0 (0.0)	0	5 (4.2)	11
Feeling Hot	0 (0.0)	0	1 (3.3)	1	4 (13.8)	4	0 (0.0)	0	5 (4.2)	5
Lacrimation Increased	2 (6.7)	2	3 (10.0)	3	0 (0.0)	0	0 (0.0)	0	5 (4.2)	5
Sneezing	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	3 (10.0)	4	4 (3.4)	5
Asthenia	3 (10.0)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	3 (2.5)	3

Abbreviations: QW, once weekly; SC, subcutaneous.

[1] Formulation A: single dose of exenatide once weekly AC2993-F17 Lot S426-2377CA 10 mg SC; Formulation B: single dose of exenatide once weekly AC2993-F17 Lot S426-2507AA 10 mg SC; Formulation C: single dose of exenatide once weekly AC2993-F28 8 mg SC; Formulation D: single dose of exenatide once weekly AC2993-F30 10 mg SC. Each single dose of exenatide once weekly was delivered using 3 injections. Exenatide once weekly doses are nominal doses.

[2] Subjects experiencing multiple episodes of a given adverse event are counted once. Percentages are based on the number of intent-to-treat subjects participating in the exenatide once weekly assessment in each treatment group or overall.

[3] MedDRA Version 11.0 terms.

Table 11. Frequent Adverse Events (Preferred Terms With Incidence ≥ 10% in Any Treatment Group) by Preferred Term and Treatment During the Treatment and Follow-Up Periods (Study 2993LAR-104; ITT Population [N = 44])

	Treatment [1]											
	Placebo LAR (N = 13)			Exenatide LAR 0.8 mg (N = 16)			Exenatide LAR 2.0 mg (N = 15)			All Exenatide LAR (N = 31)		
	Subject [4]		Events	Subject [4]		Events	Subject [4]		Events	Subject [4]		Events
Preferred Term [2, 3]	n	(%)	n	n	(%)	n	n	(%)	n	n	(%)	n
Nausea	2	(15.4)	2	3	(18.8)	8	4	(26.7)	6	7	(22.6)	14
Gastroenteritis	0	(0.0)	0	3	(18.8)	3	2	(13.3)	2	5	(16.1)	5
Hypoglycemia	0	(0.0)	0	4	(25.0)	6	0	(0.0)	0	4	(12.9)	6
Arthralgia	1	(7.7)	1	1	(6.3)	1	2	(13.3)	2	3	(9.7)	3
Injection Site Bruising	0	(0.0)	0	2	(12.5)	3	1	(6.7)	3	3	(9.7)	6
Diarrhea	1	(7.7)	1	2	(12.5)	2	1	(6.7)	1	3	(9.7)	3
Injection Site Pruritus	2	(15.4)	2	1	(6.3)	1	1	(6.7)	1	2	(6.5)	2
Tooth Abscess	0	(0.0)	0	2	(12.5)	2	0	(0.0)	0	2	(6.5)	2
Hypertension	0	(0.0)	0	2	(12.5)	2	0	(0.0)	0	2	(6.5)	2
Rash	2	(15.4)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

Abbreviations: ITT, intent-to-treat; LAR, long-acting release.
[1] The weekly LAR treatments for 15 weeks follow a 3-day lead-in period during which subjects receive exenatide 5 mcg or placebo, BID.
[2] Adverse events that occur for the first time, or exist prior to Visit 3 (Day –3) and worsen, after the first injection of lead-in medication at Visit 3 (Day –3) through study termination or within 90 days of the last LAR injection.
[3] MedDRA (version 6.1) terms.
[4] Subjects experiencing multiple episodes of a given adverse event are counted once.
Note: Percentages are based on the number of ITT subjects in each treatment group or in All Exenatide LAR group.

Table 12. Frequent Treatment-Emergent Adverse Events [1] (With Incidence ≥5% in Any Treatment Group), Excluding Hypoglycemia, During the 30-Week Assessment Period by Preferred Term and Treatment (Study 2993LAR-105; Intent-to-Treat Population Participating in 30-Week Assessment [N = 293])

	Treatment					
	BYETTA 10 mcg BID (N = 145)		Exenatide LAR 2 mg QW (N = 148)		All Subjects (N = 293)	
Preferred Term [2]	Subject n (%)	Events n	Subject n (%)	Events n	Subject n (%)	Events n
Nausea	50 (34.5)	71	39 (26.4)	67	89 (30.4)	138
Injection-Site Pruritus	2 (1.4)	2	27 (18.2)	41	29 (9.9)	43
Diarrhea	19 (13.1)	28	22 (14.9)	27	41 (14.0)	55
Vomiting	27 (18.6)	39	16 (10.8)	29	43 (14.7)	68
Constipation	9 (6.2)	9	16 (10.8)	17	25 (8.5)	26
Urinary Tract Infection	12 (8.3)	12	15 (10.1)	18	27 (9.2)	30
Dyspepsia	4 (2.8)	4	11 (7.4)	12	15 (5.1)	16
Gastroenteritis Viral	8 (5.5)	9	13 (8.8)	13	21 (7.2)	22
Upper Respiratory Tract Infection	25 (17.2)	28	12 (8.1)	13	37 (12.6)	41
Nasopharyngitis	8 (5.5)	8	10 (6.8)	15	18 (6.1)	23
Gastroesophageal Reflux Disease	6 (4.1)	6	10 (6.8)	11	16 (5.5)	17
Fatigue	4 (2.8)	5	10 (6.8)	10	14 (4.8)	15
Injection Site Erythema	0 (0.0)	0	11 (7.4)	11	11 (3.8)	11
Headache	7 (4.8)	8	9 (6.1)	21	16 (5.5)	29
Injection Site Bruising	14 (9.7)	20	7 (4.7)	8	21 (7.2)	28
Sinusitis	10 (6.9)	10	7 (4.7)	7	17 (5.8)	17
Dizziness	9 (6.2)	10	5 (3.4)	7	14 (4.8)	17

Abbreviations: BID, twice daily, LAR, long-acting release; QW, once weekly.

Table 13. Frequent Treatment-Emergent Adverse Events [1] (With Incidence ≥5% in Any Treatment Group), Excluding Hypoglycemia, During the First 22 Weeks of the Open-Ended Assessment Period by Preferred Term and Treatment (Study 2993LAR-105; Intent-to-Treat Population Participating in Open-Ended Assessment [N = 258])

	Randomized Treatment [2]					
	BYETTA 10 mcg BID (N = 130)		Exenatide LAR 2 mg QW (N = 128)		All Subjects (N = 258)	
Preferred Term [3]	Subject n (%)	Events n	Subject n (%)	Events n	Subject n (%)	Events n
Upper Respiratory Tract Infection	16 (12.3)	17	16 (12.5)	17	32 (12.4)	34
Diarrhea	9 (6.9)	10	11 (8.6)	13	20 (7.8)	23
Nasopharyngitis	6 (4.6)	8	10 (7.8)	12	16 (6.2)	20
Nausea	10 (7.7)	13	9 (7.0)	13	19 (7.4)	26
Sinusitis	9 (6.9)	10	6 (4.7)	7	15 (5.8)	17
Vomiting	6 (4.6)	6	8 (6.3)	12	14 (5.4)	18
Urinary Tract Infection	7 (5.4)	8	3 (2.3)	3	10 (3.9)	11
Injection Site Bruising	7 (5.4)	10	0 (0.0)	0	7 (2.7)	10

In Study BCB106, a total of 459 TEAEs were reported in 114 (71.3%) subjects in the exenatide group, 380 TEAEs in 103 (62.0%) subjects in the sitagliptin group and 358 TEAEs in 118 (71.5%) subjects in the pioglitazone group. Gastrointestinal AEs were more common in the exenatide group: 72 (45.0%) subjects compared with 49 (29.5%) subjects in the sitagliptin group and 40 (24.2%) subjects in the pioglitazone group (Table 14). In the exenatide group, 38 (23.8%) subjects reported nausea, 29 (18.1%) subjects reported diarrhoea and 18 (11.3%) subjects reported vomiting (Table 15).

Hypoglycaemia was uncommon with minor hypoglycaemia reported in two (1.3%) subjects and symptoms of hypoglycaemia in eight (5.0%) subjects in the exenatide group. A total of 28 injection site reactions were reported in 16 (10.0%) subjects given exenatide and 42 injection site reactions in 22 (6.6%) subjects given a placebo injection. Mean (SD) heart rate (HR) was 74.1 (9.72) at baseline in the exenatide group and this had increased to 76.4 (8.89) at Week 26. There was no significant increase in the sitagliptin or pioglitazone groups.

Table 14. All Treatment-Emergent [1] Adverse Events Summarized by System Organ Class and Treatment (Study BCB106; Intent-To-Treat Population [N = 491])

System Organ Class/ Preferred Term [3]	Treatment [2]: Exenatide QW 2 mg (N = 160) Subject [4] n (%) Events			Sitagliptin 100 mg (N = 166) Subject [4] n (%) Events			Pioglitazone 45 mg (N = 165) Subject [4] n (%) Events			All Subjects (N = 491) Subject [4] n (%) Events		
All Treatment-Emergent Adverse Events During the Double-Blind Treatment Period	**114**	**(71.3)**	**459**	**103**	**(62.0)**	**380**	**118**	**(71.5)**	**358**	**335**	**(68.2)**	**1197**
Blood and lymphatic system disorders	1	(0.6)	1	2	(1.2)	2	3	(1.8)	3	6	(1.2)	6
Cardiac disorders	3	(1.9)	3	2	(1.2)	2	5	(3.0)	6	10	(2.0)	11
Ear and labyrinth disorders	3	(1.9)	3	2	(1.2)	2	1	(0.6)	1	6	(1.2)	6
Endocrine disorders	0	(0.0)	0	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2
Eye disorders	5	(3.1)	5	6	(3.6)	6	4	(2.4)	4	15	(3.1)	15
Gastrointestinal disorders	72	(45.0)	195	49	(29.5)	90	40	(24.2)	65	161	(32.8)	350
General disorders and administration site conditions	29	(18.1)	50	28	(16.9)	53	34	(20.6)	52	91	(18.5)	155
Hepatobiliary disorders	1	(0.6)	1	0	(0.0)	0	3	(1.8)	5	4	(0.8)	6
Immune system disorders	1	(0.6)	1	2	(1.2)	2	3	(1.8)	3	6	(1.2)	6
Infections and infestations	44	(27.5)	55	46	(27.7)	69	56	(33.9)	77	146	(29.7)	201
Injury, poisoning and procedural complications	7	(4.4)	10	6	(3.6)	6	8	(4.8)	13	21	(4.3)	29
Investigations	11	(6.9)	13	7	(4.2)	9	9	(5.5)	9	27	(5.5)	31
Metabolism and nutrition disorders	12	(7.5)	14	9	(5.4)	10	9	(5.5)	11	30	(6.1)	35
Musculoskeletal and connective tissue disorders	24	(15.0)	31	30	(18.1)	39	19	(11.5)	24	73	(14.9)	94
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1	(0.6)	1	1	(0.6)	1	2	(1.2)	2	4	(0.8)	4
Nervous system disorders	29	(18.1)	34	28	(16.9)	47	18	(10.9)	26	75	(15.3)	107
Psychiatric disorders	4	(2.5)	4	8	(4.8)	11	5	(3.0)	6	17	(3.5)	21
Renal and urinary disorders	4	(2.5)	7	2	(1.2)	2	6	(3.6)	6	12	(2.4)	15
Reproductive system and breast disorders	3	(1.9)	3	2	(1.2)	2	5	(3.0)	5	10	(2.0)	10
Respiratory, thoracic and mediastinal disorders	9	(5.6)	13	8	(4.8)	8	12	(7.3)	15	29	(5.9)	36
Skin and subcutaneous tissue disorders	8	(5.0)	9	7	(4.2)	8	15	(9.1)	19	30	(6.1)	36
Social circumstances	0	(0.0)	0	0	(0.0)	0	1	(0.6)	1	1	(0.2)	1
Vascular Disorders	6	(3.8)	6	7	(4.2)	10	4	(2.4)	4	17	(3.5)	20

SC = subcutaneous; PO = per oral; QAM = once daily in the morning; QW = once weekly.

[1] Adverse events that occur for the first time, or exist prior to Day 1 and worsen, after the first randomized dose at Day 1 and prior to the first injection at Week 26.

[2] Treatment: Exenatide QW 2 mg = exenatide once weekly 2 mg SC weekly plus placebo PO QAM; Sitagliptin 100 mg = sitagliptin 100 mg PO QAM plus placebo QW SC weekly; Pioglitazone 45 mg = pioglitazone 45 mg PO QAM plus placebo QW SC weekly.

[3] MedDRA (version 11.0) terms.

[4] Subjects experiencing multiple episodes of a given adverse event are counted once.

Table 15. Frequent (Preferred Terms with an Incidence Rate ≥5% in Any Treatment Group) Treatment-Emergent [1] Adverse Events (Excluding Hypoglycemia) by Preferred Term and Treatment (Study BCB106; Intent-to-Treat Population [N = 491])

	Treatment [2]			
	Exenatide QW 2 mg (N = 160)	Sitagliptin 100 mg (N = 166)	Pioglitazone 45 mg (N = 165)	All Subjects (N = 491)
Preferred Term [3]	n (%) Events [4]	n (%) Events [4]	n (%) Events [4]	n (%) Events [4]
Nausea	38 (23.8) 62	16 (9.6) 22	8 (4.8) 9	62 (12.6) 93
Diarrhoea	29 (18.1) 39	16 (9.6) 21	12 (7.3) 13	57 (11.6) 73
Upper respiratory tract infection	6 (3.8) 7	15 (9.0)16	17 (10.3) 20	38 (7.7) 43
Headache	15 (9.4) 16	15 (9.0) 19	7 (4.2) 9	37 (7.5) 44
Vomiting	18 (11.3) 29	4 (2.4) 4	5 (3.0) 7	27 (5.5) 40
Urinary tract infection	10 (6.3) 10	9 (5.4) 10	6 (3.6) 7	25 (5.1) 27
Edema peripheral	2 (1.3) 3	5 (3.0) 5	13 (7.9) 14	20 (4.1) 22
Injection site pruritus	8 (5.0) 8	8 (4.8) 13	2 (1.2) 2	18 (3.7) 23
Sinusitis	5 (3.1) 5	2 (1.2) 2	11 (6.7) 12	18 (3.7) 19
Fatigue	9 (5.6) 10	0 (0.0) 0	5 (3.0) 9	14 (2.9) 19
Constipation	9 (5.6) 9	3 (1.8) 4	2 (1.2) 2	14 (2.9) 15

PO = per oral; QAM = once daily, in the morning; QW = once weekly; SC = subcutaneous.

[1] Adverse events that occurred for the first time, or existed prior to Day 1 and worsened, after the first injection at Day 1 and prior to the first injection at Week 26.

[2] Treatment: Exenatide QW 2 mg = Exenatide QW 2 mg SC weekly plus placebo PO QAM; Sitagliptin 100 mg = Sitagliptin 100 mg PO QAM plus placebo QW SC weekly; Pioglitazone 45 mg = Pioglitazone 45 mg PO QAM plus placebo QW SC weekly.

[3] MedDRA (version 11.0) terms.

[4] Subjects experiencing multiple episodes of a given adverse event are counted once. Percentages are based on the number of intent-to-treat subjects participating double-blind treatment assessment in each treatment group or overall.

In Study BCB108, a total of 272 TEAEs were reported in 90 (69.8%) subjects in the once weekly group and 244 TEAEs in 86 (69.9%) subjects in the twice daily group. Nausea and vomiting were less frequent in the once weekly group: n (%) 18 (14.0%) versus 43 (35.0%) subjects and six (4.7%) versus eleven (8.9%) subjects, respectively (Table 16). Diarrhoea was more common with once weekly administration: 12 (9.3%) subjects compared with 5 (4.1%) subjects, respectively. Hypoglycaemia was not observed in the once weekly group in those subjects not co-medicated with SU. With respect to injection episodes with exenatide once weekly administration, 4.4% were associated with injections site AEs: haematoma in 2.1%, nodule in 1.9%, pruritis/urticaria in 1.6%, erythema in 1.5%. One subject in the once weekly group developed pancreatitis during the study.

Table 16. Frequent Treatment-Emergent Adverse Events (Preferred Terms with an Incidence Rate ≥2% in Any Treatment Group) by Preferred Term and Treatment Population: Intent-to-Treat (N = 252)

	Treatment [1]					
	Exenatide BID 10 mcg (N = 123)			Exenatide QW 2 mg (N = 129)		
	Subject			Subject		
Preferred Term [2]	n	(%)	Events	n	(%)	Events
Nausea	43	(35.0)	51	18	(14.0)	21
Vomiting	11	(8.9)	17	6	(4.7)	14
Diarrhoea	5	(4.1)	5	12	(9.3)	13
Headache	10	(8.1)	13	6	(4.7)	6
Upper respiratory tract infection	5	(4.1)	5	9	(7.0)	9
Dizziness	8	(6.5)	10	3	(2.3)	3
Injection site haematoma	6	(4.9)	6	5	(3.9)	5
Injection site erythema	3	(2.4)	3	7	(5.4)	7
Urinary tract infection	4	(3.3)	5	4	(3.1)	5
Decreased appetite	4	(3.3)	4	4	(3.1)	4
Injection site pruritus	1	(0.8)	1	6	(4.7)	6
Constipation	5	(4.1)	5	1	(0.8)	1
Diabetes mellitus inadequate control	4	(3.3)	4	2	(1.6)	2
Dyspepsia	2	(1.6)	2	4	(3.1)	4
Nasopharyngitis	1	(0.8)	1	5	(3.9)	5
Gastroenteritis	1	(0.8)	1	4	(3.1)	5
Influenza	4	(3.3)	5	1	(0.8)	1
Arthralgia	2	(1.6)	2	3	(2.3)	3
Fatigue	3	(2.4)	3	2	(1.6)	2
Abdominal pain	3	(2.4)	3	1	(0.8)	1
Cough	1	(0.8)	1	3	(2.3)	3
Injection site nodule	0	(0.0)	0	4	(3.1)	4
Hepatic steatosis	0	(0.0)	0	3	(2.3)	3

[1] Exenatide BID 10 mcg: Exenatide 5 mcg SC BID for the first 4 weeks and 10 mcg SC BID for the next 20 weeks. Exenatide QW 2 mg: Exenatide QW 2 mg SC weekly for 24 weeks.
[2] MedDRA (version 12.0) terms.

In Study H8O-MC-GWBR, TEAEs were reported in 162 (69.5%) subjects in the exenatide-LAR group and 136 (61.0%) subjects in the glargine group (Table 17). A higher proportion of exenatide-LAR subjects than glargine subjects reported nausea: 30 (12.9%) subjects compared with three (1.3%) subjects; headache 23 (9.9%) subjects compared with 16 (7.2%) subjects, diarrhea 20 (8.6 %) subjects compared with eight (3.6%) subjects; and vomiting 10 (4.3%) subjects compared with three (1.3%) subjects in the glargine group. Injection site nodule occurred in 13 (5.6%) subjects in the exenatide-LAR group compared with none in the glargine group. A total of 70 (30.0%) subjects in the exenatide-LAR group and 21 (12.1%) subjects in the glargine group experienced treatment emergent gastrointestinal AEs. There were no clinically significant changes in vital signs. Hypoglycaemia in patients co medicated with SU was reported in 14 (20.3%) subjects in the exenatide-LAR group and 28 (42.4%) subjects in the glargine group (p=0.009). Hypoglycaemia in patients not co medicated with SU was reported in 5 (3.0%) subjects in the exenatide-LAR group and 30 (19.1%) subjects in the glargine group (p=0.009). There was one major hypoglycaemic event in the exenatide-LAR group and two in the glargine group. A mean increase in heart rate of 3.6 BPM and a mean reduction of -3.0 mm Hg in SBP were observed at endpoint for the exenatide-LAR group.

Table 17. Incidence of TEAEs in greater than or equal to 2% of Exenatide-Treated Patients by Preferred Term – Intent-to-Treat Patients.

Preferred Term	Exenatide 2 mg QW (N=233) n	(%)	Glargine QD (N=223) n	(%)	Total (N=456) n	(%)
Patients with >= 1 TEAE	162	(69.5)	136	(61.0)	298	(65.4)
Nasopharyngitis	30	(12.9)	39	(17.5)	69	(15.1)
Headache	23	(9.9)	16	(7.2)	39	(8.6)
Nausea	30	(12.9)	3	(1.3)	33	(7.2)
Diarrhoea	20	(8.6)	8	(3.6)	28	(6.1)
Influenza	9	(3.9)	8	(3.6)	17	(3.7)
Arthralgia	10	(4.3)	6	(2.7)	16	(3.5)
Back pain	9	(3.9)	5	(2.2)	14	(3.1)
Injection site nodule	13	(5.6)	0	(0.0)	13	(2.9)
Oropharyngeal pain	6	(2.6)	7	(3.1)	13	(2.9)
Vomiting	10	(4.3)	3	(1.3)	13	(2.9)
Hypertension	5	(2.1)	7	(3.1)	12	(2.6)
Musculoskeletal pain	5	(2.1)	7	(3.1)	12	(2.6)
Constipation	7	(3.0)	4	(1.8)	11	(2.4)
Gastroenteritis	5	(2.1)	4	(1.8)	9	(2.0)
Abdominal pain upper	6	(2.6)	2	(0.9)	8	(1.8)
Dyspepsia	6	(2.6)	2	(0.9)	8	(1.8)
Gastritis	7	(3.0)	1	(0.4)	8	(1.8)
Abdominal discomfort	6	(2.6)	1	(0.4)	7	(1.5)
Fatigue	6	(2.6)	1	(0.4)	7	(1.5)
Injection site reaction	7	(3.0)	0	(0.0)	7	(1.5)
Pyrexia	5	(2.1)	1	(0.4)	6	(1.3)
Decreased appetite	5	(2.1)	0	(0.0)	5	(1.1)
Injection site induration	5	(2.1)	0	(0.0)	5	(1.1)

Abbreviations: N = total number of patients; n = number of patients with at least one TEAE; QD = once daily; QW = once weekly; TEAE = treatment-emergent adverse events.

In Study H8O-JE-GWBW all the study subjects reported at least one adverse event (AE) during the treatment phase and follow-up. During the treatment phase, nine (90%) subjects in the 0.8 mg group, eight (88.9%) subjects in the 2 mg group and nine (90%) subjects in the placebo group reported TEAEs. There was a higher rate of gastrointestinal disorders in the exenatide-LAR 2 mg group: five (55.6%) subjects compared with one (10%) subject in the exenatide-LAR 0.8 mg group and one (10%) subject in the placebo group. There were no significant changes in weight or in vital signs.

In Study H8O-MC-GWDC, TEAEs were reported in 83 (61.9%) subjects during the first 26 weeks of the study. The most commonly reported TEAEs were: nausea in 20 (14.9%) subjects and injection site nodule in 14 (10.4%) subjects (Table 18). No clinically significant changes in vital signs were reported. Minor hypoglycaemia episodes were reported in three (2.2%) subjects and there were no reports of major hypoglycaemia episodes.

Table 18. Incidence of Treatment-Emergent Adverse Events Occurring in greater than or equal to 2% of Exenatide-Treated Patients – Intent-to-Treat Patients (N=134)

Preferred Term	Exenatide Once Weekly (N=134) n	(%)
Patients with >= 1 TEAE	83	(61.9)
Nausea	20	(14.9)
Injection site nodule	14	(10.4)
Anorexia	12	(9.0)
Nasopharyngitis	12	(9.0)
Headache	10	(7.5)
Upper respiratory tract infection	10	(7.5)
Vomiting	9	(6.7)
Constipation	7	(5.2)
Diarrhoea	7	(5.2)
Dyspepsia	7	(5.2)
Arthralgia	5	(3.7)
Influenza	5	(3.7)
Abdominal distension	4	(3.0)
Back pain	4	(3.0)
Dizziness	4	(3.0)
Food aversion	4	(3.0)
Injection site pruritus	3	(2.2)
Nephrolithiasis	3	(2.2)
Sinusitis	3	(2.2)

Abbreviations: N = total number of patients; n = number of patients in the specified category; TEAE = treatment-emergent adverse events.

Adverse events for exenatide in combination with TZD

In Study H8O-MC-GWAP, TEAEs were reported in 92 (76%) subjects in the exenatide group and 73 (65%) placebo subjects. Gastrointestinal AEs were more common in the exenatide group: nausea 48 (39.7%) subjects compared with 17 (15.2%) subjects and vomiting 16 (13.2%) subjects compared with 1 (0.9%) subject. Three (2%) subjects in the exenatide group reported injection site AEs. One subject in the exenatide group was reported with a lung neoplasm at Week 4. Hypoglycaemic episodes were reported in 13 (10.7%) subjects in the exenatide group and eight (7.1%) subjects in the placebo group. Nocturnal hypoglycaemia episodes were reported in two (1.7%) subjects in the exenatide group and one (0.9%) subject in the placebo group. No severe hypoglycaemia episodes were reported. There were no clinically significant changes in vital signs.

In Study H8O-BP-GWBG TEAEs were reported in 91 (77.1%) subjects in the exenatide group and 12 (10.3%) subjects in the glargine group. There was no subgroup analysis by TZD medication.

In Study H8O-US-GWAY the most common adverse events were nausea (47% exenatide, 47% exenatide plus rosiglitazone and 4% rosiglitazone), vomiting (22% exenatide, 19% exenatide plus rosiglitazone), and diarrhea (7% exenatide, 21% exenatide plus rosiglitazone and 4% rosiglitazone). Minor hypoglycemia was reported in two subjects in the exenatide group, two subjects in the exenatide plus rosiglitazone group. There were no reports of minor hypoglycemia in the rosiglitazone only group. Major hypoglycemia was reported in one subject in the exenatide plus rosiglitazone group.

In Study H8O-MC-GWCG, TEAEs were reported in 43 (38.7%) subjects in the exenatide group and 16 (29.6%) subjects in the placebo group. More subjects in the exenatide group reported nausea: 13 (11.7%) compared with 1 (1.9%) in the placebo group; and vomiting: nine (8.1%) subjects compared with none in the placebo. Hypoglycaemia was reported in four (3.6%) subjects in the exenatide group and one (1.9%) subject in the

placebo group. There were no reports of major hypoglycaemic episodes. There were no clinically significant changes in vital signs.

Serious adverse events (SAEs) and deaths

Exenatide-LAR

In Study ID: 2993LAR-102 there was one SAE: back pain following a motor vehicle accident (MVA).

In Study ID: 2993LAR-103 there were no SAEs reported in the exenatide groups during the once weekly dosing phase.

In Study BCB107, one SAE was reported: erosive oesophagitis.

In Study 2993LAR-104, there were two SAEs, one in the 0.8 mg group (ureteric calculus) and one in the 2.0 mg group (angina pectoris).

In Study 2993LAR-105, during the 30 week treatment period, nine SAEs were reported in eight (5.4%) subjects in the once weekly group and ten SAEs in five (3.4%) subjects in the twice daily group. During the 22 week follow-on phase there were 17 SAEs reported in twelve (4.7%) subjects. None of the SAEs appeared to be related to study treatment and there was no apparent pattern in SAEs.

In Study BCB106, a total of four SAEs were reported in four (2.5%) subjects in the exenatide group, six SAEs in five (3.0%) subjects in the sitagliptin group and 16 SAEs in ten (6.1%) subjects in the pioglitazone group. There did not appear to be a pattern in the SAEs reported in the exenatide group, all of which resolved (Table 19).

Table 19. Treatment-Emergent Serious Adverse Events (Study BCB106; Intent-to-Treat Population [N = 491])

Subject Number	Days of Randomized Treatment [2] Prior to Onset [3]: Exenatide QW 2 mg	Sitagliptin 100 mg	Pioglitazone 45 mg	Preferred Term [4] (Verbatim)	Intensity [5]	Causality [5]	Outcome
Exenatide Once Weekly							
102002	119	-	-	Cryptogenic organising pneumonia (Cryptogenic pneumonia)	Moderate	Related	Resolved
105002	149	-	-	Postoperative wound complication (Post surgical wound complication)	Severe	Unrelated	Resolved
139008	50	-	-	Nephrolithiasis (Kidney stone)	Moderate	Unrelated	Resolved
175016	141	-	-	Viral pericarditis (Viral pericarditis)	Moderate	Unrelated	Resolved
Sitagliptin							
120004	-	87	-	Non-cardiac chest pain (Atypical noncardiac chest pain)	Severe	Unrelated	Resolved
132002	-	66	-	Bacterial pyelonephritis (E-coli pyelonephritis)	Severe	Unrelated	Resolved
	-	66	-	Escherichia bacteraemia (E-coli bacteremia)	Severe	Unrelated	Resolved
146014	-	7	-	Cerebrovascular accident ("Stroke" per subject report)	Mild	Unrelated	Resolved
161030	-	119	-	Hypertension (Arterial hypertension non-controlled)	Severe	Unrelated	Fatal
175022	-	140	-	Papillary thyroid cancer (Papillary thyroid cancer)	Moderate	Unrelated	Resolved
Pioglitazone							
102005	-	-	61	Wound infection staphylococcal (MRSA infection of right knee wound)	Severe	Unrelated	Resolved
109009	-	-	122	Coronary artery occlusion (Coronary artery occlusion)	Severe	Unrelated	Resolved
125013	-	-	122	Pancreatitis (Pancreatitis)	Severe	Unrelated	Resolved
127006	-	-	6	Angina unstable (Chest pain suggestive of unstable angina)	Severe	Unrelated	Resolved
128003	-	-	127	Cerebrovascular accident (Cerebral vascular accident)	Mild	Unrelated	Resolved
136015	-	-	23	Non-cardiac chest pain (Non cardiac chest pain)	Mild	Unrelated	Resolved
152006	-	-	83	Coronary artery occlusion (Obstruction of 4 coronary vessels)	Severe	Unrelated	Resolved
163010	-	-	147	Viral infection (Viral fever)	Moderate	Unrelated	Resolved
168009	-	-	94	Dengue fever (Dengue fever)	Severe	Unrelated	Resolved
170002	-	-	17	Pancreatitis necrotising (Necrotizing pancreatitis)	Severe	Unrelated	Resolved
	-	-	19	Sepsis (Sepsis)	Severe	Unrelated	Resolved
	-	-	19	Renal failure acute (Acute renal failure)	Severe	Unrelated	Resolved
	-	-	23	Cholelithiasis (Cholelithiasis)	Severe	Unrelated	Resolved
	-	-	26	Clostridial Infection (Feces culture positive for C-diff)	Severe	Unrelated	Resolved
	-	-	50	Pancreatic abscess (Pancreatic abscess)	Severe	Unrelated	Resolved
	-	-	62	Bile duct obstruction (Partial common bile duct obstruction)	Severe	Unrelated	Resolved

PO = per oral; QAM = once daily, in the morning; QW = once weekly; SC = subcutaneous.

In BCB108, three SAEs were reported in three (2.3%) subjects in the once weekly group and seven SAEs in five (4.1%) subjects in the twice daily group.

In Study H8O-MC-GWBR, SAEs were reported in 11 (4.7%) subjects in the exenatide-LAR group and 10 (4.5%) subjects in the glargine group. One subject in the exenatide-LAR group had oedematous pancreatitis.

In Study H8O-MC-GWDC, SAEs were reported in five (3.7%) subjects: colon cancer, angina pectoris, urinary calculus, presyncope and intervertebral disc protrusion.

In Study H8O-JE-GWBW there were no SAEs reported.

There were no deaths reported in Study ID: 2993LAR-102, Study ID: 2993LAR-103, Study BCB107, Study 2993LAR-104, Study H8O-MC-GWBR, Study H8O-JE-GWBW.

In Study 2993LAR-105, one death was reported in the once weekly group during the 30 week treatment period (acute myocardial infarction). There were no deaths reported during the 22 week follow-on phase. In Study BCB106, one subject in the sitaglitpin group died due to uncontrolled hypertension. In BCB108, there was one death in the twice daily group: myocardial infarction. In Study H8O-MC-GWDC, there were no deaths during the first 26 weeks for treatment but one subject died from colon cancer during the follow-up period (whilst continuing exenatide-LAR 2 mg once weekly).

Exenatide in combination with TZD

In Study H8O-MC-GWAP, SAEs were reported in two (2%) subjects in the exenatide group (chest pain and allergic alveolitis).No SAEs were reported in the placebo group.

In Study H8O-BP-GWBG, SAEs were reported in five (4.2%) subjects in the exenatide group and five (4.3%) SAEs were reported in the glargine group. Two of the subjects in the exenatide group reporting SAEs were also medicated with TZD.

In Study H8O-US-GWAY narratives were provide for:

- four SAEs in the exenatide group: nausea, gastro-oesophageal reflux, haemorrhoidal haemorrhage
- ten SAEs in the exenatide and rosiglitazone group: breast cancer, depression, nausea (3), ischaemic colitis, vomiting, diverticulitis, upper gastrointestinal haemorrhage, and otitis external
- four SAEs in the rosiglitazone only group: thyroid neoplasia, cellulites/osteomyelitis, peripheral oedema, and renal failure

In Study H8O-MC-GWCG, SAEs were reported in one (0.9%) subject in the exenatide group: ischaemic stroke.

In Study H8O-MC-GWAP, Study H8O-BP-GWBG and Study H8O-MC-GWCG there were no deaths reported. It is not clear whether any deaths occurred during Study H8O-US-GWAY.

Laboratory findings

Exenatide-LAR

In Study ID: 2993LAR-102 and Study H8O-MC-GWDC there were no clinically significant abnormalities in laboratory tests reported.

In Study ID: 2993LAR-103, one subject in the exenatide 7.0 mg group had elevated creatinine, total protein, uric acid, AST, ALT, Gamma-glutamyl Transpeptidase (GGT), creatinine phosphokinase (CPK) and calcium related to pre-existing gout and therapy for recurring gout. One subject in the exenatide 7.0 mg group had elevated total

bilirubin, AST, and GGT related to pre-existing alcohol liver disease and history of elevated liver function tests. There were no clinically significant abnormal haematology values.

In Study BCB107, there was a small increase in serum amylase from baseline: mean (SD) increase of 1.6 (13.31) U/L at Day 26 and 3.8 (17.11) U/L at Day 50. There was a small increase in serum lipase from baseline: mean (SD) increase of 12.2 (29.04) U/L at Day 26 and 19.6 (43.17) U/L at Day 50. Two subjects had lipase concentrations greater than three times the upper limit of normal: 447 U/L and 220 U/L.

In Study 2993LAR-104 and Study 2993LAR-105there were no clinically significant abnormalities in laboratory values reported.

In Study BCB106, mean (SD) lipase in the exenatide group increased from 42.0 (23.77) U/L on Day 1 to 61.4 (44.56) U/L at Week 14 and 60.8 (38.39) U/L at Week 26. There were no clinical manifestations of this increase. There were no other clinically significant abnormalities in laboratory tests reported.

In Study BCB108, one subject in the once weekly group had an ALT concentration of 145 U/L and another subject had a creatinine of 2.1 mg/dL. There was an increase in mean amylase and lipase concentrations in both treatment groups and the increases were greater in the once weekly group. For amylase the mean (SD) increase was 9.0 (26.46) U/L in the once weekly group and 2.6 (17.28) U/L in the twice daily group. For lipase the mean (SD) increase was 19.1 (67.50) U/L for the once weekly group and 8.3 (39.38) U/L for the twice daily. Eight subjects in the once weekly group had elevations of lipase/amylase during the study, one of whom had elevations at baseline.

In Study H8O-MC-GWBR, there was a mean (SD) increase in serum amylase from baseline of 9.38 (20.68) U/L in the exenatide-LAR group and 1.12 (15.78) U/L in the glargine group. Baseline mean (SD) amylase was 25.62 (12.93) U/L in the exenatide-LAR group and 26.53 (14.92) U/L in the glargine group. There was a mean (SD) increase in serum lipase from baseline of 16.72 (35.98) U/L in the exenatide-LAR group and -5.06 (38.75) U/L in the glargine group. Baseline mean (SD) lipase was 44.95 (24.93) U/L in the exenatide-LAR group and 48.03 (36.84) U/L in the glargine group.

In Study H8O-JE-GWBW, an increase in serum amylase was reported in two (20%) subjects in the exenatide-LAR 0.8 mg group.

Exenatide in combination with TZD

In Study H8O-MC-GWCG, there were no clinically significant changes in mean laboratory parameters. Lipase and amylase were not reported.

Safety in special populations

No additional data in special populations were included in the submission.

Immunological events

Exenatide-LAR

In Study 2993LAR-102, anti-exenatide antibodies were detected in 11 (52.4%) subjects.

In Study ID: 2993LAR-103, the frequency of anti-exenatide antibodies at study end increased with increasing dose. In the 2.5 mg group, six (42.9%) subjects had anti-exenatide antibodies at study end.

In Study BCB107, development of anti-exenatide antibodies was common (Table 20). A total of 92 (79%) of 117 subjects in the ITT Population with available data were positive

for antibodies to exenatide during the study but of these 92 subjects, ten (11%) subjects were positive for antibodies to exenatide at baseline.

Table 20. Incidence of Treatment-Emergent Antibodies to Exenatide Titers at Last Visit, Treatment, and Titer: Descriptive Statistics Population: Intent-to-Treat (N = 120)

Visit/ Treatment Group [3]	Observed Antibody Titer >=625 n (%) [4]	125 n (%) [4]	25 n (%) [4]	Titer Group [2] Any Positive n (%) [4]	Low Titer n (%) [4]	Higher Titer n (%) [4]	
Last Visit [5]							
Exenatide QW Group A (F17) (N=30)	0 (0.0)	7 (23.3)	11 (36.7)	18 (60.0)	18 (60.0)	0 (0.0)	
Exenatide QW Group B (F17) (N=30)	4 (13.3)	7 (23.3)	11 (36.7)	22 (73.3)	18 (60.0)	4 (13.3)	
Exenatide QW Group C (F28) (N=28)	3 (10.7)	8 (28.6)	7 (25.0)	18 (64.3)	15 (53.6)	3 (10.7)	
Exenatide QW Group D (F30) (N=29)	4 (13.8)	6 (20.7)	7 (24.1)	17 (58.6)	13 (44.8)	4 (13.8)	
All Subjects (N=117)	11 (9.4)	28 (23.9)	36 (30.8)	75 (64.1)	64 (54.7)	11 (9.4)	

[5] Last visit at which a reportable titer is available.

In Study 2993LAR-104, 13 (81.3%) subjects in the 0.8 mg group and nine (60.0%) subjects in the 2.0 mg group were positive for anti-exenatide antibodies by the last visit.

In Study 2993LAR-105, 65 (51.2%) subjects in the once weekly group had developed anti-exenatide antibodies by Week 30 compared with 36 (27.7%) subjects in the twice daily group. The development of antibodies did not appear to be related to AEs or to loss of effect.

In Study BCB106, treatment emergent anti-exenatide antibodies were detected at Week 26 in 92 (60.1%) subjects in the exenatide group, 74 (48.4%) subjects in the sitagliptin group and 18 (11.8%) subjects in the pioglitazone group. The antibodies did not appear to influence efficacy.

At end of Study BCB108, 79 (64.2%) subjects in the once weekly group had treatment emergent anti-exenatide antibodies, compared with 55 (49.1%) subjects in the twice daily group. There appeared to be a trend for lesser efficacy in those subjects with higher titers of anti-exenatide antibodies. Potentially immune mediated TEAEs were reported in 20 (15.5%) subjects in the once weekly group and ten (8.1%) subjects in the twice daily group.

In Study H8O-MC-GWBR injection site nodules, induration and erythema were more common in those subjects who were antibody positive (Table 21). There were 98 (43.4%) subjects who were negative for anti-exenatide antibodies at the last visit. The baseline mean (SE) HbA1c for this group was 8.26 (0.11) % and the change from baseline to Week 26 was -1.57 (0.09), p<0.001. There were 128 (56.6%) subjects who were positive for anti-exenatide antibodies at the last visit. The baseline mean (SE) HbA1c for this group was 8.39 (0.10) % and the change from baseline to Week 26 was -1.30 (0.08), p<0.001. There was a significant difference in HbA1c response between the two groups: -0.27 (-0.48 to -0.07), p=0.01.

Table 21. Incidence of TEAEs of Interest Based on Anti-Exenatide Antibody 2-Level Status at Week 26 Endpoint by Preferred Term – Intent-to-Treat Patients Using Exenatide Once Weekly (N = 233)

	AEAB 2-Level Status					
	Negative			Positive		
Preferred Term	N	n	(%)	N	n	(%)
Patients with >= 1 TEAE	98	13	(13.3)	128	25	(19.5)
Arthralgia	98	5	(5.1)	128	5	(3.9)
Arthritis	98	1	(1.0)	128	0	(0.0)
Dermatitis allergic	98	1	(1.0)	128	0	(0.0)
Injection site erythema	98	0	(0.0)	128	3	(2.3)
Injection site induration	98	0	(0.0)	128	5	(3.9)
Injection site nodule	98	2	(2.0)	128	10	(7.8)
Injection site pruritus	98	1	(1.0)	128	1	(0.8)
Injection site reaction	98	3	(3.1)	128	3	(2.3)
Joint swelling	98	1	(1.0)	128	1	(0.8)

At the end of Study H8O-JE-GWBW, anti-exenatide antibodies were detected in five (50%) subjects in the exenatide-LAR 0.8 mg group and four (44.4%) subjects in the exenatide-LAR 2 mg group.

In Study H8O-MC-GWDC of exenatide naïve subjects at enrollment: 19 (44.2%) were positive-lower titer and two (4.7%) were positive-higher titer for anti-exenatide antibodies at the last visit.

Exenatide in combination with TZD

In Study H8O-MC-GWAP, no immunologically mediated AEs were reported.

Safety related to drug-drug interactions and other interactions

TZD did not appear to interact with exenatide other than their additive effect on efficacy.

Discontinuation due to adverse events

Exenatide-LAR

In Study ID: 2993LAR-102 and Study H8O-JE-GWBW there were no discontinuations due to Adverse Events (DAEs).

In Study ID: 2993LAR-103, three subjects withdrew from study during the lead in period but only one subject (in the placebo group) withdrew from study during the once weekly treatment phase.

In Study 2993LAR-104, one subject from the placebo group withdrew from study due to an adverse event (dizziness) during the three day lead-in period.

In Study 2993LAR-105, during the 30 week treatment period, nine (6.1%) subjects in the once weekly group and seven (4.8%) subjects in the twice daily group withdrew from study because of AEs. During the 22 week follow-on phase one (0.4%) subject withdrew because of an AE. The commonest AE leading to withdrawal was nausea (n=4), followed by vomiting (n=3) (Table 22).

Table 22. Treatment-Emergent Adverse Events Leading to Withdrawal (Study 2993LAR-105; Intent-to-Treat Population [N = 295])

Subject Number	Randomized Treatment	Treatment at Onset	Days of Treatment Prior to Onset [1]		Preferred Term (Verbatim) [2]	Intensity [3]	Causality [3]	Outcome
			BYETTA	LAR				
03309	Exenatide LAR	Exenatide LAR 2 mg QW	3	100	Weight decreased (Excessive weight loss)	Severe	Related	Resolved
05302	Exenatide LAR	Exenatide LAR 2 mg QW	3	17	Paraesthesia (Worsening of tingling of feet)	Moderate	Related	Resolved
09910	Exenatide LAR	Exenatide LAR 2 mg QW	3	159	Impaired gastric emptying (Gastroparesis)	Moderate	Related	Not resolved
09913	Exenatide LAR	Exenatide LAR 2 mg QW	2	37	Vomiting (Vomiting)	Moderate	Unrelated	Resolved
09914	Exenatide LAR	Exenatide LAR 2 mg QW	3	1	Blood potassium increased (Elevated potassium)	Moderate	Related	Resolved
10802	Exenatide LAR	Exenatide LAR 2 mg QW	3	198	Myocardial infarction (Myocardial infarction)	Severe	Unrelated	Fatal
10817	Exenatide LAR	Exenatide LAR 2 mg QW	3	249	Diabetes mellitus (Worsening Type 2 diabetes)	Severe	Unrelated	Resolved
14906	Exenatide LAR	Exenatide LAR 2 mg QW	3	45	Injection site nodule (Worsening of nodules at injection site)	Severe	Related	Resolved
50903	Exenatide LAR	Exenatide LAR 2 mg QW	3	23	Malaise (General malaise)	Moderate	Related	Not resolved
50905	Exenatide LAR	Exenatide LAR 2 mg QW	3	37	Nausea (Intermittent nausea)	Mild	Related	Resolved
00604	BYETTA	BYETTA 5 mcg BID	5	-	Nausea (Nausea)	Moderate	Related	Resolved
03311	BYETTA	BYETTA 10 mcg BID	32	-	Nausea (Nausea)	Moderate	Related	Resolved
05703	BYETTA	BYETTA 10 mcg BID	31	-	Anorexia (Loss of appetite)	Moderate	Related	Resolved
05715	BYETTA	BYETTA 10 mcg BID	82	-	Vomiting (Vomitting)	Moderate	Related	Resolved
23103	BYETTA	BYETTA 5 mcg BID	1	-	Nausea (Nausea)	Moderate	Related	Resolved
50906	BYETTA	BYETTA 5 mcg BID	14	-	Regurgitation of food (Intermittent regurgitation)	Mild	Related	Resolved
50908	BYETTA	BYETTA 10 mcg BID	98	-	Vomiting (Vomiting)	Mild	Related	Resolved
55701	BYETTA	BYETTA 10 mcg BID	162	-	Abdominal pain (Abdominal pain)	Moderate	Unrelated	Resolved

Abbreviations: BID, twice daily; LAR, long-acting release; QW, once weekly.

[1] BID calculation includes lead-in study medication. The total duration of study medication exposure prior to onset is the sum of the days of BID and LAR treatment.

[2] MedDRA Version 10.1 terms.

[3] As assessed by the investigator.

In Study BCB106, DAEs occurred in ten (6.3%) subjects in the exenatide group, five (3.0%) subjects in the sitagliptin group and six (3.6%) subjects in the pioglitazone group. In the exenatide group, three subjects withdrew from study because of diarrhoea and one subject discontinued because of an injection site mass.

In Study BCB108, six (4.7%) subjects in the once weekly group and six (4.9%) subjects in the twice daily group withdrew from study because of an AE. In addition to the subject with pancreatitis, a second subject discontinued in the once daily group because of elevated serum lipase levels.

In Study H8O-MC-GWBR, DAEs occurred for twelve (5.2%) subjects in the exenatide-LAR group and two (0.9%) subjects in the glargine group. In the exenatide-LAR group, one subject withdrew from study because of pancreatitis and four discontinued because of injection site reactions.

In Study H8O-MC-GWDC, four (3%) subjects discontinued because of an AE: constipation, injection site nodule, nausea, and vomiting.

Exenatide combined with TZD

In Study H8O-MC-GWAP, 19 (15.7%) exenatide + TZD subjects and two (1.8%) placebo + TZD subjects discontinued due to AEs. In the exenatide group nausea led to discontinuation in eleven subjects and vomiting led to discontinuation in six subjects.

In Study H8O-BP-GWBG it was not possible to determine whether study withdrawal was influenced by co medication with TZD.

In Study H8O-US-GWAY withdrawal rates due to adverse events were 4.4% in the exenatide group, 10.6% in the exenatide plus rosiglitazone group and 2.2% in the rosiglitazone group.

In Study H8O-MC-GWCG, four (3.6%) subjects in the exenatide group and one (1.9%) subject in the placebo group discontinued because of AEs.

Post marketing experience

A copy of the Risk Management Plan (Revision 9) for Bydureon was provided. A total of 779 subjects were exposed to exenatide once weekly during the development program with 112 subjects exposed for more than one year. The total duration of exposure was 432.46 patient-years. To September 2009, the sponsor estimates the total exposure to exenatide twice daily was 1,362,890 patient-years.

Evaluator's overall conclusions on clinical safety

Safety conclusions for exenatide-LAR

Gastrointestinal AEs appear to occur frequently with exenatide-LAR (30% to 45% of subjects) and are predominantly nausea, vomiting and diarrhoea. Gastrointestinal side effects occurred at a similar rate to that of exenatide twice daily treatment. The incidence of gastrointestinal side effects appears to be dose related. Injection site AEs also appear to be relatively common (around 18%) but minor in severity. Hypoglycaemia is rare.

The incidence and pattern of SAEs was no more severe than that for exenatide twice weekly administration. There were few deaths reported during the development of exenatide-LAR and none appeared to be attributable to exenatide-LAR.

Pancreatitis was reported in one subject in Study BCB108 and one subject in Study H8O-MC-GWBR.[7] In Studies BCB107, BCB108 and H8O-MC-GWBR there were small increases in

[7] The sponsor commented that this is also reported with the comparators.

mean serum amylase and lipase from baseline. In Study BCB106, the mean serum lipase increased by around 50% during the study. In Study H8O-JE-GWBW increased serum amylase was reported in two (20%) subjects. In Study BCB108, in addition to the subject with pancreatitis, a second subject withdrew from the exenatide-LAR group because of elevated serum lipase.

A large proportion of subjects treated with exenatide-LAR develop anti-exenatide antibodies. In most of the submitted studies the antibodies did not appear to be associated with adverse effects or loss of efficacy. However, in Study BCB108 there appeared to be a trend towards lesser efficacy in those subjects with higher titers of anti-exenatide antibodies. In Study H8O-MC-GWBR there was a significantly greater response for HbA1c in the antibody negative group: -0.27 (-0.48 to -0.07), p=0.01. In Study H8O-MC-GWBR injection site nodules, induration and erythema were more common in those subjects who were antibody positive.

Safety conclusions for exenatide in combination with TZD

The pattern of AEs with exenatide does not appear to be modified by co medication with TZD. In Study H8O-US-GWAY there were more subjects reporting nausea as a SAE with exenatide and rosiglitazone combined than with exenatide alone treatment. This might suggest that rosiglitazone exacerbates nausea in exenatide treated subjects.

The risk of hypoglycaemia does not appear to be increased by the combination of exenatide and rosiglitazone. The risk of cardiac failure does not appear to be increased by combining exenatide with rosiglitazone. With regard to the mechanisms of action of the two drugs it is not to be expected that hypoglycaemia or cardiac failure would be more likely when the drugs are given in combination. However, the data for cardiovascular outcomes were limited in the studies of exenatide in combination with TZD.

Pancreatitis does not appear to be more common with exenatide in combination with TZD, but the data did not include measurements for plasma lipase or amylase. The studies did not contribute additional data on renally impaired patients. The studies did not contribute additional immunogenicity data.

The duration of the studies presented for this indication were all of less than 26 weeks duration. Hence there are no long term morbidity data for the combination of exenatide and TZD.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of questions to the sponsor is generated.

Pharmacokinetics

1. Does the sponsor have additional data to support the bioequivalence of exenatide-LAR-F17 produced at different manufacturing sites?
2. Have any issues with manufacturing sites been resolved?
3. Which manufacturing site will be used to supply the formulation intended for marketing in Australia as Bydureon?

Efficacy

4. With regard to exenatide in combination with TZD, are there data that examine the duration of effect prior to the need to introduce insulin?
5. Are there data that examine the optimal sequence of treatments, or treatment combinations that include exenatide and TZD?

Safety

6. With regard to exenatide-LAR:
    a. For Study 2993LAR-105 the listings of adverse reactions and laboratory test results were not provided. Were there any reports of pancreatitis in that study?
    b. In the event of a SAE, how long would the washout period be? Would the adverse effects be prolonged?
    c. Do the ongoing studies monitor serum amylase or lipase?
7. With regard to exenatide in combination with TZD:
    a. Are there data indicating whether exenatide increases the risk of adverse cardiovascular outcomes in combination with TZD?
    b. Are there data for immunogenicity for this combination?
    c. Does the sponsor have long term morbidity data for the combination of exenatide and TZD?

Questions in general

8. Does the sponsor intend to market both products (Bydureon and Byetta) concurrently, and if so, how will the two products be placed with respect to each other in the management of Type 2 diabetes?
9. Is the formulation intended for marketing as Bydureon identical to Exenatide-LAR-F17? If not, does the sponsor have bioequivalence data for the formulation intended for marketing as Bydureon and Exenatide-LAR-F17?

Clinical summary and conclusions

Clinical aspects

The sponsor has conducted development studies for prolonged release injectable formulations of exenatide. Study 2993LAR-102 and Study BCB107 indicated that the extended release formulation with the most favourable PK profile appeared to be exenatide-LAR-F17. Study H8O-JE-GWBW indicated steady state appeared to be achieved around Week 8 of treatment for both the 0.8 mg and the 2 mg dose.

Study 2993LAR-103 indicated that the pharmacokinetics of exenatide-LAR were not dose proportional, indicating that above a 5 mg dose level there was less than expected increase in AUC, C_{max} and C_{ave}. Study 2993LAR-104 indicated dose proportional PK between the 0.8 mg and 2.0 mg dose levels. However, Study H8O-JE-GWBWindicated that AUC and C_{max} were not dose proportional between the 0.8 mg and 2 mg dose levels and there was relatively greater exposure at the higher dose.

Study 2993LAR-105 indicated that exenatide formulation LAR-F17 produced at two different manufacturing sites were not bioequivalent.[8]

The PK data did not give any indication of dose-dumping, as indicated by the relative values of SD for C_{max}.

The PD data are supportive of the choice of the 2 mg dose form for exenatide-LAR. Study 2993LAR-103 indicated a plateau in effect above the 2.5 mg dose form. Study 2993LAR-104 and Study H8O-JE-GWBW indicated greater effect with the 2 mg dose form than the 0.8 mg. Maximum reduction in HbA1c was achieved at Week 10 of treatment.

Benefit risk assessment

Benefits

Exenatide-LAR

Study 2993LAR-104 was supportive of greater efficacy, with regard to HbA1c and weight, with the 2 mg dose level of exenatide-LAR than with the 0.8 mg dose level.

Study 2993LAR-105 indicated superiority for exenatide-LAR in comparison with twice daily exenatide, with regard to the decrease from baseline in HbA1c and the treatment effect was preserved over a 52 week period. There were similar effects for the two dosage forms on FPG,[9] SMPG profile and weight loss. During Study 2993LAR-105 subjects received concurrent treatment with metformin, SU, TZD, a combination of metformin and SU, a combination of metformin and TZD or a combination of SU and TZD.

Study BCB108 also indicated superiority for exenatide-LAR in comparison with exenatide twice daily by the primary efficacy outcome measure of HbA1c.[10] There were similar effects on weight and waist circumference. Subjects were concurrently treated with metformin, SU, TZD, a combination of metformin and SU, a combination of metformin and TZD, or a combination of SU and TZD. Efficacy was not influenced by concomitant antidiabetic medication.

Data were presented that supported the efficacy of exenatide when in combination with metformin. Study BCB106 demonstrated superiority for exenatide compared with sitagliptin or pioglitazone when used in combination with metformin, for the outcome measure of HbA1c. There was also better weight control in the exenatide group than either comparator. Exenatide also had better control of FSG and SMPG profile than sitagliptin.

In Study H8O-MC-GWBR exenatide was superior to glargine with respect to HbA1c in subjects concurrently medicated with metformin or metformin plus SU. Superiority was also demonstrated in the subgroup of subjects co medicated with metformin alone. Weight control was better in the exenatide group. FSG was also lower in the exenatide group. The 8-point SMPG profile was more favourable for exenatide-LAR than glargine, with higher 03:00 and morning preprandial glucose concentrations and lower evening postprandial concentrations.

Exenatide in combination with TZD

Study H8O-MC-GWAP demonstrated efficacy for exenatide in comparison with placebo in subjects treated with TZD or TZD and metformin as assessed by HbA1c. There was also superior weight control and 7-point SMPG with exenatide. Study H8O-MC-GWCG also

[8] Sponsor commented that Study 2993LAR-108 was conducted to confirm that the Ohio material was safe and efficacious.

[9] The sponsor commented that there was a better FPG response with QW than Byetta.

[10] Sponsor comment: "As well as FPG."

demonstrated efficacy for exenatide in comparison with placebo in subjects treated with TZD or TZD and metformin as assessed by HbA1c. There was also weight loss recorded in the exenatide group but not in the placebo group. Study H8O-US-GWAY was supportive of the efficacy of exenatide in combination with rosiglitazone, in comparison with both exenatide and rosiglitazone alone. Study H8O-MC-GWDC was supportive of the efficacy of exenatide-LAR in subjects treated with TZD or TZD and metformin. However, Study H8O-BP-GWBG was an open label study that did not contribute data that could be evaluated for efficacy. This study did not appear to have been designed to support the current application.

The treatment effect was clinically significant and sustained for the duration of the studies (up to 26 weeks). The patients included in the studies were typical of those who would be considered for combination antidiabetic therapies in Australia. However, the use of glargine was only as basal insulin, whereas it would more typically be used in basal bolus regimens in combination with short acting insulin. In addition, the studies did not examine the duration of effect prior to the need to introduce insulin and did not determine the optimal sequence of treatments or treatment combinations.

Risks

Exenatide-LAR

Gastrointestinal AEs appear to occur frequently with exenatide-LAR (30% to 45% of subjects) and are predominantly nausea, vomiting and diarrhoea. Gastrointestinal side effects occurred at a similar rate to that of exenatide twice daily treatment. The incidence of gastrointestinal side effects appears to be dose related. Injection site AEs also appear to be relatively common (around 18%), but minor in severity. Hypoglycaemia is rare.

The incidence and pattern of SAEs was no more severe than that for exenatide twice weekly. There were few deaths reported during the development of exenatide-LAR and none appeared to be attributable to exenatide-LAR.

Pancreatitis was reported in one subject in Study BCB108 and one subject in Study H8O-MC-GWBR[7]. In Studies BCB107, BCB108 and H8O-MC-GWBR there were small increases in mean serum amylase and lipase from baseline. In Study BCB106 mean serum lipase increased by around 50% during the study. In Study H8O-JE-GWBW increased serum amylase was reported in two (20%) subjects. In Study BCB108, in addition to the subject with pancreatitis, a second subject withdrew in the exenatide-LAR group because of elevated serum lipase.

A large proportion of subjects treated with exenatide-LAR develop anti-exenatide antibodies. In most of the submitted studies the antibodies did not appear to be associated with adverse effects or loss of efficacy. However, in Study BCB108 there appeared to be a trend towards lesser efficacy in those subjects with higher titers of anti-exenatide antibodies. In Study H8O-MC-GWBR there was a significantly greater response for HbA1c in the antibody negative group: -0.27 (-0.48 to -0.07), p=0.01. In Study H8O-MC-GWBR injection site nodules, induration, and erythema were more common in those subjects who were antibody positive.

Risks for exenatide in combination with TZD

The pattern of AEs with exenatide does not appear to be modified by co medication with TZD. In Study H8O-US-GWAY there were more subjects reporting nausea as a SAE when given exenatide and rosiglitazone combined than when given exenatide alone. This might suggest that rosiglitazone exacerbates nausea in exenatide treated subjects.

The risk of hypoglycaemia does not appear to be increased by combining exenatide and rosiglitazone. The risk of cardiac failure does not appear to be increased by combining exenatide with rosiglitazone. With regard to the mechanisms of action of the two drugs it is not to be expected that hypoglycaemia or cardiac failure would be more likely when the

two drugs are given in combination. However, the data for cardiovascular outcomes were limited in the studies of exenatide in combination with TZD.

Pancreatitis does not appear to be more common with exenatide in combination with TZD but the data did not include measurements for plasma lipase or amylase. The studies did not contribute additional data regarding patients with renal impairment. The studies did not contribute any immunogenicity data.

The duration of the studies presented for this indication were all of less than 26 weeks duration. Hence, there are no long term morbidity data for the combination of exenatide and TZD.

Balance

Exenatide-LAR

The risk benefit assessment is in favour of exenatide-LAR.

Exenatide in combination with TZD

The risk benefit assessment is in favour of exenatide in combination with TZD.

Conclusions

It was recommended that both parts of the present application should be approved.

Recommended conditions for registration

The sponsor should provide safety updates from the ongoing studies when the data becomes available.

The evaluator also proposed changes to the PI but these discussions are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk management plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Identified important risks

- Pancreatitis
- Acute Renal Failure
- Rapid weight loss

Potential important risks

- Anti-Exenatide Antibodies (focus on anaphylactic-type reactions)
- Cardiac Events
- Malignant neoplasm (focus on pancreatic cancer and thyroid neoplasm's)

Important missing information

- Adolescents with Type 2 diabetes
- Pregnant women
- Very elderly (>75 years old)
- Combination with Thiazolidinediones
- Patients with severe gastrointestinal disease (once weekly)
- Patients with varying degrees of impaired renal function (once weekly)
- Patients with hepatic impairment (once weekly)

OPR reviewer comment:

The sponsor states that all the identified and potential risks were initially identified through the clinical development program or post marketing experience with exenatide twice daily (Byetta).

Two additional potential issues where considered by the evaluator with respect to the need for pharmacovigilance (PhV) and risk minimisation activities:

1. The interaction of exenatide with thiazolidinediones.

The clinical evaluation stated that:

> *"TZD did not appear to interact with exenatide other than their additive effect on efficacy".*

The evaluator has asked the following questions with regard to this combination:

- *"Are there data indicating whether exenatide increases the risk of adverse cardiovascular outcomes in combination with TZD?*
- *Are there data for immunogenicity for this combination?*
- *Does the Sponsor have long-term morbidity data for the combination of exenatide and TZD?"*

2. The potential for additional or exacerbated risks associated with the new formulation of once weekly dose?

The clinical evaluation stated that:

> *"The incidence and pattern of SAEs was no more severe than that for exenatide twice weekly".*

Pharmacovigilance plan

The completed premarket activities have not been assessed by the evaluator, as they will not contribute to postmarket pharmacovigilance in Australia.

All identified and potential risks will utilise the Periodic Safety Update Report (PSUR), which is considered an appropriate and routine pharmacovigilance activity[11]. The sponsor identifies that PSURs for exenatide twice daily (Byetta) are conducted six monthly in the EU and US, and will continue to be submitted every 6 months in the US and annually in the EU. The sponsor is requested to clarify the TGA timelines for PSUR submission, if known at this stage, and whether this will include Bydureon as well.

Continuing targeted surveillance for the safety concerns identified above is considered appropriate.

It is proposed that events of pancreatitis, acute renal failure, risks associated with anti-exenatide antibodies, and malignant neoplasm's that arise from the prospective cardiovascular outcome study will be analysed to inform the Identified risk, however there is no information on how this will be done. The sponsor is requested to provide further details on the methodology for this proposal, for example consider whether the events will simply be included in the ongoing surveillance analysis, or whether they will be dealt with separately in a specific analysis. A justification for the methodology should be provided, as well as a brief discussion on how this will contribute to the management of safety for this medicine.

Additional pharmacovigilance activities for specific safety concerns are discussed below.

1. Pancreatitis

The expedited reporting of cases and use of an international expert advisory panel to review evolving aggregate data on pancreatitis have evolved from postmarketing experience with Byetta (exenatide twice daily) formulation. It is agreed that these are appropriate activities to continue to identify any change in risk of pancreatitis associated with the extension of indication and the new formulation.

It is unclear what the "new once weekly" clinical studies are in which the sponsor will be measuring serum amylase and lipase. Furthermore, the amount of new information this will provide and how this information will be used to inform the epidemiology and management of pancreatitis risk is not discussed. This would benefit from clarification by the sponsor.

The mechanistic study proposed to evaluate the potential change in gallbladder emptying (Study H8O-EW-GWDP) is based on the hypothesis that the mechanism for a causal relationship between exenatide and pancreatitis might involve an increase in tone in the sphincter of Oddi. The RMP states that the new study will be conducted in the US once the clinical trial protocol has been approved by the FDA, and progress updates will be provided with each review of the RMP. While the evaluator has no objection to this study being conducted, it is not clear how the outcomes from this study will inform or assist in ensuring the safety of patients receiving exenatide. The RMP would benefit from a discussion by the sponsor on this issue, as well as including the finalised approved protocol and a mechanism and timeline by which progress updates on the study will be provided to the TGA (for example, through PSUR).

[11] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

2. Anti-exenatide antibodies

The methodology of this 3 year study (Study H8O-EW-GWBE) has not been assessed as it started in the premarket phase. It is anticipated that the final study report will be produced in the third quarter of 2011, and the commitment was made to communicate any important or new safety signals earlier (estimated start date of the study by the evaluator is early 2008). No interim reports or communications about safety signals have been provided, and the sponsor is requested to confirm that no important or new safety issues have arisen from this study to date. As part of the RMP requirements, the sponsor is requested to provide a copy of this final report, which includes a summary of how this information influences the safety specifications, pharmacovigilance and risk minimisation activities in the RMP.

3. Cardiac events

The sponsor is conducting a prospective, randomised, place controlled long-term clinical trial (GWDQ [BCB109] (EXSCEL)) to evaluate cardiovascular outcomes in subjects with Type 2 diabetes randomised to standard of care diabetes regimens with or without exenatide once weekly. Study start is anticipated by mid 2010 and completion estimated for mid 2017. It is states that the protocol is final and has been approved, however it is not stated who has provided this approval. The sponsor identifies that this study aims to address the safety concerns about cardiac events expressed in the initial Marketing Authorisation Application (MAA) submission, however it is unclear what concerns and which MAA in particular this is referring to. The sponsor was requested to provide the protocol to the TGA, indicating where and when approval was obtained, and to provide a brief discussion about the cardiac event safety concerns it seeks to address, linking the concerns to how this study will address them.

Furthermore, in light of the FDAs initial negative decision regarding a similar application for the new dosage formulation, the sponsor is requested to provide further information and discuss this issue in the Australian context particularly with respect to the implications from a RMP perspective.

4. Malignant neoplasm's

It is unclear what the "new once weekly" clinical studies are in which the sponsor will be screening and monitoring calcitonin levels. Furthermore, the amount of new information this will provide and how this information will be used to inform the epidemiology and management of malignant neoplasms is not discussed. This needs to be clarified by the sponsor.

Additional pharmacovigilance activities are proposed/in place for 2 'Missing information' safety concerns as follows:

5. Adolescents

The continuation of study (H8O-MC-GWBQ) to assess safety and efficacy of exenatide twice daily in adolescents with Type 2 diabetes, initiated in June 2008, has had very slow enrolment with 42 of the goal 195 patients randomised at July 2010. As this protocol has been finalised and the study begun before this application the protocol will not be evaluated by the RMP evaluator. However, as the proposed indication for Byetta, the twice daily formulation, is for use "in patients" (that is not restricted to adults) the information from this study will be important in monitoring this missing information. The sponsor is therefore requested to provide a copy of the final protocol so that the evaluator can be aware of the additional information that will be available, the limitations and strengths of this information, and how the sponsor will use this information in practice. In addition, the sponsor is requested to provide the timelines and mechanisms by which updates on this study progress will be provided to the TGA (this is recommended to be through the PSUR).

There is no further information provided regarding the proposed study to assess safety and efficacy of exenatide once weekly in adolescents with Type 2 diabetes. However, the indication for Bydureon (once weekly formulation) is for use "in *adults*", and so it is assumed that the information provided by this study will support an application to extend the indication of use of the weekly formulation in adolescents. It is noted that the protocol is still in draft; however the sponsor is requested to provide the draft study protocol as it stands, to clarify when and where this study will take place and the timelines and mechanisms by which updates will be provided to the TGA (recommended to be through the PSUR).

6. Pregnant women

The sponsor states that the study protocol was provided in the 30 November 2007 RMP version, which has not been submitted to the TGA as far as the evaluator was aware. The RMP identifies that the pregnancy registry has a goal to recruit 200 exenatide and 200 non exenatide drug exposed pregnant women with Type 2 diabetes, was implemented in December 2007 and currently has three patients enrolled. This is a very low number and raises the question of how well the registry will be able to supplement this missing information. The sponsor is requested to provide the study protocol to the TGA and specify which countries are involved in the register, highlighting the involvement and implications in Australia, and also address the question of the registry's ability to provide supportive data in this area. It is also stated that summary updates will be provided with each PSUR or as needed if significant safety signal is detected, and assurance is requested that this information will be provided to the TGA and the format and/or mechanisms identified.

In reviewing the size and relevance of the risk, and the information included in the product information document, the evaluator agreed there is no specific need for additional PhV activities for the following 'Missing information' safety concerns:

- very elderly,
- severe gastrointestinal disease,
- degrees of renal function impairment,
- hepatic impairment and
- use in combination with TZDs.

Risk minimisation activities

The sponsor identifies that routine risk minimisation activities are sufficient for most of the safety concerns as follows:

- Pancreatitis,
- Acute renal failure,
- Rapid weight loss,
- Anti-exenatide antibodies (focus on anaphylactic-type reactions),
- Adolescents,
- Pregnant women,
- Very elderly,
- Severe gastrointestinal disease,
- Degrees of renal function impairment, and

- Hepatic impairment.

The sponsor has identified that risk minimisation activities are not applicable for the following safety concerns:

- Cardiac events; as no association has been identified between exenatide and cardiac events to date,
- malignant neoplasm's; as no association has been identified between exenatide and malignant neoplasm's to date, and
- the use in combination with TZDs; as no differential adverse event profile has been found for patients using exenatide in combination with TZDs.

OPR reviewer comment:

As discussed above there was a recent requirement from the FDA for additional PhV and risk minimisation activities (October 2009) for the risks of pancreatitis and acute renal failure. The submitted RMP presents this information, making specific reference to the Risk Evaluation and Mitigation Strategy (REMS) agreed by the FDA which had two goals:

1. Pancreatitis: to mitigate the potential risk of undiagnosed and/or complicated pancreatitis by raising the level of patient and Health Care Professionals (HCPs) awareness of pancreatitis, and inform HCPs of the importance of timely evaluation of patients for possible pancreatitis; and
2. Renal Failure: to mitigate the potential risk of renal failure by raising the level of patient and HCP awareness of renal impairment and to use caution in treating patients with renal impairment.

To implement this, a medication guide and ongoing communication plan were instigated in the US at end 2009. A communication plan is neither identified nor discussed by the sponsor in the submitted RMP. The RMP does refer to education of HCPs in the section discussing medication errors; however there are no specifics provided about a communication plan and the safety concerns are not mentioned. The sponsor is requested to provide further comment on the need for a communication plan as an additional risk minimisation activity in Australia, given the FDA requirements and the importance they have placed on education to minimise medication errors.

Concerns have been raised about the potential for cardiac events with the use of Byetta/Bydureon, as indicated by an initial negative opinion by the FDA regarding a similar application for the additional dosage form (once weekly) and the sponsors proposed study to evaluate cardiovascular outcomes associated with exenatide exposure. This appears inconsistent with the justification that risk minimisation activities are not applicable to cardiac events (and in effect cardiac risks are not mentioned in the Summary of Product Characteristics (SmPC)/PI). The sponsor was requested to provide a further argument for this justification, addressing the above comments.

While no association has been identified between exenatide and malignant neoplasms, one of the regulatory decisions by FDA in October 2009 was for further postmarketing requirements to assess the potential risk of thyroid neoplasms in particular. The sponsor is requested to provide further argument for risk minimisation activities for this safety concern not being applicable, with particular reference to the lack of content in the PI.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application.

The OPR recommended that the implementation of the Risk Management Plan (Bydureon) version 12 (revision 11), dated 22 July 2010, was imposed as a condition of registration in

Australia with the following changes, additions and considerations that are accepted or agreed to by the OPR: The sponsor provide with respect to:

1. *Pharmacovigilance activities.*
    a. further details on the methodology for the analysis of adverse events (pancreatitis, acute renal failure, risks associated with anti-exenatide antibodies, and malignant neoplasm's) that arise from the prospective cardiovascular outcome study (include justification, discussion on contribution to management of safety),
    b. further information on what is meant by "new once weekly" clinical studies to measure serum amylase, lipase, and calcitonin levels, and explain how this information will be used to inform the epidemiology and management of pancreatitis risk and malignant neoplasm risk,
    c. the finalised approved protocol for Study H8O-EW-GWDP (mechanistic study of gallbladder emptying), an indication of how the outcomes from this study will inform the management of patient safety, and a mechanism and timeline by which progress updates will be provided to the TGA (recommended through PSUR),
    d. confirmation that no important or new safety issues have arisen from Study H8O-EW-GWBE (Anti-exenatide antibodies) to date, and a timeline and mechanism for the provision of the final to the TGA,
    e. the finalised protocol for the cardiac prospective clinical trial (GWDQ [BCB109] (EXSCEL)) to the TGA, indicating when and by whom approval was obtained, and a brief discussion about the cardiac event safety concern this seeks to address,
    f. discussion regarding the FDA concerns on the risk of cardiac events in the Australian context, and implications from an RMP perspective,
    g. the finalised protocol for continuing Study H8O-MC-GWBQ (safety and efficacy of exenatide twice daily in adolescents), a discussion of how this information will be utilised/implemented, and the timelines and mechanisms by which updates on this study progress will be provided to the TGA (recommended through PSUR),
    h. the draft study protocol (assess safety and efficacy of exenatide once weekly in adolescents) as it stands, clarify when and where this study will take place, and the timelines and mechanisms by which updates will be provided to the TGA (recommended through the PSUR), and
    i. the study protocol for the pregnancy registry, specify which countries are involved with specific mention of the involvement and implications in Australia, the timelines and mechanisms by which summary updates will be provided to the TGA, and discussion ability the ability of registry to supplement missing information given the poor enrolment to date.
2. *Risk Minimisation activities.*
    a. further argument for the justification that risk minimisation activities are not applicable to cardiac events,
    b. further argument for the justification that risk minimisation activities are not applicable for malignant neoplasm's,
    c. consideration of the following PI issues
    d. inclusion of wording in the PI addressing the potential risk of cardiac events,
    e. inclusion of wording in the PI addressing the potential risk of malignant neoplasm's, particularly thyroid neoplasm's,

f. consistency in the indications for Byetta and Bydureon with respect to reference for use "in adults" versus "in patients",

g. an updated RMP, or Australian specific annex, to adequately reflect the Australian context or discusses differences between the EU and Australian circumstance,

h. additional information outlining Australian's role in the risk minimisation activity to improve user friendliness of the pen delivery devices, and how any changes will be implemented in Australia,

i. information and results from the usability study, including details on size of the study and criteria used to measure success,

j. comment on how information on adverse issues associated with use of this kit in Australia will be collected and utilised to inform further action as necessary,

k. evidence that supports the decision to not include a safe sharps disposal device within the kit, and that leaving this up to the patient to seek advice from their HCP is adequate to minimise the risk associated with sharps disposal,

l. advice on whether there are any specific medication errors that may arise with this product (such as potential for error in transiting from a twice daily to once weekly injection for users), and

m. further comment on the need for a communication plan as an additional risk minimisation activity in Australia, given the FDA requirements and the importance placed on education to minimise medication errors, and details of the communication plan if appropriate (a communication plan is alluded to in the RMP).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator's mentioned that Bydureon is an extended release microsphere formulation of exenatide and is supplied in a single dose kit containing a vial of powder, a prefilled syringe of diluent, a vial connector and two needles (one spare).

The evaluator mentions that all outstanding chemistry and quality control issues have been resolved. The proposed shelf life for exenatide powder is 24 months at 2-8^{0}C, which includes a patient in- use (unsuspended) duration of up to 4 weeks at 30^{0}C. The stability data support this.

The evaluator discussed the biopharmaceutic studies. It was mentioned that Study BCB 107 is the only single dose study conducted with the proposed delayed release formulation and the immediate release product. The plasma concentration profiles are included in the Figure 2 above. The results indicate a multiphasic release over 10 week period. The sponsor interprets this as three peaks relating to the pharmaceutical property of the formulation; this cannot be verified as there was significant individual variability in the products release.

The results also indicated an initial burst release with a C_{max} of 200 pg/mL which is less than 1% of the overall AUC. There was a gradual increase seen over 6 to 7 weeks, after which there was minimum peak to trough fluctuation.

The evaluator also states that Study LAR 105, which assessed the comparability of batches, showed that the batches produced at the commercial site were not equivalent to the drug development product batches. *In relation to this, the sponsor should state in its pre Advisory Committee on Prescription Medicines (ACPM) response, in which clinical trial (s) each of the batches were used.*

Another issue of concern was that Study BCB 106 which examined the bioequivalence of different sites of subcutaneous injection, (upper arm, abdomen and thigh) showed ratios of plasma concentrations outside the normally accepted limits (0.8-1.25) for bioequivalence.

This submission was considered at the 141th meeting of PSC. The committee concluded that the submission was not acceptable on biopharmaceutic grounds (Recommendation 2234).

The evaluator concluded that the "acceptability of formulations from the proposed manufacturing sites must rely of clinical rather than biopharmaceutic data".

Nonclinical

The nonclinical data set relates to the new long acting formulation (LAR) of exenatide (Bydureon) only.

The evaluator mentioned that the anti-diabetic activity for this formulation was demonstrated in a "relevant rat model". Decrease in glycaemic and lipidemic indices, increased insulin sensitivity and enhanced beta cell function were observed 28 days after a single subcutaneous (SC) dose.

The evaluator considered the lack of secondary and safety pharmacology studies acceptable, based on previously submitted data.

The pharmacokinetic studies confirmed extended absorption (over weeks) after a single SC injection. Relative bioavailability of exenatide-LAR compared to exenatide-IR (immediate release) was estimated to be 63% in rats and 23% in monkeys. This is based on cross-study comparisons. Anti-exenatide antibodies were observed in the repeat dose studies in rats and monkeys. There were no toxicological consequence of antibody formation; however, there was, generally, an increase observed in exenatide exposure.

The lack of acute dose toxicity studies is considered acceptable.

The evaluator mentions that the repeat dose toxicity studies in rats (4 months) and monkeys (9 months) did not identify any novel toxicities at exposures 45-50 times those anticipated clinically (based on AUC). Local injection site reactions (both inflammatory and foreign body reactions) were observed in the active and placebo (microsphere) controlled groups. There were partial to complete resolution of these events reported and these reactions were considered as "expected" reactions of poly D,L-lactide-co-glycolide, a microsphere product.

Exenatide-LAR was not found to be genotoxic.

The two year carcinogenicity study in rats showed an increased incidence of thyroid C-cell neoplasia; this was seen with all doses of exenatide-LAR at no safety margin to clinical exposure (the relative exposure based on AUC was ≥ 3.4). This is consistent with involvement of continuous activation of GLP-1 receptors. It is noted that this was different to the observation with immediate release (IR) formulation where more marginal effects on thyroid C-cell proliferation was observed. The evaluator mentions that the potential clinical relevance is diminished as the 9 month study in monkeys using doses yielding high margins of clinical exposure (≤45 times) did not show proliferative effects on the thyroid. The RMP (see below) addresses potential safety concerns on thyroid tumours.

No reproductive studies were conducted and this was considered acceptable.

Several PI amendments were recommended.

Clinical

A full data set was submitted for exenatide-LAR. Clinical data were submitted for extension of indication for exenatide.

Exenatide-LAR (Bydureon):

Pharmacokinetics

This relates to the extended release formulation.

Five studies (2993LAR-102, 2993LAR-103, BCB 107, 2993LAR-104 and H80-JE-GWBW) are discussed under *Clinical Findings* above. The formulation proposed for marketing was used.

A summary of the studies extracted from the European Public Assessment Report (EPAR) is shown in Table 24.

Table 24. Studies providing clinical pharmacology data regarding the exenatide once weekly F17 formulation [1]. [Figure 3 in EPAR].

			Number of Subjects	
Study Identifier Study Design	Exenatide Once Weekly Dosing/Duration	Study Sample	Intent-to-Treat	Exenatide Once Weekly Treated
Clinical Pharmacology (Single-Dose) Studies				
2993LAR-102 Phase 2, randomized, open-label	Single SC injection: 2.5 mg/ 8-week observation period	Healthy subjects	21	10 [3], [8]
2993LAR-103 Phase 2, randomized, single-blind [2], placebo-controlled	Single SC injection: 2.5, 5, 7, or 10 mg/ 12-week observation period	Type 2 diabetes	62	47
BCB107 Phase 1, open-label	Single SC injection: 8 or 10 mg/ 101-day observation period	Healthy subjects	120	60 [3]
Placebo-Controlled Efficacy and Safety Studies with Pharmacokinetics and Pharmacodynamics				
2993LAR-104 Phase 2, randomized, double-blind, placebo-controlled	Weekly SC injections: 0.8 mg or 2 mg/ 15-week treatment period and 12-week follow-up period	Type 2 diabetes	45	31
H8O-JE-GWBW Phase 2, randomized, double-blind, placebo-controlled	Weekly SC injections: 0.8 mg or 2 mg/ 10-week treatment period and 11-week follow-up period	Japanese subjects, Type 2 diabetes	30	20

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

[8]: N excludes one subject who withdrew after receiving lead in exenatide BD and before receiving once weekly.

The following findings were made by the clinical evaluator;

1. Two formulations were developed: F16 and F17. Whilst the pharmacokinetics was similar in both formulations, F17 was more “favourable to sustained release formulation.

2. A dose ranging (2.5, 5.0, 7.0 and 10.0 mg) single dose study (**LAR 103**) revealed that AUC, C_{max} and C_{avg} were not dose proportional above the 5 mg dose level.
3. The study (LAR 104) comparing 0.8 mg versus 2 mg over a 15 week treatment period showed that plasma concentrations were 2.5 times higher in the 2.0 mg group. AUC and C_{max} were also 2.5 times higher.
4. Study GWBW showed that steady state was achieved in 8 weeks. There was greater plasma exposure following treatment with the 2 mg than the 0.8 mg dose.

It should be noted that the evaluator mentions the PK assessment from the follow on phase of Study LAR-105. Exenatide formulation (F 17) from two manufacturing sites was not bioequivalent. The initial release characteristics were similar (see *Sponsor's response* below).

Pharmacodynamics obtained from the above mentioned studies (LAR 103, LAR 104 and GWBW) are discussed under *Clinical Findings* above. There were no significant differences in terms of HbA_{1c} with the doses tested. However, there was a clear inverse relationship with FPG (LAR 103). The evaluator mentioned that the changes in FPG and HbA_{1c} supported the 2 mg dose over the 0.8 mg dose. In Study 104, the reduction in FPG to 6.93 mmol/L is more drastic than with the immediate release product.

Dose finding studies

One study, 2993 LAR-104 is discussed. The decrease in HbA_{1c} was greater in response to the 2 mg dose than the 0.8 mg dose. The plasma concentration of exenatide was less following a 0.8 mg dose than a 10 µg bd dose. Thus, the 2 mg dose was chosen for the Phase III studies.

Efficacy studies

There were four comparator controlled studies submitted. Studies LAR 105 and BCB 108 compared exenatide-LAR to exenatide BD in subjects with Type 2 diabetes treated with oral anti-diabetic therapy or diet and exercise alone. Study BCB 106 compared exenatide-LAR to sitagliptin and pioglitazone in subjects with Type 2 diabetes mellitus on metformin treatment and Study GWBP used insulin glargine as comparator in subjects with metformin or metformin and sulfonylurea (SU).

Exenatide (Byetta controlled studies):

Two studies, LAR 105 and BCB 108 were discussed.

Study LAR 105 was a multicentre randomised open label study of 52 weeks duration. Patients with Type 2 diabetes mellitus treated with diet modification and exercise alone or in combination with 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 were eligible to participate and t*he patient groups for which exenatide is registered in Australia, (except for TZDs).* The study treatments were exenatide-LAR 2 mg once weekly by SC or exenatide (Byetta) 5 mg twice daily for 4 weeks followed by 10 mg twice daily by SC injection for 30 weeks. At the end of this period those on exenatide (Byetta) were switched to the once weekly regimen.

The primary efficacy endpoint was the change in HbA1c from baseline to Week 30. There were several secondary endpoints including those relating to HbA_{1c}, fasting glucose and body weight. The study was a non inferiority study and the margin of non inferiority (HbA_{1c}) was a difference not greater than 0.4%. Sample size calculations are described under *Clinical Findings* above.

Results: Some 303 subjects were randomised and 295 of these were included in the ITT group. Baseline demographics were similar between groups. The mean duration of

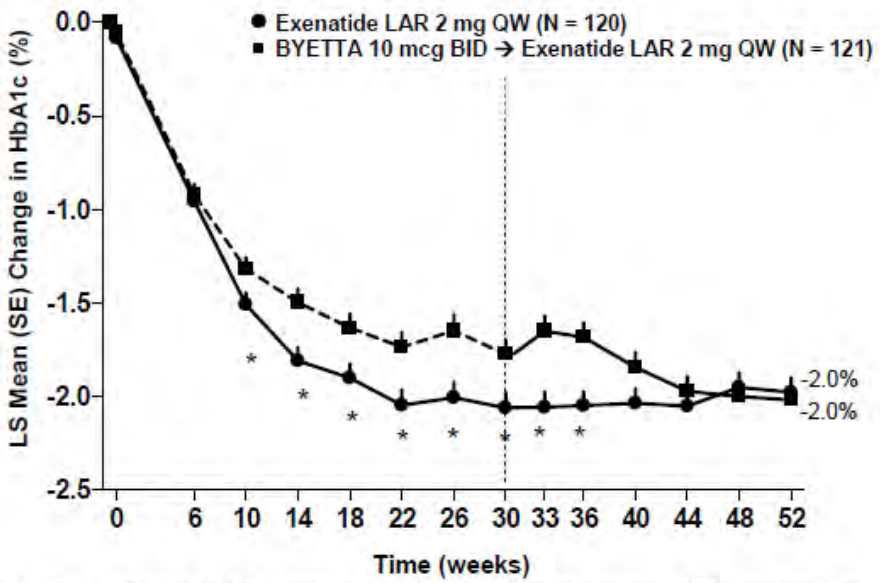
diabetes mellitus was 6.2 years and HbA_{1c} was 8.3%. The results are summarised in Table 25 and Figure 11 below.

Table 25. Efficacy results.

Group	HbA1c (%)	FPG (mmol/L)	Body weight (kg)
Exenatide-LAR (n=148)	-1.9 (0.1)*	-2.3 (0.2)*	-3.7 (0.5)
Exenatide (bd) 10mcg (n=147).	-1.5 (0.1)	-1.4 (0.2)	-3.6 (0.5)

*- p<0.05 (between groups).

Figure 11. LS Mean (SE) Change in HbA1c (%) from Baseline to Week 52 b



Abbreviations: BID, twice daily; LAR, long-acting release; LS, least squares; QW, once weekly; SE, standard error.

Notes: Mean baseline HbA1c was 8.2% and 8.3% for the BYETTA and exenatide LAR groups, respectively.
- Vertical dashed line indicates the timing of the switch from BYETTA to exenatide LAR.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

*p <0.05, exenatide LAR versus BYETTA→exenatide LAR.

Study BCB 108 was similar in design to the previous study. It was, however, only 24 weeks in duration.

In this study 254 subjects were randomised: 129 to exenatide-LAR and 125 to Byetta. The demographics were similar in both groups except for the percentage of subjects treated with TZDs; a higher percentage (15.5%) was included in the exenatide-LAR group than the Byetta group (8%). The mean duration of diabetes mellitus was 7 years and the mean HbA_{1c} was 8.4 years.

The primary efficacy endpoint indicated non inferiority relating to the PP population and superiority with the ITT population (see Table 6 above).

Comments: These two studies included the study treatment to a background of oral antidiabetic medications. Based on the clinical evaluator's report, it is not possible to

ascertain whether exenatide was added to maximum tolerated doses of other agents. *The sponsor should provide, in its pre-ACPM response a summary of the doses of anti-diabetic agents in each group, for each of these studies.*

Study 108 reported greater weight decrease (-2.3 versus -1.4 kg) at Week 24. The effect in HbA_{1c} was sustained to Week 52. Switching from exenatide to the long acting preparation produced some initial increase in HbA_{1c} which then decreased to levels observed with continuous LAR treatment.

Add on study to metformin: Exenatide versus sitagliptin or pioglitazone

Study 106 was a Phase IIIb, randomised, double blind comparator controlled three arm study with a 26 week treatment period of exenatide-LAR (2mg SC) versus sitagliptin (100 mg) or pioglitazone (45 mg). There is also a single arm, open ended assessment using exenatide-LAR for a further 26 weeks that is currently ongoing.

Those on stable treatment of metformin for a minimum of two months, with HbA_{1c} 6.5% to 10.5% were eligible to participate. Other inclusion and exclusion criteria are listed under *Clinical Findings* above. The primary efficacy endpoint was the change in HbA_{1c} from baseline to end of treatment (26 weeks). Change in body weight, waist and hip circumference, fasting and post prandial glucose, fasting lipid concentration were some of the secondary efficacy endpoints.

A total of 514 subjects were randomised to treatment group: 170 to exenatide, 172 to sitagliptin and 172 to pioglitazone. Of note the mean duration of diabetes was 5.7 years and the mean HbA1c was 8.5%.

Refer to Table 7 above.

The changes were statistically significant, favouring exenatide-LAR. The treatment effect was not influenced by country or HbA_{1c} stratum at baseline.

The change in weight from baseline was as follows: the LS Mean (95% CI) change from baseline in weight was -2.3 (-2.9 to -1.7) kg for exenatide, -0.8 (-1.4 to -0.1) kg for sitagliptin (p=0.0002) and 2.8 (2.26 to 3.4) kg for pioglitazone (p<0.0001). Similarly, there were decreases in mean hip and waist circumference in the exenatide group but no change in this measurement noted in the sitagliptin group. In contrast, increases in mean hip and waist circumference were noted in the pioglitazone group.

Add on to metformin-Lantus controlled study

Study H80-MC-GWBR was a multicentre open label randomised study of 26 weeks duration comparing exenatide-LAR with glargine. Those with HbA_{1c} of 7.1% and 11%, taking stable dose of >1500 mg of IR metformin (for three months) or extended release metformin (8 weeks) were eligible to participate. Other inclusion and exclusion criteria are discussed by the clinical evaluator above.

Those randomised to the glargine group were instructed to increase insulin doses 2-4 IU when fasting plasma glucose (FPG) > 5.5 mmol/ L for three consecutive days. If FPG was low a regimen was also in place to reduce insulin dose.

The primary efficacy variable was change in HbA_{1c}. The secondary endpoints were similar to those in previous studies.

The evaluator mentioned that 467 subjects were randomised to treatment: 233 to exenatide-LAR and 234 to glargine. A total of 209 (in each group) completed the study. These subjects had diabetes for 7.9 years and the baseline HbA_{1c} was 8.3%.

The following table summarises the results observed at Week 26. The table has been extracted from the European Public Assessment Report (EPAR) for this product.

Table 26. Efficacy results

Treatment group	HbA_{1C}: %	Fasting glucose: mmol/L	Body weight: kg
Exenatide-LAR n=223	-1.5 (0.05)*#	-2.1 (0.2)*#	-2.6 (0.2)*#
Glargine QD n=223	-1.3 (0.06)#	-2.8 (0.2)#	1.4 (0.2)#

p<0.05, exenatide-LAR versus comparator; #p <0.05, for the difference within treatment

The evaluator mentioned that, for the primary endpoint of HbA_{1c} "exenatide-LAR was superior to glargine at all time points as demonstrated by the 95% CI for the difference in HbA_{1c} between treatments (exenatide-LAR – glargine) being less than 0. At Week 26 the treatment difference (95% CI) was -0.16 (-0.29 to -0.03) %, p=0.017. Superiority was also demonstrated in the subgroup of subjects not treated with SU: treatment difference (95% CI) at Week 26 -0.18 (-0.34 to -0.02) %, p=0.031".

There were significant difference favouring exenatide-LAR over glargine in relation to fasting glucose and body weight. Results relating to other secondary endpoints are discussed by the clinical evaluator above.

Supportive study

The evaluator also discussed a supportive study, H80-MC-GWDC. This was a multicentre, uncontrolled open label study where exenatide-LAR was added to TZDs or TZDs + metformin.

A total of 134 subjects were enrolled in the ITT population. The baseline HbA1c was 7.23%. The mean duration of diabetes was 6.22 years.

The evaluator mentioned that in the complete subject group, the mean (95% CI) change from baseline in HbA1c was -0.83 (-0.99 to -0.67) %, p<0.001.

The overall efficacy summary (HbA_{1c}) from these studies is shown in Table 27 below (table extracted from the EPAR for this product).

Figure 27. LS Mean (SE) change in HbA1c (%) from baseline to Week 52 by treatment; Study 2993LAR-105, 52 week Evaluable Analysis Set (N=241). [Figure 7 in EPAR].

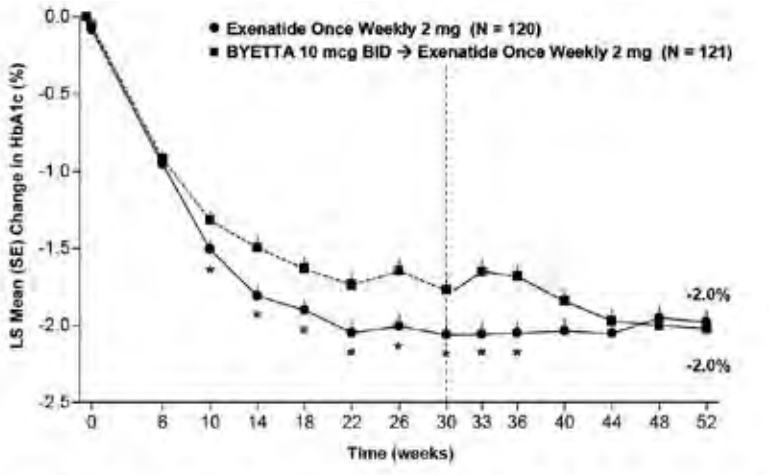
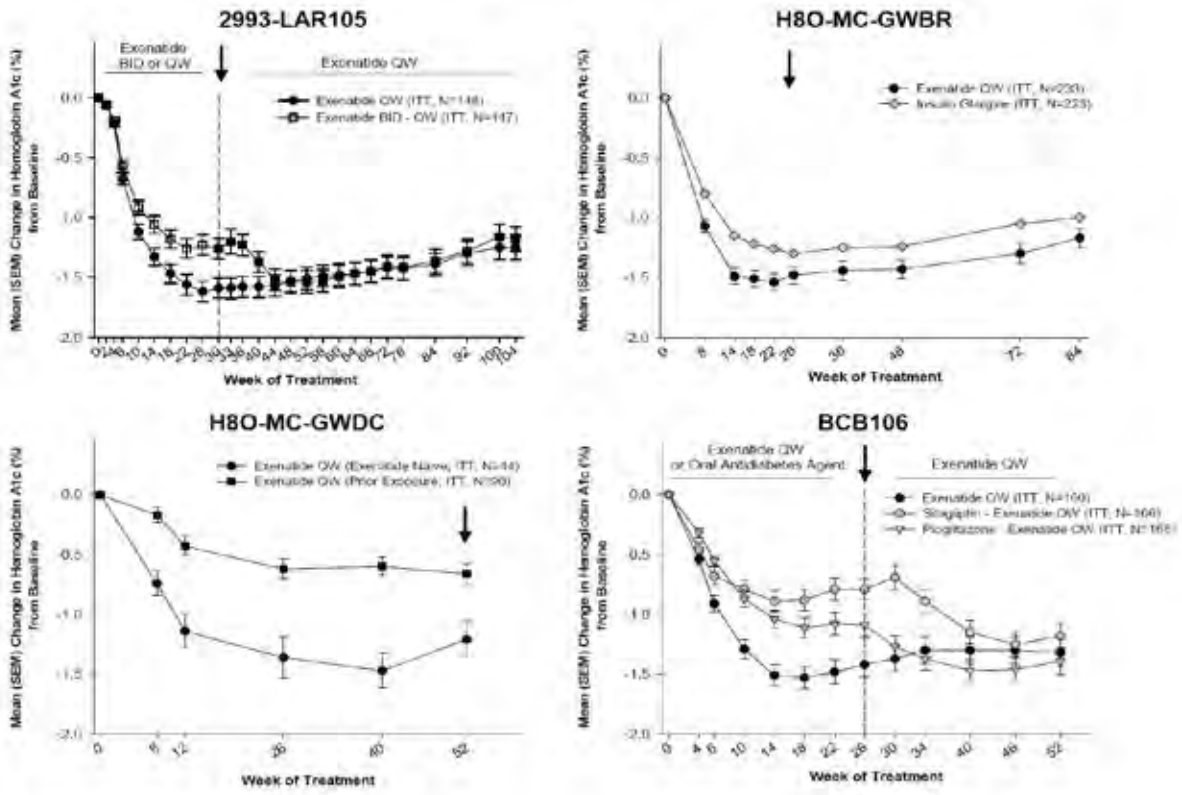


Figure 12. Time course of mean (SEM) change in hemoglobin A1c (%) from baseline to final week of response data cut off period (Studies 2993LAR-105, H80-MC-GWBR, H80-MC-GWDE, BCB106; ITT subjects). [Figure 8 in EPAR]



Please note: the extension phases depicted above, have not yet been submitted in Australia.

Efficacy studies for add on treatment with thiazolidinediones (TZDs)

Four studies were submitted:

1. Study GWAP was a multicentre double blind randomised placebo controlled superiority study on subjects taking TZDs or a combination of TZDs and metformin. This study was of 16 weeks duration.

   The inclusion criteria have been detailed by the clinical evaluator above. The evaluator notes that those "treated with a stable dose of TZD (≥4 mg/day rosiglitazone or ≥30 mg/day pioglitazone), for at least 120 days prior to Visit 1; or, with or without metformin for at least 90 days" were eligible to enroll.

   The mean HbA_{1c} was 7.89% and the mean duration of diabetes was 7.71 years. Some 21.5% of subjects had TZDs and 78.5% of subjects had a combination of TZDs. (Of these, metformin 79%, RSG 62% and pioglitazone 37%). *The dose of these drugs was not specified; the sponsor should give this in the pre-ACPM response.*

   A total of 233 subjects were randomised to treatment and received at least one dose of study drug: 121 in the exenatide group and 112 in the placebo.

   The evaluator mentioned that there was a significant improvement in HbA_{1c}: -0.88 (-1.1-0.65) p<0.0001. There was significant difference in fasting blood sugar and body weight, no significant difference was observed in relation to fasting lipids (except HDL).

Delegate's comments: In relation to the patient selection criteria, though it is specified that those with contraindications "according to product specific label" were excluded, the

exclusion criteria specify moderate to severe congestive heart failure (NYHA Class III or IV[12]). This is not aligned to current Australian PI contraindications of rosiglitazone, which excludes all grades of congestive heart failure (CHF). Similarly, the Actos PI in the Precautions section states that treatment "should be initiated at the lowest approved dose in patients with Type 2 diabetes and systolic heart failure (NYHA Class 1). If subsequent dose escalation is necessary the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, oedema or congestive heart failure exacerbation". It is not certain whether this was followed in this study.

2. Study GWCG. A multicentre, randomised placebo controlled study in patients treated with rosiglitazone (≥4 mg) or pioglitazone (≥ 30 mg) alone or in combination with metformin and on a stable dose of TZDs for three months were eligible to participate. Other inclusion and exclusion criteria have been detailed by the clinical evaluator above. This study also excluded those with NYHA Class III and IV congestive heart failure categories.

   This study was 26 weeks in duration. HbA_{1c} was the primary efficacy endpoint and there were several secondary efficacy endpoints (including waist circumference, body weight and fasting blood sugar). A total of 111 subjects were randomised to exenatide and 54 subjects were randomised to placebo. Some 94.5% took metformin, 77% took pioglitazone and 22% took RSG.

   The evaluator stated that "there was a significant decrease in HbA_{1c} from baseline in the exenatide group, and also compared to placebo: LS mean (SE) change from baseline -0.84 (0.20) % p<0.001 for exenatide and -0.10 (0.23) % for placebo: LS Mean Difference (95% CI) (exenatide-placebo) -0.74 (-1.06 to -0.41) %, p<0.001".

   There was no significant difference in fasting glucose, waist circumference or lipid levels between groups. There was a significant difference in body weight.

3. Study GWBG was an open randomised study versus glargine of 20 months duration. Those on stable combination of dual or triple therapy for at least 3 months with an

[12] In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

HbA1c of between 7.5% and 10% were eligible to participate. Local labelling requirements were considered in exclusion criteria. This study is of limited significance to this submission as glargine is not registered for use with TZDs in Australia.

A percentage of subjects (56%) were co medicated with TZDs. The evaluator mentions that, "The multivariate analysis of the primary outcome variable (HbA1c) indicated that presence of TZDs did not affect efficacy (p=0.725)".

The primary efficacy endpoint was the proportion achieving HbA1c ≤7.4% with minimal weight gain (≤1 kg) at 26 weeks or at early discontinuation. This was 52.2% versus 16.4 % (with weight loss ≤ 0.5kg). There was no significant difference in the proportion with ≤7.4% at 26 weeks. Exenatide n=64 (54.2%; 95%CI: 44.8, 63.4); Glargine n=71 (61.2%; 95% CI: 51.7, 70.1).

4. Study GWAY was an open study comparing exenatide with RSG and RSG+ exenatide on those inadequately controlled with metformin. *The mean dose of metformin should be submitted in each study group, in the sponsor's pre-ACPM response.*

   The treatment duration was 20 weeks; there were multiple outcome measures relating to glycaemic control. Exclusion criteria stipulate NYHA III and IV[12] congestive heart failure. Currently all grades of congestive heart failure are contraindicated in the Australian PI.

   Forty-five subjects were randomised to exenatide, 47 subjects were randomised to exenatide+rosiglitazone and 46 subjects were randomised to rosiglitazone. The evaluator mentioned a greater reduction in HbA1c with the combination treatment.

Safety

Exenatide-LAR

The evaluator discussed the patient exposure to exenatide-LAR and the data are summarised in Table 27 below which has been extracted from the EPAR for this product.

In the comparative studies with exenatide-IR, 592 patients were exposed to LAR and 145 patients were exposed to exenatide BD. Nausea (20% versus 34%) and vomiting (8% versus 19%) occurred less with LAR.

The duration of nausea was generally short (1 week). The majority of gastrointestinal tract (GIT) events (97%) were mild to moderate in severity.

Table 27. Adverse events [Copied form EPAR for this product].

Study Identifier	Integrated Completed Database Studies [1]		GWDC	BCB108	
Treatment	Exenatide QW	Exenatide BID	Exenatide QW	Exenatide QW	Exenatide BID
ITT Population (N)	592	145	134	129	123
Adverse Events (%)					
Gastrointestinal disorders					
Nausea	118 (20)	50 (34)	20 (15)	18 (14)	43 (35)
Diarrhoea	76 (13)	19 (13)	7 (5)	12 (9)	5 (4)
Vomiting	46 (8)	27 (19)	9 (7)	6 (5)	11 (9)
Constipation	34 (6)	9 (6)	7 (5)	1 (1)	5 (4)
General disorders and administrative site conditions					
Injection site pruritus	47 (8)	2 (1)	3 (2)	6 (5)	1 (<1)
Infections and infestations					
Nasopharyngitis	51 (9)	8 (6)	12 (9)	5 (4)	1 (<1)
Urinary tract infection	30 (5)	12 (8)	2 (2)	4 (3)	4 (3)
Nervous system disorders					
Headache	50 (8)	7 (5)	10 (8)	6 (5)	10 (8)

Abbreviations: BID = twice daily; FG = fasting glucose; ITT = intent-to-treat; N = number of subjects; QW = once weekly; SE = standard error.
[1] Consists of Studies: 2993LAR-104, H8O-JE-GWBW, 2993LAR-105, BCB106, and H8O-MC-GWBR.
Source: Integrated Completed Studies Database: smteaa11; Table GWDC.11.20; BCB108-SDS3.2.2.

Hypoglycaemia: The incidence was similar in the LAR (26.2%) and IR (30%) groups. The incidence appeared to be dependent on SU use. *Weight loss*: ≥5%, n=254: ≥10%, n=58, ≥20%, n=3. The number of *Cardiac events* was generally similar in both groups.

Injection site reactions were higher in the LAR (16%) group than the IR group (2%-7%). They included pruritus (8%), erythema (4%), induration (4%) and nodule (3%). There was also asymptomatic nodule formation (up to 77%). It is stated that approximately 73% of the first incidence of treatment emergent injection site reactions resolved within 60 days.

There was one report of oedematous pancreatitis. There was an additional report of pancreatitis.

Mean serum amylase and lipase results were discussed. *The sponsor should submit in their pre-ACPM response, the number in the exenatide-LAR studies who experienced an increase of three times the ULN of amylase and lipase. The sponsor should also submit the numbers where concomitant increase of serum amylase and lipase occurred in the same patient.*

The percentage of subjects experiencing serious adverse events was similar between the LAR and IR groups. Laboratory abnormalities were low and similar between groups. There were four deaths reported in the LAR group; they were all unrelated to treatment.

There was anti-exenatide antibodies reported. The evaluator mentions a trend to lesser efficacy in Study **BCB 108** in those with higher titres. In Study **106**, there was a greater efficacy response (HbA_{1c}) associated with higher titres. There were also higher reports of injection site nodules, induration and erythema.

Exenatide combination with TZDs

This has been discussed by the clinical evaluator above. The sponsor's summaries states that a total of 346 subjects used exenatide and TZDs alone or TZDs in combination with other oral antidiabetic agents. There were more subjects reporting nausea as a SAE with exenatide and rosiglitazone than with exenatide alone in Study H80-US-GWAY. Overall, the evaluator states that co medication with TZDs did not modify the pattern of AEs. However, the numbers were small. The duration was also short (maximum of 26 weeks). The other deficiencies were that no laboratory measurements of lipase and amylase were included. The duration of these studies was too short to assess cardiovascular outcomes.

Overall conclusions of the evaluator

Exenatide-LAR. The evaluator concluded that Study **105** showed greater efficacy with exenatide-LAR in relation to HbA_{1c} and weight compared with exenatide-IR. Studies **BCB 108, BCB 106** and **GWBR** showed statistically superior efficacy of exenatide-LAR over its comparators. Similarly, greater weight reductions were also observed with exenatide-LAR. The doses of the comparators were consistent with the registered PI in Australia. There were no safety concerns identified with this long acting formulation and the evaluator recommends approval for requested indications.

Extension of indication to include TZDs. The evaluator recommended approval, despite the comment that there was no long term morbidity data.

Risk management plan

The evaluator noted that the FDA issued a negative opinion, "and in the complete response letter (March 2010) requested a Thorough QT (TQT) study[13] with exposures of exenatide higher than typical therapeutic levels of Bydureon". This is to be submitted at the end of 2011.

The evaluator discussed the "ongoing safety concerns". The *Identified risks* are pancreatitis, acute renal failure and rapid weight loss. Some of the *Potential risks* mentioned are anti-exenatide antibodies, cardiac events and thyroid neoplasms.

Overall, the evaluator recommended that the RMP is "supportive to the application".

However, it was recommended that additional information be submitted by the sponsor as a condition of registration: of note, methodology relating to the monitoring of adverse events in the currently ongoing cardiac outcomes study, the FDA discussion on the risk of cardiac Risk-Benefit Analysis

Sponsor's response

The sponsor has responded to the questions of the evaluator.

In relation to the question regarding the lack of bioequivalence from the two manufacturing sites, the sponsor has compared the HbA_{1c}, FPG and C_{ss} from Study LAR 105 where batches from these two sites were used. The results are stated as being similar. Efficacy results from Study BCB 108 were also submitted (commercial site) to support the claim that they are similar to those of Study LAR 105 (both sites).

Delegate considerations

Exenatide in combination with TZDs

The dataset is limited. The number included is 346 and is insufficient to detect rare adverse events that may arise in combination with TZDs; of note, cardiovascular events. Duration spans 12-26 weeks and is not adequate to assess long term morbidity. The patient selection may also not reflect the currently approved PIs for TZDs in Australia, based on ongoing safety concerns with TZDs. Longer term studies addressing morbidity outcomes should be submitted to support registration.

Based on the data submitted the Delegate recommended rejection due to insufficient data on long term safety.

[13] Since 2005 the FDA and European regulators have required that nearly all new molecular entities are evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval. The TQT study serves to assess the potential arrhythmia liability of a drug. See Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. ICH. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf

Exenatide LA

Efficacy has been shown with exenatide-LAR. Adequate efficacy data in two studies (LAR 105 and BCB 108) show that Bydureon was statistically significantly better than Byetta in relation to the primary efficacy endpoint. (It appears that the minimum effective dose has not been used in these studies). In addition, there were two studies that showed exenatide-LAR was superior to TZDs and insulin glargine, in relation to the primary efficacy endpoint.

Safety, in this population, did not reveal any concerns; however, the safety data set is limited by the small number of subjects.

The significant issues relate to the biopharmaceutic data submitted. This is captured in the Pharmaceutical Subcommittee (PSC) Recommendation 2234, dot point 4:

The Committee considered that the deficiencies in the biopharmaceutic data provided in support of the submission were significant. In particular, the PSC agreed that:

- The extended release profile for the proposed formulation was not clearly defined.
- The lack of bioequivalence for the products manufactured at the nominated two manufacturing sites, the observed large variability in the release of drug substance from the product, the different pharmacokinetic profiles obtained for exenatide when the product was administered at different sites and the different pharmacokinetic profiles obtained from different batch sizes of the drug product were concerning.
- Efficacy and tolerability could be adversely impacted by the variable drug release characteristics inherent with the proposed product. The Committee therefore concluded that it is important to ensure that the proposed product displays consistent release profile/properties.

The chemistry evaluator states that the acceptability of formulations must rely on clinical rather than biopharmaceutic data.

This is difficult to do as the clinical data set is limited to approximately 850 patients receiving exenatide-LAR formulation. As it is stated that the extended release profile was not clearly defined, a potential concern is dose dumping. This would not be easy to detect in relation to the efficacy endpoints as the glycaemic indices are not sensitive to detect small anomalies in the release characteristics of the formulation.

Similarly, the safety information is submitted on a limited number of patients. This number is insufficient to detect events relating to erratic release characteristics unless the effect is marked. Larger number of subjects is needed; or, the results of a study examining a rare adverse effect of exenatide, which could manifest if there is dose dumping. It is stated in the EPAR that the sponsor undertook a QT study with exenatide BD, " which showed a moderate increase of the QTc interval". It is noted that the FDA has requested a QT study to be conducted, prior to registration. The results of this study would reassure the TGA that the variable release characteristics would not adversely affect the safety of the product.

Proposed action

The Delegate recommended rejection of Bydureon on quality grounds.

Advice from the Advisory Committee on Prescription Medicines was sought. Should the Committee recommend registration of Bydureon, the submission of the QT study should be submitted to the TGA as a condition of registration.

The Delegate recommended rejection of the extension of indication of Byetta to include combination therapy with thiazolidinediones as there are inadequate safety data to support registration.

Response from sponsor

Proposed indication for exenatide-IR and exenatide once a week (LAR)

The request to expand the indication for Byetta (exenatide twice daily [bd]) to include the use of thiazolidinediones (TZDs) was made in parallel to the request for a new dosage form to allow the bridging of data with combination TZD therapy generated with exenatide twice a day (exenatide-IR) to that of exenatide once weekly (exenatide-LAR) and to request the same indication for the two presentations. Therefore, patients using TZDs were included in the exenatide-LAR Studies LAR105 and LAR108.

The following proposed indication is aligned with the indication of exenatide-IR and exenatide-LAR in Europe:

> *Exenatide is indicated for treatment of patients with Type 2 diabetes mellitus (T2DM) in combination with metformin (MET); sulfonylureas (SUs); TZDs; MET plus an SU; and MET plus a TZD in adults who are not achieving adequate glycaemic control.*

Extension of indication exenatide-IR

Exenatide-IR in combination with TZDs. Duration of studies

The clinical evaluation of this indication concluded "*the risk benefit assessment is in favour of exenatide in combination with TZD*". Exenatide-IR and TZDs produce their antihyperglycaemic pharmacological actions by two distinctly different mechanisms of action. Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that enhances glucose-dependent insulin secretion, suppresses glucagon secretion and slows gastric emptying. TZDs (rosiglitazone, pioglitazone) produce their antihyperglycaemic pharmacological effect by improving insulin sensitivity in peripheral tissues. TZDs are potent agonists for peroxisome proliferator activated receptor gamma (PPARγ). These receptors modulate the transcription of several insulin-responsive genes involved in control of glucose and lipid metabolism in adipose tissue, skeletal muscle, and the liver. To the sponsor's knowledge, there is no overlap of these two pathways that would result in pharmacological synergism/interaction of exenatide-IR and TZDs. In addition, exenatide being a therapeutic peptide has no known effect on the cytochrome P450 enzyme mediated metabolism of small molecule drugs such as TZDs. The co administration of a TZD with or without MET with exenatide-IR in the 16 and 26 week studies (GWAP and GWCG, respectively) in 398 subjects resulted in an increase in efficacy, without any signs of additive safety concerns, confirming a lack of clinically relevant interactions.

The sponsor will gain additional safety data on the use of exenatide plus TZD in two long term studies: EUREXA [GWBE] and EXSCEL (EXenatide Study of Cardiovascular Event Lowering [Study BCB 109]). EUREXA compares patients on exenatide-IR and MET to an SU and MET.

Subjects can add a TZD or an SU to exenatide-IR if they do not achieve target haemoglobin A1c (HbA_{1c}) at 6 months. In the EXSCEL study, subjects taking a TZD will take part in the long term, placebo controlled, double blinded study that seeks to characterize the effects of exenatide-LAR on cardiovascular related outcomes in patients with Type 2 Diabetes mellitus (T2DM) when added to the current usual care for glycaemic control in a standard care setting. Both studies are ongoing; copies of the study reports can be provided as a post approval commitment. Furthermore, information on the use of exenatide in combination with TZDs is also available from postmarketing spontaneous reports and the Risk Management Plan (RMP). Cumulative reports, as of 31 March 2010, of the total spontaneous cases reporting adverse events (AEs) show 17% of subjects using exenatide were on concomitant TZDs (either single entity or combination products). Adverse event profiles were similar in the rank order of AE occurrence and the proportion of subjects with AEs in subjects with concomitant TZD versus no concomitant TZD (RMP). Given the

small number of spontaneous reports for concomitant TZD use relative to non concomitant TZD use, these spontaneous data reflect a qualitative assessment.

Study inclusion criteria

Consistent with the current labels in the United States (US), the GWAY, GWBG study designs contraindicated the use of rosiglitazone and pioglitazone in patients with established heart failure. In Study GWCG, patients on pioglitazone and rosiglitazone were included per NYHA criteria in the local label. Furthermore, at the time of designing the studies, pioglitazone was not contraindicated in patients with NYHA Class I and II cardiac disease, as reflected in the Australian pioglitazone labelling in 2005. In Studies GWAY and GWBG subjects were to be on a stable dose of TZD for at least 120 days prior to study entry. In Study GWCG, patients had to be on ≥4 mg/day rosiglitazone or ≥30 mg/day pioglitazone. In all three studies, escalations (or decrease) of TZD dose for 7 days were disallowed by the protocol. Although patients had more severe cardiac disease classification than allowed by current Australian PI contraindications for rosiglitazone and pioglitazone, which exclude all grades of congestive heart failure, no significant safety concerns were observed during the studies.

Mean dose of oral antidiabetic medications (OAMs)

A summary OAM doses in Studies 105, 108, and GWAY has been submitted to the TGA. In Study 105, subjects were required (if taking MET, a TZD, or an SU) to be on a stable dose at randomization.

Subjects taking a TZD and MET were taking near maximum doses with the doses remaining relatively constant throughout the study. Subjects taking SUs were instructed to decrease their SU dose to the minimum dose to examine the incidence and rate of hypoglycaemic events associated with the proactive approach to SU management. After reducing SU doses to minimum levels, doses were progressively increased during the study, per protocol.

In Study 108, subjects were required (if taking MET, a TZD, or an SU) to be on a stable dose of ≥1500 mg/day MET, ≥4 mg/day rosiglitazone, or ≥30 mg/day pioglitazone. Subjects taking an SU were required to be taking at least the maximally effective dose (BCB 108 study protocol). During the study, subjects typically met or exceeded OAMs doses described in the protocol. Prior to screening in Study GWAY, the only oral concomitant medication allowed was MET. Subjects had to be on a stable dose of MET (no minimum dose required).

New dosage form (Exenatide-LAR)

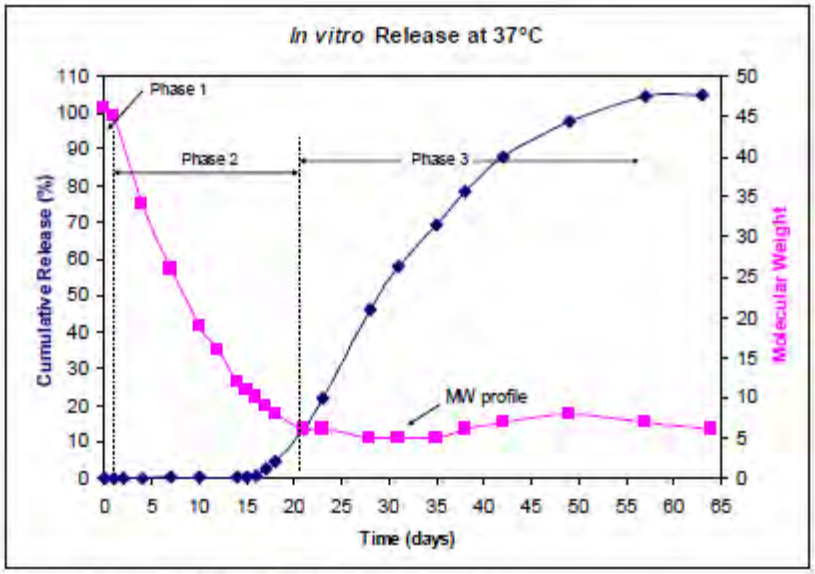
The clinical, nonclinical and quality evaluations concluded in favour of exenatide-LAR. The biopharmaceutical evaluation identified potential concerns in relation to the extended release profile for the exenatide-LAR formulation; drug release characteristics and potential dose dumping; bioequivalence of the commercial to smaller scale material and of the different injection sites, recommending that acceptability of the new dose form must be based on clinical rather than biopharmaceutical data.

Chemistry and dose dumping

Dose dumping is an unlikely mechanism for poly-(D,L-lactide-co-PLG microspheres after SC injection based on the known physical characteristics of drug release. The release occurs in three phases:

1. Initial release of loosely bound surface exenatide,
2. Hydration phase where the polymer begins to be hydrolysed providing for a controlled manner for exenatide release, and
3. Extended release phase as the polymer matrix erodes (Figure 13).

Figure.13. *In vitro* release and polymer molecular weight.



Abbreviation: MW = molecular weight of PLGA polymer. Extended release phase of exenatide from the PLGA polymer microspheres does not begin until the polymer molecular weight drops to about 25-30kD.

Controls are in place to confirm all three phases will consistently occur for each batch manufactured. Initial release of exenatide is controlled by the dispersion of the exenatide through the polymer matrix. This homogeneous dispersion has been demonstrated with the validated manufacturing process and is also confirmed at batch release with the *in vitro* initial release test, which quantifies the amount of surface exenatide released[14] [15].

Consistency of the hydration and extended-release phase is controlled by the molecular weight of the polymer, which is confirmed for every batch. All three phases, including the extended release phase, is confirmed with the *in vitro* complete release test, which involves incubation of the microspheres in aqueous buffer at 37°C to erode the porous polymer matrix and release exenatide, which is controlled by monitoring release at several timepoints during this incubation. The use of PLGA polymer microspheres has been extensively studied[14] and no mechanism for dose dumping has been proposed or observed. In fact, the release of encapsulated drug from lamellar microspheres is limited to the rate of polymer degradation, which occurs homogenously from the exterior of the microsphere inward. This is supported by the observed slow release of drug *in vitro/in vivo*, along with no dose dumping reported in labels for other approved PLGA microsphere products such as Vivitrol® and Risperdal® Consta®.

Therefore, the pool of available exenatide is limited with this delivery technology in contrast to extended release oral or patch delivery systems, where rapidly solubilised drug can lead to dose dumping into the systemic circulation.

Tolerability and safety

Since high exposure levels are closely related to gastrointestinal (GI) side effects, significant dose dumping would be expected to result in acute worsening of GI adverse events. The exenatide-LAR formulation compared to exenatide-IR (unmodified release formulation used as comparators in Studies 105 and 108) showed exenatide-LAR had

[14] Anderson J.M and Shive M.S. ()Biodegradation and biocompatibility of PLA and PLGA microspheres. Advanced Drug Delivery Reviews 28 (1997) 5–24

[15] S.K.Senthilkumar et al (2010). Formulation, Characterization and In vitro Evaluation of Floating Microsphere Containing Rabeprazole Sodium. JITPS 1:274-282.

better tolerability compared to exenatide-IR as evidenced by fewer subjects experiencing GI AEs in the exenatide-LAR versus bd group (nausea: 26% versus 35% in Study 105 and 14% versus 35% in Study 108; vomiting: 11% versus 19% in Study 105 and 5% versus 9% in Study 108). These data suggest no significant increases in exenatide exposure and/or spikes leading to acute worsening of GI AEs profile compared to exenatide-IR.

The Delegate has suggested that QT study data may be informative with respect to the long term safety profile of the extended release formulation. These studies are briefly summarised below and can be provided in full as post approval commitment. Synopses of the two studies were provided to the TGA with this pre ACPM response. To address both the general concern raised about QT prolongation and relevance to unexpected high concentrations of exenatide, a randomised, three period, placebo and positive controlled, double blind, crossover study (BCB 112) assessed the electrophysiological effects of exenatide at therapeutic (~200 and ~300 pg/mL) and supratherapeutic (~500 pg/mL) concentrations on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects. Study BCB113 was a pilot study to identify infusion parameters for intravenous (IV) infusion of exenatide for Study BCB112. The stepped IV infusion paradigm was then implemented in Study BCB112 resulting in the achieved steady state plasma exenatide concentrations of (geometric mean [min, max]): 253 [77, 834] pg/mL (Day 1), 399 [184, 1337] pg/mL (Day 2), and 627 [299, 1904] pg/mL (Day 3).

The primary objective of Study BCB112 was to determine in healthy subjects that exenatide administered at therapeutic and supratherapeutic concentrations does not differ from placebo in the mean change from predose in 12-lead ECG corrected QT interval measurements (such that the upper bound of the one-sided 95% confidence interval [CI] between exenatide and placebo is <10 ms). Results showed that the least-squares (LS) mean difference in the change from baseline in average QTcP between exenatide and placebo (ΔΔQTcP) was -1.36, -2.02, and -1.13 ms with an upper limit of the two-sided 90% CI (equivalent to one-sided 95% CI) of <10 ms at all three steady state target plasma exenatide concentrations predefined for the primary analysis and below the threshold of regulatory concern defined in the International Conference on Harmonisation (ICH) E14 Guidance[13], indicating no effect of exenatide-LAR on prolonging the QT interval.

Additional data from Studies 105, 106, BCB112, GWBR, and GWDC are available and can be provided as a post approval commitment. Review of the data provides no new additional safety signal(s) of concern. Potential exenatide safety topics that have been identified are discussed in the RMP. The dataset of approximately 850 subjects receiving exenatide-LAR formulation is felt to be reasonable for an active ingredient with an established AE profile. No safety topics have been identified that are specific to the exenatide-LAR formulation.

Finally, as requested by the TGA, Table 28 includes the number of subjects who experienced >3 times the upper limit of normal amylase and lipase values.

Table 28. Incidences of lipase and amylase >3 times ULN.

Study	Lipase levels >3xULN n (%)	Amylase levels >3xULN n (%)	Lipase and Amylase levels >3xULN n (%)
BCB 106 controlled period	5 (3)	0 (0)	0 (0)
BCB 106 extension (All)	16 (5)	3 (1)	3 (1)
H8O-MC-GWBR	4 (2)	2 (1)	1 (0)
BCB 108	7 (6)	2 (2)	2 (2)
H8O-MC-GWDC	4 (3)	0 (0)	0 (0)

Abbreviations: EQW = exenatide once weekly; PIO = pioglitazone; SITA = sitagliptin; ULN = upper limit of normal. Note: BCB106 extension and H8O-MC-GWDC include all EQW arms combined.

Efficacy

Studies 105 and 108 were designed to compare glucose control, as measured by HbA_{1c}, of exenatide-LAR, using the small scale (1 kg) and commercial scale (15 kg) formulation, respectively to exenatide-IR formulations in subjects with Type 2 Diabetes mellitus. In both studies, exenatide-LAR showed superiority in HbA_{1c} reduction (0.3% and 0.7% superiority of HbA_{1c} lowering relative to exenatide-IR in Studies 105 and 108, respectively).

Bioequivalence of the commercial to smaller scale material

The comparability of commercial scale (15 kg) to smaller scale (1 kg) material was established by physicochemical comparability evaluations showing that the change in manufacturing site and associated scale up to 15 kg scale did not affect product performance. The pivotal support for clinical comparability of commercial scale material is based on results from Study BCB108 and *in vitro in vivo* correlation (IVIVC [Study BCB107]).

Study 108 (15 kg material) showed a -1.6% change from baseline HbA1c that is a similar efficacy response in the other studies supporting this submission, which all used 1 kg material in the controlled 24 to 30 week treatment periods (-1.9% for Study 105, -1.6% for Study 106, and -1.5% for Study GWBR). Further, the treatment difference (exenatide-LAR - exenatide-IR) was -0.3% in Study 105 compared with -0.7% in Study 108, confirming that a statistically significant and clinically relevant treatment difference compared with exenatide-IR is maintained in the 15 kg material. Study 105-c (extension of Study 105) compared the 15 kg material with 1 kg material. The primary prespecified analysis of HbA1c change from re-randomisation to 18 weeks after re-randomisation on the evaluable population showed a treatment difference (15 kg material - 1 kg material) of 0.17% with 95% CI (0.01%, 0.34%) achieving the prespecified non inferiority margin of 0.4% for comparability. Table 29 shows the batches used in the clinical trials supporting the proposed indication.

Table 29. Summary of Exenatide QW use.

Study	Production Scale
2993LAR-105	105 g, 1 kg and 15 kg
BCB106	1 kg
H8O-MC-GWBR	1 kg and 15 kg
BCB108	15 kg
H8O-MC-GWDC	1 kg and 15 kg

Comparability of the different injection sites

A substudy was conducted in the open label assessment period of Study BCB106 to assess the effects of exenatide-LAR administered SC in the upper arm, thigh, and abdomen on glycaemic control and exenatide pharmacokinetics.

Plasma exenatide concentrations at baseline (Week 40) were comparable between anatomical sites (geometric mean: 232.74 pg/mL, 220.23 pg/mL, and 205.52 pg/mL for abdomen, upper arm, and thigh, respectively). Following 12 weeks of treatment, the geometric LS mean ratio of exenatide plasma concentrations between upper arm and abdomen was 1.01 with a 90% CI of (0.79, 1.29). Similarly, the geometric LS mean ratio of exenatide plasma concentrations between thigh and abdomen was 0.93 with a 90% CI of (0.73, 1.18). Although the CIs of these geometric LS mean ratios are not strictly between 0.80 and 1.25, the studies were prospectively powered to detect a 100 pg/mL difference. The CIs not being contained in (0.80, 1.25) does not indicate a lack of bioequivalence because the study was not powered to show bioequivalence. The slight differences in the exenatide plasma concentrations among the three anatomical sites did not result in clinically significant differences in HbA1c or fasting plasma glucose.

RMP evaluation

EXSCEL study (BCB 109) was initiated on the 18 June 2010 and is actively enrolling in multiple countries, including Australia. Assessment of the composite primary endpoint (time to occurrence of a major macrovascular event: cardiovascular death, non-fatal stroke, non-fatal myocardial infarction) will be done using prospective, blinded adjudication of potential endpoint events. Prior to and following the initiation of the trial, the sponsor engaged in active dialog with the FDA regarding the planned oversight of subjects and the assessment of macrovascular outcomes. This ongoing dialog has included submission of the trial's statistical analysis plan (SAP), data safety monitoring board (DSMB) charter, event adjudication plan (that is, clinical events committee charter), and amendments to the protocol. Regarding assessment of cardiovascular events, FDA's feedback has not resulted in changes to the planned conduct of event assessment or adjudication. Every 6 months, the DSMB will review serious adverse events (SAEs) (pancreatitis, pancreatic cancer and thyroid carcinoma will be reported as SAEs in this trial); clinical events defined in the protocol; non serious overdoses if they are not captured in SAEs; and severe hypoglycaemic events.

Conclusion

The LAR formulation of exenatide provides patients therapeutic concentrations of exenatide with a better tolerability and efficacy profile versus exenatide-IR. The release of encapsulated drug from lamellar microspheres is limited to the rate of polymer degradation. The sponsor concludes that the LAR formulations of exenatide used in pivotal Studies 105 and 108 are comparable based on quality testing and clinical outcomes. Based on the tolerability, safety, microspheres structure and controls in place for exenatide-LAR, there is a low potential for dose dumping and the sponsor does not believe that dose dumping is of concern. The site of injection data supports the use of the three anatomical sites for the SC administration of exenatide-LAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM considered these products to have a negative benefit-risk profile for the proposed indication, for the following reasons:

The clinical rationale for combined use of Byetta with a TZD unclear and is not supported by adequate nonclinical data.

Specific long term safety and efficacy data on this combination is considered to be essential owing to the changing safety profile of TZDs. The ACPM expressed concern about cardiovascular adverse events and the impact of long term use.

The ACPM noted that the Bydureon efficacy was statistically better than Byetta in relation to the primary endpoint; nonetheless, the committee agreed with the Delegate that the evidence to demonstrate a positive benefit-risk profile for the combination with a TZD is inadequate in terms of demonstrating safety.

It is noted that the trend to better efficacy could be consistent with the higher dose of Bydureon; however, this matter cannot be resolved on the current data. As the higher dose raises potential safety concerns this further emphasises the need for caution.

The evidence of variable release rates and generally the poor quality of the biopharmaceutical data for the formulation of Bydureon is unacceptable.

The considerable safety issues associated with the risk of dose dumping of Bydureon have not been resolved due to inadequate bioavailability data. The clinical data do not address the deficiencies noted by the Pharmaceutical Subcommittee (Recommendation 2234). The suggested bioavailability of Bydureon is approximately 22% of the registered injection solution, Byetta. The sponsor needs to clarify this matter.

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Byetta, exenatide (5 µg/20 µL and 10 µg/40 µL) solution for injection multidose cartridge, for combination with thiazolidinediones (TZDs) for the treatment of Type 2 diabetes mellitus in patients who have not achieved adequate glycaemic control, and the new once weekly dosage form: Bydureon exenatide 2 mg powder for injection vial with diluents syringe.

The reasons for the Delegate's decision are that there were inadequate data submitted on quality and safety. In particular,

Bydureon

Lack of quality

The extended release profile for the proposed formulation was not clearly defined. As indicated in the adopted Guideline[16] on modified release formulations, dose dumping is a concern with modified release formulations. The sponsor's pre-ACPM response that dose dumping is an unlikely mechanism for poly-(D, L –lactide-co-glycolide) microspheres, based on the physical characteristics of drug release is noted. However, due to the variable release characteristics this cannot be taken at face value, for this product. Larger number of subjects is needed to address this, where attention needs to be given to the occurrence of rare events. However, even in the absence of large numbers, more sampling at various times after injection would have been of assistance in defining the release characteristics.

Dose dumping is also a concern as the suggested bioavailability of Bydureon is approximately 22% of the registered injection solution, Byetta indicating a higher dose of exenatide with Bydureon. Thus, safety concerns due to a higher dose clearly are an issue that need to be dealt with in relation to all modified release products. Incomplete dose

[16]Note for guidance for modified release oral and transdermal dosage forms:Section II (Pharmacokinetic and Clinical evaluation). CPMP/EWP 280/96. http://www.tga.gov.au/pdf/euguide/ewp028096en.pdf

finding for Bydureon means that there are no data to support the registration of the lower dose.

The sponsor's response relating to gastrointestinal effects which were favourable in comparison with the registered immediate release exenatide is noted. These are crude indices that do not provide the assurance that dose dumping does not occur in treated patients. The commonly reported adverse events per se are inadequate to detect small anomalies in relation to dose dumping or to higher dose related serious events. You have stated that there is "no evidence from either the safety database or the pharmacokinetic data that dose dumping is a possibility with Bydureon". The Delegate does not agree with this statement as a total of 850 subjects is inadequate to detect rare or uncommon adverse events that may arise due to dose dumping. A study is needed where rare events are assessed as this would better support the claim of no dose dumping with Bydureon.

The lack of bioequivalence for the products manufactured at the nominated two manufacturing sites, the observed large variability in the release of drug substance from the product, the different pharmacokinetic profiles obtained for exenatide when the product was administered at different sites and the different pharmacokinetic profiles obtained from different batch sizes of the drug product were of concern. The sponsor stated that the change in manufacturing site and associated scale up to production batch did not affect the performance of Bydureon. To support this, the sponsor compared HbA1c reductions observed with these batches to state that the performance was similar. It is the Delegate's view that HbA1c is not a sensitive index to detect significant variability in pharmacokinetics. However, the trend for superiority of Bydureon over Byetta, that is the dose delivered is effectively significantly higher. There are insufficient data on relative bioavailability but the suggestion is that the dose is higher, pointing to potential safety concerns.

Another concern is that there was no bioavailaibility study of different sites of injection. This is not allayed in the sponsor's pre-ACPM response as the sponsor stated that such a study was not submitted.

Insufficient safety:

The safety information is submitted on a limited number of patients. This number is insufficient to detect events relating to erratic release characteristics unless the effect is marked. Larger number of subjects is needed; or, the results of a study examining a rare adverse effect of exenatide, which could manifest if there is dose dumping.

Resubmission:

A minimum data requirement, should the sponsor resubmit, would be the submission of a bioequivalence study versus the registered formulation; this study should also assess bioavailability from different sites of injection.

Exenatide in combination with TZDs

Insufficient safety:

The dataset is limited. The number included is 346 and is insufficient to detect uncommon to very uncommon adverse events that may arise in combination with TZDs; of note, cardiovascular events. Duration of the studies spans 12-26 weeks and is not adequate to assess long term morbidity or to detect uncommon but serious events. The sponsor stated in the pre-ACPM response, that the studies to support registration were undertaken prior to the labelling changes adopted in Australia. This reinforces the fact that patient selection may not reflect the currently approved PIs for TZDs in Australia, based on ongoing safety concerns with TZDs. There is a need for longer term studies addressing morbidity outcomes to be submitted to support registration. The sponsor has indicated that two long term studies, EUREXA and EXSCEL are underway. These studies on completion, may address the concerns currently expressed with this data-set. The sponsor was encouraged

to complete and submit these studies when available. In the interim, Byetta is registered in this country.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The Delegate of the Minister noted that Study BCB108 compared the proposed commercial Bydureon product with Byetta twice daily as in Study 105 (which involved the investigational Bydureon product). The primary objective of this study was to demonstrate non-inferiority of Bydureon compared with Byetta using a non-inferiority margin in HbA1c of 0.4% for a one sided test at a significance level of 0.025. The clinical evaluation is in agreement with the sponsor's appeal submission that for the primary efficacy outcome measure the per-protocol evaluation indicated non-inferiority and the ITT evaluation indicated superiority for the Bydureon weekly injection. "For the ITT population, the LS mean (95% CI) change in HbA1c from baseline to Week 24 was -1.6 (-1.8 to -1.4) % for exenatide LAR and -0.9 (-1.1 to -0.7) % for twice daily, LS mean (95% CI) difference -0.7 (-0.9 to -0.4), $p<0.0001$. The relative improvement in HbA1c with exenatide LAR exenatide was significant from Week 8 through to Week 24. In the exenatide LAR group, 75 (58.1%) subjects achieved an HbA1c of <7% at Week 24 compared with 37 (30.1%) in the twice daily ($p<0.0001$). In the exenatide LAR group, 48 (43.6%) subjects achieved an HbA1c of <6.5% at Week 24 compared with 18 (19.6%) in the twice daily ($p=0.0002$). Efficacy was not influenced by baseline severity or concomitant diabetes medication."

Although the bioavailability of exenatide is less from the commercial product than the investigational product, an adequate, albeit open label, study has shown that Bydureon commercial product demonstrated a superior efficacy to Byetta 5 µg twice daily for 4 weeks, then 10 µg twice daily. Thus, the fact of lower bioavailability of the commercially produced product compared with the investigation product does not preclude registration.

Concerning dose-dumping the review by the Delegate of the Minister included reviewing the plasma concentrations following injection of the F17 formulation proposed for marketing at ten time stations between 15 minutes and 24 hours after injection and at the time stations Week 14, Week 20 and Week 24.

Data for the 24 hours following injection are very limited. Data are available from individual patient listings for Amylin study REST080475. The plasma exenatide concentrations were consistent with the early release of active drug (~ 1%) and comparable to the mean exenatide concentrations from a 10 mcg immediate release injection.

Data for plasma exenatide concentrations at Weeks 14, 20 and 24 in the study report for BCB108 (Supporting Data Summary 2.8.2) appear to include only Intention To Treat analyses which are not readily reconcilable with the Bydureon 2 mg SC data in Figure 4 of the sponsor's appeal documentation. Both, however, show a wide range of plasma exenatide concentrations at these times but the Delegate has not regarded these as suggestive of dose-dumping.

The Delegate also noted the comments of the clinical evaluator and was of the view that there were not sufficient concerns about possible dose-dumping raised by the data as to preclude registration.

The Delegate of the Minister decided that the quality, efficacy and safety of the product had been adequately demonstrated and that that the Bydureon (exenetide-LAR) could be included on the Australian Register of Therapeutic Goods (ARTG).

Concerning injection at sites other than the abdomen the sponsor's application included a report titled 'Exenatide Once Weekly Site of Injection Assessment Interim Analysis' Final Date: 05 February 2010". All subjects received at least 14 weeks of exenatide once weekly treatment (injected into the abdomen) to allow all subjects to achieve steady-state exenatide once weekly concentrations prior to entry into the Site of Injection substudy. Subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 injection-site groups (abdomen, upper arm, or thigh).

The Delegate noted that this report of an interim analysis includes details of effects on HbA1c and Fasting Plasma Glucose. In each case the data suggest that the difference in HbA1c and Fasting Plasma Glucose for both comparisons (thigh versus abdomen; upper arm versus abdomen) was not clinically significant and the confidence intervals were both relatively narrow given the sample sizes.

The Delegate noted, however, that the sponsor's pre-ACPM Response refers to pharmacokinetic data, but the submitted interim report states that "Plasma exenatide concentrations are pending at the time of this interim report. Pharmacokinetic results will be presented in the final report."

The Delegate noted that although the sponsor included reference to a Final Analysis report in the appeal documentation, it did not submit the report as part of the appeal documentation. The Delegate had not been afforded an opportunity to review the complete set of data about efficacy and safety concerning the Site of Injection assessment or, depending on the circumstances, remit the study report for evaluation. The Delegate decided that although these circumstances do not preclude registration of Bydureon, the failure to date to submit the Final Analysis report precludes approval of the alternative thigh and deltoid injection sites in the approved Product Information. The sponsor may wish to submit a subsequent application with the Final Analysis report seeking approval of alternative injection sites.

Concerning the Delegate of the Secretary's rejection of inclusion of use in combination with TZDs in the approved indications, the sponsor submitted as part of the appeal a report of Study H80-MC-GWDC titled "Safety of Exenatide Once Weekly in Parients with Type 2 Diabetes Mellitus Treated with Thiazolidinedione Alone or Thiazolidinedione in Combination with Metformin" was included. The submitted document was an "Abbreviated Clinical Study Report".

The design of this study assumes that there will be no difference in long term efficacy or safety between the combinations of exenatide and rosiglitazone with, or without, metformin and exenatide and pioglitazone with or without metformin. In the Delegate's view, that is a flawed assumption. As early as September 2007, differences between these two thiazolidinediones (TZDs) were being highlighted[17]. That was more than one year prior to the first enrolment in H80-MC-GWDC.

An important consequence of the assumption is that the submitted data in the abbreviated study report provide only pooled information concerning the characteristics of the subjects of the study. The Delegate was of the view that it is essential that the efficacy and

[17] Solomon DH, Winkelmayer WC. Cardiovascular Risk and the Thiazolidinediones. New England Journal of Medicine. 2007; 298: 1216-1218

safety of combinations including rosiglitazone and combinations including pioglitazone be considered separately. The study report does not provide separate analyses or tabulations of these two combinations for even the most basic distributions of demographics such as age and sex.

This report provides information about the experiences of only 28 patients exposed to rosiglitazone at Baseline, falling to 24 at Week 91 and 9 at Week 104.

It was the Delegate's view that this poverty of information about the long term safety of combinations including rosiglitazone precludes approved of indications that include rosiglitazone and, as a consequence, indications including the name of the class of drugs ("thiazolidinediones").

The Delegate considered the information in this abbreviated study report concerning subjects exposed to combinations including pioglitazone. The Delegate made the following observations:

- The number of patients exposed to combinations including pioglitazone was 105 at Week 1. It had fallen to 98 patients by Week 12 and 90 by Week 52. A study of 90 subjects has a very low power to detect adverse effects. Using the Rule of 3's, for example, such a study has 95% power to detect an event occurring in 1 in 30 subjects or more commonly. In the Delegate's view, this is too few subjects to provide an assurance of the safety of the long-term safety of the combination of exenatide and pioglitazone with or without concomitant metformin. It was the Delegate's view that, given the documented, albeit different, safety concerns with exenatide and with pioglitazone, a reasonable expectation on the part of prescribers and patients would be that adverse events attributable to combinations including pioglitazone and exenatide with an incidence of 1% (1 in 100) or more commonly following one year of therapy should have been sought prior to registration. That would require about 300 patients rather than the 90 subjects reported at one year in H80-MC-GWDC;
- The presentation of the data did not permit the Delegate to know the basic demographics of subjects exposed to combinations including pioglitazone;
- Concerning treatment in the study for longer than 52 weeks the Delegate noted that the numbers of patients taking combinations including pioglitazone fall further, such that at Week 91, prior to the transfer of some subjects from rosiglitazone to pioglitazone, the number exposed to pioglitazone was 85 subjects;

The Delegate also noted several other specific issues concerning the conduct of the study.

The Delegate was of the view that these matters preclude an adequate assessment of the long term safety of combinations of exenatide and pioglitazone and consequently preclude the approval of the requested extension of the indications for Byetta and Bydureon to include use in combination with pioglitazone and more broadly thiazilodinediones.

The delegate of the Minister's decision

Pursuant to section 60 of the *Therapeutic Goods Act 1989* (the Act), the Delegate decided to revoke the initial decision concerning registration of Bydureon and make the following decision in substitution for that initial decision:

The application by Eli Lilly Australia Pty Ltd to register Bydureon exenatide 2 mg powder for injection vial with diluents syringe should be approved for the following additional indications:

Exenatide is indicated for the treatment of type 2 diabetes mellitus in combination with:

- *metformin*
- *sulfonylureas*

· *metformin and a sulfonylurea*

in patients who have not achieved adequate glycaemic control.

The Delegate was only satisfied of the safety and efficacy of Bydureon for these indications subject to a condition that the site of administration stated in the Australian Product Information be the abdomen only and to a condition that the company implement the Risk Management Plan titled Bydureon Risk Management Plan (Revision 15) and any modifications subsequently required by the TGA.

Pursuant to section 60 of the *Therapeutic Goods Act 1989* (the Act), The Delegate decided to confirm the original decision refusing the application to extend the indications for Byetta 5 and Byetta 10 and for Bydureon to include use with thiazolidinediones and with metformin and a thiazolidinedione.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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