16 February 2012
EMA/363251/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BYETTA

exenatide

Procedure No.: EMEA/H/C/000698/II/0029

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Background information on the procedure

1.1. Requested variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 7 June 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
BYETTA	exenatide	See Annex A

The following variation was requested:

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

The MAH proposed the update of sections 4.1, 4.2, 4.4., 4.6, 4.7, 4.8 and 5.1 of the SmPC in order to extend the indication for the use of Byetta in combination with a basal insulin with or without metformin and/or a thiazolidinedione. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH proposed minor changes for the Product Information.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Kristina Dunder

Co-Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	7 June 2011
Start of procedure:	26 June 2011
Rapporteurs' joint assessment report circulated on:	22 August 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 September 2011
MAH's responses submitted to the CHMP on:	30 September 2011
Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on:	24 November 2011
Rapporteurs' final joint assessment report on the MAH's responses circulated on:	7 December 2011
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2011
MAH's responses submitted to the CHMP on:	12 January 2012

Rapporteurs' joint assessment report on the MAH's responses circulated on:	26 January 2012
CHMP opinion:	16 February 2012

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/21/2011) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/21/2011) was not yet completed as some measures were deferred.

List of Abbreviations

BID	twice daily
BMI	body mass index
CHMP	Committee on Medicinal Products for Human Use
DPP-4	dipeptidyl peptidase 4
EU	European Union
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSG	fasting serum glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1c
ILPS	insulin lispro protamine suspension
ITT	intent to treat
LS	least squares
LOCF	last observation carried forward (also referred to as "mean change analysis")
MAA	marketing authorization application
OAD	oral antidiabetes drug
PSUR	periodic safety update report
RMP	risk management plan
SC	subcutaneously
SMBG	self-monitored blood glucose
SmPC	summary of product characteristics
SU	sulphonylurea
TZD	thiazolidinedione

2. Scientific discussion

2.1. Introduction

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Endogenous incretins, like GLP-1, enhance insulin secretion following their release from the gut into the circulation in response to food intake.

BYETTA (exenatide) injection is currently approved in the Union as a treatment for type 2 diabetes in combination with the following agents in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies:

- *metformin*
- *sulphonylureas*
- *thiazolidinediones*
- *metformin and a sulphonylurea*
- *metformin and a thiazolidinedione.*

The current application aimed to extend the indication of exenatide to include combination with basal insulin to support the following proposed additional indication:

> *BYETTA is indicated to improve glycaemic control in patients with type 2 diabetes mellitus in combination with a basal insulin with or without metformin and/or a thiazolidinedione.*

The data submitted in support of this extension of indication application are discussed within the hereafter assessment report.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

The MAH considered exenatide, as a moderately sized peptide, to be exempt from the Environmental Risk Assessment requirement, and this was agreed by CHMP.

2.3. Clinical aspects

2.3.1. Introduction

Support for the additional indication requested is based on 2 studies: H8O US GWCO (GWCO) and F3Z-US-IOPB (IOPB):

Table 1. Summary of Studies Supporting Use of Exenatide in Combination with Basal Insulin

Exenatide versus Placebo in Subjects Treated with Basal Insulin	
Study GWCO	Phase 3, 30-week, double-blind, efficacy and safety in subjects with type 2 diabetes and suboptimal glycaemic control with insulin glargine treatment with or without concomitant oral antidiabetes therapies
Insulin Lispro Protamine Suspension versus Insulin Glargine in Subjects Treated with Exenatide	
Study IOPB	Phase 3, 24-week, open-label, efficacy and safety of basal analog ILPS in subjects with type 2 diabetes and suboptimal glycaemic control with exenatide BID treatment in combination with oral antidiabetes therapies

Abbreviations: BID = twice daily; ILPS = insulin lispro protamine suspension.

GCP

The confirmatory clinical trials were performed in accordance with GCP as claimed by the MAH

2.4. Clinical efficacy

2.4.1. Methods – analysis of data submitted

A Randomized Trial Comparing Exenatide with Placebo in Subjects with Type 2 Diabetes on Insulin Glargine with or without Oral Antihyperglycemic Medications (Study GWCO)

Study design

Study GWCO was a multicenter, randomized, double-blind, two-arm, parallel, placebo-controlled study in 259 subjects with suboptimal glycaemic control.

Study population

Key inclusion criteria for participation in the study included: stable body weight with a body mass index ≤45 kg/m^2, suboptimal glucose control evidenced by HbA1c ≥7.1% and ≤10.5%, and if taking OADs, treatment with stable doses of metformin or pioglitazone, or a combination of metformin and pioglitazone. Key exclusion criteria included: treatment with specifically excluded glucose-lowering medication or insulin other than glargine within 3 months of participation in the study, and more than 1 major hypoglycaemia episode within 6 months.

Subjects were randomly assigned to add exenatide BID or placebo BID before morning and evening meals to their current therapy regimens (insulin glargine, with or without metformin, pioglitazone, or both). Stratification was performed by investigative site and baseline HbA1c ≤8.0%, ≥8.1%). According to their treatment assignment, subjects received exenatide 5 mcg BID for 4 weeks followed by exenatide 10 mcg BID for the remaining 26 weeks or placebo (equivalent volume) for 30 weeks.

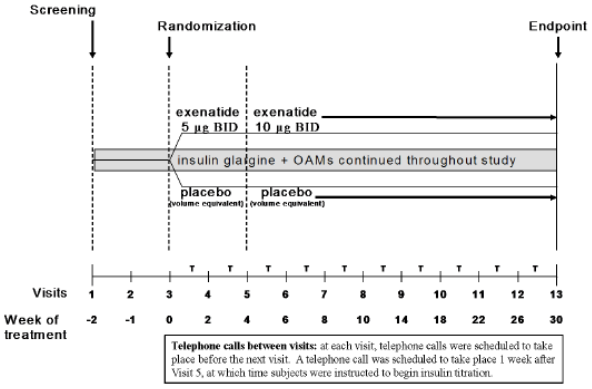
During the initial 4 weeks of treatment (exenatide or placebo), subjects with an HbA1c ≤8.0% decreased their prestudy dose of insulin glargine by 20% and subjects with an HbA1c ≥8.1% maintained their prestudy insulin dose. Beginning at Week 5, insulin doses for the exenatide and placebo treatment groups were actively titrated with guidance from the investigator toward predefined fasting plasma glucose (FPG) targets.

Endpoints

The primary objective of the study was to test the hypothesis that exenatide plus titrated insulin glargine was superior to placebo plus titrated insulin glargine on glycaemic control as measured by change in HbA1c from baseline to Week 30, with or without OADs.

Secondary efficacy measures included the proportion of subjects achieving HbA1c target values (≤7.0%, and ≤6.5%) at Week 30; preprandial and postprandial glucose derived from 7-point SMBG profiles (glucose measurements before and 2 hours after the start of the morning, midday, and evening meals, and at the 0300 hour), change from baseline in FSG, body weight, blood pressure, serum lipids and insulin dose. Additional efficacy analyses included assessment of the proportion of subjects achieving HbA1c <7% and postprandial blood glucose excursions (from 7-point SMBG profiles).

Figure 1. Illustration of design for Study GWCO.



Abbreviations: BID = twice daily within 60 minutes before morning and evening meals; OAMs = oral antidiabetes medications, specifically metformin and/or pioglitazone; T = telephone calls.

The design of study GWCO was considered as adequate for the objective to assess whether the addition of exenatide to ongoing insulin treatment can provide additional effect in comparison to placebo for patients treated with metformin or pioglitazone, or a combination of metformin and pioglitazone. In subjects with an HbA1c ≤8.0%, the insulin dose was reduced by 20%, the impications of which is discussed further below.

A Randomized Trial Comparing Insulin Lispro Protamine Suspension with Insulin Glargine in Subjects with Type 2 Diabetes on Oral Antihyperglycemic Medications and Exenatide (Study IOPB)

Study design

Study IOPB was a multicenter, randomized, open-label, two-arm, 24-week clinical trial which examined 337 subjects with type 2 diabetes with suboptimal glycaemic control.

Study population

Key inclusion criteria for participation in the study included: body mass index ≤45 kg/m2 and suboptimal glucose control evidenced by HbA1c ≥7.0% and ≤10.0%. Patients should have been taking exenatide therapy at a dose of 10 µg twice daily (BID) for at least 3 months prior to Visit 1 as well as receiving metformin or a combination of metformin and a sulfonylurea or a combination of metformin and pioglitazone 3 months prior to Visit 1

Key exclusion criteria included treatment with a maximum dose of OADs that were not allowed with concurrent use of insulin according to the label, insulin treatment within 2 years prior to study entry, treatment with excluded glucose-lowering medication within 3 months of participation in the study, and more than 1 severe hypoglycaemia episode within 6 months.

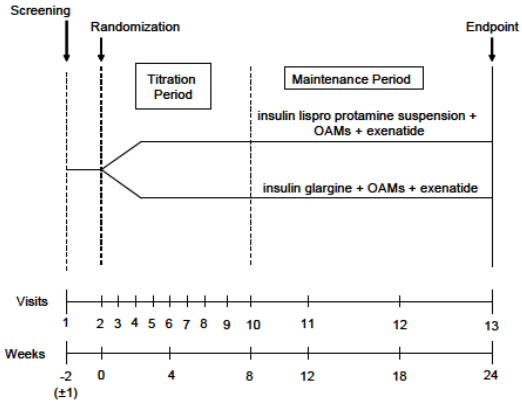
Subjects were randomly assigned with stratification (based on use of an SU and baseline HbA1c strata [≤8.5%, >8.5%]) to add a single evening dose of insulin glargine or ILPS to their current treatment regimen: exenatide (BID, before morning and evening meals) alone or exenatide in combination with metformin, metformin and an SU, or metformin and pioglitazone. The insulin dose was titrated to reach FPG targets over 8 weeks (titration period) and continued treatment for a 16-week maintenance period. The insulin titration regimen for insulin glargine was the same as that used in GWCO (Riddle et al. 2003) and a slightly modified insulin titration regimen was used for ILPS.

Endpoints

The primary objective of the study was to test the noninferiority margin (0.4%) of bedtime dosing with ILPS versus bedtime dosing with insulin glargine on glycaemic control, as measured by change in HbA1c from baseline to endpoint (last observation carried forward [LOCF]) when added to OADs plus exenatide in subjects whose type 2 diabetes was suboptimally controlled (HbA1c ≥7.0% and ≤10.0%).

Secondary efficacy measures included actual HbA1c value at endpoint (LOCF) and actual and change from baseline HbA1c value at Week 24; percentage of patients with target HbA1c at Weeks 12, 18, and 24, and at endpoint (LOCF); 7-point SMBG profiles; mean blood glucose (BG) measurement based on 7-point SMBG, and glycaemic variability (measured as SD of a subject's intraday mean BG levels) from these profiles at endpoint (LOCF). In addition, insulin dose at endpoint (LOCF) was examined.

Figure 2. Illustration of design for Study IOPB.



Abbreviation: OAMs = oral antidiabetes medications.
Note: Visits 3, 4, 5, 7, 8, and 9 were weekly telephone visits.

The design of study IOPB does not provide any data on the efficacy of exenatide in combination with insulin, but will contribute safety data for the combination +/- different OADs.

2.4.2. Results

Disposition of subjects

Table 3. Summary of Reasons for Discontinuation by Treatment (Studies GWCO [N = 261] and IOPB [N = 339]) - All Randomized Subjects

	Study GWCO[1]		Study IOPB	
Subject Disposition	Exenatide n (%)	Placebo n (%)	ILPS n (%)	Insulin Glargine n (%)
Completed	112 (81.2)	101 (82.1)	154 (90.1)	151 (89.9)
Withdrew	26 (18.8)	22 (17.9)	17 (9.9)	17 (10.1)
Adverse Event	13 (9.4) [3]	2 (1.6) [2]	3 (1.8)	2 (1.2)
Entry Criteria Not Met	2 (1.4)	2 (1.6)	1 (0.6)	0 (0.0)
Loss of Glucose Control	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Lost to Follow-up	1 (0.7)	3 (2.4)	0 (0.0)	1 (0.6)
Physician Decision	2 (1.4)	1 (0.8)	2 (1.2)	6 (3.6)
Subject Decision	7 (5.1)	11 (8.9)	3 (1.8)	3 (1.8)
Protocol Violation	1 (0.7)	1 (0.8)	6 (3.5)	5 (3.0)
Sponsor Decision	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)

Abbreviation: ILPS = insulin lispro protamine suspension.

[1] All subjects received insulin glargine therapy in addition to randomized study medication. Two subjects (1 per treatment arm) withdrew prior to receiving study medication.

[2] One subject was withdrawn from the study due to a fatal event of myocardial infarction.

[3] Subject 2800 (exenatide) withdrew from the study due to the adverse event of diarrhea that was not treatment emergent (onset >1 year prior to first dose of study medication and no increase severity post treatment).

Demographics and baseline characteristics

Table 4. Subject Demographics at Baseline (Studies GWCO [N = 259] and IOPB [N = 337]) – Intent-to-Treat Population

Variable Statistic	Study GWCO		Study IOPB	
	Exenatide N = 137	Placebo N = 122	ILPS N = 170	Insulin Glargine N = 167
Age (years)				
Mean (SD)	58.7 (8.91)	59.4 (9.96)	56.5 (9.75)	56.3 (9.35)
Minimum, Maximum	30.8, 77.7	29.9, 84.9	28.8, 73.8	28.7, 74.4
Age Group (n [%])				
>65 years	37 (27.0)	38 (31.1)	37 (21.8)	29 (17.4)
≤65 years	100 (73.0)	84 (68.9)	133 (78.2)	138 (82.6)
Origin; n(%)				
American Indian or Alaska Native	13 (9.5)	13 (10.7)	0 (0.0)	1 (0.6)
Asian	5 (3.6)	2 (1.6)	7 (4.1)	6 (3.6)
Black or African American	14 (10.2)	9 (7.4)	13 (7.6)	14 (8.4)
Multiple	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
White	103 (75.2)	98 (80.3)	129 (75.9)	130 (77.8)
Ethnicity; n(%)				
Hispanic or Latino	44 (32.1)	43 (35.2)	21 (12.4)	16 (9.6)
Not Hispanic or Latino	93 (67.9)	79 (64.8)	149 (87.6)	151 (90.4)
Gender (n [%])				
Female	67 (48.9)	44 (36.1)	95 (55.9)	74 (44.3)
Male	70 (51.1)	78 (63.9)	75 (44.1)	93 (55.7)
Duration of Diabetes (years)				
Mean (SD)	12.3 (6.88)	12.4 (7.13)	9.5 (5.98)	10.3 (6.65)
Minimum, Maximum	0.8, 33.0	1.0, 39.0	0.3, 40.0	0.4, 37.0
Body Weight (kg)				
Mean (SD)	95.4 (20.44)	93.4 (21.21)	101.6 (18.67)	102.4 (19.76)
Minimum, Maximum	47.2, 151.9	49.4, 140.6	45.8, 158.8	54.9, 157.9
BMI (kg/m^2)				
Mean (SD)	33.8 (5.80)	33.1 (6.18)	34.9 (5.21)	34.7 (5.15)
Minimum, Maximum	20.1, 45.6	21.1, 54.4	19.7, 46.6	19.7, 44.9
HbA1c (%)				
Mean (SD)	8.3 (0.85)	8.5 (0.96)	8.2 (0.78)	8.2 (0.80)
Minimum, Maximum	6.9, 10.4	6.7, 10.7	7.0, 10.2	7.0, 10.0
Fasting Glucose (mmol/L)				
Mean (SD)	7.3 (2.6)	7.5 (2.6)	n/a	n/a
Minimum, Maximum	2.6, 14.6	2.5, 16.3	n/a	n/a
Insulin Dose (U)				
Mean (SD)	49.5 (29.88)	47.4 (25.38)	n/a	n/a
Minimum, Maximum	20.0, 200.0	20.0, 130.0	n/a	n/a

Abbreviations: n/a = not applicable; ILPS = insulin lispro protamine suspension; SD = standard deviation, U = units.

Patients had a rather long duration of disease. The proportion of males/females differed between the placebo and exenatide groups in study GWCO.

In study GWCO patients had to be included at screening with a body mass index of ≤45 kg/m2. However there were patients included at baseline(time of randomization) with a BMI of 54.4 kg/m2. In study GWCO, inclusion criteria had to be suboptimal glucose control evidenced by HbA1c ≥7.1% (and ≤ 10.5%). However at baseline, minimum in the exenatide group was 6.9%, in the placebo group 6.7%. This 2 points have been addressed by the applicant during the procedure and are discussed below in the section Discussion.

Table 5 Baseline Diabetes Management Method (Study GWCO [N=259]) –ITT Population

Variable Statistic	Exenatide N = 137	Placebo N = 122	Total N=259
Baseline Diabetes Management Method			
Metformin	91 (66.4%)	91 (74.6%)	182 (70.3%)
Pioglitazone	2 (1.5%)	6 (4.9%)	8 (3.1%)
Metformin + Pioglitazone	23 (16.8%)	8 (6.6%)	31 (12.0%)
Diet and Exercise	21 (15.3%)	17 (13.9%)	38 (14.7%)

Table 6 Summary of Concomitant OAD in Study IOPB – All Randomized Subjects (N=339)

Pre-Treatment Drug Name	ILPS N=171	Glargine N = 168	Total N=339	p-value*
Patients with 3 Drugs	2 (1.17%)	5 (2.98%)	7 (2.06%)	0.2572
Patients with 2 Drugs	128 (74.85%)	114 (67.86%)	242 (71.39%)	0.0092
SU/Metformin	105 (61.40%)	104 (61.90%)	209 (61.65%)	0.9493
TZD/Metformin	22 (12.87%)	10 (5.95%)	32 (9.44%)	0.0289
SU/TZD	1 (0.58%)	0 (0.00%)	1 (0.29%)	0.3390
Patients with 1 Drug	40 (23.39%)	48 (28.57%)	88 (25.96%)	0.0224
Metformin	40 (23.39%)	47 (27.98%)	87 (25.66%)	0.0334
SU	0 (0.00%)	1 (0.60%)	1 (0.29%)	0.3138

Abbreviation: ILPS = insulin lispro protamine suspension; TZD = thiozolidinedione, SU = sulphonylurea.
*Frequencies are analyzed using CMH test with the stratification variables of baseline A1C strata (8.5%, >8.5%) and use of sulfonylurea (yes/no).

In the 2 studies, exenatide and insulin has mainly been given together with metformin, metformin+pioglitazone and SU+metformin.

Primary and secondary efficacy endpoints

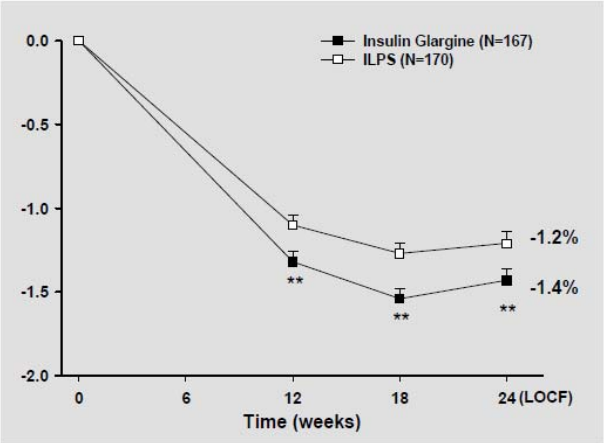
Table 7. Summary of Efficacy Results for Study GWCO (Intent-to-Treat Population)

	Least-Squares Mean or Percentage of Subjects		
Variable	**Exenatide (N=137)**	**Placebo (N=122)**	**Estimated Treatment Difference (95% CI)**
Haemoglobin A1c (%)			
Baseline	8.3	8.5	-0.20
Week 30	6.7	7.4	-0.71 (-0.95 to -0.47)*
Change	-1.7	-1.0	
Proportion reaching glycaemic target			
Haemoglobin A1c <7.0%	56%	29%	--*
Haemoglobin A1c ≤6.5%	42%	13%	--*
Body weight (kg)			
Baseline	95.4	93.8	1.6
Week 30	93.6	96.3	-2.74 (-3.74 to -1.74)*
Change	-1.78	+0.96	
Change in insulin dose at Week 30			
U/day	13	20	-6.5 (-12.24 to -0.79)**
U/kg	0.15	0.20	-0.05 (-0.10 to 0.00)
Fasting serum glucose(mmol/L)			
Baseline	7.4	7.4	-0.01
Week 30	6.1	6.5	-0.41 (-0.99 to 0.18)

Abbreviations: CI = confidence interval.
Between-treatment difference: * p<0.001, ** p<0.05

The proportion of patients reaching HbA1c < 7.0 % in the placebo group is 29%, indicating that no exenatide therapy at all would have been necessary for these patients. In addition, in the exenatide group HbA1c<7.0% is 56%, HbA1c ≤6.5% is 42%. Therefore, in study GWCO there seems to be a number of patients that had already reached their HbA1c target at baseline. This hinders the interpretation of efficacy. The MAH provided clarification on these points during the procedure (see section Discsussion).

Figure 3. LS mean (SE) change in HbA1c from baseline to Endpoint (Week 24 [LOCF]) by treatment (Study IOPB [N = 337]) – ITT population.



Abbreviations: LS = least squares; ILPS = insulin lispro protamine suspension; LOCF = last observation carried forward; SE = standard error.
**p<0.01, insulin glargine vs. insulin ILPS.

Insulin dose

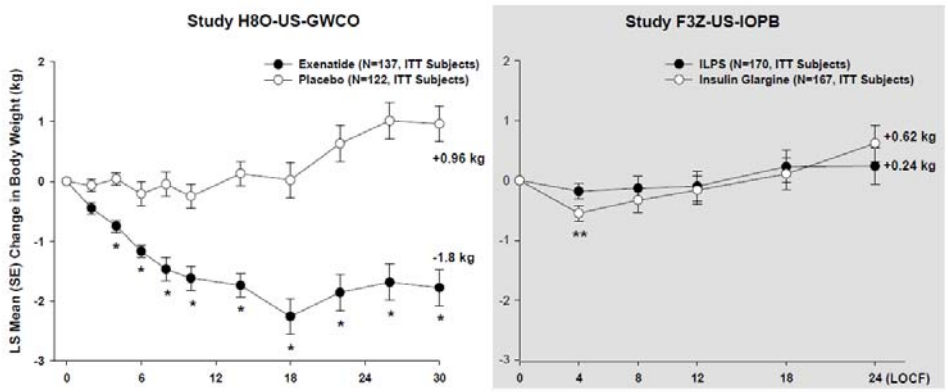
In study GWCO, subjects receiving exenatide, administered statistically significantly lower insulin doses in units (U) at Weeks 8, 10, 14, 18, 22, 26, and 30 compared to placebo ($p<0.05$). The LS mean (SE) insulin dose per day in U was statistically significantly lower for exenatide-treated subjects (62 [2] U) compared to placebo-treated subjects (69 [2] U, $p=.026$) at Week 30.

In Study IOPB, insulin dose at endpoint (LOCF) was analyzed by 24-hour total daily insulin.

The mean (SE) treatment difference at endpoint for ILPS (31 [1.5] U) compared to insulin glargine (38 [1.4] U; $p<.001$) resulted in statistically significantly greater insulin doses for the insulin glargine treatment group.

In study GWCO, during the initial 4 weeks of treatment (exenatide or placebo), subjects with an HbA1c ≤8.0% decreased their prestudy dose of insulin glargine by 20% and subjects with an HbA1c ≥8.1% maintained their prestudy insulin dose. Beginning at Week 5, insulin doses for the exenatide and placebo treatment groups were actively titrated with guidance from the investigator toward predefined fasting plasma glucose (FPG) targets. In both groups, the mean daily insulin dose increased from baseline to week 30 with the final dose being higher in the placebo group. Despite this, there was a statistically significant difference in favour of exenatide with respect to reduction of HbA1c.

Figure 4. LS mean (SE) change in body weight from baseline to endpoint by treatment (Studies GWCO [N = 259] and IOPB [N = 337]) – ITT population.



Abbreviations: ITT = intent-to-treat; LS = least squares; ILPS = insulin lispro protamine suspension; LOCF = last observation carried forward; SE = standard error.
Notes: Detailed explanation of the statistical analyses can be found in Study GWCO CSR and Study IOPB CSR (Section 5.3.5.1).
*p<0.001, treatment vs. placebo.
**p=.036, insulin glargine vs. ILPS

The LS mean (SE) change in body weight from baseline at Week 30 was a reduction of -1.8 (0.3) kg for subjects treated with exenatide, which was significantly different from the weight gain of +1.0 (0.3) kg observed for the placebo-treated subjects (p<0.001).

As expected, in study GWCO there was a statistically significant difference in favour of exenatide with respect to weight lowering.

Table 8 Summary of Blood Pressure Values in Studies GWCO (N = 259) and IOPB (N=337) – ITT Population

	Least Squares Mean (Standard Error)			
	Study GWCO		Study IOPB	
	Exenatide (N=137)	Placebo (N=122)	ILPS (N=170)	Insulin Glargine (N=167)
Systolic Blood Pressure (mm Hg)				
Baseline	130.02 (1.26)	127.85 (1.35)	128.74 (1.20)	125.86 (1.04)
Change from Baseline to Last Scheduled Visit (Week 30, GWCO; Endpoint [LOCF], IOPB [1]	-2.74 (1.25)*,**	1.71 (1.31)	n/a	n/a
Diastolic Blood Pressure (mm Hg)				
Baseline	75.76 (0.79)	74.40 (0.85)	75.66 (0.69)	75.82 (0.70)
Change from Baseline to Last Scheduled Visit (Week 30, GWCO; Endpoint [LOCF], IOPB [1])	-1.73 (0.66)*,†	1.69 (0.70)*	n/a	n/a

Abbreviation: ILPS = insulin lispro protamine suspension.
[1] Analyses of change in systolic and diastolic blood pressure were not conducted in Study IOPB. At endpoint, mean systolic blood pressure was 127.25 mm Hg for the ILPS treatment group, 127.95 mm Hg for the insulin glargine treatment group. Diastolic blood pressure at endpoint was 74.97 mm Hg for the ILPS treatment group, 76.06 mm Hg for the insulin glargine treatment group.
*p-value <0.05, change from baseline within treatment.
**p-value <0.05, †p-value <0.001, exenatide compared to placebo.

The addition of exenatide to insulin did not result in any signs of a detrimental effect on blood pressure, but rather a moderate reduction compared to placebo.

Clinical studies in special populations (study GWCO)

Table 9 LS Mean (SE) Change in HbA1c From Baseline to Week 30 by Treatment and Intrinsic Factors: Gender, Age, Ethnicity, Renal Function, Baseline HbA1c Stratum, and Duration of Diabetes

	Exenatide			Placebo		
Subgroup	N	Mean (SD) Baseline (%)	LS Mean (SE) Change (%) [1]	N	Mean (SD) Baseline (%)	LS Mean (SE) Change (%) [2]
Overall Population [2]	131	8.4 (1.0)	-1.7 (0.1)	113	8.5 (1.0)	-1.0 (0.1)
Gender						
Male	67	8.3 (0.9)	-1.7 (0.1)	71	8.5 (1.0)	-1.1 (0.1)
Female	64	8.4 (0.8)	-1.8 (0.1)	42	8.5 (0.9)	-0.9 (0.2)
Age (Screening)						
≤65 Years	97	8.4 (0.9)	-1.7 (0.1)	78	8.6 (0.9)	-1.0 (0.1)
>65 Years	34	8.2 (0.7)	-1.7 (0.2)	35	8.5 (1.0)	-1.1 (0.2)
Ethnicity						
Hispanic or Latino	39	8.4 (0.9)	-1.9 (0.2)	39	8.6 (1.0)	-0.8 (0.2)
Not Hispanic or Latino	76	8.3 (0.9)	-1.6 (0.1)	66	8.5 (1.0)	-1.1 (0.1)
Race						
Caucasian	82	8.3 (0.1) [3]	-1.8 (0.1)	85	8.5 (0.1) [3]	-1.0 (0.1)
Not Caucasian	33	8.4 (0.2) [3]	-1.5 (0.2)	20	8.8 (0.2) [3]	-0.8 (0.3)
Renal Function (Baseline)						
Normal [4]	52	8.3 (0.1) [3]	-1.7 (0.1)	45	8.7 (0.1)[3]	-1.1 (0.1)
Mild Impairment [4]	50	8.4 (0.1) [3]	-1.7 (0.1)	51	8.4 (0.1) [3]	-0.9 (0.1)
Moderate Impairment [4]	13	8.2 (0.3) [3]	-1.7 (0.3)	9	8.5 (0.3) [3]	-1.1 (0.3)
HbA1c Stratum (Baseline)						
≤8.0%	56	7.6 (0.3)	-1.4 (0.2)	38	7.5 (0.4)	-1.0 (0.2)
>8.0%	75	8.9 (0.6)	-1.9 (0.1)	75	9.1 (0.7)	-1.0 (0.1)
Duration of Diabetes						
<10 years	48	8.0 (0.8)	-1.6 (0.1)	42	8.4 (1.0)	-1.4 (0.1)
≥10 years	83	8.5 (0.8)	-1.8 (0.1)	71	8.6 (0.9)	-0.8 (0.1)

Abbreviations: GRF = estimated glomerular filtration rate; LS = least squares; SD = standard deviation; SE = standard error.

Note: Detailed explanation of the statistical analyses can be found in Study GWCO CSR (Section 5.3.5.1).

[1] LS mean change in HbA1c from baseline at Week 30 based on a MMRM analysis.

[2] Only patients with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in the analysis.

[3] Baseline values expressed as LS mean (SE) based on an ANOVA model.

[4] Normal renal function defined as eGRF >90 mL/min, mild impairment as 60 to 90 mL/min, and moderate impairment as 30 to 59 mL/min. There were no subjects with severe (<30 mL/min) renal impairment.

There were no major differences with respect to efficacy in the subgroups examined, although the number of patients in some of the groups was rather limited.

Table 10 Change from Baseline in HbA1c at Week 30 by Treatment and Extrinsic Factors: Baseline Dose and Baseline OAD (GWCO, Intent-to-Treat Population [N = 259])

	Exenatide			Placebo		
Subgroup	N	Mean (SD) Baseline (%)	LS Mean (SE) Change (%) [1]	N	Mean (SD) Baseline (%)	LS Mean (SE) Change (%) [1]
Overall Population [2]	131	8.4 (1.0)	-1.7 (0.1)	113	8.5 (1.0)	-1.0 (0.1)
Baseline Insulin Dose						
≤0.5 U/kg	77	8.3 (0.9)	-1.7 (0.1)	65	8.6 (0.9)	-1.2 (0.1)
>0.5 U/kg	54	8.5 (0.8)	-1.8 (0.1)	48	8.4 (1.0)	-0.8 (0.1)
Baseline OAD						
Metformin	87	8.4 (0.9)	-1.7 (0.1)	84	8.5 (0.9)	-1.1 (0.1)
Metformin + Pioglitazone	21	8.2 (0.8)	-1.8 (0.2)	8	8.9 (0.9)	-1.3 (0.4)
Diet and Exercise	21	8.3 (0.9)	-1.6 (0.2)	15	8.7 (1.0)	-0.6 (0.3)
Pioglitazone	2	8.7 (0.3)	-0.4 (0.7)	6	7.9 (1.0)	-0.8 (0.5)

There were no major differences with respect to efficacy based on baseline insulin dose or OAD. The number of patients with only pioglitazone was very limited.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.4.3. Discussion

This application aims to extend the indication of exenatide to include combination with basal insulin.

Support for this additional indication is based on 2 studies: H8O-US-GWCO (GWCO) and F3Z-US-IOPB (IOPB). The design of study GWCO, in which exenatide and placebo is added to ongoing insulin therapy (+/- OAD) was considered as adequate for the objective to assess whether the addition of exenatide can provide additional effect in comparison to placebo. The design of study IOPB, in which insulin is added to ongoing exenatide treatment, does not provide any substantial data on the efficacy of exenatide in combination with insulin, but contributes safety data for the combination +/- different OADs.

In studies GWCO and IOPB a number of subjects were included being in excess of BMI criteria (BMI >45 kg/m2) at baseline. Since this concerned only 6 (1%) subjects, and the changes in HbA1c and body weight for these patients were similar to the overall results for subjects, the CHMP agreed that the inclusion of these 6 subjects in the ITT analyses has not affected the final conclusion of the studies.

In study GWCO, in the placebo group as well as in the exenatide group, 13 subjects had a HbA1c ≥

7.1% at screening that subsequently decreased to below this target by baseline. Per definition, these patients had already reached treatment target when they were randomised to treatment. However, since the number of patients was low and there was no imbalance between treatment groups, this would not have had affected the overall results.

For add-on studies, it is recommended to select patients not meeting therapeutic targets on the established agent alone at maximal tolerated or recommended dose. In study GWCO, during the initial 4 weeks of treatment, subjects with an HbA1c ≤8.0% decreased their prestudy dose of insulin glargine by 20% and subjects with an HbA1c ≥8.1% maintained their prestudy insulin dose. Beginning at Week 5, insulin doses for the exenatide and placebo treatment groups were actively titrated with guidance from the investigator toward predefined fasting plasma glucose (FPG) targets. In both groups, the

mean daily insulin dose increased from baseline to week 30 with 13 and 20/U per day in the exenatide and placebo groups respectively. Apparently, the patients were not optimally titrated at study start.

Looking at the results in the placebo group, 29% of the patients reached a HbA1c below 7% and were therefore not in need of additional treatment. It could therefore be argued that it may have been more adequate to optimize the insulin dose before randomization and add exenatide to "true" non-responders. However, the insulin doses in the placebo group was higher compared to the exenatide group at week 30 and despite this difference, there was a statistically significant difference in favour of exenatide with respect to reduction of HbA1c compared to placebo (-0.71%, CI -0.95% to -0.47%). There was also a higher proportion of patients reaching a HbA1c below 7%, demonstrating that exenatide does provide additional glucose lowering effect on top of insulin treatment.

As expected, in study GWCO there was a statistically significant difference in favour of exenatide with respect to weight lowering.

In conclusion, adding exenatide to ongoing insulin therapy in combination with optimization of insulin therapy resulted in a clinically relevant reduction of HbA1c and, albeit to a lesser extent, body weight compared to placebo.

2.5. Clinical Safety

2.5.1. Methods – analysis of data submitted

Patient exposure

A total of 600 subjects were randomly assigned to a treatment in Studies GWCO and IOPB. Of these subjects, 596 received at least 1 dose of randomly assigned study drug. Two subjects (1 from each treatment group) in Study IOPB received study drug but did not have any post baseline data, therefore 307 subjects are in the intent-to-treat (ITT) data set. These subjects who were exposed to study drug constitute the ITT sample and serve as the primary population of interest for analyses. Of the 596 ITT subjects, 474 (80%) received exenatide treatment in combination with basal insulin (ILPS or insulin glargine). Subjects in these studies were exposed to randomly assigned study treatment for a mean of at least 22 weeks across studies and treatment groups.

Table 11 Subject Numbers and Mean Treatment Duration in Studies GWCO and IOPB

	Randomized Subjects	Intent-to-Treat Subjects	
Study	N	N	Mean Duration of Treatment (Weeks)
H8O-US-GWCO (Insulin glargine with or without OADs) – 30 Weeks of Treatment[1]			
Exenatide	138	137	25.98
Placebo	123	122	26.85
F3Z-US-IOPB (Exenatide with OADs) – 24 Weeks of Treatment[2]			
Insulin ILPS	171	170	22.93
Insulin glargine	168	167	23.39
Total	600	596	--

Abbreviations: CSR = clinical study report; ILPS = insulin lispro protamine suspension; N = number of subjects; OAD = oral antidiabetes drug.

[1] Mean days of exposure to insulin glargine: 183, exenatide group; 189, placebo group. Subjects 1802 (exenatide) and 7200 (placebo) discontinued study participation after random assignment to treatment but before the first dose of insulin glargine and therefore are not included in the insulin glargine exposure estimate.

[2] Mean weeks of exposure to insulin glargine and insulin ILPS: 24 weeks (ILPS 65.9%: insulin glarine 70.1%).

The number of patients exposed to the combination of insulin and exenatide was considered as adequate while the mean duration of exposure is rather short which may be of importance concerning the occurrence of rare adverse events.

2.5.2. Results

Adverse events

In Study GWCO, TEAEs were reported in 109 (79.6%) exenatide subjects and 86 (70.5%) placebo subjects. A total of 94 (36.3%) subjects experienced adverse events that the investigator considered to be possibly related to study medication (50.4% exenatide subjects; 20.5% placebo subjects). Eight exenatide subjects and 11 placebo subjects experienced treatment-emergent SAEs, of which 1 event in a placebo subject (myocardial infarction) resulted in death. Twelve exenatide subjects and 2 placebo subjects (including 1 death) discontinued due to TEAEs. One exenatide subject withdrew due to an adverse event that was not treatment emergent. All other subjects withdrew due to vomiting or nausea, except one subject due to headache.

In Study IOPB, TEAEs were reported in 86 (50.3%) ILPS subjects and 110 (65.5%) insulin glargine subjects. Of these, 13 (3.8%) were considered related to study drug as assessed by the investigator (10 [5.8%] ILPS subjects; 3 [1.8%] insulin glargine subjects). Serious adverse events were reported by 9 (5.3%) ILPS subjects, while 5 (3.0%) insulin glargine subjects reported SAEs. There were no deaths reported in either treatment group. Five (1.5%) of all subjects withdrew from the study due to an adverse event (3 [1.8%] ILPS subjects; 2 [1.2%] insulin glargine subjects).

Common adverse events

In Study GWCO, nausea was the most common adverse event reported, occurring in 40.9% and 8.2% of exenatide and placebo subjects, respectively. Consistent with the known safety profile of exenatide, the incidence of nausea, diarrhea, and vomiting were higher in subjects treated with exenatide compared to those treated with placebo. Headache and constipation also occurred at higher frequency in exenatide subjects compared to placebo subjects. The majority of adverse events were mild to moderate in intensity.

Table 12. Number (%) of Subjects With Treatment-Emergent Adverse Events with an Incidence Equal to or Greater than 2% in Any Treatment Group (GWCO; ITT [N=259])

Preferred Term	Exenatide N=137 n (%)	Placebo N=122 n (%)	Total N=259 n (%)
Nausea	56 (40.9)	10 (8.2)	66 (25.5)
Diarrhoea	25 (18.2)	10 (8.2)	35 (13.5)
Vomiting	25 (18.2)	5 (4.1)	30 (11.6)
Headache	19 (13.9)	5 (4.1)	24 (9.3)
Upper respiratory tract infection	11 (8.0)	9 (7.4)	20 (7.7)
Constipation	14 (10.2)	2 (1.6)	16 (6.2)
Cough	7 (5.1)	7 (5.7)	14 (5.4)
Nasopharyngitis	8 (5.8)	6 (4.9)	14 (5.4)
Dizziness	6 (4.4)	7 (5.7)	13 (5.0)
Back pain	9 (6.6)	2 (1.6)	11 (4.2)
Dyspepsia	9 (6.6)	2 (1.6)	11 (4.2)
Abdominal pain	4 (2.9)	4 (3.3)	8 (3.1)
Asthenia	7 (5.1)	1 (0.8)	8 (3.1)
Fatigue	5 (3.6)	3 (2.5)	8 (3.1)
Toothache	4 (2.9)	4 (3.3)	8 (3.1)
Bronchitis	4 (2.9)	3 (2.5)	7 (2.7)
Hypertension	3 (2.2)	4 (3.3)	7 (2.7)
Oropharyngeal pain	2 (1.5)	5 (4.1)	7 (2.7)
Abdominal distension	5 (3.6)	1 (0.8)	6 (2.3)
Abdominal pain upper	3 (2.2)	3 (2.5)	6 (2.3)
Chest pain	2 (1.5)	4 (3.3)	6 (2.3)
Influenza	2 (1.5)	4 (3.3)	6 (2.3)
Myalgia	3 (2.2)	3 (2.5)	6 (2.3)
Oedema peripheral	2 (1.5)	4 (3.3)	6 (2.3)
Anorexia	5 (3.6)	0 (0.0)	5 (1.9)
Pain in extremity	3 (2.2)	2 (1.6)	5 (1.9)
Sinusitis	3 (2.2)	2(1.6)	5 (1.9)
Tremor	2 (1.5)	3 (2.5)	5 (1.9)
Arthralgia	3 (2.2)	1 (0.8)	4 (1.5)
Decreased appetite	4 (2.9)	0 (0.0)	4 (1.5)
Flatulence	3 (2.2)	1 (0.8)	4 (1.5)
Gastrooesophageal reflux disease	3 (2.2)	1 (0.8)	4 (1.5)
Hypoasthesia	3 (2.2)	1 (0.8)	4 (1.5)
Joint sprain	3 (2.2)	1 (0.8)	4 (1.5)
Muscle spasms	1 (0.7)	3 (2.5)	4 (1.5)
Musculoskeletal pain	4 (2.9)	0 (0.0)	4 (1.5)

In Study IOPB, for subjects who had ≥1 TEAE (n=196, 58.2%), a significantly greater percentage was reported for the insulin glargine treatment group (n=110, 65.9%) versus the ILPS treatment group (n=86, 50.6%) (p=.006). The most common TEAEs (occurring ≥3%) were headache (7.4%), nausea (6.5%), diarrhoea (6.2%), nasopharyngitis (5.9%), upper respiratory tract infection (5.9%), sinusitis (4.7%), gastroenteritis viral (4.2%), vomiting (4.2%), arthralgia (3.9%), nasal congestion (3.3%), abdominal discomfort (3%), and oropharyngeal pain (3%); with the exception of viral gastroenteritis, there were no statistically significant differences between the treatment groups for any of these events. Viral gastroenteritis was reported significantly more often in the insulin glargine treatment group (n=12, 7.2%) versus the ILPS treatment group (n=2, 1.2%) (p=.006).

Table 13. Number (%) of Subjects With Treatment-Emergent Adverse Events With an Incidence ≥2% in Any Treatment Group (Study IOPB; Intent-to-Treat Population [N = 337])

Preferred Term	Insulin ILPS N = 170 n (%)	Insulin Glargine N = 167 n (%)	Total N = 337 n (%)
Headache	11 (6.5)	14 (8.4)	25 (7.4)
Nausea	12 (7.1)	10 (6.0)	22 (6.5)
Diarrhoea	9 (5.3)	12 (7.2)	21 (6.2)
Nasopharyngitis	11 (6.5)	9 (5.4)	20 (5.9)
Upper respiratory tract infection	11 (6.5)	9 (5.4)	20 (5.9)
Sinusitis	7 (4.1)	9 (5.4)	16 (4.7)
Gastroenteritis viral	2 (1.2)	12 (7.2)	14 (4.2)
Vomiting	6 (3.5)	8 (4.8)	14 (4.2)
Arthralgia	8 (4.7)	5 (3.0)	13 (3.9)
Nasal congestion	3 (1.8)	8 (4.8)	11 (3.3)
Abdominal discomfort	6 (3.5)	4 (2.4)	10 (3.0)
Oropharyngeal pain	3 (1.8)	7 (4.2)	10 (3.0)
Cough	4 (2.4)	5 (3.0)	9 (2.7)
Pain in extremity	3 (1.8)	5 (3.0)	8 (2.4)
Influenza	4 (2.4)	3 (1.8)	7 (2.1)
Sinus congestion	6 (3.5)	1 (0.6)	7 (2.1)
Urinary tract infection	5 (2.9)	2 (1.2)	7 (2.1)
Bronchitis	1 (0.6)	5 (3.0)	6 (1.8)
Pyrexia	1 (0.6)	5 (3.0)	6 (1.8)
Dyspepsia	1 (0.6)	4 (2.4)	5 (1.5)
Fall	0 (0)	4 (2.4)	4 (1.2)
Myalgia	0 (0)	4 (2.4)	4 (1.2)

Overall, as expected, patients who initiated exenatide in study GWCO had a high incidence of GI symptoms. These adverse events are to a large extent transient, which is confirmed in study IOPB in which the incidence of nausea was 6-7%.

Serious adverse events and deaths

One death was reported during Study GWCO. Subject 8001 (placebo), a 65-year-old Mexican male with a medical history of arterial hypertension, unspecified arrhythmia, atrioventricular block, and complete right bundle branch block, experienced a fatal myocardial infarction approximately 3 months after initiation of study medication.

In Study GWCO, a total of 8 (5.8%) exenatide and 11 (9.0%) placebo-treated subjects experienced at least 1 treatment-emergent serious adverse event during the study.

Two serious adverse events (Subject 2700 [placebo], urticaria; Subject 9100 [exenatide], accidental overdose) were assessed by the investigator as related to study medication. With the exception of the fatal myocardial infarction, none of the serious adverse events resulted in discontinuation from the study, and the majority of serious adverse events resolved during the study, without interruption of study medication treatment. With the exception of 3 events of chest pain (1 exenatide subject, 1 placebo subject [2 events]) and 2 exenatide subjects who experienced osteoarthritis, serious adverse events occurred as a single instance for that Preferred Term category. One placebo subject experienced the serious adverse event of hypoglycaemia. There were no serious adverse events of hypoglycaemia reported among exenatide subjects.

Table 14. Treatment-Emergent Serious Adverse Events (Study GWCO; Intent-to-Treat Population [N = 259])

Treatment	Subject	Treatment Duration Prior to Event Onset (days)	Preferred Term [1]	Intensity	Causality [2]	Outcome
Exenatide	801	9	Staphylococcal Infection	Severe	No	Recovering/ Resolving
	2203	150	Osteoarthritis	Moderate	No	Recovered with Sequelae
	2702	138	Herpes zoster	Severe	No	Recovered with Sequelae
	3002	10	Dyspnoea	Mild	No	Recovered
		10	Chest pain	Mild	No	Recovered
	4007	25	Coronary artery occlusion	Severe	No	Recovering/ Resolving
	4601	201 [3]	Osteoarthritis	Severe	No	Ongoing
	7001	43	Eye Penetration	Severe	No	Recovered
		43	Fall	Severe	No	Recovered
	9100	6	Accidental overdose	Mild	Yes	Recovered
Placebo	1006	100	Cystitis	Severe	No	Recovered
		100	Sepsis	Mild	No	Recovered
	1203	11	Suicide attempt	Severe	No	Recovered
	2204	47	Ankle fracture	Severe	No	Recovering/ Resolving
	2700	49	Urticaria	Severe	Yes	Recovered
	3003	57	Pulmonary Embolism	Moderate	No	Recovered
	3703	180	Hypoglycaemia	Severe	No	Recovered
	3903	115	Transient ischemic attack	Moderate	No	Recovered
	5209	195	Small intestinal obstruction	Moderate	No	Recovered
	6013	103	Chest Pain	Severe	No	Recovered
		103	Palpitations	Severe	No	Recovered
		184	Chest Pain	Mild	No	Recovered
	7205	89	Angina unstable	Mild	No	Ongoing
	8001	79	Myocardial infarction	Severe	No	Fatal

In Study IOPB, a total of 14 patients (4.2%) reported SAEs: 9 (5.3%) in the ILPS treatment group and 5 (3.0%) in the insulin glargine treatment group. Most of the events were severe in intensity. One patient in the ILPS treatment group reported an SAE of hypoglycaemia during the study. The most commonly reported SAE in the ILPS treatment group was atrial fibrillation, which was reported in 2 patients (1.2%); the events were severe in both patients but were considered to be not related to study treatment by the investigator. All other SAEs for ILPS treatment were reported only once. There was no significant difference between treatment groups on incidence of any reported SAEs.

Table 15. Treatment-Emergent Serious Adverse Events (Study IOPB; Intent-to-Treat Population [N=337])

Treatment	Subject	Treatment Duration Prior to Event Onset (days)	Preferred Term [1]	Intensity	Causality [2]	Outcome
Insulin ILPS	313	82	Cystitis bacterial	Moderate	No	Recovered
	604	58	Colon cancer	Severe	No	Not recovered
	1018	132	Appendicitis	Severe	No	Recovered
	2708	108	Nephrolithiasis	Severe	No	Recovering/ resolving
	2907	11	Atrial fibrillation	Severe	No	Recovered
	2908	83	Pneumonia pneumococcal	Severe	No	Recovered
	3006	163	Joint injury	Severe	No	Recovering/ resolving
	4427	146	Atrial fibrillation	Severe	No	Recovering/ resolving
	5107	42	Hypoglycaemia	Severe	Yes	Recovered
Insulin Glargine	911	41	Heat exhaustion	Severe	No	Recovered
	1101	86	Ankle fracture	Severe	No	Recovered
		86	Fall	Mild	No	Recovered
	4436	43	Drug exposure during pregnancy	Severe	No	Not recovered
	5403	84	Chest pain	Severe	No	Recovered
	5711	12	Cholelithiasis	Severe	No	Recovered

In study GWCO, there was no difference in the incidence of SAE between the placebo and exenatide groups and overall in both studies there was no clustering of any SAE. There was one case of malignancy in study IOPB. This clinical trial case regarded a 53 year old Caucasian female. Rectal bleeding was present at time of screening, no diagnosis of cancer was made (despite being a symptom). Several months history of recurring rectal bleeding. The patient's risk factors for colon cancer were high fat diet and obesity. She received multiple concomitant medications. The patient received study drug 24 units daily on 28Jan08 via a device. On 18Mar08 she had a colonoscopy which showed a tumor and a biopsy was taken. The biopsy was found to be malignant. Thus, the patient received the combination of insulin and exenatide for 3 months and it is not likely that this was related to the malignancy. Overall, the time of exposure in the referred studies is too short to draw any conclusions on the risk of neoplasms.

Adverse events of special interest

Table 16. Overview of Treatment-Emergent Adverse Events of Clinical Interest (Study GWCO; Intent-to-Treat Population [N = 259])

Event Type	Exenatide N = 137 n (%)	Placebo N = 122 n (%)	Total N = 259 n (%)
Gastrointestinal Events	79 (57.7)	33 (27.0)	112 (43.2)
Hypoglycaemia [1]	34 (24.8)	36 (29.5)	70 (27.0)
Cardiac Events	8 (5.8)	9 (7.4)	17 (6.6)
Loss of Consciousness and Other Neurological Symptoms	6 (4.4)	7 (5.7)	13 (5.0)
Loss of Efficacy [2]	0 (0.0)	0 (0.0)	0 (0.0)
Potentially Immune-Related Events	9 (6.6)	9 (7.4)	18 (6.9)
Abdominal Pain	10 (7.3)	9 (7.4)	19 (7.3)

[1] Includes both minor and major hypoglycaemia. Most events collected were not adverse events. Minor hypoglycaemia defined as symptoms consistent with hypoglycaemia that a concurrent finger stick blood glucose concentration <3.0 mmol/L (54 mg/dL). Major hypoglycaemia defined as symptoms consistent with hypoglycaemia that resulted in loss of consciousness or seizure that showed prompt recovery in response to administration of glucagon or glucose **or** documented hypoglycaemia (blood glucose concentration <3.0 mmol/L [54 mg/dL]) that required the assistance of another person because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycaemia were detected by the subject).

Hypoglycaemic adverse events

In Studies GWCO and IOPB, hypoglycaemia events were categorized as the following.

- Major hypoglycaemia - any episode with symptoms consistent with hypoglycaemia resulting in loss of consciousness or seizure that shows prompt recovery in response to administration of glucagon or glucose **or** documented hypoglycaemia (blood glucose <3.0 mmol/L [54 mg/dL]) requiring the assistance of another person because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycaemia are detected by the subject).
- Minor hypoglycaemia - any time a subject feels that he or she is experiencing a sign or symptom associated with hypoglycaemia that is either self-treated by the subject or resolves on its own **and** has a concurrent fingerstick blood glucose <3.0 mmol/L (54 mg/dL).
- Symptoms of hypoglycaemia - all other reported hypoglycaemic adverse events that did not fit the definitions of major or minor hypoglycaemia.
- Non-nocturnal hypoglycaemia - any hypoglycaemic episode that occurred after breakfast and before bedtime.
- Nocturnal hypoglycaemia – any hypoglycaemic episode that occurred after bedtime and before breakfast.

Table 17. Summary of Hypoglycaemia Events (Study GWCO;Intent-to-Treat Population [N=259])

	Exenatide N=137 n (%) Events	Placebo N=122 n (%) Events
Major Hypoglycaemia	0 (0.0) 0	1 (0.8) 2
Minor Hypoglycaemia	34 (24.8) 92	35 (28.7) 82
Symptoms of Hypoglycaemia [1]	78 (56.9) 419	71 (58.2) 340

Table 18. Summary of Hypoglycaemia Events (Study IOPB; Intent-to-Treat Population [N=337])

	ILPS N=170 n (%) Events	Insulin Glargine N=167 n (%) Events
Major Hypoglycaemia	2 (1.2) 2	0 (0.0) 0
Minor Hypoglycaemia	63 (37.1) 246	64 (38.3) 220
Symptoms of Hypoglycaemia [1]	71 (41.8) 1112	89 (53.3) 1268

There was no difference in the incidence of hypoglycaemia between exenatide and placebo in study GWCO. Cases of major hypoglycaemia were few.

In study IOPB, the incidence of hypoglycaemia was somewhat higher in the glargine group compared to ILPS.

Cardiac events

Eight (5.8%) exenatide and 9 (7.4%) placebo subjects experienced at least 1 adverse event categorized as a cardiac event; 22 total events. The majority of these events were mild or moderate in intensity; 5 events were severe in intensity (Subject 6013 [placebo], palpitations and chest pain; Subject 4007 [exenatide], coronary artery occlusion; Subject 5001 [exenatide], left ventricular hypertrophy; Subject 8001 [placebo], myocardial infarction). Seven of the 22 cardiac events were serious adverse events. With the exceptions of 1 event of palpitations (Subject 6100 [exenatide]), and 2 chest pain events (Subjects 1401 [exenatide] and 1400 [placebo]), the cardiac adverse events were assessed by the investigator as unrelated to study medication.

In Study GWCO, the mean baseline heart rate was 75 and 73 beats per minute in the exenatide and placebo groups, respectively. A small increase in LS mean heart rate from baseline to Week 30 of +2.3 beats per minute was noted in exenatide subjects compared to a change from baseline to Week 30 of -0.7 beats per minute in placebo subjects.

Overall, nothing unexpected was found concerning cardiac events. A minor increase in heart rate has been seen in previous exenatide studies, but this does not seem to translate into an increase in blood pressure.

Potentially Immune-Related Adverse Events

The list of eligible terms for potentially immune-related events includes terms related to injection-site events, generalized pruritus and urticaria, rash, angiooedema, and anaphylaxis.

In Study GWCO, 9 (6.6%) exenatide and 9 (7.4%) placebo subjects experienced a total of 20 potentially immune-related TEAEs. Events of arthralgia (1 exenatide, 1 placebo), injection site reaction

(1 exenatide), pruritus (1 exenatide, 1 placebo), rash erythematous (1 exenatide) and urticaria

(2 placebo) were assessed by the investigator as related to study medication; the remaining events were assessed as unrelated to study medication. With the exception of 2 events of severe urticaria (placebo subjects), all events were mild or moderate in intensity, 1 event of urticaria (Subject 2700 [placebo]) was also a serious adverse event, and 1 event of joint swelling (Subject 3407 [placebo]) led to withdrawal from the study. Fourteen of the 20 total events resolved. Antibodies to exenatide were not measured in Study GWCO.

It is known that patients developing high anti exenatide antibodies have an increased risk of injection site reactions, and already taken into account in the SmPC.

Abdominal pain, pancreatitis

In Study GWCO, the incidence of abdominal pain was similar between the 2 treatment groups.

A total of 10 (7.3%) exenatide subjects and 9 (7.4%) placebo subjects experienced at least 1 TEAE of abdominal pain. All of these events were assessed as mild to moderate in intensity by the investigator. There were no treatment-emergent events of pancreatitis reported during Study GWCO or IOPB.

Laboratory findings

In Study GWCO, no clinically meaningful changes from baseline to endpoint were noted in haematology, chemistry, or urinalysis assessments in any treatment group.

Safety in special populations

Age

In Study GWCO, 184 (71%) subjects were <65 years of age and 75 (29%) subjects were ≥65 years of age, with the mean age comparable between the treatment groups.

Review of TEAEs by age category indicated adverse event profiles that were generally comparable between the age groups and consistent with the primary study results and also consistent with previous clinical trials of exenatide. The incidence of nausea was higher in exenatide subjects <65 years of age (44.0%) compared to exenatide subjects ≥65 years of age (32.4%), but comparable to the incidence of nausea in exenatide subjects in the overall ITT Population (40.9%).

In Study IOPB, among all randomized patients (n=339), the mean age of the sample was 56.4 years and most patients (n=273, 80.5%) were under 65 years of age, with the mean age comparable between treatment groups.

Reviews of TEAEs by age category were generally comparable between age groups.

Treatment-emergent adverse events between age groups were similar as related to nausea (<65 = 6.64%; >65 = 6.06%) and diarrhoea (<65 = 6.27%; >65 = 6.06%).

In study GWCO, 75 patients were ≥65 years.

There were no indications of major differences in the adverse events based on age.

Gender

In Study GWCO, there were 148 male subjects and 111 female subjects, with approximately

10% more female subjects in the exenatide group relative to the placebo group. In general, the incidence of gastrointestinal side effects (such as nausea and vomiting), headache, and dizziness was greater among female subjects compared to male subjects in both treatment groups. This difference by gender was also observed in previous clinical trials of exenatide.

In Study IOPB, there were 169 male subjects and 170 female subjects, with 95 (55.6%) females

and 76 (44.4%) males in the ILPS group. There were 75 (44.6%) females and 93 (55.4%) males

in the insulin glargine group. In general, events such as nausea, diarrhea, vomiting, and headache were greater among female subjects compared to male subjects in both treatment groups.

Renal Function

In Study GWCO, 225 subjects had normal renal function (defined as estimated glomerular filtration rate [eGFR] ≥80mL/minute [min]), 28 subjects had mild impairment of renal function (eGFR ≥50 mL/min and <80 mL/min), and 6 subjects had moderate impairment of renal function (eGFR <30 to 50 mL/min). The proportions of subjects with normal, mild, or moderate renal impairment were generally balanced across the treatment groups. There were no subjects with severe impairment of renal function (eGFR <30 mL/min).

In general, adverse event profiles were comparable in subjects with normal renal function or mild or moderate impairment of renal function with the exceptions that gastrointestinal adverse events such as nausea and vomiting occurred at higher incidence in exenatide subjects with moderate renal impairment and events of minor hypoglycaemia occurred at higher incidence in exenatide and placebo subjects with moderate renal impairment. These results were consistent with observations in previous clinical trials of exenatide.

In Study IOPB, 315 subjects had normal renal function (defined as eGFR ≥80mL/min) and 22 subjects had mild impairment of renal function (eGFR ≥50 mL/min and <80mL/min). The proportions of subjects with normal and mild renal impairment were generally balanced across the treatment groups. There were no subjects with severe impairment of renal function (eGFR <30 mL/min). In general, adverse event profiles were comparable in subjects withnormal renal function or mild impairment of renal function, with the exception of gastroenteritis viral which occurred more frequently in the insulin glargine group (10) than in the ILPS group (2) in those subjects with normal renal function.

The current product information already recommends careful dose titration in patients with moderate renal impairment while the treatment of patients with severe impairment is not recommended. Therefore the current results were not considered to have an impact of these recommendations.

Exposure in published studies

The MAH has performed a literature search to identify clinical studies or case reports that describe the use of exenatide with short-acting and/or basal insulins.

The final search results identified 15 manuscripts and 33 abstracts (including those for Studies GWCO and IOPB) that reported information potentially relevant to understanding the clinical use, particularly safety, of exenatide in combination with insulin in humans.

Overall, the publications, excluding those for Studies GWCO and IOPB, describe exposure of more than 5000 subjects to exenatide in combination with short-acting and/or basal insulins, including (when specified) insulin glargine and insulin detemir. The results of the reported studies do not indicate any

safety findings unique to the use of exenatide in combination with insulin and are consistent with the results of Studies GWCO and IOPB.

2.5.3. Discussion

A total of 600 subjects were randomly assigned to a treatment in Studies GWCO and IOPB. Of the 596 ITT subjects, 474 (80%) received exenatide treatment in combination with basal insulin (ILPS or insulin glargine). Subjects in these studies were exposed to randomly assigned study treatment for a mean of at least 22 weeks across studies and treatment groups.

In the clinical study GWCO, the insulin dose was reduced by 20% in subjects with an HbA1c ≤8.0%. This standard dose reduction of insulin in patients with a relative low HbA1C for the risk of hypoglycaemia was considered to be relevant with regard to safety. To alleviate concerns by the CHMP, guidance on this is now provided in section 4.2 of the SmPC. Overall, CHMP agreed that insulin treatment should be individualized and too strict recommendations are not warranted.

There was no difference in the incidence of hypoglycaemia between exenatide and placebo in study GWCO. In study IOPB, the incidence of hypoglycaemia was somewhat higher in the glargine group compared to ILPS. In study IOPB, an increased incidence of hypoglycaemia in combination with SU was found. Even though combined use with SU is not part of the requested indication, information on the incidence of hypoglycaemia in patients where existing therapy included SU is now included in section 4.8 of the SmPC to address this concern.

No unexpected safety findings were recorded in the studies. Gastrointestinal adverse event were common in patients initiating exenatide. One case of malignancy was reported, most likely not related to treatment.

An association of GLP 1 analogues and the finding of c-cell tumours in rats has been extensively discussed in the past with no firm conclusion as to whether this is relevant to humans or not. The possible risk of pancreatic cancer with GLP 1 analogues has also been included in the RMP as a safety concern. Considering a possible tumour promoting effect of insulin analogues, the risk of malignant neoplasm following combination treatment with insulin has been identified and is now included as a potential risk in the RMP. As the time of exposure in the referred studies was too short to draw any conclusions concerning this potential safety issue, this is addressed within the RMP by relevant pharmacovigilance criteria: All events of pancreatic cancer and thyroid neoplasms are captured in patients using exenatide in an ongoing CV outcome study. The same approach is taken in an epidemiological study aimed at investigating pancreatic cancer and thyroid neoplasms events. Both events will now be also specifically captured with regard to cases on combination treatment with exenatide and insulin (see sections below).

Overall, no unexpected safety findings were recorded in the studies with the combined use of exenatide and insulin, and possible identified risks are adequately addressed in the RMP.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety Concern	Agreed Pharmacovigilance Activities	Agreed Risk Minimization Activities
Pancreatitis	• Routine pharmacovigilance • Targeted surveillance of pancreatitis events • Additional information from ongoing clinical trials • Completed a mechanistic study to evaluate potential change in gallbladder emptying following exenatide administration as a surrogate measure of increased tone of the sphincter of Oddi is onging.	• SmPC 4.4 and 4.8, includes an appropriate description of the observed events of pancreatitis.
Acute Renal Failure	• Routine pharmacovigilance • Additional information from ongoing clinical trials • Targeted surveillance of acute renal failure/insufficiency, dehydration, and hypovolaemia events.	• SmPC 4.4 and 4.8, includes an appropriate description of the observed events of acute renal failure.
Rapid Weight Loss	• Routine pharmacovigilance	• SmPC 4.4 and 4.8 includes an appropriate description of the observed event of rapid weight loss.
Risks Associated with Anti-exenatide Antibodies (focus on anaphylactic-type reactions)	• Routine pharmacovigilance • Targeted surveillance of allergic/immunologic events (anaphylaxis, angiooedema, laryngeal oedema). • Additional information from ongoing clinical trials	• In general no association has been identified between anti-exenatide antibodies and SAEs. An association has been identified for nonserious injections-site reactions. • SmPC 4.8 includes language on anti-exenatide antibodies and injection site reactions. • SmPC 4.3 includes contraindication for use in individuals with known hypersensitivity to exenatide or formulation excipients
Cardiac Events	• Routine pharmacovigilance	• No association identified between exenatide and cardiac events to date.
Pancreatic cancer	• Routine pharmacovigilance • Additional information from ongoing clinical trials • Targeted surveillance for treatment-emergent malignancies and neoplasms with focus on pancreatic cancer. • Initiate a pharmaepidemiologic study in the US to assess the absolute and relative risk of pancreatic cancer and thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide twice daily as compared to other antidiabetes drugs	• No association identified between exenatide and pancreatic cancer to date.
Thyroid neoplasms (C-	• Routine pharmacovigilance • Additional information from ongoing clinical	• No association identified between exenatide and thyroid neoplasms to

Safety Concern	Agreed Pharmacovigilance Activities	Agreed Risk Minimization Activities
cell hyperplasia and Non-C-cell cancer)	trials • Targeted surveillance for treatment-emergent malignancies and neoplasms with focus on thyroid neoplasms. • Initiate a pharmaepidemiologic study in the US to assess the absolute and relative risk of pancreatic cancer and thyroid neoplasms among type 2 diabetes mellitus patients who initiate exenatide twice daily as compared to other antidiabetes drugs	date.
Malignant neoplasm following combination treatment with insulin	• Routine pharmacovigilance. • Continued targeted surveillance for treatment-emergent malignancies and neoplasms. • Initiate a pharmacoepidemiological study in the US to assess the absolute and relative risk of pancreatic cancer and thyroid neoplasms among type 2 diabetic patients who initiate exenatide twice daily as compared to other antidiabetes drugs.	• No association identified between exenatide and combination insulin use and malignant neoplasms to date.
Adolescents	• Conduct a double blind, placebo controlled study to assess safety and efficacy of exenatide twice daily (as monotherapy and adjunctive therapy to oral antidiabetic agents) in children and adolescents with type 2 diabetes.	• SmPC 4.2 states with respect to children and adolescents, "The safety and effectiveness of exenatide have not been established in patients under 18 years of age."
Pregnant Women	• Implemented a pregnancy registry beginning in December 2007 to determine whether exenatide poses a risk to pregnant women or their developing foetuses.	• SmPC 4.6 states with respect to pregnancy and lactation, That there are no adequate data from the use of BYETTA in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 [of the SmPC]). The potential risk for humans is unknown. BYETTA should not be used during pregnancy and the use of insulin is recommended.
Very Elderly (≥75 years of age)	• Routine pharmacovigilance	• SmPC 4.2 states with respect to the elderly, "BYETTA should be used with caution and dose escalation from 5 µg to 10 µg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.""
Use of Exenatide in Combination with TZDs or insulins	• Routine pharmacovigilance	• No differential adverse event profile has been found for patients taking exenatide in combination with TZDs or insulins.
Severe Gastrointestinal	• Routine pharmacovigilance	• SmPC 4.4 states with respect to patients with severe gastrointestinal

Safety Concern	Agreed Pharmacovigilance Activities	Agreed Risk Minimization Activities
Disease		disease, "BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease."
Various Degrees of Impaired Renal Function	• Routine pharmacovigilance	• SmPC 4.2 states with respect to patients with varying degrees of renal function impairment, "No dosage adjustment is necessary inr patients with mild renal impairment (creatinine clearance 50 – 80 ml/min). • In patients with moderate renal impairment (creatinine clearance: 30-50 ml/min), dose escalation from 5µg to 10µg should proceed conservatively (see section 5.2). • BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).
Hepatic Impairment	• Routine pharmacovigilance	• SmPC 5.2 states with respect to patients with hepatic impairment, "No pharmacokinetic study has been performed in patients with hepatic insufficiency. Exenatide is cleared primarily by the kidney, therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide." In addition, SmPC 4.2 states "No dose adjustment is necessary for patients with hepatic impairment."

Abbreviations: SAE = serious adverse event; SmPC = Summary of Product Characteristics; TZDs = thiazolidinediones.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Inclusion of patients on insulin comedication in the ongoing CV outcome study GWDQ [BCB109]	unchanged

Description	Due date
All events of pancreatic cancer and thyroid neoplasms on combination treatment with exenatide and insulin will be analysed in patients using exenatide in the epidemiological studies	unchanged

These pharmacovigilance activities are in addition to those already requested.

No additional risk minimisation activities were required beyond those included in the product information.

2.7. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (underlined = new text, strikethrough = deleted text):

Section 4.1 Therapeutic indications of the SmPC

. . .

BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

Section 4.2 Posology and method of administration of the SmPC

Posology

. . .

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, pioglitazone and/or a basal insulin. One can continue to use BYETTA when a basal insulin is added to existing therapy. . . . When BYETTA is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia consider reducing the dose of basal insulin (see section 4.8).

The dose of BYETTA does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas or the dose of basal insulin.

. . .

Method of administration

Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

BYETTA and basal insulin must be administered as two separate injections.

4.6 Effects on ability to drive and use machines

. . . When BYETTA is used in combination with a sulphonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

Section 4.8 Undesirable effects of the SmPC

Table 1: Adverse reactions reported in long term phase 3 controlled studies[1] and spontaneous adverse reactions[3]

. . .

[3] Post marketing reports

When BYETTA was used in combination with basal insulin therapy the incidence and types of other adverse events observed were similar to those seen in the controlled clinical trials with exenatide as monotherapy, with metformin and/or sulphonylurea or a thiazolidinedione, with or without metformin.

. . .

In a 30 week study, when BYETTA or placebo was added to existing basal insulin therapy(insulin glargine), the dose of basal insulin was decreased by 20 % in patients with an HbA_{1c} ≤ 8.0 %, per protocol design in order to minimize the risk of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels (see section 5.1). There were no clinically significant differences in the incidence of hypoglycaemic episodes in the BYETTA compared to the placebo group (25% and 29% respectively). There were no episodes of major hypoglycaemia in the BYETTA arm.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin or metformin plus thiazolidinedione the incidence of patients with at least one minor hypoglycaemic episode was 18% and 9% respectively and one patient reported major hypoglycaemia. In patients where existing therapy also included a sulphonylurea the incidence of patients with at least one minor hypoglycaemic episode was 48% and 54% respectively and one patient reported major hypoglycaemia.

Section 5.1 Pharmacological properties

. . .

Studies of BYETTA with metformin, a thiazolidinedione or both as background therapy

Two placebo-controlled studies were conducted: one of 16 and one of 26 weeks duration, with 121 and 111 BYETTA and 112 and 54 placebo treated patients respectively, added to existing thiazolidinedione treatment, with or without metformin. Of the BYETTA patients, 12% were treated with a thiazolidinedione and BYETTA and 82% were treated with a thiazolidinedione, metformin and BYETTA. BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.7% versus +0.1%) as well as significant reductions in body weight (-1.5 versus 0 kg) in the 16 week study. The 26 week study showed similar results with statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus -0.1%). There was no significant difference in body weight between treatment groups in change from baseline to endpoint (-1.4 versus -0.8 kg).

When BYETTA was used in combination with a thiazolidinedione, the incidence of hypoglycaemia was similar to that of placebo in combination with a thiazolidinedione. The experience in patients > 65 years and in patients with impaired renal function is limited. The incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with a sulphonylurea, metformin or both.

Studies of BYETTA in combination with basal insulin

In a 30 week study, either BYETTA (5 µg BID for 4 weeks, followed by 10 µg BID) or a placebo was added to insulin glargine (with or without metformin, pioglitazone or both). During the study both treatment arms titrated insulin glargine using an algorithm reflecting current clinical practice to a target fasting plasma glucose of approximately 5.6 mmol/l. The mean age of subjects was 59 years and the mean duration of diabetes was 12.3 years.

At the end of the study, BYETTA (n=137) demonstrated a statistically significant reduction in the HbA_{1c} and weight compared to placebo (n=122). BYETTA lowered HbA_{1c} by 1.7 % from a baseline of 8.3 % while placebo lowered HbA_{1c} by 1.0 % from a baseline of 8.5 %. The proportion of patients achieving HbA_{1c} <7% and HbA_{1c} ≤6.5% was 56 % and 42 % with BYETTA and 29 % and 13 % with placebo.

Weight loss of 1.8 kg from a baseline of 95 kg was observed with BYETTA whereas a weight gain of 1.0 kg from a baseline of 94kg was observed with placebo.

In the BYETTA arm the insulin dose increased by 13 units/day compared to 20 units/ day on the placebo arm. BYETTA reduced fasting serum glucose by 1.3 mmol/l and placebo by 0.9 mmol/l. BYETTA arm compared to placebo had significantly lowered postprandial blood glucose excursions at the morning meal (- 2.0 versus - 0.2 mmol/l) and evening meal (- 1.6 versus + 0.1 mmol/l), there was no difference between treatments at midday.

In a 24 week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin, metformin and sulphonylurea or metformin and pioglitazone, HbA1c was lowered by 1.2 % (n=170) and by 1.4 % (n=167) respectively from a baseline of 8.2 %. Weight increase of 0.2 kg was observed for patients on insulin lispro protamine suspension and 0.6 kg for insulin glargine treated patients from a baseline of 102 kg and 103 kg respectively.

Previous reference to use of insulin in the SmPC was changed as appropriate. Some sections have been deleted as they have been replaced by new sections (see above). The Package Leaflet has been updated accordingly. In addition minor changes have been made throughout the Product Information.

2.8. User consultation

No user consultation with target patient groups on the package leaflet has been performed because the changes in the package leaflet were considered to be minor by the MAH, to which the CHMP agreed.

3. Overall conclusion and impact on the benefit/risk balance

The current application aims to extend the indication of Byetta (Exenatide, as injection twice daily) to include the combination with basal insulin with or without metformin and/or a thiazolidinedione. The thiazolidinedione used in the underlying studies was in most cases pioglitazone.

Support for this additional indication is based on 2 studies: H8O-US-GWCO (GWCO) and F3Z-US-IOPB (IOPB). The design of study GWCO, in which exenatide (as injection, twice daily) or placebo is added to ongoing insulin therapy (+/- OAD) was considered as adequate for the objective to assess whether the addition of exenatide can provide additional effect in comparison to placebo. The design of study IOPB, in which insulin is added to ongoing exenatide treatment, does not provide any substantial data on the efficacy of exenatide in combination with insulin, but does contribute safety data for the combination +/- different OADs.

Benefits

For add-on studies, it is recommended to select patients not meeting therapeutic targets on the established agent alone at maximal tolerated or recommended dose. In study GWCO, during the initial 4 weeks of treatment, subjects with an HbA1c ≤8.0% decreased their prestudy dose of insulin glargine by 20% and subjects with an HbA1c ≥8.1% maintained their prestudy insulin dose. Beginning at Week 5, insulin doses for the exenatide and placebo treatment groups were actively titrated with guidance from the investigator toward predefined fasting plasma glucose (FPG) targets. In both groups, the mean daily insulin dose increased from baseline to week 30 with 13 and 20/U per day in the exenatide and placebo groups respectively. Thus, apparently the patients were not optimally titrated at study start. In the placebo group, 29% of the patients reached a HbA1c below 7% and were therefore not in need of additional treatment, and thus may have been not "true" non-responders.

However, the insulin doses in the placebo group was higher compared to the exenatide group at week 30. Despite this difference, there was a statistically significant difference in favor of exenatide with respect to reduction of HbA1c, as the primary outcome parameter, compared to placebo (-0.71%, CI -0.95% to -0.47%). There was also a higher proportion of patients reaching a HbA1c below 7%, showing that exenatide does provide additional glucose lowering effect on top of insulin treatment. Further,it was taken into account by CHMP that the fact that insulin doses were not optimised before randomisation in study GWCO may provide a better reflection of clinical practice.

As expected, in study GWCO there was a statistically significant difference in favor of exenatide with respect to weight lowering, which was a secondary outcome parameter.

Risks

A total of 600 subjects were randomly assigned to a treatment in Studies GWCO and IOPB. Of the 596 ITT subjects, 474 (80%) received exenatide treatment in combination with basal insulin (ILPS or insulin glargine). Subjects in these studies were exposed to study treatment for a mean of at least 22 weeks across studies and treatment groups. The treatment duration is thus rather short, especially concerning potential rare risks such as a possible tumour promoting effect.

There was no difference in the incidence of hypoglycaemia between exenatide and placebo in study GWCO.

Gastrointestinal adverse event were common in patients initiating exenatide. No unexpected safety findings were recorded in the studies. One case of malignancy was reported, most likely not related to treatment.

The association of GLP 1 analogues and the finding of c-cell tumours in rats has been extensively discussed in the past with no firm conclusion as to whether this is relevant to humans or not. The possible risk of pancreatic cancer had already been covered by the RMP. The MAH has committed to address this issue within an ongoing CV safety study and in a planned epidemiological study, to which the MAH had agreed previously. All events of pancreatic cancer and thyroid neoplasms are captured in patients using exenatide in these studies, and also specifically with regard to cases of combined treatment with exenatide and insulin. The MAH has provided an updated RMP within this procedure to that regard. The risk of malignant neoplasm following combination treatment with insulin has therefore now been included as a potential risk in the updated RMP, as this has been the case for other GLP-1 analogues.

Balance

In conclusion, even though the pivotal trial did not include exclusively "true" non-responders to insulin treatment, the results do show that exenatide provides additional glucose lowering effect on top of insulin treatment with a reduction of HbA1c of -0.71%, compared to placebo. No unexpected safety issues have been identified. The benefit/risk balance for this extension of indication was therefore considered to be positive.

4. Recommendations

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

Variation accepted		**Type**
C.I.6.a	Change to therapeutic indication - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include Byetta as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

As a consequence, update of sections 4.1, 4.2, 4.4., 4.6, 4.7, 4.8 and 5.1 of the SmPC. The Package Leaflet is updated in accordance.

Furthermore, the MAH took this opportunity to introduce minor editorial updates throughout the PI.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include Byetta as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents. As a consequence, update of sections 4.1, 4.2, 4.4., 4.6, 4.7, 4.8 and 5.1 of the SmPC. The Package Leaflet is updated in accordance. Furthermore, the MAH took this opportunity to introduce minor editorial updates throughout the PI.

Summary

For further information please refer to the scientific conclusion: Byetta-H-698-II-29-AR.