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APPLICATION NUMBER:

022200Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	22-200 SDN 43
Priority or Standard	Standard
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Division / Office	DMEP / ODE II
Reviewer Name(s)	Valerie S. W. Pratt, M.D.
Review Completion Date	12-12-11
Established Name	Exenatide LAR
(Proposed) Trade Name	Bydureon
Therapeutic Class	GLP-1 agonist
Applicant	Amylin Pharmaceuticals Inc.
Formulation(s)	Injection
Dosing Regimen	2 mg SC once weekly
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adult type 2 diabetics

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this new drug application for exenatide for extended-release injectable suspension (Bydureon). The proposed indication is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

1.2 Risk Benefit Assessment

The applicant proposes 2 mg Bydureon subcutaneously weekly as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Based on my review of the clinical data, the benefits of Bydureon, compared to the immediate release form of exenatide, include convenient once weekly dosing and fewer gastrointestinal adverse events (specifically, nausea and vomiting). Supportive trial BCB108 demonstrated that the commercial formulation of Bydureon is non-inferior (NI) and statistically superior to Byetta. The primary objective in study BCB108 was to compare the effect on glucose control (HbA1c) of Bydureon (commercial formulation) to that of Byetta in T2DM subjects at week 24. The mean baseline HbA1c in the intent to treat (ITT) and Evaluable treatment groups was 8.3-8.5%. Bydureon resulted in a statistically significant mean decrease in HbA1c of 0.7% when compared to Byetta in both the ITT and Evaluable populations. The 95% confidence interval (CI) for the ITT population was (-0.9, -0.4). Thus, the commercial formulation of Bydureon is non-inferior and statistically superior to Byetta for up to 24 weeks, based on the pre-defined NI margin of 0.4%. Secondary endpoint analysis supported the primary analysis.

The risks of Bydureon include the following:

- Thyroid tumors: Like another approved long acting glucagon-like-peptide-1 (GLP-1 agonist), nonclinical studies suggest that Bydureon may increase the risk of thyroid tumors. Although more Bydureon subjects (n=6) were diagnosed with thyroid neoplasms, all but one was benign; that diagnosis was papillary thyroid microcarcinoma, not medullary thyroid carcinoma (MTC). I do, though, recommend a risk mitigation strategy similar to that of liraglutide. The product should not be used as first-line therapy, and it should be contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2). I also recommend that the applicant continue to analyze thyroid neoplasms events as adverse events (AEs) of special interest in Periodic Safety Update Reports (PSURs). The long term cardiovascular (CV) safety study BCB109 will analyze thyroid carcinoma as an AE of special interest and should include screening, annual, and endpoint

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calcitonin measurements as well as safeguards to protect subjects from unnecessary thyroidectomies.

- Injection site nodules and reactions: Bydureon is (b) (4) exenatide, (b) (4) sucrose, and (b) (4) polymer (poly-D,L-lactide-coglycolide or PLG) microspheres. PLG and its degradation products are associated with local inflammatory reactions. To further assess this safety issue after approval, I recommend the PSURs and CV safety study BCB109 analyze serious injection site reactions, including nodules, as AEs of special interest.
- Cardiovascular: Exenatide, like other long acting GLP-1 agonists, is associated with a small increase in heart rate. A postmarketing trial of Bydureon is necessary to definitively show that the upper bound of the two-sided 95% CI for the estimated risk ratio is <1.3. The applicant initiated CV study BCB109 in June 2010. The applicant should also analyze CV events in the PSURs.
- Pancreatitis: Although the incidence of pancreatitis in T2DM patients is debated in the literature, exenatide is associated with pancreatitis, including hemorrhagic and necrotizing forms. I therefore recommend a Warning and Precaution in the label and continued vigilance via the postmarketing requirements (PMRs) described below and summaries in the PSURs to mitigate this risk.
- Hypersensitivity: Like Byetta, subjects using Bydureon are at risk of serious hypersensitivity reactions. Antibody-positive Bydureon subjects were nearly twice as likely to experience potentially immune-related AEs than antibody-negative Bydureon subjects and antibody positive and negative Byetta subjects. To mitigate this risk, the label will include Warnings and Precautions related to the immunogenicity and serious hypersensitivity, as well as a contraindication for patients who had experienced prior severe hypersensitivity with exenatide products. I also recommend changes to the proposed label as described in section 7.4.6. To monitor this risk post approval, I recommend the applicant analyze hypersensitivity events as an event of special interest in PSURs and CV study BCB109.
- Hypoglycemia: Like Byetta, there is a risk of hypoglycemia when Bydureon is used in combination with a sulfonylurea (SU). This is described in the Warnings and Precautions section of the label. Serious hypoglycemia will be analyzed in CV trial BCB109.
- Renal impairment: tQT study BCB112 demonstrated no clinically significant QT prolongation with exenatide exposures up to ~500 pg/ml. Bydureon is not recommend for subjects with severe and end stage renal impairment. It should be used with caution in subjects with moderate renal impairment. Renal disorders will be analyzed as an AE of special interest in CV study BCB109 and PSURs.
- Gastrointestinal (GI) AEs: GLP-1 agonists, including exenatide, are associated with gastrointestinal AEs. However, the frequency of withdrawals in this system organ class (SOC) and incidence of nausea and vomiting were lower with Bydureon when compared to Byetta. The Bydureon label will contain a Warning

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and Precaution regarding use in patients with severe GI disease and Adverse Reactions language.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Because of 1) the risk of thyroid tumors associated with GLP-1 analogues identified in preclinical studies, including exenatide LAR Study REST060229 ([redacted] (b) (4) #840-040) and 2) post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide, and in order to ensure that the benefits of exenatide continue to outweigh these serious risks, I recommend a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide (MG), communication plan, and timetable for assessments.

The applicant proposed the following REMS:

- Medication Guide
- Communication plan:
  - A Dear Healthcare Provider (DCHP) letter
  - A direct mail letter
  - Highlighted information for prescribers will be provided by the applicant's representatives during the first discussion of Bydureon with all HCPs detailed during the first six months after launch.
- Timetable of assessments: 1, 2, 3, and 7 years from the date of approval of the REMS

I recommend that the proposed letters be sent by email, as this delivery method has the potential to reduce waste and cost while increasing the likelihood that the document will be read. I also recommend that the assessments report on use of Bydureon as a first-line antidiabetic agent.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the following PMRs. Please note that these are preliminary PMRs at the time of filing the review, pending additional internal discussion and negotiations with the applicant.

- A deferred randomized, double-blind, adequately controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy, safety, and pharmacokinetics (PK) of Bydureon for the treatment of T2DM in pediatric patients ages 10 to 17 years (albeit with a limited number of 17 year olds). This study should not be initiated until at least 1 month after the completed study report for the rodent study to determine if Bydureon-induced c-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation has been submitted to FDA and found to conclude no likely effects on human thyroid.

- MTC case series registry of at least 15 years duration to systematically monitor the annual incidence of MTC in the United States and to identify any increase related to the introduction of Bydureon into the marketplace. This study will also establish a registry of incident cases of MTC and characterize their medical histories related to diabetes and use of Bydureon.
- A randomized, double-blind, controlled trial evaluating the effect of Bydureon on the incidence of major adverse cardiovascular events in patients with T2DM. This trial must also assess adverse events of interest including the long-term effects of Bydureon on potential biomarkers of MTC (e.g. serum calcitonin) as well as the long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and/or necrotizing forms), pancreatic cancer, serious injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

I also recommend the applicant continue to analyze the following as AEs of special interest in the PSURs: cardiovascular events, thyroid neoplasms, pancreatic cancer, serious injection site reactions (including nodules), allergic/hypersensitivity events, pancreatitis events, and renal failure.

2 Introduction and Regulatory Background

2.1 Product Information

Amylin Pharmaceuticals, Inc. first submitted a new drug application (NDA) for the use of exenatide for extended-release injectable suspension as an adjunct to diet and exercise to improve glycemic control in patients with T2DM on May 4, 2009. The drug product is also referred to exenatide once weekly or long-acting release (LAR) injection. The proposed trade name is Bydureon.

Bydureon contains the same active ingredient as the commercial product exenatide (Byetta) injection (NDAs 21-773 and 21-919). Exenatide injection, an incretin mimetic (specifically, GLP-1 agonist), is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, the Bydureon NDA submission references the safety and efficacy information in the Byetta NDA.

Bydureon was produced using drug substance from (b) (4) different suppliers during its development: (b) (4) Mallinckrodt, Inc. and Lonza, SA. It was also manufactured at (b) (4) different scales ((b) (4) and at 2 different manufacturing sites (Alkermes, Inc. in Wilmington, Ohio and Amylin Ohio, LLC in West

Chester, Ohio. Please refer to the CMC review and my previous NDA reviews (dated February 22 and September 15, 2010) for full details.

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of T2DM include the following:

- Insulin
- Sulfonylureas (SUs)
    - Tolazamide (Tolinase)
    - Chlopropramide (Diabinese)
    - Glyburide (Micronase)
    - Glipizide (Glucotrol and Glucotrol XL)
    - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones (TZDs)
    - Rosiglitazone (Avandia)
    - Pioglitazone (Actos)
- α-Glucosidase inhibitors
    - Acarbose (Precose)
    - Miglitol (Glyset)
- Incretin-mimetics
    - Exenatide (Byetta)
    - Liraglutide (Victoza)
- Amylinomimetics
    - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 (DPP4) inhibitors
    - Sitagliptin (Januvia)
    - Saxagliptin (Onglyza)
    - Linagliptin (Tradjenta)
- Bile acid sequestrants
    - Colesevelam (WelChol)
- Dopamine receptor agonists
    - Bromocriptine mesylate (Cycloset)
- FDCs of the various oral medications listed above

2.3 Availability of Proposed Active Ingredient in the United States

Although it was approved for use in Europe on June 21, 2011, Bydureon is not currently approved for use in the United States. Two complete responses (CR) letters were issued on March 12 and October 18, 2010. However, exenatide has been approved in

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the United States since March 2005 and is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Exenatide is currently being studied under (b) (4) active INDs:

1) IND 57,725 Exenatide injection for the treatment of T2DM
2) IND 67,092 Exenatide LAR injection for the treatment of T2DM

(b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

Exenatide is used to improve glycemic control in T2DM patients. Labeled safety concerns with exenatide include:

1. Acute pancreatitis
2. Gastrointestinal side effects
3. Hypoglycemia, especially when used in combination with a sulfonylurea
4. Hypersensitivity reactions occurring predominantly in patients with anti-exenatide antibodies
5. Renal failure

The division recently approved NDA 22-341 for liraglutide, another GLP-1receptor agonist. Liraglutide causes thyroid c-cell tumors in rats and mice. Please refer to my February 22, 2011 review of the original NDA submission for more details.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Bydureon was developed for the treatment of T2DM under IND 67,092, which was opened March 17, 2003. As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, NDA 22-200 references the safety and efficacy information in Byetta NDA 21-773.

This is a Class 2 resubmission to the Bydureon NDA. Two complete response letters were issued on March 12, 2010 (due to the lack of a REMS and CMC and microbiology deficiencies) and October 18, 2010 (due to an uncertain benefit: risk ratio and the need for a tQT study and results from study BCB108). The resubmission consists of clinical study reports (CSRs) BCB108 amendment (date October 11, 2010), tQT pilot BCB113, and tQT study BCB112 as well as the safety updates (original and supplemental) and proposed REMS.

Please refer to my February 22, 2010 review of the original NDA submission and my September 15, 2010 review of the first complete response for a summary of regulatory activities up until March 12, 2010 and October 18, 2010, respectively.

The following is a summary of key presubmission regulatory activity related to this submission:

- On October 29, 2010, the applicant submitted to Bydureon IND 67,092 a protocol synopsis for tQT study BCB112. This was reviewed by the QT Interdisciplinary Review Team (QT IRT) on November 22, 2010. Although the protocol was acceptable, comments were conveyed to the applicant via a teleconference on November 23, 2010. The applicant was also informed that any new analyses of tQT study GWCI would likely require a clinical audit by the Office of Scientific Investigation (OSI).
- On November 19, 2010, the applicant submitted to the IND CV protocol BCB109 amendment 1 which included calcitonin monitoring.
- On December 3, 2010, the applicant submitted to the IND protocol amendment BCB113, a tQT pilot study, which I reviewed on December 8, 2010.
- On December 7, 2010, the applicant submitted a December 6, 2010 email to Dr. Mary Parks which explained the status of the reanalysis of tQT study GWCI due to a programming error and the intent to not rely on data from study GWCI in the complete response.
- On December 8, 2010, the applicant submitted to the IND draft tQT protocol BCB112, which was reviewed by QT-IRT on January 10, 2011.
- On December 15, 2010, the applicant submitted to the IND a discussion of the validated immunoenzymetric assay (IEMA) used to measure exenatide concentrations and an amended CSR for BCB108 and a report documenting the data in study BCB106. According to the applicant, during a limited period in the 3.5 year phase 3 Bydureon program, the assay was inaccurately calibrated by a contract research facility. This calibration drifted over multiple lot changes in the standards for the assay. Thus, a revised method for preparation and qualification of the calibration samples was established. This required the new standards to be compared to an invariant comparator rather than the previously prepared standards. Key samples during the erroneous period were retested and consistent with data from the periods before and after the miscalibration. Relevant plasma exenatide samples from studies BCB108 and BCB106 were retested and concentrations were found to be higher than previously reported.
- On January 4, 2011, the applicant withdrew its request for the End of Review meeting, which was scheduled for January 11 on the condition that submission of study BCB108 and the safety update be considered a complete response, although the applicant pledged to complete the tQT study.
- On January 5, 2011, during a teleconference with the applicant, the agency reiterated the need to submit both study BCB108 and the tQT study in the complete response. Rolling submission of the NDA Complete Response would

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not be acceptable. Although the possibility of submitting the tQT study post-approval was still being discussed internally, the Agency's recommendation was to conduct the tQT pre-approval. If the Agency's recommendation changed, the applicant would be notified.

- On January 11, 2011, the agency conveyed comments on tQT protocol BCB112 and clarified that the results from the tQT study must be submitted in conjunction with study BCB108 to be considered a complete response.
- On January 21, 2011, the applicant submitted to the IND final tQT protocol BCB112, *A randomized, three period, placebo and positive controlled, double blind, crossover study to assess the electrophysiological effects of exenatide at therapeutic and supratherapeutic concentrations on the 12-lead ECG QT interval in healthy subjects.*
- On February 3, 2011, the applicant submitted its first formal dispute resolution request. A meeting to discuss whether the application should be approved without the need for additional clinical data was held with Dr. Curtis Rosebraugh on March 4, 2011. The request was denied on March 30, 2011.
- On February 11, 2011, OSE completed its review of a protocol for a case-series registry of MTC for exenatide. These comments were conveyed on March 29, 2011.
- On May 11, 2011, the applicant submitted its second formal dispute resolution request, which was denied by Dr. John Jenkins on May 11, 2011.
- On May 17, 2011, the applicant submitted the IND CV study BCB109 amendment 2 to allow insulin use prior to randomization, lower calcitonin exclusion criteria to >40 ng/L, define the calcitonin exit threshold as ≥50 ng/L, and clarify even reporting. I reviewed this amendment on June 21 and my comment pertaining to the calcitonin exclusion criteria was conveyed on June 28, 2011.
- On May 20, 2011, the applicant submitted to the IND amended CSR BCB108 and relevant module 2 documents for review.
- On May 25, 2011, the Agency conveyed comments QT IRT's comments on BCB112's statistical analysis plan (SAP).
- On May 26, 2011, a teleconference was held to discuss the proposed contents and timing of the NDA resubmission. On June 3, 2011, the Agency conveyed the meeting minutes with the following key comments:
    - The PDUFA clock will not start until the application is complete. However, the applicant may submit materials to the IND whereupon the FDA will review in advance of the complete response NDA submission.
    - If labeling is sought based on additional study reports, the reports need to be submitted as separate supplements after approval.
    - The CR should also include an analysis of BCB108 efficacy by subpopulation, a cumulative analysis of pancreatitis events, a safety analysis by subpopulation including renal impairment, and an analysis of ischemic and arrhythmic CV events.

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  - The applicant may submit embryo-fetal development and toxicokinetic study REST110051 for review.
  - Provided there are no additional safety issues, a medication guide will be required for Bydureon but it need not be part of the REMS.
- On June 3, 2011, the applicant's request for a CMC meeting was denied as the questions in the briefing document were straightforward and written responses were provided on June 6.
- On June 6, 2011, the applicant submitted to the IND questions regarding the Agency's May 25 feedback on BCB112's SAP and a teleconference request. The QT-IRT's responses from their June 8 consult were conveyed on June 16.
- On June 30, 2011, the applicant submitted the safety update and supplement safety update for review.

2.6 Other Relevant Background Information

On August 25, the applicant submitted a revised pediatric plan as requested.

On October 20, 2011, the applicant submitted draft protocol *Medullary thyroid carcinoma surveillance study: a case-series registry*, which was consulted to OSE.

On October 24, 2011, the applicant responded to our pediatric study BCB114 information request.

On November 3, 2011, the applicant responded to our pancreatitis information request.

On December 8, 2011, the applicant submitted a proposed REMS amendment.

Please refer to the relevant sections of this review for more information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of appropriate quality. As negotiated with the applicant, CSR BCB108, tQT study BCB112, and the relevant safety updates were submitted.

CSR BCB108 was an amended version (date October 11, 2010) for the reasons described in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission. In the original report, PK data were summarized and listed but not calculated. The exenatide test method was then reestablished and validated at (b) (4) . Plasma exenatide concentrations were reanalyzed and PK

parameters calculated. The treatment group of subject 137005 (Byetta) was also corrected. The amended CSR is acceptable because the commercial formulation of Bydureon was used in study BCB108 and the exenatide concentrations were only supportive in nature.

3.2 Compliance with Good Clinical Practices

All clinical trials were conducted according to the principles of Good Clinical Practices (GCPs). One study site in studies 105 and BCB106 was closed after the discovery of suspected GCP violations. The FDA was notified under IND 67, 092 on December 17, 2008. The violations were identified after completion of the 52-week CSR. However, only 3 subjects from this study participated in study 105. Analyses indicated that removal of these subjects would have not effect on the primary endpoint.

OSI investigated the following clinical sites involved in study BCB108:

- Dario Altamirano's site in Hialeah, FL which enrolled 22 subjects
- Ernesto Fuentes' site in Miami, FL which enrolled 17 subjects
- Douglas Denham's site in San Antonio, TX which enrolled 14 subjects

No action was indicated at the Denham site. However, the duration and stability of the diabetes treatment in the eligibility criteria were not well documented at the Altamirano and Fuentes sites; it is not clear if these criteria were met for the 39 subjects at those sites. However, even if the eligibility criteria were not met at the Altamirano and Fuentes sites, this would not affect the primary efficacy results. Janice Derr's statistical analysis below indicates the results are not appreciably affected by excluding the two sites.

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Table 1. BCB108: Change in HbA1c at week 24 in the ITT/LOCF population with 1) all study sites in the ITT population and 2) excluding sites 126 and 131

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 24 ± SE[1]	Exenatide QW – Byetta Difference in adjusted mean change (95% CI)[1]	P-value
1. ITT analysis set with LOCF, all sites included (primary analysis)					
Exenatide QW	128	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-0.9, -0.4)	<0.0001
Byetta	122	8.4 ± 0.1	-0.9 ± 0.1		
2. ITT analysis set with LOCF, sites 126 and 131 excluded					
Exenatide QW	108	8.5 ± 0.1	-1.7 ± 0.1	-0.8 (-1.0, -0.5)	<0.0001
Byetta	104	8.4 ± 0.1	-0.9 ± 0.1		

Excluded sites	Site ID	Randomized to Exenatide QW (code A)	Randomized to Byetta (code B)	Totals
E. Fuentes	126	10	7	17
D. Altamirano	131	10	12	22
				39

Analysis:
The primary analysis model was an analysis of variance including treatment and the two stratification factors used in randomization: baseline HbA1c stratum, and concomitant SU use at screening.

Source:
1. Study BCB108 clinical report, Table 7
2. Analysis by Janice Derr

Source: Janice Derr's statistical analysis

3.3 Financial Disclosures

The applicant submitted financial discloser information for studies [redacted] (b) (6) The following [redacted] (b) (6) investigators were identified as having disclosable financial interests:

- [redacted] (b) (6) has a common stock IRA account >$50,000. [redacted] (b) (6) enrolled [redacted] (b) (6) subjects at site [redacted] (b) (6)
- [redacted] (b) (6) owns 4,000 shares of Amylin stock ($116,000). [redacted] (b) (6) enrolled [redacted] (b) (6) subjects at site [redacted] (b) (6).
- [redacted] (b) (6) has honoraria unrelated to research >$50,000 [redacted] (b) (6) enrolled [redacted] (b) (6) subjects at site [redacted] (b) (6).
- [redacted] (b) (6) received speaker and consulting fees (total $31,000). [redacted] (b) (6) enrolled [redacted] (b) (6) subjects at site [redacted] (b) (6)

As [redacted] (b) (6) was [redacted] (b) (6) (Bydureon ITT n = [redacted] (b) (6)), randomized study, the likelihood that data drawn from one of the study sites significantly altered the outcome is low.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

As agreed, the resubmission includes the following CMC changes:

- Proposal to conduct the in vitro complete release test at 37ºC and new acceptance limits
- Stability data and proposed retest or expiry periods for drug substance, drug product, and diluent
- Revision of the appearance specification for the excipient polylactide co-glycolide to be consistent with the supplier's drug master file

Please refer to Dr. Olen Stephens' CMC reviews of the NDA submission and resubmissions for full details.

4.2 Clinical Microbiology

Please refer to Dr. Steven Fong's microbiology review, which recommends approval.

4.3 Preclinical Pharmacology/Toxicology

The applicant submitted one nonclinical study, *An embryo-fetal development and toxicokinetic study of subcutaneously administered exenatide LAR in Sprague-Dawley rats*. Please refer to B. Timothy Hummer's nonclinical review of the resubmission. Please also refer to his review of the original NDA submission for a description of the thyroid c-cell tumor findings associated with GLP-1 agonists.

4.4 Clinical Pharmacology

The applicant submitted PK data for the commercial (Amylin-manufactured) material from study BCB108 as well as results from tQT study GWCI and LAR105.

Comment: On October 29, 2010, the applicant was also informed that any new analyses of tQT study GWCI would likely require a clinical audit by the Division of Scientific Investigation.

Please refer to Dr. Jaya Vaidynathan's clinical pharmacology review of the original NDA and resubmissions for full details.

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4.4.1 Mechanism of Action

Exenatide is a GLP-1 receptor agonist that improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with T2DM. It does this through the following mechanisms of action:

- Enhances glucose-dependent insulin secretion
- Restores first-phase insulin response
- Suppresses inappropriately elevated glucagon secretion
- Slows gastric emptying
- Reduces food intake

Bydureon is (b) (4) exenatide and (b) (4) sucrose encapsulated within (b) (4) biodegradable (b) (4) polymer (poly-D,L-lactide-coglycolide or PLG) microspheres that are designed to release therapeutic concentrations of exenatide over an extended period of time. PLG is a common, biodegradable medical polymer that has been previously used in human sutures, bone plates, and extended release pharmaceuticals, such as Vivitrol and Risperdal Consta (b) (4) fold versus Bydureon, respectively). Please refer to section 2.6.6.8 of Dr. B. Timothy Hummer's nonclinical review for more information regarding the safety of PLG microspheres.

In short, the pharmaceutical industry has used polymer microspheres for sustained release formulations for over 20 years. The microspheres are suspected in an aqueous diluent prior to injection. Once in the body, the PLG degrades over time to lactic and glycolic acid and releases exenatide by a combination of drug diffusion and polymer erosion. PLG and its degradation products do not cause systemic toxicity, reproductive or developmental effects, genotoxicity, or carcinogenicity at clinically relevant doses, although local inflammatory reactions can occur. Please refer to section 7.3.3 Dropouts and/or Discontinuations for more details.

4.4.2 Pharmacodynamics

Phase 2 study 104 evaluated 0.8 and 2 mg Bydureon once weekly for 15 weeks in 43 T2DM subjects (12 placebo, 16 Bydureon 0.8 mg, 15 Bydureon 2 mg). Reductions in FPG were observed in both Bydureon groups throughout the treatment period. At week 15, the 0.8 mg and 2 mg Bydureon groups had mean reductions of 42.7 mg/dl and 39.0 mg/dl, respectively, whereas the placebo group's fasting plasma glucose (FPG) concentrations increased by 18.2 mg/dl at week 15. The mean overall daily average self-monitored blood glucose concentration was also reduced for both the 0.8 mg (164.6 mg/dl) and 2 mg (149.1 mg/dl) Bydureon groups compared to baseline and to the placebo group (220.5 mg/dl).

Please refer to section 6.1.4 Analysis of Primary Endpoint for a discussion of Bydureon's (Amylin's commercial formation) effect on HbA1c.

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4.4.3 Pharmacokinetics

A single dose of Bydureon exhibits multiphasic release over approximately 10 weeks with complex release characteristics:

- Phase 1: Initial release of surface-bound exenatide
- Phases 2 and 3: Subsequent release peaks representing hydration and erosion, respectively, in weeks 2 and 6

Repeated once weekly injection of 2 mg Bydureon results in overlap of the single-dose release profiles and a gradual increase in the average plasma exenatide concentration, until steady state is achieved after approximately 7 weeks. At weeks 14-15, the average steady state concentration ($C_{ss\ ave}$) of the 2 and 0.8 mg doses are 289 and 118 pg/ml, respectively. There is a concentration-dependent decrease in HbA1c from baseline with maximal response at exenatide concentrations > 200 pg/ml. I therefore agree with the proposed 2 mg dose (EC_{50} ~83 pg/ml).

Age, gender, race, and body mass index (BMI) do not influence the PK. However, there was a 53% increase in exenatide exposure in the subjects with moderate renal impairment (n=10) in study 105 (versus 24% increase in subjects with mild renal impairment). No dosage adjustment is proposed by the applicant in patients with mild to moderate renal impairment. This is acceptable since tQT study BCB112 demonstated no clinically significant QT prolongation with exenatide exposures up to ~500 pg/ml

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. NDA 22-200 SDN 23: Tabular listing of completed clinical studies in the complete response safety update

Study No. No. Centers- Country	Study Design Primary Objective	Population No. and Type	Treatment Duration
2993LAR-104 (104)*	Phase 2, randomized, double blind, placebo controlled, multiple dose Safety and PK	45 T2DM subjects 31 Bydureon	3 day Byetta 5 mcg BID or placebo lead in followed by 0.8 or 2 mg exenatide (F17) or placebo once weekly x 15 wks
H8O-JE-GWBW (GWBW)*	Phase 1, randomized, double blind, placebo controlled, multiple dose Safety in T2DM Japanese subjects	30 T2DM Japanese subjects 20 Bydureon	0.8 or 2 mg Bydureon (F17) or placebo once weekly x 10 wks

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Study No. No. Centers- Country	**Study Design Primary Objective**	**Population No. and Type**	**Treatment Duration**
2993LAR-105 (105)*	Phase 3, randomized, open label, comparator controlled, multiple dose Safety and efficacy	295 T2DM subjects 148 Bydureon 147 Byetta	3 day Byetta 5 mcg BID lead in followed by 2 mg Bydureon or Byetta x 30 wks and ongoing, uncontrolled, open-ended assessment period (completed through 3 years)
BCB106*	Phase 3, randomized, double blind, comparator controlled, parallel group study	491 T2DM subjects 160 Bydureon + Met 166 sitagliptin + Met 165 pioglitazone + Met	2 mg exenatide LAR weekly, sitagliptin 100 mg daily, or pioglitazone 45 mg daily x 26 wks followed by ongoing, uncontrolled, open-ended assessment period (completed through 1 year)
BCB108*	Phase 3, randomized, open label, Byetta-controlled	252 T2DM subjects on stable oral meds or diet and exercise 129 Bydureon	Bydureon or Byetta x 24 wk
H8O-MC-GWBR (GWBR)*	Phase 3, randomized, open label, glargine-controlled	456 T2DM subjects on Met or Met+SU 233 Bydureon	26 wks followed by ongoing, controlled open-ended assessment period (completed through week 84)
H8O-JE-GWBX (GWBX)	Phase 3, randomized, open label, glargine-controlled	456 Japanese T2DM subjects on Met, SU, TZD or a combo	26 wks (ongoing)
H8O-MC-GWCH (GWCH)*	Phase 3b, randomized, double blind, comparator (Met, SU, or pioglitazone)-controlled	820 T2DM subjects	26 wks
H8O-MC-GWCK (GWCK)	Phase 3, randomized, open label, Byetta-controlled	Approx 680 Asian T2DM subjects on Met, SU, TZD, or a combo	26 wks (ongoing)
H8O-FW-GWCL (GWCL)	Phase 1, open label, single arm	Approx 30 Chinese T2DM subjects on Met or diet & exercise	10 wk (ongoing)
H8O-MC-GWDC (GWDC)*	Phase 3, open label, single arm	134 T2DM subjects on TZD or TZD+Met	52 wks (ongoing, uncontrolled, open ended assessment period)
H8O-MC-GWDE (GWDE)	Phase 3, randomized, open label, liraglutide-controlled	Approx 907 T2DM subjects on Met, SU, Met+SU, or Met+pioglitazone	26 weeks (ongoing)
H8O-FW-GWDL (GWDL)	Phase 3, randomized, open label, Detemir-controlled	Approx 258 T2DM subjects on Met or Met+SU	26 wk (ongoing)

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Study No. No. Centers- Country	Study Design Primary Objective	Population No. and Type	Treatment Duration
BCB109	Phase 3b/4, randomized, double blind, placebo-controlled, CV outcomes trial	Approx 9500 T2DM subjects on up to 3 oral antidiabetic medications or diet & exercise	Median follow up 4 – 5 years (ongoing)

*Eight controlled and uncontrolled safety and efficacy studies included in the pooled safety analysis.

5.2 Review Strategy

My review focused on the clinical study report BCB108, tQT study BCB112 and QT IRT consult, and the controlled data in the complete response safety update and supplemental safety update.

The original NDA submission and safety update cutoff dates were November 15, 2008 and March 31, 2009, respectively. The first CR's safety update cutoff date was December 31, 2009. The cutoff date for the second CR's safety update was September 30, 2010. Data for ongoing clinical studies were included in the second CR's safety update from December 31, 2009 through September 30, 2010. In the 9-month period between cutoff dates for two CR safety updates, two clinical studies were completed, H8O-MC-GWCH (GWCH) and H8O-MC-GWDC (GWDC).

5.3 Discussion of Individual Studies/Clinical Trials

1) BCB108: A randomized, open label, parallel group, comparator-controlled, multicenter, study to evaluate the glycemic effects, safety, and tolerability of exenatide once weekly in subjects with T2DM (Amendment 2)

Study phase and dates conducted: March 23, 2009 through October 27, 2009

Objectives:
Primary: To compare the effect on glucose control (HbA1c) of Bydureon to that of Byetta in T2DM subjects
Secondary:

- To examine the effects of Bydureon in T2DM subjects on FPG concentration and body weight
- To examine the PK of Bydureon in T2DM subjects
- To examine the safety and tolerability of Bydureon in T2DM subjects

Study design: Study BCB108 was an open-label, randomized (1:1), comparator-controlled study comparing the safety, tolerability, and glucose control of Bydureon (manufactured by Amylin) and Byetta over 24 weeks. Subjects were randomized to either a 2 mg Bydureon subcutaneously (SC) once weekly or 5 mcg Byetta SC twice

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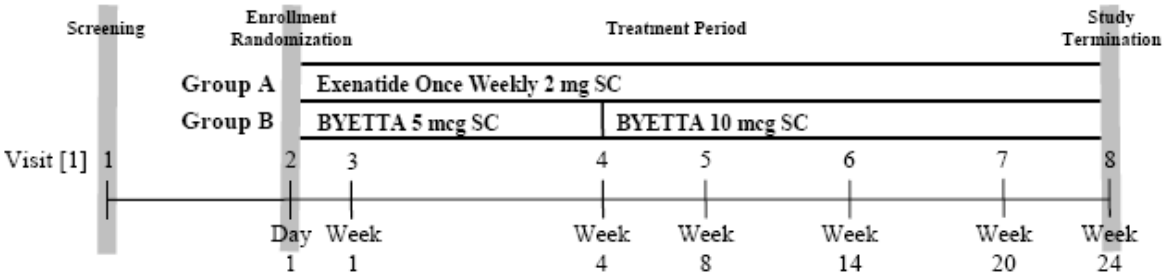
daily (BID) for 4 weeks followed by 10 mcg Byetta SC BID for 20 weeks. Randomization was stratified by HbA1c (<9% or ≥9%) and concomitant use of SU at screening. Applicant personnel were blinded to the efficacy data (HbA1c and FPG) during the 24-week assessment period. Subjects returned to the study site at one to six week intervals for safety, efficacy, pharmacodynamic (PD), anthropometric, and PK assessments.



Abbreviation: SC, subcutaneous.
[1] Visit 2 (Day 1) occurred within 14 days following Visit 1 (Screening). Subsequent visits occurred at the indicated interval (± 2 days) relative to Visit 2.

Figure 1. BCB108: Study design

Source: CSR BCB108 amendment Figure 1

Table 3. BCB108: Study schedule

Procedure	Visit 1 (Screening)	Treatment Period [1]				Study or Early Termination	
		Visit 2 (Day 1)	Visit 3 (Week 1)	Visit 4 (Week 4)	Visits 5-7 (Weeks 8-20)	Visit 8 (Week 24/ Study Termination)	Early Termination
Informed Consent/HIPAA/Stored Blood Forms	X						
Complete Medical History/Height	X						
Physical Examination and ECG [2]		X				X	X
Serum βhCG Test (Nonhysterectomized Females)	X					X	X
Urine βhCG Test (Nonhysterectomized Females)		X	X	X	X		
Verify Inclusion/Exclusion Criteria	X	X					
Enrollment/Randomization		X					
Body Weight, Waist/Hip Circumference, and Vital Sign Assessments	X [3]	X	X	X	X	X	X
Chemistry, Hematology, Urinalysis	X	X [4]			X [5]	X	X
Fasting Plasma Glucose Concentration	X	X		X	X	X	X
HbA1c	X	X		X	X	X	X
Spare Blood Samples		X				X	X
Plasma Exenatide Concentration [6]		X		X	X	X	X
Antibodies to Exenatide Assessments [7]		X		X	X	X	X
Fasting Serum Lipid Concentration		X				X	X
Adverse Event Review		X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Administer Study Medication		X	X	X	X		
Study Medication Compliance Review			X	X	X	X	X

Abbreviations: βhCG, beta subunit of human chorionic gonadotropin; ECG, electrocardiogram; HIPAA, Health Insurance Portability and Accountability Act.
[1] Visit 2 (Day 1) occurred within 14 days of Visit 1 (Screening). All other visits occurred within required time period, relative to Visit 2 (Day 1) (±2 days).
[2] A 12-lead ECG was performed at Visit 2 (Day 1) only.
[3] Waist and hip circumference were not measured at Visit 1 (Screening).
[4] Calcitonin assessment was not performed at Visit 2 (Day 1).
[5] Chemistry, hematology, and urinalysis assessments were performed at Visit 6 (Week 14) only. Calcitonin assessment was not performed at Visit 6 (Week 14).
[6] For Group B subjects, plasma exenatide concentration was assessed only at Visit 7 (Week 20) at -15 minutes, 1, 2, and 3 hours, relative to study medication administration at time = 0. For Group A subjects, a blood sample for plasma exenatide concentration assessment was collected prior to study medication administrations at all visits but Visit 3 (Week 1).
[7] For Group B subjects, antibodies to exenatide were assessed at Visit 2 (Day 1), Visit 6 (Week 14), and Visit 8 (Week 24/Study Termination) or Early Termination.

Source: CSR BCB108 amendment Table 1

Inclusion criteria:

1. Is at least 18 years old at screening (visit 1)
2. Has been diagnosed with T2DM
3. Has HbA1c of 7.1% to 11.0%, inclusive, at screening
4. Has a BMI of 25 to 45 kg/m^2, inclusive, at screening
5. Has stable body weight, i.e., not varying by >3% for at least 3 months prior to screening, as documented by the investigator
6. Has FPG concentration <280 mg/dL at screening
7. Has been treated with diet and exercise alone or in combination with a stable regimen of metformin, an SU, a TZD, a combination of metformin and an SU, a combination of metformin and a TZD, or a combination of an SU and a TZD for a minimum of 2 months prior to screening; metformin dose must be ≥1500 mg/day for 2 months prior to screening, SU dose must be at least the maximally effective dose for 2 months prior to screening, and TZD dose must be ≥4 mg/day for rosiglitazone or ≥30 mg/day for pioglitazone for 2 months prior to screening
8. 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 prior to screening:
    a. Hormone replacement therapy (female subjects)
    b. Oral contraceptives (female subjects)
    c. Antihypertensive agents
    d. Lipid-lowering agents
    e. Thyroid replacement therapy
    f. Antidepressant agents
    g. Drugs known to affect body weight, including prescription medications (e.g. orlistat, sibutramine, topiramate) and over-the-counter antiobesity agents
9. Is male, or if female, meets all the following criteria:
    a. Not breastfeeding and not lactating
    b. Negative pregnancy test result (human chorionic gonadotropin, beta subunit [ßhCG]) at screening (not applicable to hysterectomized females)
    c. If of childbearing potential (including perimenopausal women who have had a menstrual period within one year), must practice and be willing to continue to practice appropriate birth control (defined as a method which results in a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as implants, injectables, oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, tubal ligation, or a vasectomized partner) during the entire duration of the study through 90 days following the final injection of exenatide once weekly or 30 days following the final injection of exenatide BID

Exclusion criteria:

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1. Has a 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:
    a. Hepatic disease
    b. Renal disease
    c. Cardiovascular disease
    d. Gastroparesis
    e. Organ transplantation
    f. Active or untreated malignancy, or in remission from clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinoma of the cervix, or in situ prostate cancer) for less than 5 years prior to screening
    g. Evidence of known or suspected chronic infections (e.g., human immunodeficiency virus or tuberculosis)
2. Has clinical laboratory test values (clinical chemistry, hematology, and urinalysis) judged as clinically significant by the investigator at screening
3. Has a physical examination or ECG results judged as clinically significant by the investigator at day 1
4. Currently abuses drugs or alcohol or has a history of abuse that in the investigator's opinion would cause the individual to be noncompliant with study procedures
5. Has ever been exposed to exenatide (Bydureon, Byetta, or any other formulation) or any GLP-1 analog
6. Has donated blood within 2 months of screening or is planning to donate blood during the study
7. Has had a major surgery or a blood transfusion within 2 months of screening
8. Has received any investigational drug within one month (or five half-lives of the investigational drug, whichever is greater) of screening
9. Has known allergies or hypersensitivity to any component of study treatment (including PLG and Microsphere Diluent)
10. Has been treated, is currently being treated, or is expected to require or undergo treatment with any of the following treatment-excluded medications:
    a. Any DPP-4 inhibitor within 3 months prior to screening
    b. Alpha-glucosidase inhibitor, meglitinide, nateglinide, or pramlintide within 30 days of screening
    c. Insulin within 2 weeks of screening or for more than 1 week within 3 months of screening
    d. Systemic corticosteroids by oral, intravenous, or intramuscular route; or potent, inhaled, or intrapulmonary (including Advair) steroids known to have a high rate of systemic absorption

<u>Treatments and management:</u> Subjects were randomized to either a 2 mg Bydureon subcutaneously (SC) once weekly or 5 mcg Byetta SC twice daily (BID) for 4 weeks

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followed by 10 mcg Byetta SC BID for 20 weeks. Exenatide was injected into the abdomen. Injection sites were rotated.

Subjects continued their current oral antidiabetic, antihypertensive, and lipid lowering agents at the current dosages. However, the dose reduction of concomitant SUs was considered in the event of hypoglycemia. Changes in any concomitant medications were reported to the applicant.

Hypoglycemia was defined as follows:

- Mild: Usually transient, requires no special treatment, and does not interfere with the subject's daily activities.
- Moderate: Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- Severe: Requires the assistance of another person to obtain treatment (e.g., intravenous glucose, intramuscular glucagon, or oral carbohydrate) for the event.

According to protocol amendment 2, at any time during the study, subjects were to be withdrawn if their blood glucose was unacceptable in the opinion of the investigator. Rescue therapy was not specified in the protocol but left to the discretion of the investigator.

Study sites including enrollment: BCB108 was conducted at 43 study sites in 254 T2DM subjects.

Efficacy (exposure/response) assessments:
Efficacy: HbA1c
Anthropometric Measures: Body weight; waist and hip circumferences
Pharmacodynamic: FPG and lipid concentrations; sitting systolic and diastolic blood pressure
Pharmacokinetic: Plasma exenatide concentrations (Week 20 only for Byetta subjects)

Safety assessments: Adverse events, hematology, chemistry, and urinalysis assessments; pancreatic amylase and lipase concentrations; calcitonin concentration; physical examinations; vital signs; antibodies to exenatide

2) BCB112: A randomized, three period, placebo- and positive-controlled, double blind, crossover study to assess the electrophysiological effects of exenatide at therapeutic and supratherapeutic concentrations on the 12-lead ECG QT interval in healthy subjects (January 17, 2011)

Comments:

- *Prior to conducting study BCB112, study BCB113, A pilot study to identify infusion parameters for intravenous infusion of exenatide for the study of 12-lead*

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electrocardiogram (ECG) QT intervals in healthy subjects, was conducted. Please refer to my December 8, 2010 review under exenatide INDs 57,725 and 67,092.

- *Protocol BCB112 and its statistical plan were reviewed by QT-IRT on November 22, 2010; January 10, 2011; May 25, 2011; and June 14, 2011. Comments were conveyed to the applicant and a teleconference was held on November 23, 2010. Please refer to the QT-IRT consults, in particular the discussion regarding the selection of the best QT correction method.*

Study phase and dates conducted: Phase 1 study conducted February 21 – April 26, 2011.

Objectives:
Primary: To determine, in healthy subjects, that exenatide administered at therapeutic and supratherapeutic concentrations does not differ from placebo in the mean change fro predose in 12-lead ECG corrected QT interval (such that the upper bound of the one-sided 95% CI between exenatide and placebo is <10 ms)
Secondary:

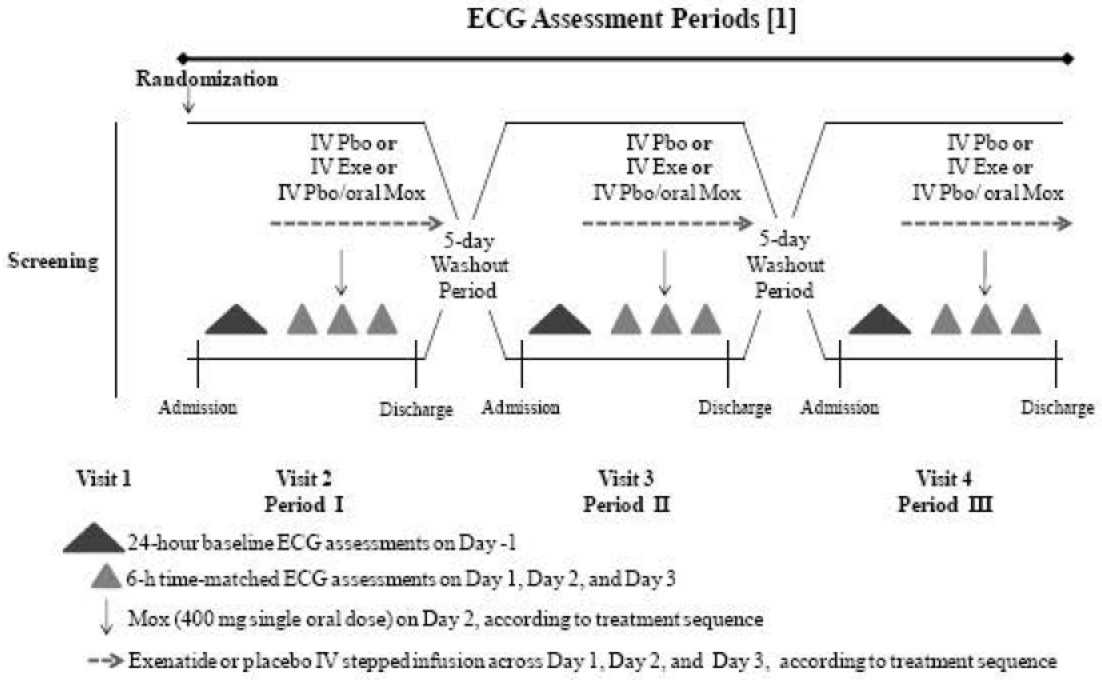
- To evaluate the relationship between plasma exenatide concentrations and QT interval at therapeutic and supratherapeutic concentrations
- To evaluate the influence of physiological covariates such as serum glucose, serum insulin, and serum potassium on the correct QT interval
- To evaluate the safety and tolerability of exenatide administered at therapeutic and supratherapeutic concentrations

Study design: This was a randomized sequence (1:1:1:1:1:1), three-period, placebo- and positive-controlled crossover study. The intravenous (IV) exenatide and placebo infusion ECG assessment periods were double-blind to subjects, the investigator, most study site personnel, and the applicant. The ECG assessment period when moxifloxacin was administered was open label. The cardiologists who overread the ECGs were blinded to all study treatments.

The study included three five-day ECG assessment periods separated by two five-day washout periods, as shown in Figure 2. The IV infusion of exenatide (t=0 at day -1 2000h) was stepped through t=67 h (day 5 1500h) in periods I, II, and III. The goal of the stepped infusion was to achieve steady-state exenatide concentrations ~200 pg/ml (day 1), ~300 pg/ml (day 2), and ~500 pg/ml (day 3), which approximate the exenatide exposure in subjects with normal and mild to moderate renal impairment and a supratherapeutic concentration, respectively. The stepped infusion also maximized tolerability and stabilized potential confounders such as heart rate, insulin, potassium, and glucose concentrations. See Table 5 for the treatment sequence.

Reference ID: 3057015

Figure 2. Study BCB112: Study design



Exe = exenatide; IV = intravenous; Mox = moxifloxacin; Pbo = placebo.

Note: Subjects will be discharged at approximately 1800 h on Day 3. Washout period should be a minimum of 5 and maximum of 7 days.

[1] A 24-hour baseline ECG assessment will be collected using a 12-lead digital Holter recorder at t = -24 h on Day -2 (approximately 2000 h) during each ECG assessment period. On Day -1 through Day 3 of each ECG assessment period, continuous 12-lead ECGs will be collected in a similar manner. Exenatide will be delivered by stepped IV infusion to gradually deliver levels of exenatide at concentrations of approximately 200 pg/mL (Day 1), 300 pg/mL (Day 2), and 500 pg/mL (Day 3). Placebo will be infused at the same volume rate (mL/min) as that of active study medication. IV infusion concentration and volume rate (mL/min) were designed to optimize tolerability and maximize stabilization of potentially confounding physiological covariates of QT/QTC, including heart rate, insulin, potassium and glucose concentrations, as confirmed in Study BCB113. Moxifloxacin will be administered orally, but accompanied by placebo infusion to standardize experimental conditions across treatment periods.

Source: BCB112 study protocol

Table 4. BCB112: Study schedule

Study Procedure	Screening	ECG Assessment Period [1]											Study [2]/Early Termination
	Visit 1	Visit 2 (Period I)			W/O	Visit 3 (Period II)			W/O	Visit 4 (Period III)			
		Day -2	Day -1	Days 1 to 3		Day -2	Day -1	Days 1 to 3		Day -2	Day -1	Days 1 to 3	
Fast (~10 h overnight) prior to visit/treatment day	X		X	X			X	X			X	X	
Informed Consent/HIPAA	X												
Confirm Inclusion/Exclusion Criteria	X	X											
Complete Medical History/Height	X												
Urine Drug and Alcohol Screen	X	X				X				X			
Randomization		X											
Adverse Event Assessment		X	X	X		X	X	X		X	X	X	X
Concomitant Medication Review	X	X	X	X		X	X	X		X	X	X	X
Physical Examination		X											X
ECG	X [3]	X [4]	X [4,5]	X [5]		X [4]	X [4,5]	X [5]		X [4]	X [4,5]	X [5]	X [3]
Chemistry, Hematology, Urinalysis	X	X		X [2]		X		X [2]		X			X
Serum βhCG test (Females)	X												
Urine βhCG Test (Females)		X				X				X			
Body Weight and Vital Signs	X	X	X [6]	X [6]		X	X [6]	X [6]		X	X [6]	X [6]	X
Plasma Exenatide [8]			X	X			X	X			X	X	X
Serum Mg^{2+}	X												
Serum Glucose and K^+ [8]	X		X	X			X	X			X	X	
Serum Insulin [8]			X	X			X	X			X	X	
Antibodies to Exenatide			X [7]				X [7]				X [7]		X
Exenatide or placebo infusion [9]			X	X			X	X			X	X	
Plasma Moxifloxacin [10]				X				X				X	
Moxifloxacin administration [11]				X				X				X	

ECG = electrocardiogram; h = hours; K^+ = potassium; Mg^{2+} = magnesium; W/O = washout.

Notes: Each ECG assessment period is 5 days in duration (Day -2 to Day 3) including a primary ECG period on Days -1 to 3 over a 6-h period from approximately 0900 to 1500 h; Washout between ECG assessment periods should be 5 days. During each of the three 5-day ECG assessment periods, continuous ECG assessments will be performed at baseline (pre-dose; Day -2 to Day -1) and on Days -1 to 3. According to assigned treatment sequence, exenatide will be delivered by stepped intravenous infusion to gradually deliver levels of exenatide at concentrations of approximately 200 pg/mL (Day 1), 300 pg/mL (Day 2), and 500 pg/mL (Day 3). Placebo will be infused at the same volume rate (mL/min) as that of active study medication. ECGs should be performed at the same relative time on treatment days. Standardized meals will be provided at specified times and should be consumed within 30 minutes.

[1] Continuous 12-lead ECGs will be collected using a 12-lead digital Holter recorder. ECGs should be performed at the same relative time on treatment days.
[2] On ECG assessment Day 3 prior to discharge and following completion of all other ECG assessment period-specific Day 3 measures. Study termination procedures completed at the end of Period III only.
[3] Safety only.
[4] Continuous ECG assessments performed over 24 h (from t = -24 to t = 0).
[5] Continuous ECG assessments performed over 67 h (from t = 0 to t = 67 h); 6-h primary ECG period from 0900 h to 1500 h, with ECG measures extracted hourly.
[6] Vital signs only.
[7] Single baseline sample just prior to initiating exenatide/placebo infusion at t = 0 h on Day -1.
[8] Timed serial sampling coincident to hourly serial ECG measurements.
[9] According to randomized treatment sequence; stepped intravenous exenatide or placebo infusion will begin at t = 0 h and continue through time = 67 h.
[10] According to randomized treatment sequence; timed serial sampling on Day 2 during the period of positive control assessments.
[11] According to randomized treatment sequence; moxifloxacin (400-mg tablet; single oral dose) administered during the period of positive control assessments at t = 37 h.

Source: BCB112 protocol Appendix 1

Inclusion criteria:

1. Are between the ages of 18 and 65 years, inclusive.
2. Are overtly healthy, as determined by medical history and physical examination.
3. Is male or is females and is non-menstruating due to bilateral oophorectomy or postmenopausal status; women with an intact uterus are deemed postmenopausal if they have had cessation of menses for at least 1 year or 6 to 12 months of spontaneous amenorrhea with follicle stimulating hormone >40 IU/mL; age ≥45 years; not taking oral contraceptives for at least 1 year; and otherwise healthy.
4. Has BMI between 25 and 35 kg/m^2, inclusive at screening.
5. Has fasting serum glucose <100 mg/dl at screening

6. Has no clinically significant blood pressure or heart rate readings as judged by the investigator at screening
7. Serum magnesium and potassium are within normal limits at screening
8. Has clinical laboratory test values judged as not clinically significant by the investigator at screening
9. Has ECG results judged as not clinically significant by the investigator at screening
10. Has physical examination results judged as not clinically significant by the investigator at Visit 2 (Period I)

Exclusion criteria:

1. Has a 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:
    a. Cardiac arrhythmia
    b. Hepatic disease (defined by aspartate or alanine transaminase >3.0 times the upper limit of normal)
    c. Renal disease or estimated glomerular filtration rate <60 mL/min, as assessed by the Modification of Diet in Renal Disease (MDRD) equation
    d. Gastrointestinal disease
    e. Organ transplantation
    f. Chronic infection (e.g., tuberculosis, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus)
    g. Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of screening
2. Has an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risk of participating in the study, such as a Bazett's corrected QT (QTcB) interval >450 ms. The following conduction abnormalities may confound QTc analysis and should be avoided:
    a. PR >220 ms
    b. 2nd or 3rd degree atrioventricular block
    c. Intraventricular conduction delay with QRS >120 ms
    d. Complete left bundle branch block, right bundle branch block, or Wolfe-Parkinson-White Syndrome (left anterior fascicular block and left posterior fascicular block are acceptable)

    In addition, the screening ECG should also be acceptable (that is, no diffuse flat T waves, biphasic T-wave or pronounced U-wave).
3. Family history of sudden death
4. Personal history of unexplained syncope within last year
5. Personal or family history of Long QT Syndrome
6. History of significant active cardiac disease (e.g., arrhythmia, hypertension, congestive heart failure, hypokalemia, mitral valve regurgitation, endocarditis, coronary artery heart disease), or symptoms of angina pectoris or transient ischemic attacks within the previous 6 months

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7. Current or recent history of (within 2 weeks) clinically significant infection or inflammatory process, at the discretion of the investigator
8. Has donated blood or had a significant blood loss within 56 days of first dose of study medication or is planning to donate blood during the study
9. Has had a major surgery or a blood transfusion within 2 months of screening
10. Has donated plasma within 7 days of first dose of study medication
11. Has ever been exposed to exenatide (Bydureon, Byetta, or any other formulation) or any GLP-1 analog
12. Has received any investigational drug within one month (or five half-lives of the investigational drug, whichever is greater) of screening
13. Currently abuses drugs or alcohol or has a history of abuse that in the investigator's opinion would cause the individual to be noncompliant with study procedures
    a. Has an average weekly alcohol intake that exceeds 28 units per week (males) and 21 units per week (females), or subject unwilling to stop alcohol consumption for the duration of the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
14. Positive urine drug screen (including screen for cocaine, amphetamines, and cannabinoids)
15. Currently uses tobacco products
16. Is unable to refrain from consuming caffeinated beverages during the inpatient portion of the study
17. Intends to use any over-the-counter medication (other than, for example, occasional intake of acetaminophen, or vitamin or mineral supplements) for 7 days prior to dosing and throughout the study or any prescription medication (no exceptions) for 14 days prior to dosing and throughout the study
18. Has known allergies or hypersensitivity to heparin or any component of study treatment

Treatments and management: Subjects were randomized (1:1:1:1:1:1) to the treatment sequence in Table 5. The exenatide infusion was 0.2% human albumin and 0.2 mcg/ml exenatide in saline (0.9% sodium chloride). The IV infusion (t=0 at day -1 2000h) was stepped through t=67 h (day 5 1500h) in periods I, II, and III, so as to achieve a steady-state exenatide concentration ~200 pg/ml (day 1), ~300 pg/ml (day 2), and ~500 pg/ml (day 3). The infusion parameters were based on the results of pilot study BCB113. An adjusted flow rate of 5 – 19.5 ml/h was used to deliver exenatide concentrations at 1 – 3.9 mcg/h to achieve the targeted concentrations.

The placebo infusion contained 0.2% human albumin in saline (0.9% sodium chloride) and was infused at the same stepped concentration and volume rate as the exenatide infusion.

Moxifloxacin (400 mg tablet) was provided at 0900h on day 2 (t=37 h) of the positive ECG assessment period.

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Table 5. BCB112: Treatment sequence

Sequence Group	Electrocardiogram Assessment Periods [1]		
	Period I	Period II	Period III
1	Placebo	Exenatide	Placebo/Moxifloxacin
2	Exenatide	Placebo/Moxifloxacin	Placebo
3	Placebo/Moxifloxacin	Placebo	Exenatide
4	Placebo/Moxifloxacin	Exenatide	Placebo
5	Placebo	Placebo/Moxifloxacin	Exenatide
6	Exenatide	Placebo	Placebo/Moxifloxacin

Notes: Each ECG assessment period is approximately 5 days in duration (Day -2 to Day 3). Duration of washout between ECG assessment periods is a minimum of 5 days and a maximum of 7 days. Exenatide and placebo will be administered intravenously; moxifloxacin will be administered orally, but accompanied by placebo infusion to standardize experimental conditions across ECG assessment periods.

[1] Continuous 12-lead ECGs will be collected using a 12-lead digital Holter recorder. During each of the 3 ECG assessment periods, ECGs will be extracted at the same relative time of day at baseline (pre-dose; Day -1) and when exenatide concentrations have achieved steady-state concentrations of approximately 200 pg/mL (Day 1), 300 pg/mL (Day 2), and 500 pg/mL (Day 3) or comparable time points during placebo infusion; between approximately 0900 h and 1500 h each day.

Source: BCB112 study protocol

Table 6. BCB112: Infusion parameters for IV infusion of exenatide or placebo

Step	Time (h)	Duration (h)	Infusion Rate (mL/h)	Exenatide Infusion (mcg/h)	Target plasma exenatide concentration (pg/mL) at end of infusion period
1	0	6	5.0	1.0	100
2	6	24	9.0	1.8	200
3	30	18	12.5	2.5	300
4	48	6	16.0	3.2	400
5	54	18	19.5	3.9	500

Note: Placebo infusions will be at rate and duration equivalent to the exenatide infusion.

Source: BCB112 protocol Table 2

If a subject experienced clinically significant nausea or one or more episode of vomiting coinciding with ECG measurements during a primary ECG assessment period, the IV infusion, PD, PK, and ECG (not safety) assessments were suspended and the subject withdrawn.

Comment: Subject 1048 was withdrawn for nausea. Subject 2019 was withdrawn for vomiting. Subject 1092 withdrew due to intermittent emesis.

If hypoglycemia occurred, clinical judgment and standard of care measures were used to treat. Subjects who experienced hypoglycemia with a finger stick blood glucose <54 mg/dl were withdrawn.

Study sites including enrollment: The study was conducted in Indiana and Florida in 94 enrolled subjects.

Efficacy (exposure/response) assessments:
Pharmacokinetic: Plasma exenatide and moxifloxacin concentrations
Pharmacodynamic: Serum glucose, insulin, and potassium concentrations

Safety assessments: Adverse events, concomitant medications, 12-lead ECGs (for QT measurement and safety assessment), physical examination, vital signs, clinical chemistry, hematology, and urinalysis

Please refer to section 7.4.4 Electrocardiograms for a discussion of study BCB112's results.

6 Review of Efficacy

Efficacy Summary

The second NDA resubmission included CSRs BCB108 and BCB112, the safety update, and supplemental safety update. My efficacy review of the applicant's second complete response focused on phase 3 study BCB108, which compared the effect on glucose control (HbA1c) of Bydureon (Amylin's commercial formulation) to that of Byetta in T2DM subjects at week 24. BCB108 was required in the complete response to enable a more accurate assessment of the efficacy of Bydureon and labeling of its safety and effectiveness.

The applicant proposes 2 mg Bydureon subcutaneously weekly as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. Due to the risk of thyroid tumors based on nonclinical studies, I recommend Bydureon not be used as first-line therapy and be contraindicated in patients with a personal or family history of MTC or in patients with MEN type 2.

A total of 254 subjects were randomized in study BCB108. Two subjects withdrew consent prior to the first dose of study drug. Thus, BCB108's ITT population was comprised of 252 subjects with a mean duration of T2DM of 5.3 years and mean HbA1c of 8.4%. Forty-seven (18.7%) subjects were treated with diet and exercise, 118 (46.8%) were treated with a single oral ADA, and 87 (34.5%) were treated with a combination of oral ADA. The use of use of oral ADA varied slightly between treatment groups.

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Of the 252 ITT subjects, 48 (19.0%) withdrew during the 24 week treatment period and 204 (80.9%) completed treatment. More Byetta subjects withdrew during treatment, when compared to Bydureon subjects (24.0% vs. 15.5%). The majority (5 of 6, 83.3%) of Bydureon subjects who withdrew consent did so for personal reasons, although one (#113012) withdrew consent due to injection site nodules.

The primary endpoint in study BCB108 was to compare the effect on glucose control (HbA1c) of Bydureon (commercial formulation) to that of Byetta in T2DM subjects at week 24. The mean baseline HbA1c in the ITT and Evaluable treatment groups was 8.3-8.5%. Bydureon resulted in a statistically significant mean decrease in HbA1c of 0.7% in both the ITT and Evaluable populations. The 95% confidence interval (CI) for the ITT population was (-0.9, -0.4). Thus, the commercial formulation of Bydureon is non-inferior and statistically superior to Byetta for up to 24 weeks, based on the pre-defined non-inferiority margin of 0.4%.

Analysis of secondary endpoints supported the primary analysis:

- Significantly more Bydureon subjects achieved HbA1c ≤6.5% and <7% in both the ITT and Evaluable populations, when compared to Byetta subjects (Bydureon 41.1 and 60.9% vs. Byetta 16.3 and 35.9%).
- Compared to Byetta, Bydureon resulted in a statistically significant improvement in FPG concentration in both the ITT and Evaluable populations (LS mean difference -20 to -22 mg/dL).

Efficacy (change in HbA1c) was also analyzed by subpopulations based on baseline HbA1c stratum, T2DM management method, and intrinsic factors. These analyses generally supported the primary analysis.

6.1 Indication

The applicant proposes 2 mg Bydureon subcutaneously weekly as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Like Victoza, Bydureon is a long-acting GLP-1 agonist. Based on nonclinical studies, it is thought that these agents may increase the risk of thyroid tumors. I therefore recommend that the product labeling include the important limitation of use “not recommended as first-line therapy for patients inadequately controlled on diet and exercise”. In addition, I recommend Bydureon be contraindicated in patients with a personal or family history of MTC or in patients with MEN type 2.

6.1.1 Methods

My efficacy review of the applicant’s second complete response focused on phase 3 study BCB108, *A randomized, open label, parallel group, comparator-controlled, multicenter, study to evaluate the glycemic effects, safety, and tolerability of exenatide*

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once weekly in subjects with T2DM. The Bydureon used in study BCB108 was manufactured by Amylin (commercial product). BCB108 was required in the complete response to enable a more accurate evaluation of the efficacy of the to-be-marketed Bydureon and labeling of its safety and effectiveness.

6.1.2 Demographics

BCB108's ITT population was comprised of 252 subjects. The majority were male (57.5%) and Caucasian (59.1%). The mean age and BMI were 55.7 years and 33.3 kg/m^2, respectively. The mean duration of T2DM was 5.3 years with a mean HbA1c of 8.4%. The majority (71.2%) had HbA1c <9%. Although there were slightly more Caucasians in the Bydureon group, characteristics were generally similar between the Bydureon and Byetta groups, as shown in Table 7.

Table 7. BCB108: Demographic and baseline characteristics by treatment (ITT)

	Treatment		
Baseline [1] Characteristics	BYETTA (N = 123)	Exenatide Once Weekly (N = 129)	All Subjects (N = 252)
Gender - n (%)			
Male	68 (55.3)	77 (59.7)	145 (57.5)
Female	55 (44.7)	52 (40.3)	107 (42.5)
Age at Consent (years)			
Mean (SD)	55.2 (10.3)	56.1 (11.1)	55.7 (10.7)
Minimum, Maximum	23, 79	23, 83	23, 83
Race/Ethnicity - n (%)			
Caucasian	68 (55.3)	81 (62.8)	149 (59.1)
Black	9 (7.3)	6 (4.7)	15 (6.0)
Asian	5 (4.1)	5 (3.9)	10 (4.0)
Hispanic	41 (33.3)	37 (28.7)	78 (31.0)
Mean (SD) Weight (kg)	94.3 (18.9)	97.0 (20.7)	95.7 (19.8)
Mean (SD) BMI (kg/m^2)	33.0 (5.3)	33.6 (5.5)	33.3 (5.4)
Mean (SD) HbA1c (%) [2]	8.4 (1.2)	8.5 (1.1)	8.4 (1.2)
HbA1c Stratum –n [2]	122	128	250
<9.0% - n (%)	88 (72.1)	90 (70.3)	178 (71.2)
≥9.0% - n (%)	34 (27.9)	38 (29.7)	72 (28.8)
Mean (SD) Fasting Plasma Glucose (mg/dL)	168 (47)	173 (47)	171 (47)
Mean (SD) Duration of Diabetes at Screening (years) [3]	7.1 (5.4)	6.9 (5.3)	7.0 (5.3)

Source: CSR BCB108 Table 4

In the ITT population, the most commonly used concomitant medications, excluding ADA medications, were 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (n=103, 40.9%), platelet aggregation inhibitors excluding heparin (n=9,

35.7%), plain angiotensin-converting enzyme (ACE) inhibitors (n=75, 29.8%), propionic acid derivatives (n=46, 18.3%), and plain multivitamins (n=41, 16.3%).

- Of the 118 subjects that used a lipid lowering medication, 112 (94.9%) did not change their dose.
- Of the 135 subjects that used an antihypertensive agent at baseline, 129 (95.6%) did not change their dose.

Of the 252 ITT subjects, 47 (18.7%) were treated with diet and exercise, 118 (46.8%) were treated with a single oral ADA, and 87 (34.5%) were treated with a combination of oral ADA. The use of use of oral ADA varied slightly between treatment groups. More Bydureon subjects used metformin, SU, or TZD alone or in combination when compared to Byetta subjects. (See Table 6.) Of the 252 ITT subjects, 23 (9.1%) added a new ADA or change the dosage of an existing one during the study. The majority of these changes were changes in SU dosage, as was consistent with the protocol (see section 5.3 Discussion of Individual Studies/Clinical Trials).

Table 8. BCB108: Use of concomitant ADA at screening (ITT)

	Treatment		
Diabetes Management Method	BYETTA (N = 123) n (%) [1]	Exenatide Once Weekly (N = 129) n (%) [1]	All Subjects (N = 252) n (%) [1]
Diet and Exercise Alone	26 (21.1)	21 (16.3)	47 (18.7)
Metformin Alone	52 (42.3)	51 (39.5)	103 (40.9)
Sulfonylurea Alone	8 (6.5)	1 (0.8)	9 (3.6)
Thiazolidinedione Alone	2 (1.6)	4 (3.1)	6 (2.4)
Metformin plus Sulfonylurea	25 (20.3)	34 (26.4)	59 (23.4)
Metformin plus Thiazolidinedione	9 (7.3)	13 (10.1)	22 (8.7)
Metformin, Sulfonylurea, and Thiazolidinedione [2]	1 (0.8)	5 (3.9)	6 (2.4)
Metformin Alone or in Combination	87 (70.7)	103 (79.8)	190 (75.4)
Sulfonylurea Alone or in Combination	34 (27.6)	40 (31.0)	74 (29.4)
Thiazolidinedione Alone or in Combination	12 (9.8)	22 (17.1)	34 (13.5)

Notes: Subjects are included in individual categories and in the "Metformin Alone or in Combination," "Thiazolidinedione Alone or in Combination," and "Sulfonylurea Alone or in Combination" categories.
- 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.

[1] Percentages are based on the number of intent-to-treat subjects in each treatment group and overall.
[2] The diabetes management method of metformin, sulfonylurea, and thiazolidinedione at screening for 6 subjects represented a protocol deviation (violation of Inclusion Criterion #7); the subjects were allowed to continue study participation.

Source: CSR BCB108 Table 5

6.1.3 Subject Disposition

A total of 254 subjects were randomized in study BCB108. Two subjects withdrew consent prior to the first dose of study drug. Of the 252 ITT subjects, 48 (19.0%) withdrew during the 24 week treatment period and 204 (80.9%) completed treatment.

Table 9. BCB108: Study populations (Randomized population)

	Treatment		
Population	BYETTA (N = 125) n (%)	Exenatide Once Weekly (N = 129) n (%)	All Subjects (N = 254) n (%)
Randomized [1]	125 (100.0)	129 (100.0)	254 (100.0)
Intent-to-Treat [2]	123 (98.4)	129 (100.0)	252 (99.2)
Evaluable [3]	93 (74.4)	111 (86.0)	204 (80.3)

Note: 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.

[1] All subjects who were randomly assigned to a treatment group.

[2] Subjects who received at least one injection of randomized study medication.

[3] Subjects who completed study procedures at Week 20 or beyond in compliance with the protocol and received adequate study medication exposure during the 24-Week Treatment Period.

Source: CSR BCB108 Table 3

More Byetta subjects withdrew during treatment, when compared to Bydureon subjects (24.0% vs. 15.5%). This was due to more Byetta withdrawals due to the withdrawal of consent, investigator decision, protocol violation, and loss of glucose control. A similar percent (4.75%) of subjects in both groups withdrew due to AEs. More Byetta than Bydureon subjects (4 vs. 3) were withdrawn due to loss of glucose control.

Table 10. BCB108: Subject disposition (Randomized population)

Disposition	Treatment: BYETTA (N = 125) n (%)	Treatment: Exenatide Once Weekly (N = 129) n (%)	All Subjects (N = 254) n (%)
Completed 24-Week Treatment Period	95 (76.0)	109 (84.5)	204 (80.3)
Withdrew During 24-Week Treatment Period	30 (24.0)	20 (15.5)	50 (19.7)
Withdrawal of Consent	12 (9.6)	6 (4.7)	18 (7.1)
Adverse Event	6 (4.8)	6 (4.7)	12 (4.7)
Investigator Decision	2 (1.6)	0 (0.0)	2 (0.8)
Protocol Violation	1 (0.8)	0 (0.0)	1 (0.4)
Lost to Follow-up	5 (4.0)	5 (3.9)	10 (3.9)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Loss of Glucose Control	4 (3.2)	3 (2.3)	7 (2.8)

Note: 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.

Source: CSR BCB108 Table 2

The majority (5 of 6, 83.3%) of Bydureon subjects who withdrew consent did so for personal reasons, although one (#113012) withdrew consent due to injection site nodules (i.e. an AE). Withdrawals due to AEs are shown in Table 11. More Byetta subjects experienced withdrawals due to nausea, vomiting, or diarrhea (5/6 events). More Bydureon subjects were withdrawn due to laboratory abnormalities (lipase, creatinine, ALT), pancreatitis, or injection site pruritis. The laboratory events (increased lipase, creatinine, and ALT) either did not resolve or had an unknown outcome.

Table 11. BCB108: AEs leading to withdrawal (ITT)

Treatment	Subject	Event	Day	Intensity	Outcome
Bydureon	118010	Injection site pruritis	20	Mild	Resolved
	126015	Post-traumatic pain	28	Moderate	Resolved
	143005	Blood creatinine increased	100	Moderate	Not resolved
	152006	Pancreatitis	61	Severe	Resolved
	156005	ALT increased	100	Moderate	Unknown
	156013	Lipase increased	99	Moderate	Not resolved
Byetta	103002	Nausea	29	Severe	Resolved
	127003	Diarrhea	2	Moderate	Resolved
	130006	Nausea	1	Mild	Recovered
	147005	Myocardial infarction	19	Severe	Fatal
	151001	Vomiting	2	Mild	Resolved
	156010	Vomiting	32	Severe	Resolved

Source: CSR BCB108 Table 16

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint in BCB108 was to compare the effect on glucose control (HbA1c) of Bydureon (commercial formulation) to that of Byetta in T2DM subjects at week 24. The change in HbA1c was analyzed using a general linear model (GLM), which included factors for treatment group, baseline HbA1c stratum (<9%or ≥9%), and concomitant SU use at screening. It was predefined that noninferiority would demonstrated if the upper limit of the 2-sided 95% CI for the difference between treatment groups fell beneath 0.4%. Superiority of Bydureon to Byetta was demonstrated if the CI was entirely below zero. Although protocol BCB108 was submitted to the agency on March 12, 2009 and reviewed, no comments were conveyed regarding the adequacy or inadequacy of these definitions.

The mean baseline HbA1c in the ITT and Evaluable treatment groups was 8.3-8.5%. Bydureon resulted in a statistically significant mean decrease in HbA1c of 0.7% when compared to Byetta in both populations. The 95% CI for the ITT population was (-0.9, -0.4). Thus, the commercial formulation of Bydureon is non-inferior and statistically superior to Byetta.

Table 12. BCB108: Change in HbA1c (%) from baseline to week 24 (ITT and Evaluable populations)

		Baseline	**Week 24**		**Difference**		
		Mean (SE)	**Mean (SE)**	**LS Mean (SE)**	**LS Mean (SE)**	**95% CI for LS Mean**	**p-value**
ITT	252						
Byetta	123	8.4 (0.1)	-0.7 (0.1)	-0.9 (0.1)			
Bydureon	129	8.5 (0.1)	-1.4 (0.1)	-1.6 (0.1)	-0.7 (0.1)	-0.9, **-0.4**	<0.0001
Evaluable	204						
Byetta	93	8.3 (0.1)	-0.8 (0.1)	-0.9 (0.1)			
Bydureon	111	8.5 (0.1)	-1.4 (0.1)	-1.6 (0.1)	-0.7 (0.2)	-1.0, -0.3	<0.0001

Source: CSR BCB108 Table 7

6.1.5 Analysis of Secondary Endpoints(s)

Proportion of Subjects Reaching HbA1c Targets (<7% and ≤6.5%) at Week 24:

The applicant analyzed the proportion of subjects reaching HbA1c targets using the Cochran-Mantel-Haenszel test adjusting for baseline HbA1c strata (<9% or ≥9%) and concomitant SU use at screening. Significantly more Bydureon subjects achieved HbA1c ≤6.5% and <7% in both the ITT and Evaluable populations, when compared to Byetta subjects (Bydureon 41.1-60.9% vs. Byetta 16.3-35.9%).

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Table 13. BCB108: N (%) of subjects achieving HbA1c ≤6.5% or <7% at week 24 (ITT and Evaluable)

HbA1c category	Byetta (n=123)	Bydureon (n=129)	p-value
ITT			
≤6.5%	20 (16.3)	53 (41.1)	<0.001
<7%	37 (30.1)	75 (58.1)	<0.001
Evaluable			
≤6.5%	18 (19.6)	48 (43.6)	0.002
<7%	33 (35.9)	67 (60.9)	0.001

Source: CSR BCB108's SDS 2.1.3.1.1 and 2.1.3.1.2

Fasting Plasma Glucose Concentration:

The applicant conducted a parametric analysis based on the GLM including treatment, baseline HbA1c stratum, concomitant SU use at screening, and the baseline FPG value. The mean baseline FPG concentrations in the Byetta and Bydureon ITT groups were 168 and 173 mg/dl, respectively. Compared to Byetta, Bydureon resulted in a statistically significant improvement in FPG concentration in both the ITT and Evaluable populations (LS mean difference -20 to -22 mg/dL). (See Table 14.)

Table 14. BCB108: Parametric analysis of change in FPG (mg/dl) from baseline to week 24 (ITT and Evaluable)

		Baseline	Week 24		Difference		
		Mean (SE)	Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI for LS Mean	p-value
ITT	252						
Byetta	123	168 (4)	-10 (5)	-5 (5)			
Bydureon	129	173 (4)	-33 (4)	-25 (4)	-20 (6)	-31, -10	0.0003
Evaluable	204						
Byetta	93	165 (5)	-9 (5)	-5 (5)			
Bydureon	111	175 (5)	-37 (5)	-27 (4)	-22 (6)	-24, -11	0.0001

Source: CSR BCB108 Table 9

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The applicant analyzed efficacy (change in HbA1c) by baseline HbA1c stratum, T2DM management method, and intrinsic factors.

Change in HbA1c by Baseline HbA1c Stratum:

The applicant analyzed the change in HbA1c and the percent of subjects in each stratum achieving HbA1c <7% and ≤6.5% by baseline HbA1c stratum (<9% and ≥9%). The change in HbA1c by baseline HbA1c stratum was calculated using a GLM including treatment and concomitant SU use at screening. The last observation carried forward (LOCF) was used to estimate missing values. Using this approach, Bydureon subjects achieved a greater decrease in HbA1c regardless of baseline HbA1c stratum (HbA1c <9% stratum: Bydureon -1.2% vs. Byetta -0.5%). Subjects with higher baseline HbA1c (≥9%) had a greater reduction in HbA1c (Bydureon: -1.9% vs. -1.2%). Proportionately more Bydureon subjects achieved HbA1c ≤6.5% or <7% regardless of baseline HbA1c stratum. (See Table 15.)

Table 15. BCB108: Change in HbA1c by baseline HbA1c stratum (ITT)

Category	**HbA1c Stratum**			
	<9% (n=178)		**≥9% (n=72)**	
	Byetta (n=88)	**Bydureon (n=90)**	**Byetta (n=34)**	**Bydureon (n=38)**
Change in HbA1c				
Baseline mean (SE)	7.7 (0.1)	7.9 (0.1)	10.0 (0.2)	9.9 (0.1)
Week 24 LS mean (SE)	-0.5 (0.1)	-1.2 (0.1)	-1.3 (0.3)	-1.9 (0.2)
LS mean difference		-0.7 (0.1)		-0.6 (0.3)
95% CI		-0.99, -0.44		-1.28, 0.08
Number (%) achieving ≤6.5%	18 (20.5)	45 (50.0)	2 (5.9)	8 (21.1)
p-value		<0.0001		0.0783
Percent achieving <7%	34 (38.6)	62 (68.9)	3 (8.8)	13 (34.2)
p-value		<0.0001		0.0102

Source: CSR BCB108 SDS 2.1.2.3 and 2.1.3.2

Change in HbA1c by T2DM Management Method:

The applicant analyzed the change in HbA1c by T2DM management method using a GLM including treatment and baseline Hb1c stratum. Both Bydureon and Byetta improved glycemic control regardless of ADA use at screening. Greater improvement was seen with Bydureon in both the ADA monotherapy and combination subgroups (-1.3 to -1.7% vs. -0.8 to -0.9%). This trend was also observed when the ADA combination group was further broken down into specific ADA therapies (see Figure 3).

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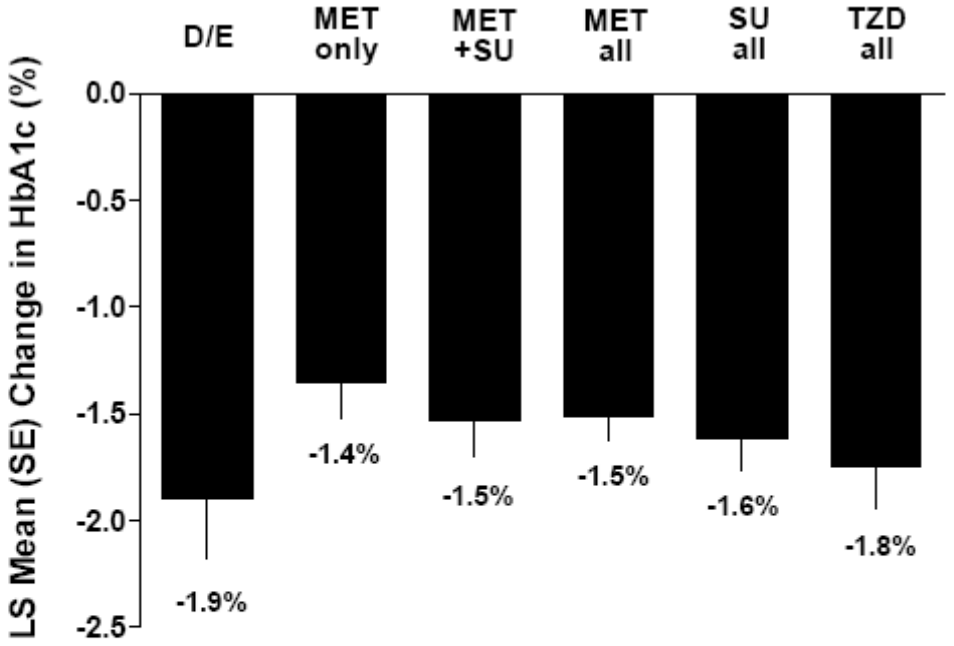
Table 16. BCB108: LS mean change in HbA1c (%) at week 24 by treatment group and ADA use at screening (ITT)

ADA(s) at screening	Byetta			Bydureon		
	n	Baseline mean (SE)	LS mean change (SE)	n	Baseline mean (SE)	LS mean change (SE)
ADA monotherapy	62	8.1 (0.1)	-0.8 (0.2)	56	8.4 (0.2)	-1.3 (0.2)
ADA combination	35	8.5 (0.2)	-0.9 (0.2)	52	8.6 (0.2)	-1.7 (0.1)

Source: CSR BCB108 SDS 2.1.2.5



Abbreviations: D/E, diet and exercise only; LOCF, last observation carried forward; LS, least squares; MET, metformin; SE, standard error; SU, sulfonylurea; TZD, thiazolidinedione.

Notes: -Based on a general linear model including treatment and baseline HbA1c stratum. 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% for D/E group (N = 21), Met only group (N = 51), and TZD all group (N = 22); mean baseline HbA1c was 8.7% for Met +SU group (N = 34) and SU all group (N = 40); mean baseline HbA1c was 8.5% for Met all group (N = 103).
- The LOCF approach was applied to estimate missing values at postbaseline time points.
- The HbA1c values from 1 exenatide once weekly intent-to-treat subject 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.

Figure 3. BCB108: LS mean (SE) change in HbA1c (%) in Bydureon subjects from baseline at week 24 by ADA(s) used at screening (ITT)

Source: CSR BCB108 Figure 5

Change in HbA1c by Intrinsic Factors:

The applicant also analyzed the change in HbA1c by subpopulations based on intrinsic factors (i.e. gender, age, race, renal function, BMI, and antibody status at baseline). Similar to the subpopulations analyses above, Bydureon resulted in greater LS mean change in HbA1c when compared to Byetta (Bydureon -1.0 to -1.9% vs. Byetta -0.7 to -1.3%). Notable observations when the change in HbA1c was analyzed by intrinsic subpopulations are as follows (see Table 17):

- Gender: Gender did not alter the effect of exenatide on the change in HbA1c from baseline.
- Age: Subjects ≥65 years had greater reductions in HbA1c in both treatment groups than subjects <65 years (-1.3 to -1.9% vs. -0.9 to -1.5%). However, this was not observed in previous study 105 (see my review of the original NDA).
- Race: The two largest race subgroups were compared. Caucasian subjects had a greater LS mean reduction in HbA1c than Hispanic subjects in both treatment groups (Caucasian -1.1 to -1.8% vs. Hispanic -0.7 to -1.1). However, the reverse was observed in study 105.
- Renal impairment: Subjects with mild and moderate renal impairment treated with Bydureon had similar reductions in HbA1c as those with normal renal function. Exenatide is not recommended for use in patients with severe renal impairment.
- BMI: Bydureon subjects with BMI <30 kg/m^2 had similar LS mean reductions in HbA1c from baseline compare to subjects with BMI ≥30 kg/m^2 (Bydureon -1.5 to -1.8% vs. Byetta -0.7 to -1.0%).
- Antibody status: More Bydureon subjects had high titers when compared to Byetta subjects. Most antibody-positive subjects treated with Bydureon had low antibody titers (≤125) and reductions in HbA1c similar to those observed in antibody-negative subjects (-1.7% both antibody groups). The response to Bydureon varied in subjects with high antibody titers (≥625), although the mean effect was slightly reduced (-1.0%).

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Table 17. BCB108: Change in HbA1c (%) by intrinsic subpopulations

	Study BCB108 (24 Weeks)					
	Exenatide Once Weekly 2 mg			BYETTA 10 mcg BID [1]		
Subgroup	N	Mean (SE) Baseline (%)	LS Mean (SE) Change (%) [2]	N	Mean (SE) Baseline (%)	LS Mean (SE) Change (%) [2]
Overall Population	128	8.5 (0.1)	-1.6 (0.1)	122	8.4 (0.1)	-0.9 (0.1)
Gender						
Male	77	8.6 (0.1)	-1.6 (0.1)	68	8.4 (0.1)	-0.8 (0.2)
Female	51	8.4 (0.2)	-1.5 (0.2)	54	8.4 (0.2)	-1.0 (0.2)
Age (Screening)						
<65 Years	102	8.5 (0.1)	-1.5 (0.1)	101	8.5 (0.1)	-0.9 (0.1)
≥65 Years	26	8.3 (0.2)	-1.9 (0.2)	21	7.9 (0.2)	-1.3 (0.2)
Race						
Caucasian	81	8.4 (0.1)	-1.8 (0.1)	68	8.2 (0.1)	-1.1 (0.1)
Hispanic	37	8.7 (0.2)	-1.1 (0.2)	41	8.5 (0.2)	-0.7 (0.2)
Renal Function (Baseline)						
Normal [3]	63	8.9 (0.2)	-1.6 (0.2)	59	8.5 (0.2)	-0.8 (0.2)
Mild Impairment [3]	56	8.2 (0.1)	-1.4 (0.2)	55	8.3 (0.1)	-1.0 (0.2)
Moderate Impairment [3]	8	7.9 (0.2)	-1.5 (0.3)	8	8.0 (0.2)	-0.9 (0.3)
BMI Stratum (Baseline)						
<30 kg/m^2	39	8.7 (0.2)	-1.8 (0.2)	45	8.5 (0.2)	-0.7 (0.2)
≥30 kg/m^2	89	8.4 (0.1)	-1.5 (0.1)	77	8.3 (0.1)	-1.0 (0.1)
Antibody Status [4]						
Negative Titer	44	8.3 (0.1)	-1.7 (0.2)	57	8.2 (0.1)	-0.9 (0.2)
Low Positive Titer (≤125)	51	8.6 (0.2)	-1.7 (0.2)	46	8.4 (0.2)	-0.9 (0.2)
Higher Titer (≥625)	28	8.5 (0.2)	-1.0 (0.3)	9	8.3 (0.4)	-0.8 (0.5)

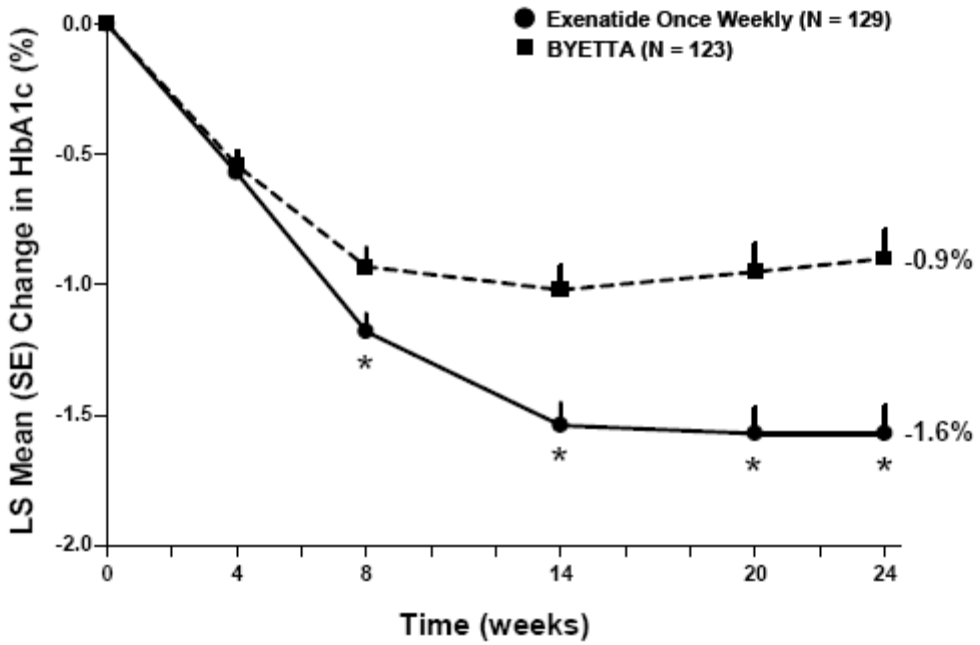
Source: Summary of Clinical Efficacy Table 14

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable. See my review of the original NDA submission.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study BCB108 evaluated the effect of Bydureon and Byetta up to 24 weeks. A greater reduction in HbA1c was seen in the Bydureon group, compared to the Byetta group, from week 4 through week 24; this difference was statistically significant from week 8 through week 24 (see Figure 4). Improvements in FPG were observed in both treatment groups at the first post-treatment measurements (week 4), as shown in Figure 5, although we prefer the longitudinal analysis (effect over time) to be conducted among completers, given the differential dropout rates among treatment groups.



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.

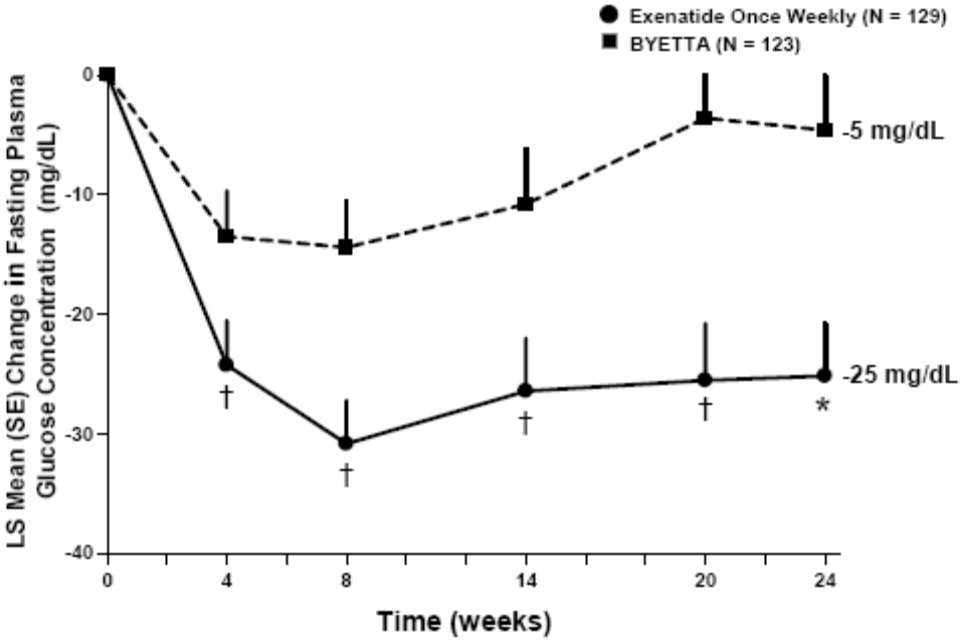
-Mean baseline HbA1c was 8.4% and 8.5% in the BYETTA and exenatide once weekly groups, respectively.

- 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.

Figure 4. BCB108: LS mean (SE) change in HbA1c (%) from baseline to week 24 by treatment (ITT)

Source: CSR BCB108 Figure 3



Abbreviations: LOCF, last observation carried forward; LS, least squares; SE, standard error.
Notes: Based on a general linear model including treatment, baseline HbA1c stratum, concomitant SU use at screening, and the baseline value of fasting plasma glucose concentration. Baseline = Day 1; if unavailable, a value from an earlier visit (the last measurement prior to the first injection) was used.
-Mean baseline fasting plasma glucose was 173 mg/dL for the exenatide once weekly group and 168 mg/dL for the BYETTA group.
- The LOCF approach was applied to estimate missing values at postbaseline time points.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.
*Adjusted p = 0.0006, exenatide once weekly versus BYETTA (based on the Hochberg procedure).
† p <0.05 (non-adjusted), exenatide once weekly versus BYETTA.

Figure 5. BCB108: LS mean (SE) change in FPG (mg/dl) from baseline to week 24 (ITT)

Source: CSR BCB108 Figure 7

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

In the 9-month period between cutoff dates for two CR safety updates (12/31/09 – 9/30/10), two clinical studies were completed, H8O-MC-GWCH (GWCH) and H8O-MC-GWDC (GWDC). Both studies were included in the pooled safety analysis of 2,520 subjects (1,478 Bydureon) in eight controlled and uncontrolled safety and efficacy studies as shown in Table 18.

My review focused on the controlled data in the complete response safety update and supplemental safety update, specifically the deaths, SAEs, AEs leading to withdrawal, AEs of special interest, and other relevant data that was not consistent with my two previous Bydureon reviews. I also summarized the QT IRT's review of tQT study BCB112 and pilot study BCB113.

Studies of Bydureon excluded subjects with moderate, severe and end stage renal failure as described in section 7.2.1. The applicant proposes not recommending Bydureon in subjects with severe and end stage renal impairment. This is acceptable given the results of tQT study BCB112 which demonstrated no clinically significant QT prolongation with exenatide exposures up to ~500 pg/ml.

The overall incidence of serious AEs (SAEs) in Bydureon-treated subjects in controlled efficacy and safety studies was less than that of Byetta-, pioglitazone-, insulin-, and metformin-treated subjects, although it was slightly greater than the incidence of SAEs in sitagliptin-treated subjects. The system organ classes (SOCs) with the most Bydureon SAEs were Infections and Infestations (n=6, 0.7%), Cardiac (n=4, 0.4%), GI (n=3, 0.3%), Neoplasms (n=3, 0.3%), and Renal and Urinary (n=3, 0.3%).

The withdrawal rate due to AEs in completed, controlled trials was greater for Bydureon and Byetta (4.9%) when compared to pioglitazone (3.4%), sitagliptin (1.8%), metformin (1.6%), and insulin (0.9%). Discontinuation due to GI AEs occurred less frequently than with Byetta (4.1%). However, General Disorders events (including injection site events) occurred more frequently in the Bydureon group when compared to other treatment groups. I recommend 1) revising the proposed language to include the percentage of subjects withdrawn due to this AE and 2) the Periodic Safety Update Reports (PSURs) analyze serious injection site reactions (including nodules).

Slightly more Bydureon subjects were discontinued due to events in the Investigations SOC when compared to other treatment groups (Bydureon 0.5% vs. pioglitazone 0.3%). However, all were single events. When uncontrolled/extension data (out to 3 years) was reviewed, the incidence of Investigation SOC events did not increase (0.5% in n=1,478).

The following is a summary of the adverse events (AEs) of special interest:

- Thyroid neoplasms: Although more Bydureon subjects (n=6) were diagnosed with thyroid neoplasms, all but one was benign. Subject GWCK-4307 received only one dose before being diagnosed with papillary thyroid microcarcinoma.
    - I recommend Bydureon be contraindicated in subjects with a personal or family history of MTC or in patients with MEN2, it not be used as a first-line antidiabetic therapy, a MTC case series registry of at least 15 years duration, and the applicant analyze thyroid tumors as an AE of special interest in the PSURs.

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- Pancreatitis: The incidence in the Bydureon- and Byetta-treated subjects is similar to comparator-treated subjects in completed, long-term, controlled studies. Although GLP-1 agonists (and DPP-4 inhibitors) have been associated with pancreatitis, it is unclear at this time the extent to which they cause or exacerbate the condition, as T2DM patients may be at increased risk regardless of medical therapy used. However, I agree with the applicant's proposal to include pancreatitis-related Warnings and Precautions language that is similar to Byetta's in the Bydureon label. I also recommend that the Bydureon CV trial (BCB109) and PSURs include an assessment of pancreatitis events.
- GI AEs: GI SAEs and discontinuation due to GI AEs occurred less frequently with Bydureon than with Byetta.
- Hypoglycemia: As seen with Byetta and proposed in the Bydureon label, there is an increased risk of hypoglycemia when used in combination with a SU.
- Hypersensitivity: Of the 918 Bydureon subjects in tested in 5 studies, 654 (71.2%) were positive for antibodies to exenatide, with 202 (22.0%) having a high titer (≥625) and 452 (49.2%) having lower titer (≤125). Antibody-positive (Ab+) Bydureon subjects were nearly twice as likely to experience potentially immune-related AEs than antibody-negative (Ab-) Bydureon subjects and antibody positive and negative Byetta subjects (23.7% Bydureon Ab+ vs. 13.2% Bydureon Ab- and 10.1-10.2% Byetta). The increase in overall AEs is attributed to the significant increase in General Disorders and Administration Site Conditions AEs in antibody-positive Bydureon subjects (17.7%). I recommend changes to the proposed labeling as described in section 7.4.6.
- Renal failure: The shifts in renal function observed with Bydureon from baseline to last visit were similar to that seen with comparators. In controlled studies, the incidence of AE and AEs leading to withdrawal was slightly greater in Bydureon subjects with normal renal function or mild renal impairment than non-exenatide comparator subjects with similar renal function.
- Arrhythmia: The percentage of Bydureon subjects with normal renal function and mild impairment who experienced events in the Torsade de Pointes/QT prolongation Standard MedDRA Query (SMQ) in controlled and uncontrolled studies was similar (0.6% vs. 0.7%).

Consistent with my previous reviews, a small mean increase (2.6 beats per minute) in heart rate (HR) and decrease in blood pressure (BP) (-2.6/0.9 mm Hg) were observed in completed controlled studies of Bydureon. A CV safety trial of Bydureon has been initiated and will be required of the applicant.

In tQT study BCB112, no significant QTc prolongation was detected with exenatide exposures up to ~500 pg/ml. The largest upper bounds of the two-sided 90% CI for the mean difference between exenatide (~200, 300, and 500 pg/ml) and placebo were below 10 ms, the threshold for regulatory concern (see Table 32).

The incidence of AEs was generally similar between treatment groups and demographic subgroups, when sample size was taken into account.

The pediatric plan was discussed with PeRC on February 17, 2010. The applicant's revised plan, which was submitted on August 25, 2011, is consistent with the PeRC's recommendations although it proposes evaluation of one (2 mg) not two Bydureon doses. As discussed with clinical pharmacology, this is acceptable.

Bydureon was approved for use by the European Medicines Agency (EMA) on June 21, 2011. As the CR was submitted on July 28, 2011, European post-marketing data were not available at the time of submission.

Please also refer to section 7 Review of Safety in my review of the original NDA and first CR.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The original NDA submission and safety update cutoff dates were November 15, 2008 and March 31, 2009, respectively. The first CR's safety updates' cutoff date was December 31, 2009. The cutoff date for this, the second CR's, safety update is September 30, 2010. Data for ongoing clinical studies were included in the second CR's safety update from December 31, 2009 through September 30, 2010.

In the 9-month period between cutoff dates for two CR safety updates, two clinical studies were completed, GWCH and GWDC. Both studies were included in the pooled safety analysis of 2,520 subjects (1,478 Bydureon) in eight controlled and uncontrolled safety and efficacy studies as shown in Table 18.

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Table 18. CR 2011: Overview of safety data for Bydureon

Source of data	Details
Complete response safety update	Controlled studies (repeat-dose studies over 15-30 weeks): • Placebo-controlled: 104 and GWBW • Comparator-controlled: 105, BCB106, BCB108, GWBR, and GWCH Uncontrolled studies/extension periods: • Uncontrolled: GWDC (through week 52) • Extension periods: o 105: week 30 through year 3 (uncontrolled) o BCB106: week 26 through year 1 (uncontrolled) o GWBR: weeks 26-84 (glargine-controlled)
tQT studies	BCB112 and pilot study BCB113

Clinical pharmacology studies 2993LAR-102, -103, and BCB107 were previously pooled in the original 4-month safety update. No additional clinical pharmacology studies have been conducted. Thus, the applicant did not submit additional clinical pharmacology safety data; this is acceptable.

My review focused on the controlled data in the complete response safety update and supplemental safety update, specifically the deaths, SAEs, AEs leading to withdrawal, AEs of special interest, and other relevant data that was not consistent with my two previous Bydureon reviews. I also compare deaths, SAES, and AEs leading to withdrawal in the Bydureon and Byetta groups in study BCB198. Furthermore, I summarized the QT IRT's review of tQT study BCB112 and pilot study BCB113.

7.1.2 Categorization of Adverse Events

The applicant's coding and categorization of adverse events was adequate. The original NDA used MedDRA version 10.1. The complete response safety update used MedDRA version 13.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Please refer to section 7.1.1 above for a description of the studies pooled.

I generally agree with the pooled study groups. However, it must be noted that studies 104 and 105 used a Byetta lead-in. Study GWBW was conducted in 30 Japanese, T2DM subjects.

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7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of the September 30, 2010 cutoff date for this safety update, 2622 subjects have been exposed to Bydureon in completed and ongoing trials (see Table 19). This includes the 1,478 subjects exposed to Bydureon in the eight pooled, completed, safety and efficacy studies (total n = 2,520).

Table 19. CR 2011: Number of subjects in completed and ongoing studies who received at least one dose of Bydureon as of September 30, 2010

Study	Subjects in Completed Studies	Additional Subjects in Ongoing Studies	Total Exenatide Once Weekly Subjects
2993LAR102 [1]	10	—	10
BCB107 [1]	60	—	60
2993LAR103	47	—	47
2993LAR104	**31**	—	**31**
H8O-JE-GWBW	**20**	—	**20**
2993LAR-105	**278 [2]**	—	**278**
BCB106	**160**	**245 [3]**	**405**
BCB108	**129**	—	**129**
BCB109 [4]	—	111	111
(b) (4) [5]	—	(b) (4)	(b) (4)
H8O-MC-GWBR	**233**	—	**233**
H8O-MC-GWCH	**248**	—	**248**
H8O-MC-GWCK	—	204	204
H8O-FW-GWCL	—	42	42
H8O-MC-GWDC	**134**	—	**134**
H8O-FW-GWDL	—	83	83
H8O-JE-GWBX	—	95	95
H8O-MC-GWDE	—	462	462
Total	1350	1272	2622

Notes: Due to ongoing enrollment of some of the studies, the numbers of subjects treated as of the cutoff date are approximate.
- Studies indicated by **bold font** are included in the integrated analysis of this safety update.

[1] Includes only those subjects who received the F17 formulation of exenatide once weekly.
[2] Includes 130 subjects in Study 2993LAR-105 randomized to BYETTA comparator who received open-label exenatide once weekly during open-ended assessment period.
[3] Includes subjects randomized to sitagliptin and pioglitazone comparator who received open-label exenatide once weekly during open-ended assessment period.
[4] Study BCB109 is a blinded study; the number of subjects that received exenatide once weekly is an estimate.
[5] (b) (4) safety information for these subjects is included as part of the ongoing studies.

Source: CR safety update 2011 Table 3

Table 20. CR 2011: Cumulative number (%) of subjects exposed to Bydureon as of September 30, 2011 (ITT, n=1595). (Source: CR safety update 2011 Table 4.)

Study Grouping		Cumulative Duration of Administration (Weeks) [1]						
Study	Any Duration	≥12	≥26	≥52	≥78	≥104	≥130	≥156
Clinical Pharmacology Studies [2]								
2993LAR-102 [3]	10	—	—	—	—	—	—	—
BCB107 [3]	60	—	—	—	—	—	—	—
2993LAR-103	47	—	—	—	—	—	—	—
Clinical Pharmacology Subtotal	**117**	—	—	—	—	—	—	—
Efficacy and Safety Studies								
Controlled Studies								
Placebo-controlled								
2993LAR-104	31	31 (100.0)	—	—	—	—	—	—
H8O-JE-GWBW	20	—	—	—	—	—	—	—
Comparator-controlled								
2993LAR-105 [4]	278	268 (96.4)	251 (90.3)	233 (83.8)	218 (78.4)	208 (74.8)	198 (71.2)	155 (55.8)
BCB106 [4]	405	369 (91.1)	337 (83.2)	99 (24.4)	—	—	—	—
H8O-MC-GWBR [4]	233	218 (93.6)	207 (88.8)	185 (79.4)	176 (75.5)	1 (0.4)	—	
BCB108	129	118 (91.5)	18 (14.0)	—	—	—	—	—
H8O-MC-GWCH	248	226 (91.1)	201 (81.0)	—	—	—	—	—
Uncontrolled Studies								
H8O-MC-GWDC [4]	134	126 (94.0)	123 (91.8)	101 (75.4)	—	—	—	—
Efficacy and Safety Subtotal	**1478**	**1356 (91.7)**	**1137 (76.9)**	**618 (41.8)**	**394 (26.7)**	**209 (14.1)**	**198 (13.4)**	**155 (10.5)**
Grand Total	**1595**	**1356 (85.0)**	**1137 (71.3)**	**618 (38.7)**	**394 (24.7)**	**209 (13.1)**	**198 (12.4)**	**155 (9.7)**

Note: Percentages are based on the number of subjects in the "Any Duration" column.

[1] Duration of Administration in weeks = (Date of the last exenatide once weekly administration – Date of the first exenatide once weekly administration)/7+1, rounded to the nearest integer. For studies with single exenatide once weekly injection, the duration of administration is counted as 1 week. Subjects are counted in multiple columns up to their maximum duration of administration.

[2] Includes both healthy volunteers and subjects with type 2 diabetes.

[3] Includes only the subjects who received the F17 formulation of exenatide once weekly.

[4] Includes exenatide once weekly duration of administration from comparator-controlled and open-ended assessment periods through Week 52 (BCB106 and H8O-MC-GWDC), Week 84 (H8O-MC-GWBR), and Year 3 (Study 2993LAR-105).

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Comment: As alluded to in footnote 4 above, only the extension period of study GWBR (not 105 or BCB106) was controlled (with glargine). Thus, the longest, controlled Bydureon exposure is 176 subjects to ≥76 weeks (1.5 years).

The total exposure of Bydureon subjects (n=1,595) is less than the 2,500 exposed subjects recommended in the draft February 2008 diabetes mellitus guidance. However, the Bydureon NDA references Byetta NDA 21-773 for a different formulation with the same active ingredient (exenatide). As of September 30, 2010, over (b) (4) patients have been exposed to exenatide in the United States. More than 6,500 subjects and healthy volunteers have been exposed to exenatide in clinical trials. Thus, the exposure is adequate.

The demographic and baseline characteristics of subjects in controlled trials are shown below. Approximately half of subjects were male. The mean age ranged from 52.3 – 58.3 years; the majority of subjects were <65 years. The distribution of races varied by study but, overall, was diverse. The mean BMI ranged from 30.69 – 34.12. The mean HbA1c and duration of diabetes ranged from 8.0 – 8.6% and 2.6 years on metformin to 8.0 years on insulin, respectively. The majority of subjects were on background antidiabetic medication in addition to diet and exercise. The majority of subjects had normal renal function or mild renal insufficiency.

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Table 21. CR 2011: Demographic and baseline characteristics treatment by controlled study and treatment (ITT)

	Placebo-controlled		Comparator-controlled					
	Bydureon (n=51)	Placebo (n=23)	Bydureon (n=918)	Byetta (n=268)	Sitagliptin (n=329)	Pioglitazone (n=328)	Insulin (n=223)	Metformin (n=246)
Male	35 (68.6)	9 (39.1)	507 (55.2)	142 (53.0)	180 (54.7)	176 (53.7)	123 (55.2)	154 (62.6)
Mean age (y)	54.3	57.3	55.0	55.0	52.3	54.1	58.3	53.7
Age								
≥18-65	40 (78.4)	17 (73.9)	766 (83.4)	224 (83.6)	293 (89.1)	278 (84.8)	167 (74.9)	215 (87.4)
≥65	11 (21.6)	6 (26.1)	152 (16.6)	44 (16.4)	36 (10.9)	50 (15.2)	56 (25.1)	31 (12.6)
Race								
Caucasian	18 (35.3)	9 (39.1)	616 (67.1)	173 (64.6)	163 (49.5)	175 (53.4)	189 (84.8)	160 (65.0)
Black	5 (9.8)	1 (4.3)	43 (4.7)	28 (10.4)	23 (7.0)	17 (5.2)	1 (0.4)	11 (4.5)
Asian	21 (41.2)	10 (43.5)	110 (12.0)	6 (2.2)	75 (22.8)	74 (22.6)	14 (6.3)	51 (20.7)
Native Am	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (1.2)	0 (0.0)	0 (0.0)	2 (0.8)
Hispanic	6 (11.8)	3 (13.0)	147 (16.0)	61 (22.8)	62 (18.8)	59 (18.0)	19 (8.5)	21 (8.5)
Other	1 (2.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.6)	3 (0.9)	0 (0.0)	1 (0.4)
Mean BMI	31.95	31. 89	32.58	34.12	31.78	31.80	32.27	30.69
Mean HbA1c (%)	8.0	8.1	8.4	8.3	8.5	8.5	8.3	8.6
Mean T2DM duration (y)	4.9	5.2	6.0	6.7	4.0	4.2	8.0	2.6
Background diet & exercise only	22 (43.1)	6 (26.1)	290 (31.6)	49 (18.3)	163 (49.5)	163 (49.7)	0 (0.0)	246 (100.0)
Renal function								
Normal	35 (68.6)	13 (56.5)	628 (68.4)	142 (53.0)	227 (69.0)	205 (62.5)	171 (76.7)	213 (86.6)
Mild	16 (31.4)	9 (39.1)	254 (27.7)	107 (39.9)	88 (26.7)	107 (32.6)	51 (22.9)	33 (31.7)
Moderate	0 (0.0)	0 (0.0)	34 (3.7)	19 (7.1)	11 (3.3)	15 (4.6)	1 (0.4)	47 (4.9)
Severe	0 (0.0)	1 (4.3)	1 (0.1)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.1)

Source: CR safety update 2011 SDS 2.
Note: Includes subjects from GWDC and subjects who completed 105, BCB106, GWBR controlled periods and enrolled in the extension period.

With regard to withdrawals due to AEs, more Byetta subjects discontinued due to nausea, vomiting, or diarrhea (5/6 events), whereas more Bydureon subjects discontinued due to laboratory abnormalities (lipase, creatinine, ALT), pancreatitis, or injection site pruritis (5/6 events).

Byetta (exenatide) should not be used in patients with severe renal impairment or ESRD. It should be used with caution in patients with renal transplantation. Caution should be applied when initiating exenatide or escalating the dose in patients with moderate renal failure. The applicant proposes similar language for the Bydureon label. Studies of Bydureon excluded subjects with renal failure as follows:

- Studies 104, 105, 105c: Included male and female subjects with serum creatinine ≤ 1.6 and 1.4 mg/dl, respectively. Excluded subjects with creatinine clearance (CrCl) ≤ 30 mL/min
- Study GWBW: Excluded subjects with a history of renal transplantation, currently receiving dialysis, or serum creatinine ≥ 1.5 or 1.4 mg/dl for males or females, respectively

- Study BCB106: Excluded subjects with serum creatinine level > 1.5 or 1.4 mg/dl in men and women, respectively
- Study BCB108: Excluded subjects with clinically significant, as judged by the investigator, renal disease
- Studies GWBR and GWCH: Excluded subjects with a history of renal transplantation or are currently receiving renal dialysis or have serum creatinine ≥1.5 mg/dL for males and ≥1.2 mg/dL for females
- Study GWDC: Excluded subjects with a history of renal transplantation or are currently receiving dialysis or have serum creatinine ≥1.5 mg/dl for males and ≥1.25 mg/dl for females.

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide. The proposed Bydureon label also states these points. However, studies of Bydureon excluded subjects with hepatic impairment as follows:

- Studies 104, 105, 105c, BCB106: Hepatic disease or an ALT or AST >3x ULN
- Studies GWBW GWDC, and GWCH: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or ALT or AST ≥ 2.5x ULN
- Study BCB108: Excluded subjects with clinically significant, as judged by the investigator, hepatic disease
- Study GWBR: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, ALT or AST >3x ULN

7.2.2 Explorations for Dose Response

Please refer my review of the original NDA submission.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to section 4.3 Preclinical Pharmacology/Toxicology of my original NDA review for a discussion of the relevant animal thyroid data with Bydureon and related products, exenatide and liraglutide. A thyroid cancer registry to assess the relative risk of thyroid neoplasm with exenatide will be required of the applicant.

Although the incidence of pancreatitis in T2DM patients is debated in the literature, exenatide is associated with pancreatitis, including hemorrhagic and necrotizing pancreatitis. The applicant did not conduct special animal or in vitro studies of pancreatitis with Bydureon. However, please refer to B. Timothy Hummer's July 19, 2011 review of PMR 1559-4, *Potential effects of twice-daily (BID) subcutaneous injection of exenatide (AC2993) for 3 months on pancreatic exocrine structure and function in obese diabetic (ZDF) rats*. (b) (4)

7.2.4 Routine Clinical Testing

The applicant obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. Limitations of this testing included the following:

- Serum amylase and lipase was not drawn in studies 104, 105, and GWBW. However, on July 21, 2010, as requested by the agency, the applicant submitted an analysis of all calcitonin data obtained in ongoing, terminated, and completed clinical trials of Bydureon, which I reviewed with the first CR. No additional studies in which pancreatic enzyme concentrations were collected were completed as of September 30, 2010. The clinical significance of routine amylase and lipase monitoring in asymptomatic patients is not clear. The incidence of pancreatitis was summarized again in the complete response safety update.
- As there were no concerns about MTC when the majority of studies were planned, calcitonin was not measured in studies submitted to the original NDA. On August 25, 2010, as requested by the agency, the applicant submitted an analysis of all calcitonin data obtained in ongoing, terminated, and completed clinical trials of Bydureon, which I reviewed with the first CR. No additional studies in which calcitonin concentrations were collected were completed as of September 30, 2010. However, the incidence of thyroid neoplasms was discussed in the complete response resubmission.

Please refer to section 7.4.2 Laboratory Findings of my previous reviews.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to my review of the original NDA submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As discussed in section 2.4 Important Safety Issues with Consideration to Related Drugs, GLP-1 mimetics currently approved in the United States include exenatide and liraglutide. Labeled safety concerns with exenatide include:

- Acute pancreatitis
- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions as a result of anti-exenatide antibodies
- Renal failure

Liraglutide and other longer acting GLP-1 receptor agonists are associated with thyroid c-cell tumors in rats and mice.

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7.3 Major Safety Results

7.3.1 Deaths

Twelve deaths (7 Bydureon, 2 liraglutide, 1 Byetta, 1 sitagliptin, 1 metformin) were reported in the Bydureon development program. This includes liraglutide subject GWDE-4052, who died after September 30, 2010.

The following five deaths were previously reported:

- BCB106-161030 (sitagliptin): Died of "hypertension" after 119 days of study medication
- 2993LAR-105-10802 (Bydureon): Died of a fatal myocardial infarction after approximately 198 days of study medication. The subject was a 67 year old American male with a history of T2DM (8 years) and hyperlipidemia who was overweight.
- BCB108-147005 (Byetta): Died of a myocardial infarction (MI)
- H8O-MC-GWDC-5001 (Bydureon): The subject was diagnosed with stage II descending colon adenocarcinoma <1 month after the first dose of Bydureon. The subject was subsequently diagnosed with stage 2 right lung adenocarcinoma and died.
- H8O-MC-GWCH-1043 (metformin): The subject discontinued blinded injectable and oral study medication after ~5 months due to abdominal pain, which remained ongoing. Approximately 1 month later, the subject was hospitalized for severe abdominal pain and distension and was diagnosed with gastric adenocarcinoma with carcinomatosis ascites. The subject died of multiple organ failure ~1 month later.

Six deaths occurred during completed or ongoing studies:

- GWDC-3302 (Bydureon): The subject experienced a brain neoplasm after ~9 months of Bydureon use. The drug was discontinued and surgery performed to remove the left frontal tumor. Approximately four months later, the subject died.
- GWDC-5117 (Bydureon): The subject was hospitalized for weakness, hypotension, anemia, and cardiomegaly with INR of 4 on anticoagulants approximately 16 months after initiating Bydureon. Past medical history (PMH) was hypertension (HTN), hyperlipidemia, ischemic cardiomyopathy, atrial fibrillation, and coronary artery disease (CAD). The subject died 2 days later due to cardiopulmonary arrest secondary to iatrogenic coagulopathy, Barrett's esophagus, and gastrointestinal (GI) hemorrhage.
- GWBX-0212 (Bydureon): The subject, who had a history of HTN, died from ischemic cardiac failure ~8 days after the first Bydureon dose. Autopsy was not performed.

- GWDE-6707 (Bydureon): The subject, who had a history of obesity and HTN, received ~3 weeks of Bydureon and was discontinued due to a protocol violation (baseline HbA1c greater than inclusion criteria in Argentina). Approximately 10 weeks later, the subject was found dead at home. No autopsy was performed. The cause of death was non-traumatic cardiorespiratory arrest.
- GWDE-1558 (Bydureon): The subject had a history of depression that worsened to severe depression after ~6 months Bydureon use, at which time the drug was discontinued due to completion of the treatment period. The subject committed suicide approximately 12 days later.
- GWDE-9153 (liraglutide): The subject had a history of HTN, atherosclerosis, and obesity and completed 26 weeks liraglutide treatment. Approximately 1.5 months later, the subject was admitted to the hospital with headache. Computed tomography (CT) scan two days later revealed significant ischemia on the right cerebellum, compression of the brain stem and fourth ventricle, and internal hydrocephalus. Intubation, mechanical ventilation, and anti-edematous therapy were initiated and surgery was conducted to drain the ventricles. The subject died of cardiac arrest on day 7 of the hospitalization. Autopsy revealed the death was due to a massive pulmonary embolism (PE).

One death occurred after the data cut-off date:

- GWDE-4052 (liraglutide): The subject completed 26 weeks of liraglutide treatment and experienced a cerebral stroke and died ~4.5 weeks after discontinuation of study drug.

In study BCB108, one Byetta subject (147005) was found dead at home approximately 190 days after the first dose. Autopsy revealed the cause of death as MI and coronary artery disease.

Although there more Bydureon subjects died when compared to comparator subjects in the Bydureon development program, these deaths are inconclusive.

7.3.2 Nonfatal Serious Adverse Events

The SAEs which occurred in the completed studies in the pooled analysis are shown in Table 22. The percentage of subjects who experienced an SAE was lower with Bydureon than most other comparators. The SOCs with the most Bydureon SAEs were Infections and Infestations (n=6, 0.7%), Cardiac (n=4, 0.4%), GI (n=3, 0.3%), Neoplasms (n=3, 0.3%), and Renal and Urinary (n=3, 0.3%). Except for viral pericarditis, prostate cancer, and calculus ureteric (n=2), events within those SOCs were single events.

In study BCB108, eight subjects experience 10 SAEs. Three Bydureon subjects experienced three SAEs (cellulitis, calculus ureteric, pancreatitis). Five Byetta subjects experienced seven SAEs (gastrointestinal hemorrhage and cholelithiasis, myocardial

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ischemia, cholecystitis, chest pain, CAD and MI). The MI in the Byetta subject was fatal, as described above.

Table 22. CR 2011: SAEs by SOC and treatment in completed, controlled efficacy and safety studies

	Placebo-Controlled		Comparator-Controlled					
System Organ Class [1]	EQW (N = 51) n (%)	Placebo (N = 23) n (%)	EQW (N = 918) n (%)	BYETTA (N = 268) n (%)	Sitagliptin (N = 329) n (%)	Pioglitazone (N = 328) n (%)	Insulin (N = 223) n (%)	Metformin (N = 246) n (%)
All Serious Treatment-Emergent Adverse Events	0 (0.0)	0 (0.0)	28 (3.1)	10 (3.7)	8 (2.4)	19 (5.8)	10 (4.5)	12 (4.9)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	4 (0.4)	3 (1.1)	0 (0.0)	5 (1.5)	1 (0.4)	2 (0.8)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.4)	0 (0.0)	5 (1.5)	1 (0.4)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.7)	1 (0.3)	2 (0.6)	2 (0.9)	1 (0.4)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.7)	0 (0.0)	2 (0.6)	1 (0.4)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	6 (0.7)	0 (0.0)	1 (0.3)	7 (2.1)	0 (0.0)	2 (0.8)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.8)
Nervous system disorders	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.9)	2 (0.8)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CR safety update 2011 Table 8

Bydureon does not appear to be associated with an increase in SAEs.

7.3.3 Dropouts and/or Discontinuations

The withdrawal rate due to AEs in completed, controlled trials was greater for Bydureon and Byetta (4.9%) when compared to pioglitazone (3.4%), sitagliptin (1.8%), metformin (1.6%), and insulin (0.9%). SOCs with ≥2 withdrawals due to AEs were as follows: GI (1.7%), General Disorders (1.1%), Investigations (0.5%), Nervous System (0.5%), and Injury/Poisoning/Procedural Complications (0.2%). Discontinuation due to GI AEs occurred less frequently than with Byetta (4.1%). However, General Disorders events occurred more frequently in the Bydureon group when compared to other treatment groups. Nine of the 10 events were injection-site related (1 mass, 5 nodules, 1 puritis, and 2 reactions).

Slightly more Bydureon subjects were discontinued due to events in the Investigations SOC when compared to other treatment groups (Bydureon 0.5% vs. pioglitazone 0.3%). However, all were single events: ALT, blood creatinine, blood potassium, and lipase increased and weight decreased. When uncontrolled/extension data (out to 3 years) was reviewed, the incidence of Investigation SOC events did not increase (0.5% in n=1,478).

In study BCB108, 12 subjects withdrew due to AEs (6 each Bydureon and Byetta), as shown in Table 24. More Byetta subjects withdrew due to nausea and vomiting. The Bydureon events were all singe events.

Table 23. BCB108: AEs leading to withdraw (ITT; n=1 unless otherwise noted)

Bydureon	Byetta
Injection site pruritis	Nausea (n=2)
Post-traumatic pain	Vomiting (n=2)
Blood creatinine increased	Diarrhea
Pancreatitis	MI
Alanine aminotransferase increased	
Lipase increased	

Bydureon appears to be associated with an increased risk of withdrawal due to AEs. However, in controlled clinical trials, this rate is equal to that of Byetta. As described in my two prior reviews of Bydureon NDA 22-200, Bydureon contains PLG which is associated with local inflammatory reactions. Although one PLG-containing approved product (Vivitrol, NDA 21-897) contains an injection site Warning and Precaution, that product is administered through a different route and the microsphere dose (mg/injection) significantly exceeds that of Bydureon (b) (4)-fold). The labeling of most products containing PLG includes Adverse Reactions language regarding possible injection site reactions.

The applicant-proposed labeling includes the following injection site language:

- Highlights Adverse Reactions: Injection site pruritis and nodule were among the most common (≥5%) adverse reactions and occurred more frequently than comparator in clinical trials
- 6.1 Clinical Trial Experience: *Small, asymptomatic subcutaneous injection site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24 out of 31 subjects (77%) experienced at least one injection site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.*

COMMENT: I recommend the following regarding injection site reactions:

- **Revising the proposed language to include the percentage of subjects withdrawn due to this AE**
- **The Periodic Safety Update Reports (PSURs) analyze serious injection site reactions (including nodules)**

Table 24. CR 2011: AEs leading to withdrawal by SOC and treatment in completed, controlled safety and efficacy studies

	Placebo-Controlled		Comparator-Controlled					
System Organ Class [1]	EQW (N = 51) n (%)	Placebo (N = 23) n (%)	EQW (N = 918) n (%)	BYETTA (N = 268) n (%)	Sitagliptin (N = 329) n (%)	Pioglitazone (N = 328) n (%)	Insulin (N = 223) n (%)	Metformin (N = 246) n (%)
All Treatment-Emergent Adverse Events Leading to Withdrawal	0 (0.0)	0 (0.0)	45 (4.9)	13 (4.9)	6 (1.8)	11 (3.4)	2 (0.9)	4 (1.6)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	16 (1.7)	11 (4.1)	4 (1.2)	4 (1.2)	2 (0.9)	2 (0.8)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	10 (1.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)
Nervous system disorders	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.4)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CR safety update 2011 Table 9

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7.3.4 Significant Adverse Events

As described in section 2.4, thyroid tumors are an adverse event of special interest with regard to long acting GLP-1 analogues. The exenatide label contains the following safety concerns:

- Acute pancreatitis
- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions, predominantly as a result of anti-exenatide antibodies
- Renal failure

Thyroid tumors: The following thyroid neoplasms have been reported to date:

- Bydureon:
  - Subject 2993LAR-105-22415: Benign thyroid mass
  - Subject BCB108-150001: Thyroid nodule. Although no AEs occurred in this subject, his screening calcitonin concentration of 59 pg/ml increased to 91 pg/mol at week 24 (normal 0-8.4 pg/ml). Approximately 11 weeks after study termination, the subject's calcitonin was 121 pg/ml (normal 0-7.5 pg/ml). Thyroid ultrasound revealed a heterogenous thyroid with complex nodules. Fifteen weeks after study termination, his calcitonin concentration was 80.5 pg/ml. Eighteen weeks after study termination, a thyroid uptake and scan was unremarkable, with no focal areas of increased or decreased uptake. An ultrasound-guided thyroid fine needle aspiration revealed no evidence of malignancy.
  - Subject BCB106-145023: Thyroid nodule
  - Subject GWCK-1624: SAE of thyroid nodule. Baseline calcitonin was 18.3 pg/ml (normal 0-18.2 pg/ml) and 24.1 pg/ml on day 85. At the end of treatment, calcitonin was 26.1 pg/ml. One month after last dose of Bydureon, ultrasound (US) revealed a small, right thyroid nodule.
  - Subject GWCK-5408: Thyroid cyst.
- Byetta → Bydureon: Subject GWCK-4307: SAE of papillary thyroid microcarcinoma. The subject received a single dose of Bydureon during an extension period prior to the diagnosis of the malignancy. A right thyroid (subtotal thyroid) lobectomy was performed.
- Byetta: Subject GWCK-5410: Thyroid nodule
- Sitagliptin: Subject BCB106-175022: SAE of papillary thyroid cancer
- Pioglitazone: Subject GWCH-0500: Thyroid neoplasm (worsening of pre-existing)

Although more Bydureon subjects (n=6) were diagnosed with thyroid neoplasms, all but one was benign. The Bydureon subject with papillary thyroid microcarcinoma only

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received one dose suggesting it was pre-existing (although the subject had been exposed to Byetta).

In completed, controlled efficacy and safety studies, the exposure-adjusted incidence rate for thyroid neoplasms[1] is 2.2 events per 1000 subject years for Bydureon compare to 6.6 and 7.0 events per 1000 subject years for sitagliptin and pioglitazone, respectively.

On August 25, 2010 as requested by the agency, the applicant submitted an analysis of all calcitonin data obtained in ongoing, terminated, and completed clinical trials of Bydureon. The submission included data from 4 completed or ongoing clinical trials (BCB108, GWBR, GWCH, and GWDC) for which an interim data cut (July 5, 2010) was available. Mean calcitonin values remained within the normal range (up to 84 weeks). Approximately 3% of subjects had elevated postbaseline calcitonin levels, although the mean change seen with Bydureon was small (~0.3 pg/ml). Calcitonin measurements >20 pg/ml were more common in men, but they also had a higher normal range (ULN = 18.2 pg/ml). Please refer to my review of the first CR. No additional studies in which calcitonin data were collected were completed as of September 30, 2010.

In summary:

- Although more Bydureon subjects (n=6) were diagnosed with thyroid neoplasms, all but one was benign. Subject GWCK-4307 received only one dose before being diagnosed with papillary thyroid microcarcinoma.
- In completed, controlled efficacy and safety studies, the exposure-adjusted incidence rate for thyroid neoplasms[1] is 2.2 events per 1000 subject years for Bydureon compare to 6.6 and 7.0 events per 1000 subject years for sitagliptin and pioglitazone, respectively.
- [redacted] (b) (4)

Based on this and the nonclinical information, I recommend the following:

- The label clearly state that Bydureon is contraindicated in subjects with a personal or family history of MTC or in patients with MEN2
- Bydureon not be used as a first-line antidiabetic therapy for patients inadequately controlled on diet and exercise

1 Preferrred terms (PTs): benign neoplasm of thyroid gland, metastases to thyroid, thyroglossal cyst, thyroid adenoma, thyroid cancer, thyroid cancer metastatic, thyroid cyst, thyroid mass, and thyroid neoplasm

- A MTC case series registry of at least 15 years duration as described in section 1.4
- The applicant analyze thyroid tumors as an AE of special interest in the PSURs

NOTE: As the human relevance of the animal thyroid c-cell tumors is unknown and (b) (4) [redacted] described adverse exocrine pancreatic effects expressed as necrotizing pancreatitis, the applicant was asked to conduct an epidemiologic study of thyroid neoplasms and pancreatic cancer under exenatide (Byetta) monotherapy NDA PMR 1559-3.[2] (b) (4), (b) (5) [redacted]

Regarding pancreatic tumors, two cases of pancreatic cancer have been reported in the Bydureon and Byetta clinical programs:

- GWBX-2103 (Bydureon): The subject was hospitalized for jaundice 38 days after initiating Bydureon, which was discontinued. Five weeks later, cancer of the head of the pancreas was diagnosed and bile duct cancer suspected. One month later, pancreatic head resection and duodenectomy were performed. Cancer was detected in the pancreatic duct. *Comment: Due the extent of malignancy at the time of diagnosis, it is unlikely that the cause is 38 days' exposure to Bydureon.*
- GWCK-5203 (Byetta): The subject experienced an intraductal papillary mucinous neoplasm of the pancreas. The event was ongoing with no additional information available at the time of the report.

Although it does not appear as if there is a signal for pancreatic cancer in the exenatide development programs, I recommend monitoring events of pancreatic cancer in the CV trial and PSURs.

Acute pancreatitis: Nine cases of pancreatitis (including PTs for edematous, acute, chronic, or necrotizing forms) occurred in the Bydureon clinical development program. In completed, comparator-controlled trials, the following five events occurred (2 Bydureon [0.2%], 2 pioglitazone [0.6%], and 1 sitagliptin [0.3%]). All but the chronic pancreatitis resolved. The pancreatitis symptoms in the Bydureon subjects 5802 and 152006 resolved within 3 days while exenatide was still in circulation at therapeutic concentrations.

2 Matveyenko, AV et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes. Diabetes 2009, 58:1604-1615.

- BCB106- 170002 (pioglitazone): Necrotizing pancreatitis which resulted in withdrawal
- BCB106-125013 (pioglitazone): Pancreatitis
- GWBR-5802 (Bydureon): Moderate edematous pancreatitis which led to withdrawal but resolved within 3 days.
- GWCH-3181 (sitagliptin): Chronic pancreatitis 9 days after starting blinded study medication which lead to withdrawal
- BCB108-152006 (Bydureon): The subject presented to the emergency room approximately 61 days after starting Bydureon with moderate perumbilical pain. Amylase and lipase were 160 and 324, respectively (units not provided). The subject had a history of dyslipidemia but did not experience nausea or vomiting. CT scan showed no acute inflammatory abnormality. The pancreatitis resolved in 3 days, while the subject was receiving study mediation. However, the subject was subsequently withdrawn due to the pancreatitis. *Comment: This was the only event of pancreatitis in study BCB108.*

In the completed, controlled efficacy and safety studies, the exposure-adjusted incidence rate for pancreatitis is 4.4 events per 1000 subject years for Bydureon compared to 6.6 events and 13.9 events per 1000 subject years for sitagliptin and pioglitazone, respectively (0 events per 1000 subject years for Byetta, placebo, insulin, and metformin). However, four additional events occurred in Bydureon subjects in ongoing studies:

- GWBR-9090 (Bydureon): The subject experienced mild epigatric pain with amylase 119 u/l (normal [nl] 28-100 u/l) and lipase 127 U/l (nl <60 u/l) after >2 years Bydureon use. Abdominal US showed no abnormalities. The subject recovered ~11 days later and continued study participation and Bydureon use. *Comment: Due to the mild symptoms, pancreatic enzymes <3x the upper limit of normal (ULN), and negative US, this may not have been a true case of pancreatitis by current diagnostic standards.*
- GWCK-1209 (Bydureon): This subject was diagnosed with pancreatitis ~6 months after initiating Bydureon. Lipase was 188 u/l (nl 0-60 u/l). A CT scan revealed the pancreas was diffuse and mildly enlarged but without duct dilation, parenchymal calcification, calculi, and per-pancreatic fluid. Bydureon was discontinued. The subject withdrew and recovered 2.5 months later.
- GWDE-8703 (Bydureon): The subject was hospitalized with vomiting and elevated pancreatic enzymes (amylase 438 u/l [nl 28-100 u/l] and lipase 2155 [nl 13-60 u/l]) and diagnosed with acute pancreatitis ~3 months after initiating Bydureon. US revealed cholelithiasis. Study medication was discontinued. The subject was withdrawn and, at the time of submission, had not recovered.
- GWDE-3115 (Bydureon): The subject had elevated pancreatic enzymes (see below) but was asymptomatic. CT scan six days after the enzyme test revealed an enlarged pancreas without evidence of a discrete mass, fluid collection, or acute pancreatitis. The subject was withdrawn.

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- Baseline: Amylase 110 u/l (nl 20-112 u/l) and lipase 99 u/l (nl 0-60 u/l)
- Week 4: Amylase 335 u/l and lipase 694 u/l
- Week 4 + 4 days: Amylase 238 u/l and lipase 299 u/l
- Week 8: Amylase 217 u/l and lipase 244 u/l

As requested, the applicant analyzed events of pancreatitis associated with Byetta and compared this to Bydureon. As of September 30, 2010, the global exposure to Byetta was (b) (4) patient-years with more than 6500 subjects and healthy volunteers exposed to Byetta in 70 completed and ongoing trials. More than 2160 subjects have been exposed for ≥6 months, more than 1200 subject for ≥1 year, and ~400 subjects for ≥3 years (>1400 patient-years of exposure). In long-term (>28 days), controlled studies, there were 4 (0.1%) events of pancreatitis[3] in Byetta subjects and 1 (0.1%) event in both placebo and insulin subjects:

- 2993-112-151212 (Byetta 5 mcg BID): The subject experienced pancreatitis ~130 days after initiating Byetta The subject was withdrawn due to lithium overdose.
- 2993-115-08606 (Byetta 10 mcg BID): The subject experienced a pancreatic pseudocysts 158 days after initiation of Byetta.
- 2993-115-10511 (Byetta 5 mcg BID): The subject was hospitalized for acute pancreatitis 156 days after initiation of Byetta. The event resolved after 9 days. The subject continued study participation.
- GWBB-1005 (Byetta 5 mcg BID): The subject experienced an SAE of acute pancreatitis 175 days after initiation of Byetta. The event resolved after 8 days. The subject was withdrawn.
- 2993-113-30401 (placebo): The subject was hospitalized for an SAE of acute pancreatitis which occurred 18 days after Byetta initiation and resolved 9 days later.
- GWAA-6773 (glargine): The subject was hospitalized for acute pancreatitis that occurred 9 days after initiating glargine. The event resolved in 4 days. The subject was withdrawn.

The exposure-adjusted incidence rate (95% CI) for pancreatitis in the long-term, controlled studies of the BYETTA program is 2.7 (0.7, 6.9) events per 1000 subject-years for Byetta compared with 1.8 (0.05, 10.3) and 1.8 (0.05, 10.1) events per 1000 subject-years for placebo and insulin, respectively. In uncontrolled, long term extension studies of Byetta, six additional events occurred in Byetta subjects. No deaths related to pancreatitis have been reported in the Byetta clinical development program.

When Byetta and Bydureon data from completed, long-term, controlled studies were pooled, there was a similar incidence of pancreatitis in both treatment groups (Byetta/Bydureon 6 [0.1%] vs. placebo/comparator 5 [0.1%]). The exposure-adjusted

3 PTs: pancreatitis and autoimmune, hereditary, ischaemic, edematous, acute, chronic, hemorrhagic, necrotizing, and repleasing pancreatitis

incidence rate (95% CI) per 1000 subject years is 2.9 (1.1, 6.3) for Byetta/exenatide once weekly and 3.1 (1.0, 7.2) for placebo/non-exenatide comparators.

On July 21, 2010, the applicant submitted an analysis of all amylase and lipase data in ongoing, terminated, and completed trials of Bydureon (cutoff June 30, 2010). Please refer to my review of the first CR for a discussion of these data. No additional studies in which pancreatic enzyme data were collected were completed as of September 30, 2010.

In summary, the incidence of pancreatitis in the Bydureon- and Byetta-treated subjects is similar to comparator-treated subjects in completed, long-term, controlled studies. Although GLP-1 agonists (and dipeptidyl peptidase-4 [DPP-4] inhibitors) have been associated with pancreatitis, it is unclear at this time the extent to which they cause or exacerbate the condition, as T2DM patients may be at increased risk regardless of medical therapy used. However, I agree with the applicant's proposal to include pancreatitis-related Warnings and Precautions language that is similar to Byetta's in the Bydureon label. I also recommend that the Bydureon cardiovascular trial (BCB109) and PSURs include an assessment of pancreatitis events.

Please also refer to related OSE reviews of tracked safety issue (TSI) #892 (GLP-1 agonists and pancreatitis).

Gastrointestinal side effects: GI SAEs and discontinuation due to GI AEs occurred less frequently with Bydureon than with Byetta

- SAEs: 0.3% vs. 0.4%
- SAEs leading to discontinuation: 1.7% vs. Byetta 4.1%

Hypoglycemia: There were no events of major hypoglycemia, defined as loss of consciousness, seizure, or severe impairment in consciousness or behavior. In comparator-controlled trials, 16.4% of Bydureon subjects using a concomitant SU experienced minor hypoglycemia, compared to <2% of Bydureon subjects not using a SU. The planned labeling includes a Warning and Precaution about the increased risk of hypoglycemia when used in combination with a SU.

Hypersensitivity reactions as a result of anti-exenatide antibodies: Please refer to section 7.4.6 Immunogenicity.

Renal failure: The exposure to Bydureon in controlled and uncontrolled/extension studies by baseline renal status subgroup is shown in Table 25.

Table 25. Bydureon exposure in controlled and uncontrolled/extension studies by baseline renal status subgroup (ITT)

CKD Stage	n	Exposure

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		≥6 months	≥1 year	≥3 years
Normal	982	772	417	70
Mild impairment	430	311	176	73
Moderate/Severe impairment	63	51	23	12
Total	**1475**			

Source: CR supplemental safety update 2011 SDS 12

No Bydureon subjects with renal impairment died during the completed clinical safety and efficacy trials.

In the controlled and uncontrolled safety and efficacy studies, the incidence of SAEs increased with worsening renal function (normal n=59 [6.0%], mild impairment n=30 [7.0%], moderate/severe impairment n=8 [12.7%]). However, in controlled studies, the incidence of renally impaired Bydureon subjects who experienced SAEs was 3.0%, 2.4%, and 8.6%, respectively; this is similar to or lower than the rates associated with comparators.

Table 26. SAEs by treatment and baseline renal function in completed safety and efficacy studies

	Placebo-Controlled		Comparator-Controlled						Uncontrolled/Extension [1]		
System Organ Class	EQW n (%)	Placebo n (%)	EQW n (%)	BYETTA n (%)	Sitagliptin n (%)	Pioglitazone n (%)	Insulin n (%	Metformin n (%	EQW n (%)	Insulin [2] n (%)	All EQW [3] n (%)
Baseline Renal Function: Normal [4] (N = 1760)											
	(N = 35)	(N = 13)	(N = 628)	(N = 142)	(N = 227)	(N = 205)	(N = 172)	(N = 213)	(N = 598)	(N = 152)	(N = 982)
All Serious Treatment-Emergent Adverse Events	0 (0.0)	0 (0.0)	19 (3.0)	5 (3.5)	4 (1.8)	10 (4.9)	6 (3.5)	10 (4.7)	42 (7.0)	11 (7.2)	59 (6.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	3 (0.5)	3 (2.1)	0 (0.0)	2 (1.0)	1 (0.6)	1 (0.5)	9 (1.5)	2 (1.3)	12 (1.2)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)	0 (0.0)	4 (0.7)	1 (0.7)	6 (0.6)
Neoplasms	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.3)	1 (0.7)	3 (0.3)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.3)	0 (0.0)	4 (0.4)
Baseline Renal Function: Mild Impairment [4] (N = 672)											
	(N = 16)	(N = 9)	(N = 254)	(N = 107)	(N = 88)	(N = 107)	(N = 51)	(N = 33)	(N = 301)	(N = 44)	(N = 430)
All Serious Treatment-Emergent Adverse Events	0 (0.0)	0 (0.0)	6 (2.4)	3 (2.8)	4 (4.5)	6 (5.6)	4 (7.8)	2 (6.1)	26 (8.6)	5 (11.4)	30 (7.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	1 (3.0)	4 (1.3)	0 (0.0)	4 (0.9)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	3 (0.7)
Neoplasms	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (3.0)	5 (1.7)	0 (0.0)	6 (1.4)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.5)
Baseline Renal Function: Moderate/Severe Impairment [4] (N = 83)											
	(N = 0)	(N = 1)	(N = 35)	(N = 19)	(N = 12)	(N = 16)	(N = 0)	(N = 0)	(N = 48)	(N = 0)	(N = 63)
All Serious Treatment-Emergent Adverse Events	0 (0.0)	0 (0.0)	3 (8.6)	2 (10.5)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	6 (12.5)	0 (0.0)	8 (12.7)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.2)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CR supplemental safety update 2011 Table 7

In the completed safety and efficacy studies, the incidence of AEs leading to withdrawals increased slightly with worsening renal function (normal n=41 [4.2%], mild impairment n=26 [6.0%], moderate/severe impairment n=4 [6.3%]. In controlled studies, the incidence of AEs leading to withdrawal was greater in Bydureon subjects with normal renal function (4.1%) or mild renal impairment (7.1%) than comparator subjects with similar renal function and Bydureon subjects with moderate/severe renal impairment (2.9%).

Table 27. AEs leading to withdrawal by treatment and baseline renal function in completed safety and efficacy studies

	Placebo-Controlled		Comparator-Controlled						Uncontrolled/Extension [1]		
System Organ Class	EQW n (%)	Placebo n (%)	EQW n (%)	BYETTA n (%)	Sitagliptin n (%)	Pioglitazone n (%)	Insulin n (%)	Metformin n (%)	EQW n (%)	Insulin [2] n (%)	All EQW [3] n (%)
Baseline Renal Function: Normal [4] (N = 1760)											
	(N = 35)	(N = 13)	(N = 628)	(N = 142)	(N = 227)	(N = 205)	(N = 172)	(N = 213)	(N = 598)	(N = 152)	(N = 982)
All Adverse Events Leading to Withdrawal	0 (0.0)	0 (0.0)	26 (4.1)	4 (2.8)	3 (1.3)	2 (1.0)	2 (1.2)	2 (0.9)	15 (2.5)	2 (1.3)	41 (4.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.2)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	7 (1.1)	3 (2.1)	2 (0.9)	1 (0.5)	2 (1.2)	1 (0.5)	8 (1.3)	0 (0.0)	15 (1.5)
Neoplasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.7)	1 (0.1)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Renal Function: Mild Impairment [4] (N = 672)											
	(N = 16)	(N = 9)	(N = 254)	(N = 107)	(N = 88)	(N = 107)	(N = 51)	(N = 33)	(N = 301)	(N = 44)	(N = 430)
All Adverse Events Leading to Withdrawal	0 (0.0)	0 (0.0)	18 (7.1)	7 (6.5)	3 (3.4)	7 (6.5)	0 (0.0)	2 (6.1)	8 (2.7)	0 (0.0)	26 (6.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	9 (3.5)	7 (6.5)	2 (2.3)	3 (2.8)	0 (0.0)	1 (3.0)	3 (1.0)	0 (0.0)	12 (2.8)
Neoplasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.3)	0 (0.0)	1 (0.2)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Renal Function: Moderate/Severe Impairment [4] (N = 83)											
	(N = 0)	(N = 1)	(N = 35)	(N = 19)	(N = 12)	(N = 16)	(N = 0)	(N = 0)	(N = 48)	(N = 0)	(N = 63)
All Adverse Events Leading to Withdrawal	0 (0.0)	0 (0.0)	1 (2.9)	2 (10.5)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	3 (6.3)	0 (0.0)	4 (6.3)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.2)
Neoplasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CR supplemental safety update 2011 Table 8

The incidence of AEs in comparator-controlled trials was slightly greater in the Bydureon and Byetta groups in subjects with normal renal function and mild impairment. However, more Byetta subjects than Bydureon subjects with normal renal function experienced AEs (79.6% vs. 70.4%). The incidence of AEs in subjects with mild impairment was similar (Bydureon 74.8% vs. Byetta 71.0%). Although more Bydureon and Byetta subjects experienced GI AEs than comparator subjects, the incidence of AES in other SOCs (including Cardiac Disorders) was less than with comparators. When Cardiac Disorders were reviewed, all but two events (palpitations [n=2, 0.3%] and tachycardia [n=2, o.3%]) in subjects with normal renal function were single events.

Table 28. AE by treatment and baseline renal function in completed safety and efficacy studies

Category or System Organ Class	Placebo-Controlled		Comparator-Controlled						Uncontrolled/Extension [1]		
	EQW n (%)	Placebo n (%)	EQW n (%)	BYETTA n (%)	Sitagliptin n (%)	Pioglitazone n (%)	Insulin n (%	Metformin n (%	EQW n (%)	Insulin [2] n (%)	All EQW [3] n (%)
Baseline Renal Function Subgroup: Normal [4] (N = 1760)											
	(N = 35)	(N = 13)	(N = 628)	(N = 142)	(N = 227)	(N = 205)	(N = 172)	(N = 213)	(N = 598)	(N = 152)	(N = 982)
All Treatment-Emergent Adverse Events	21 (60.0)	12 (92.3)	442 (70.4)	113 (79.6)	138 (60.8)	136 (66.3)	108 (62.8)	139 (65.3)	438 (73.2)	86 (56.6)	731 (74.4)
Cardiac Disorders	0 (0.0)	1 (7.7)	10 (1.6)	4 (2.8)	3 (1.3)	5 (2.4)	3 (1.7)	7 (3.3)	22 (3.7)	5 (3.3)	29 (3.0)
Gastrointestinal Disorders	8 (22.9)	3 (23.1)	225 (35.8)	66 (46.5)	51 (22.5)	51 (24.9)	26 (15.1)	53 (24.9)	193 (32.3)	20 (13.2)	375 (38.2)
Neoplasms	0 (0.0)	0 (0.0)	4 (0.6)	1 (0.7)	1 (0.4)	2 (1.0)	1 (0.6)	2 (0.9)	12 (2.0)	2 (1.3)	16 (1.6)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	13 (2.1)	4 (2.8)	4 (1.8)	3 (1.5)	5 (2.9)	3 (1.4)	31 (5.2)	0 (0.0)	43 (4.4)
Baseline Renal Function Subgroup: Mild Impairment [4] (N = 672)											
	(N = 16)	(N = 9)	(N = 254)	(N = 107)	(N = 88)	(N = 107)	(N = 51)	(N = 33)	(N = 301)	(N = 44)	(N = 430)
All Treatment-Emergent Adverse Events	15 (93.8)	7 (77.8)	190 (74.8)	76 (71.0)	55 (62.5)	71 (66.4)	29 (56.9)	19 (57.6)	228 (75.7)	30 (68.2)	340 (79.1)
Cardiac Disorders	0 (0.0)	0 (0.0)	5 (2.0)	1 (0.9)	1 (1.1)	5 (4.7)	1 (2.0)	1 (3.0)	6 (2.0)	0 (0.0)	10 (2.3)
Gastrointestinal Disorders	7 (43.8)	1 (11.1)	106 (41.7)	48 (44.9)	24 (27.3)	24 (22.4)	7 (13.7)	9 (27.3)	109 (36.2)	7 (15.9)	193 (44.9)
Neoplasms	0 (0.0)	0 (0.0)	5 (2.0)	0 (0.0)	3 (3.4)	1 (0.9)	0 (0.0)	1 (3.0)	15 (5.0)	0 (0.0)	20 (4.7)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	7 (2.8)	4 (3.7)	1 (1.1)	2 (1.9)	0 (0.0)	0 (0.0)	18 (6.0)	2 (4.5)	24 (5.6)
Baseline Renal Function Subgroup: Moderate/Severe Impairment [4] (N = 83)											
	(N = 0)	(N = 1)	(N = 35)	(N = 19)	(N = 12)	(N = 16)	(N = 0)	(N = 0)	(N = 48)	(N = 0)	(N = 63)
All Treatment-Emergent Adverse Events	0 (0.0)	1 (100.0)	27 (77.1)	17 (89.5)	8 (66.7)	13 (81.3)	0 (0.0)	0 (0.0)	36 (75.0)	0 (0.0)	51 (81.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.3)	0 (0.0)	4 (6.3)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	18 (51.4)	13 (68.4)	6 (50.0)	3 (18.8)	0 (0.0)	0 (0.0)	22 (45.8)	0 (0.0)	34 (54.0)
Neoplasms	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
Renal and Urinary Disorders	0 (0.0)	0 (0.0)	3 (8.6)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.3)	0 (0.0)	6 (9.5)

Source: CR supplemental safety update 2011 Table 5

When controlled and uncontrolled studies were searched for events in the Torsade de Pointes/QT prolongation Standard MedDRA Query (SMQ) by baseline renal function subgroup, a similar percentage of Bydureon subjects with normal (0.6%) and mild renal impairment (0.7%) experienced events. (See Table 27.) No subjects with moderate/severe renal impairment experienced events within the SMQ.

Table 29. AEs in the Torsade de Pointes/QT prolongation SMQ by baseline renal status subgroup (n=1 unless otherwise indicated)

Normal Renal Function	Mild Renal Impairment
Cardiac arrest	Syncope (n=3)
Ventricular tachycardia	
Loss of consciousness	
Syncope (n=3)	

Source: Supplemental safety update SDS 14

Studies of Bydureon excluded subjects with mioderate or severe renal failure as described in section 7.2.1.

In the proposed labeling, the applicant does not recommend using Bydureon in subjects with severe and end stage renal impairment. It recommends using Bydureon with caution in subjects with moderate renal impairment. This is acceptable given the results of tQT study BCB112 which demonstated no clinically significant QT prolongation with exenatide exposures up to ~500 pg/mml.

When the percentage of subjects' whose renal function improved or decreased was reviewed, the observed shifts were less than those seen with Byetta and were similar to comparators.

Table 30. Change in renal function from baseline to last visit using C-G formula (ITT)

	Placebo Controlled		Comparator Controlled						Uncontrolled [2]	
n (%)	EQW (N = 51)	Placebo (N = 23)	EQW (N = 918)	BYETTA (N = 268)	Sitagliptin (N = 329)	Pioglitazone (N = 328)	Insulin (N = 223)	Metformin (N = 246)	EQW (N = 950)	Insulin [3] (N = 196)
No Change	44 (86.3)	20 (87.0)	698 (76.0)	201 (75.0)	251 (76.3)	229 (69.8)	169 (75.8)	186 (75.6)	753 (79.3)	145 (74.0)
Improved Renal Function	0 (0.0)	1 (4.3)	56 (6.1)	21 (7.8)	18 (5.5)	22 (6.7)	23 (10.3)	21 (8.5)	53 (5.6)	20 (10.2)
Decreased Renal Function	7 (13.7)	2 (8.7)	96 (10.5)	34 (12.7)	25 (7.6)	35 (10.7)	20 (9.0)	12 (4.9)	115 (12.1)	23 (11.7)
Missing Data [4]	0 (0.0)	0 (0.0)	66 (7.2)	12 (4.5)	32 (9.7)	40 (12.2)	11 (4.9)	20 (8.1)	29 (3.1)	8 (4.1)

Source: CR safety update 2011 Table 9

In summary, the shifts in renal function observed with Bydureon from baseline to last visit were similar to that seen with comparators. In controlled studies, the incidence of AE and AEs leading to withdrawal was slightly greater in Bydureon subjects with normal renal function or mild renal impairment than non-exenatide comparator subjects with similar renal function. However, the incidence of fatalities, SAEs, AEs, and AEs leading to withdrawal in the Cardiac Disorders SOC were less than with comparators. The percentage of Bydureon subjects with normal renal function and mild impairment who experienced events in the Torsade de Pointes/QT prolongation Standard MedDRA Query (SMQ) in controlled and uncontrolled studies was similar (0.6% vs. 0.7%). (See also 7.4.4 Electrocardiograms (ECGs).)

7.3.5 Submission Specific Primary Safety Concerns

See section 7.4.4 Electrocardiograms (ECGs).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The data contained in the complete response safety update 2011 are generally consistent with those presented in the previous safety updates. The most common AEs were GI events, infections (specifically nasopharyngitis and upper respiratory infection),

and injection site related AEs. In comparator-controlled trials, the incidence of nausea and vomiting was lower in Bydureon than Byetta subjects (16.9% vs. 34.3% and 6.8% vs. 14.2%, respectively). Injection-site related AEs such as pruritis, nodule, and erythema were more common with Bydureon than Byetta (3.7-5.9% vs. 0-1.1%).

See also my reviews of the original NDA 22-200 and the first CR submission.

7.4.2 Laboratory Findings

Please refer to my review of NDA 22-200.

7.4.3 Vital Signs

Consistent with my previous reviews, a small mean increase (2.6 beats per minute) in HR and decrease in BP (-2.6/0.9 mm Hg) were observed in completed controlled studies of Bydureon.

The etiology of these changes is unclear. The slight decrease in BP and increase in HR could result from volumetric changes, since GLP-1 agonists are associated with nausea and diarrhea. However, Bydureon is associated with less GI effects than Byetta and the changes in HR and BP were similar. A more likely explanation is that the central GLP-1 system is a regulator of sympathetic outflow.[4] This potential association deserves additional study. A cardiovascular safety trial of Bydureon has been initiated and will be required of the applicant. However, as described in my initial review of NDA 22-200, Bydureon is not a new molecular entity but a reformulation of exenatide which has been on the market since April 2005 without a signal for increased CV risk. Thus, the overall risk-benefit analysis supports approval with a required postmarketing CV trial.

7.4.4 Electrocardiograms (ECGs)

In the October 18, 2010 CR letter, the applicant was required to conduct a tQT study following treatment with exenatide at exposures comparable to those observed in renal impaired patients taking Bydureon. As outlined in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, the agency worked closely with the applicant to design pilot study BCB113 and tQT study BCB112. (See also section 5.3 Discussion of Individual Studies/Clinical Trials.)

tQT studies BCB113 and BCB112 were reviewed by the QT-IRT, which concluded that no significant QTc prolongation effect of exenatide (~200, 300, and 500 pg/ml) was detected. The largest upper bounds of the two-sided 90% CI for the mean difference

4 Yamamoto, H et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. Journal of Clinical Investigation 2002, 110:43-52.

Reference ID: 3057015

between exenatide (~200, 300, and 500 pg/ml) and placebo were below 10 ms, the threshold for regulatory concern (see Table 32).

Table 31. The point estimates and 90% CI corresponding to the largest upper bounds for exenatide (~200, 300, and 500 pg/ml) and the largest lower bound for moxifloxacin (QT-IRT analysis)

Treatment	Time (hour)	ΔΔQTcP (ms)	90% CI (ms)
Exenatide (~200pg/mL)	9	5.0	(3.7, 6.3)
Exenatide (~300pg/mL)	9	3.6	(2.3, 5.0)
Exenatide (~500pg/mL)	9	2.7	(1.4, 4.0)
Moxifloxacin 400 mg*	3	11.4	(9.0, 13.8)

* Multiple endpoint adjustment was applied for 3 time points.

7.4.5 Special Safety Studies/Clinical Trials

CV AEs were reviewed in the CR safety update 2011. In 24- to 30-wk comparator-controlled treatment periods, the incidence of AEs in the Cardiac Disorders SOC was similar between treatment groups (1.7% Bydureon, 1.9% Byetta, 2.3% comparators [sitagliptin, pioglitazone, insulin, and metformin]). In the Bydureon group, all events except for atrial flutter, palpitations, sinus tachycardia, and tachycardia (n=2 events each) were single events. The incidence of Cardiac Disorder SAEs was 0.4% Bydureon, 1.1% Byetta, and 0.7% comparators.

Please also refer to Dr. Fiona Callaghan's statistical review of the applicant's MACE analysis.

7.4.6 Immunogenicity

Of the 918 Bydureon subjects in studies 105, BCB106, BCB018, GWBR, and GWCH, 654 (71.2%) were positive for antibodies to exenatide, with 202 (22.0%) having a high titer (≥625) and 452 (49.2%) having lower titer (≤125). These numbers are similar to those reviewed in the first CR and the original NDA.

When potentially immune-related AEs were identified in exenatide-antibody positive and negative subjects, the incidences were similar to my previous review. Antibody-positive (Ab+) Bydureon subjects were nearly twice as likely to experience potentially immune-related AEs than antibody-negative (Ab-) Bydureon subjects and antibody positive and negative Byetta subjects (23.7% Bydureon Ab+ vs. 13.2% Bydureon Ab- and 10.1-10.2% Byetta). The increase in overall AEs is again attributed to the significant increase in General Disorders and Administration Site Conditions AEs in antibody-

Reference ID: 3057015

positive Bydureon subjects (17.7%). This is expected, as discussed section 7.3.3 Dropouts and/or Discontinuations. The injection sites were localized and not associated with systemic reactions.

In study BCB108, 17 (13.2%) of Bydureon subjects experienced 27 injection-site related AEs. Only 12 (9.8%) of Byetta subjects experienced 14 injection-site related AEs.

The applicant proposes the following Immunogencity labeling in section 6.1 Clinical Trials Experience: *Antibody levels were measured at defined intervals (4-14 weeks) in all subjects in the five controlled studies of BYDUREON. In the five trials, 405 patients (45%) had low titer antibodies (<* (b) (4) *) to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 patients (43%) without antibody titers. An additional 107 patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies [see Warnings and Precautions]. In the study with the most comprehensive evaluation of antibody titers (30-week), the mean antibody titer peaked at week 6 and was reduced by 56% by week 30.*

Two hundred forty six patients with antibodies to exenatide in the BYETTA and BYDUREON clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

(b) (4)

COMMENTS:

- **I recommend that labeling section 6.1 Adverse Reactions include the number of subjects tested for antibodies.**
- **As the applicant defines low and high titers as ≤125 and ≥625 in the safety update, I disagree with the description of low titers as** (b) (4) **in the proposed prescribing information (PI). The text should be revised.**
- **Antibody data should be displayed as the percent of subjects with positive antibodies at any time during the study, not just at study endpoint.**

Please also refer to section 7.3 above for my recommendations pertaining to injection site reactions.

Reference ID: 3057015

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please refer to my review of the original NDA submission.

7.5.2 Time Dependency for Adverse Events

Please refer to my review of the original NDA submission.

7.5.3 Drug-Demographic Interactions

As requested, the applicant analyzed AE data for possible subgroup differences based on age (<65 year vs. ≥65 years), gender, race/ethnicity (Caucasian, Asian, Black, or Hispanic), and duration of diabetes (<10 year vs. ≥10 years). The incidence of AEs was generally similar between treatment groups and demographic subgroups, when sample size was taken into account (see Table 32).

Table 32. Incidence of AEs (%) by treatment and demographic subgroup in controlled clinical trials (ITT)

Category	Placebo-Controlled		Comparator-Controlled					
	Bydureon	Placebo	Bydureon	Byetta	Sitaglip	Pioglit	Insulin	Met
Age								
<65y (n=2144)	67.5	88.2	71.4	75.0	61.1	68.0	62.3	64.2
≥65y (n=406)	81.8	83.3	74.3	86.4	66.7	62.0	58.9	64.5
Gender								
M (n=1400)	62.9	100.0	69.4	69.0	58.3	64.2	59.3	62.3
F (n=1120)	87.5	78.6	74.9	85.7	65.8	70.4	64.0	67.4
Race/ethnicity								
Caucasian (n=1615)	61.1	77.8	74.0	80.3	65.6	66.9	58.2	63.1
Black (n=140)	20.0	100.0	74.4	75.0	73.9	64.7	100.0	72.7
Asian (n=365)	85.7	90.0	59.1	100.0	45.3	67.6	64.3	62.7
Hispanic (n=378)	83.3	100.0	71.4	65.6	66.1	89.5	71.4	67.1
DM Duration								
<10y (n=2066)	76.7	84.2	70.2	76.6	62.1	67.2	61.0	64.9
≥10y (n=454)	37.5	100.0	78.3	77.6	58.1	65.9	62.3	53.3

Source: CR supplemental safety update 2011 Tables 1, 2, 3, and 4

7.5.4 Drug-Disease Interactions

Please refer to section 7.3.4 Significant Adverse Events above and my review of the original NDA submission.

7.5.5 Drug-Drug Interactions

Please refer to my review of the original NDA submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to my review of the original NDA submission.

7.6.2 Human Reproduction and Pregnancy Data

In most clinical studies of Bydureon pregnancy or lactation were exclusion criteria, and pregnancy during the study was cause for withdrawal. Six pregnancies were previously reported in the following Bydureon studies:

- BCB107: Healthy volunteer treated with a single dose of Byetta and Bydureon
- GWBR: Two Bydureon subjects
- BCB106: Two Bydureon subjects
- BCB108: Byetta subject

Of these six pregnancies, two ended in elective abortion, two in spontaneous abortions, one subject was lost to follow up, and one pregnancy (Byetta subject) was progressing without complication.

During this reporting period, three additional pregnancies were reported in the following studies:

- GWCH: Bydureon subject's pregnancy was without complication
- GWCK:
    - Bydureon subject experienced a spontaneous abortion.
    - Byetta subject chose an elective abortion.

Two of these reports (one each in studies BCB107 and GWBR) were described in my review of the original NDA submission. The four new reports are as follows:

- BCB106:
    - Pregnancy ended in a spontaneous abortion at approximately 10 weeks
    - Pregnancy ended with an elective abortion due to personal reasons

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- BCB108: Pregnancy was progressing without complications as of December 31, 2009
- GWBR: Pregnancy ended in a spontaneous abortion after an unknown duration

Bydureon will be labeled pregnancy category C. There are no adequate and well-controlled studies of Bydureon use in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Exenatide LAR has not been studied in pediatric subjects. However, the pediatric program for Byetta (NDA 21-773) is currently ongoing. Protocol 2993-124 is a completed clinical PK/PD study in T2DM adolescents; the final report was submitted September 27, 2007. Protocol H8O-MC-GWBQ (GWBQ) is an ongoing long-term safety and efficacy study in T2DM adolescents. As described in Written Request #3 Amendment 2 (dated October 27, 2010), the final GWBQ report will be submitted on or before December 31, 2014.

The applicant's previous Bydureon pediatric plan was discussed with the Pediatric Research Committee (PeRC) on February 17, 2010. PeRC concurred with my recommendations to 1) include T2DM subjects ages 10-16 years 11 months in the pediatric safety and efficacy study and 2) defer initiation of that study until after completion of a rodent study to determine if Bydureon-induced c-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation. In addition, PeRC recommended the applicant conduct a PK study in the same population and evaluate 0.8 mg.

On August 25, 2011, the applicant submitted a revised pediatric plan. It seeks a waiver of Bydureon studies in pediatric T2DM subjects aged 0-9 years because the pathogenesis of T2DM is such that it rarely occurs in patients <10 years of age. I agree with this waiver for the reason provided and the fact that it is consistent with our approach to Byetta NDA 21-773.

The applicant requests a deferral of pediatric studies in subjects 10-17 years, until Bydureon has been approved for use in adults. It proposes the pediatric study (b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to my review of the original NDA submission.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Bydureon was approved for use by the European Medicines Agency (EMA) on June 21, 2011. As the CR was submitted on July 28, 2011 European post-marketing data were not available at the time of submission.

9 Appendices

9.1 Literature Review/References

The applicant submitted the following list of recently published literature relevant to the clinical safety of Bydureon (January 1, 2010 – December 31, 2010):

- Bergenstal RM, Wysham C, MacConell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. The Lancet. August 2010;376 (9739):431-439.
- Bruce S, Han J, Brown C, et al. Safety and Tolerability of Exenatide Once Weekly Pooled Summary of 1095 Patients from DURATION-1, 2, and 3. Diabetes. Jun 2010;59(Suppl. 1):A16-A17.
- Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes care. Jun 2010;33 (6):1255-1261.
- Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. The Lancet. 2010;375 (9733):2234-2243.
- Fineman M, Mace K, Diamant M, et al. Antibodies to exenatide did not cross-react with human GLP-1 or glucagon or alter the efficacy or safety of exenatide. Diabetologia. September 2010;53:S342.
- Horton E, Taylor K, Booker Porter TK, Han J, Wilhelm K, Harris C. Once-Weekly Exenatide Used for 6 Months Provided Both Improved Glycemic Control and Weight Loss Compared to Sitagliptin, Pioglitazone, or Insulin Glargine in Metformin-Treated Patients with Type 2 Diabetes. Diabetes. Jun 2010;59(Suppl. 1):A163.
- Horton E, Walsh B, Han J, et al. Treatment with Once-Weekly Exenatide for 52 Weeks Resulted in Improvements in Glycemic Control, Body Weight, and Markers of Cardiovascular Risk and Hepatic Injury. Diabetes. Jun 2010;59(Suppl. 1):A159.
- Mondick JT, Kothare P, Gastonguay MR, Cirincione B. Disease progression modelling to quantify the effects of exenatide twice daily and once weekly formulations on HbA1c in patients with type 2 diabetes. Diabetologia. September 2010;53:S335.
- Norwood P, Pintilei E, Pop L, et al. Safety of Exenatide Once Weekly in Patients with Type 2 Diabetes Treated with a Thiazolidinedione. Diabetes. Jun 2010;59(Suppl. 1):A195.

- Okerson T, Yan P, Miller S, Kim T. Exenatide once weekly reduced A1c, weight, and cardiovascular risk factors across a wide BMI range. Diabetic Medicine. March 2010;27 (2 SUPPL. 1):76-77.
- Pullman J, Blevins TC, Malloy J, et al. DURATION-5: Exenatide once weekly resulted in significantly greater improvement in glycaemic ci ontrol than exenatide twice daily in patients with type 2 diabetes. Diabetologia. September 2010;53:S336.
- Wysham C, Bergenstal RM, Malloy J, et al. DURATION-2: Effect of Switching to Once-Weekly Exenatide from Maximum Daily Doses of Sitagliptin or Pioglitazone. Diabetes. Jun 2010;59(Suppl. 1):A162.

9.2 Labeling Recommendations

Please refer to my review of the original NDA submission and the following sections of this review for my proposed changes and the rationale underlying those changes.

- 1.2 Risk Benefit Assessment
- 6.1 Indication
- 7.3.3 Dropouts and/or Discontinuations
- 7.3.4 Significant Adverse Events
- 7.4.4 Electrocardiograms
- 7.4.6 Immunogenicity

9.3 Advisory Committee Meeting

Not applicable.

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/s/

VALERIE S PRATT
12/12/2011

ILAN IRONY
12/12/2011
I concur with Dr. Pratt's review and recommendation. Please see the CDTL memo.

Summary Review for Regulatory Action

Date	October 15, 2010
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-200
Applicant Name	Amylin
Date of Submission	Original NDA submission date May 4, 2009 Complete Response date 4/22/2010
PDUFA Goal Date	10/22/2010
Proprietary Name / **Established (USAN) Name**	Bydureon® (exenatide LAR)
Dosage Forms / Strength	2 mg SC once weekly
Proposed Indication(s)	Improve glycemic control in T2DM
Action/Recommended Action for NME:	Complete Response

1. Introduction

Bydureon is the long-acting formulation of exenatide, an approved glucagon-like peptide 1 (GLP-1) receptor agonist marketed as an immediate-release formulation under the tradename, Byetta. Both products control hyperglycemia in type 2 diabetes in a glucose-dependent fashion through GLP-1 receptor activation. GLP-1 is an incretin hormone which increases insulin secretion in response to an ingested meal. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPPIV), it has limited clinical use.

Exenatide is a synthetically manufactured 34-amino acid GLP-1 agonist that has 53% homology with human GLP-1. Agonistic activity at the human GLP-1 receptor is retained with exenatide while being naturally resistant to DPP-IV, allowing for twice-daily administration. Bydureon is comprised of exenatide encapsulated in a biodegradable polymer microsphere. After subcutaneous injection the polymer degrades slowly allowing for the delayed release of exenatide reducing the frequency of injections over Byetta. The recommended dosing regimen for Bydureon is 2 mg once weekly.

Since the active ingredient in Bydureon is the approved exenatide, the nonclinical and clinical development program relies, in part, on previous studies involving Byetta, supplemented by studies of Bydureon to specifically evaluate the unique characteristics of this formulation, to bridge between the two products, or to provide data intended for labeling claims with this product.

During the course of the original review of this NDA, the agency was confronted with a nonclinical safety issue of thyroid C-cell tumors with liraglutide, another GLP-1 receptor

agonist with sustained activation of GLP-1 receptor. That clinical development program also evaluated the carcinogenicity of exenatide administered via a sc pump which allowed for a sustained pharmacologic effect. In such an evaluation, exenatide was also noted to induce C-cell tumors in rodents. These findings, alongside the carcinogenicity results of Bydureon summarized later in this memo and the ongoing concerns of pancreatitis with exenatide, led the agency to recommend a more comprehensive Risk Evaluation and Mitigation Strategy (REMS) than proposed by the applicant. Dr. Amy Egan, Deputy Director of Safety summarized this in her memo dated February 16, 2010.

In addition, the microbiology review in the original NDA also noted deficiencies. Consequently, the applicant received a *complete response* action letter on March 12, 2010, citing the need for an expanded REMS and the microbiology issues as deficiencies for non-approval.

On April 22, 2010, the applicant submitted its complete response to the action letter. The submission addressed the microbiology deficiencies and included draft labeling, including revised carton and container labeling, and a proposed REMS, including a medication guide and communication plan. Because the response included a REMS, this resubmission was classified as a Class 2 resubmission with a PDUFA goal date of October 22, 2010.

In April 2010, FDA was notified by HealthCanada of a thorough QT (tQT) study conducted for Byetta that was not conducted under a U.S. IND. Byetta was approved before the requirements for a tQT study were put in place for new molecular entities. HealthCanada did not approve Byetta on the basis of its conclusion that exenatide prolonged the QT interval as observed in mean increases exceeding 5 ms at some time intervals. As a consequence of HealthCanada's communication, FDA requested Amylin to submit the completed results and datasets for this study to its NDA for review. These data were provided to FDA on April 13, 2010, and reviewed by the Interdisciplinary Review Team (IRT) for QT Studies. Although the IRT concluded that there was no significant QT prolongation effect for Byetta, a similar conclusion could not be made for Bydureon because the mean maximum concentration of exenatide in this tQT study was only half the steady state concentration achieved with Bydureon and clinical exposure of Bydureon is expected to be 50-60% higher in patients with moderate renal impairment. In addition, extrapolation of QT effect through modeling suggested a potential for QTc prolongation resulting in the IRT's recommendation that a tQT study be required of this NDA in which exenatide is administered to achieve maximum therapeutic dosing of Bydureon.

During development, the company utilized different manufacturing sites for its different scale up from clinical batch to commercial batch. The clinical batches included the (b) (4) (b) (4) scales manufactured at the Alkermes site and the to-be-marketed product includes the (b) (4) scale manufactured at the Amylin Ohio site. The drug product manufactured at the (b) (4) scale was used in many of the Phase 2 trials whereas the (b) (4) scale product was used in the pivotal efficacy and safety trial comparing the once-weekly product to Byetta. Since efficacy data for the to-be-marketed product are not available from this trial, the applicant needed to bridge between the (b) (4) scale product to the (b) (4) scale product. The applicant was not able to bridge the different drug products between the different manufacturing sites via in vitro/in vivo correlation (IVIVC) and was therefore required to demonstrate bridging through a BE study

and a clinical study. This aspect of the evolving manufacturing of the exenatide long-acting formulation has contributed to the difficulties in labeling for Bydureon, as it could not be concluded that Bydureon was superior to Byetta from any of these bridging studies. Although this information was known at the time of the initial review for this NDA, it must now be considered in light of the new information from the tQT study.

The E14/Guidance for Industry outlines the FDA's views on the assessment of proarrhythmic potential for non-antiarrhythmic drugs through the conduct of a tQT study. As stated previously, Byetta was approved prior to the implementation of this guidance which is primarily focused on the development of novel agents. However, the guidance also specifically states that the recommendations from the guidance might also be applicable to approved drugs when a new dose or route of administration is being developed that results in significantly higher exposure (i.e., Cmax or AUC). Given the observation that Bydureon administration does have a higher exposure than Byetta; there is a potential for a QT effect at these higher exposures based on modeling of data from the Byetta tQT study; and there is insufficient evidence to conclude superior efficacy over Bydureon over Byetta to justify dismissing the potential for QT prolongation, it is difficult to ignore the uncertainty of CV safety raised by currently available data and not require a tQT study of this NDA as a premarketing trial.

Consequently, NDA 22-200 will receive a 2nd complete response action and this summary memo will highlight the issues pertaining to the complete response.

2. Background

Please see Dr. Ilan Irony's Cross Discipline Team Leader memo of the original NDA and the complete response submission for a thorough summary of the NDA.

3. CMC/Device

Please see Dr. Stephen Owen's chemistry review for details and recommendations from ONDQA. Overall recommendation from CMC is "acceptable". Office of Compliance completed its recommendation on September 20, 2010 and Dr. Robert Mello has confirmed that microbiology deficiencies identified in the initial review cycle have been adequately addressed in his memo dated July 22, 2010.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology program for exenatide immediate-release was relied upon, in part, in the review of this NDA. However, additional studies were also conducted to bridge the two products and to evaluate the unique characteristics of the long-acting preparation of exenatide. These studies included repeat-dose studies in rats and monkeys, a 2-year rat carcinogenicity study, and *in vitro* genotoxicity studies. Dr. Hummer has summarized

these additional studies in pages 18 and 19 of his review. Details of these studies are also discussed in his review.

For this NDA (22-200), Amylin was only required to conduct one carcinogenicity study in rats as the applicant had already performed two 2-year rodent bioassays with exenatide immediate-release formulation under NDA 21-773 for Byetta.

Under NDA 21-773, rats and mice were studied for the carcinogenic potential of exenatide administered as once-daily sc injection. It should be noted that the approved clinical dosing regimen for Byetta is twice-daily sc injection; however, pharmacology/toxicology reviewers considered the dosing regimen in the carcinogenicity program acceptable because higher exposure multiples were achieved relative to the maximum recommended human dosing (MRHD) with Byetta based on AUC. Doses selected in the rat study achieved up to 130x the MRHD and doses selected in the mouse study achieved up to 95x the MRHD. They also pointed out that multiple daily injections in life-time studies are difficult to perform.

No tumors were observed in the mouse carcinogenicity study for exenatide immediate-release; however, benign thyroid C-cell adenomas were observed in female rats at all exenatide dose levels: 14% (low); 11% (medium); and 23% (high) versus 8% and 5% in the two control groups.

Under NDA 22-200, rats were administered exenatide long-acting release formulation sc once every other week to achieve 2x (0.3 mg/kg), 10x (1.0 mg/kg) and 26x (3.0 mg/kg) MRHD by AUC. Two control groups (diluent control and microsphere control) were employed to separate out the effect of microspheres in this formulation from the drug product.

Statistically significant increases in thyroid C-cell adenomas were noted in male rats dosed at 1 mg/kg (10x MRHD) and 3.0 mg/kg (26x MRHD) and at all doses in female rats. No C-cell carcinomas were observed in diluent control animals whereas 6% of female rats in the high-dose group (26x MRHD) and 3%, 7%, and 4% of the male rats in the low, mid, and high-dose groups, respectively, had C-cell carcinomas. A statistically significant difference relative to controls was only observed in the mid-dose group in male rats. When all neoplasms were considered (adenoma and carcinoma) there was a statistically significant higher incidence noted in both male and female rats, including at clinical exposures in the female low-dose group.

Table 1. Thyroid C-cell Findings from 104-week Rat Carcinogenicity Study (Adapted from Reviews of Drs. Davis-Bruno and Hummer) – Bolded red font cells represent statistically significant findings

	Male Rats					Female Rats					
	DC	MC	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	DC	MC	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	Historical controls
No. of animals	70	70	70	70	70	70	70	70	70	70	-
Exposure margin	-	-	2x	10x	26x	-	-	1x	8x	25x	-
Adenoma	9 (14%)	9 (14%)	20 (29%)	**32 (46%)**	**33 (47%)**	5 (7.1%)	9 (13%)	**22 (31%)**	**19 (27%)**	**21 (30%)**	2.0-15.4%*

Carcinoma	0	1 (1.4%)	2 (2.9%)	**5 (7.1%)**	3 (4.3%)	0	1 (1.4%)	1 (1.4%)	1 (1.4%)	4 (5.7%)	0-4.0%*
Adenoma + carcinoma	9 (13%)	10 (14%)	22 (31%)	**34 (49%)**	**35 (50%)**	5 (7%)	10 (14%)	**23 (33%)**	**20 (29%)**	**25 (36%)**	?

*combined data for males and females

Although the findings summarized in the above table do not reveal any significant difference in incidence of C-cell carcinoma compared to controls at clinical exposures, FDA's pharmacology/toxicology discipline has noted that distinctions can not be made between adenomas and carcinomas as these findings may represent a continuum in the progression of cancer. Furthermore, Dr. Davis-Bruno argues that differences in veterinary histopathology and clinical pathology sampling may result in a less sensitive detection of cancerous tissue in the nonclinical program.

Although their final recommendation is against approval, the pharmtox reviewers acknowledge the recent approval of liraglutide, another GLP-1 receptor agonist which has prolonged activation of GLP-1 receptors that had nonclinical findings of thyroid C-cell tumors. Similar to Bydureon, there was a higher incidence of C-cell adenomas in liraglutide-treated animals than controls and a statistically significant higher rate of C-cell carcinoma was only observed in male rats receiving liraglutide at doses achieving 8x the MRHD. However, it was the consideration of both adenomas and carcinomas which led them to conclude that C-cell tumors occur in a treatment and dose-related fashion. It is their recommendation that should Bydureon be approved, similar labeling and post-marketing requirements in the liraglutide NDA be put in place for Bydureon.

Although the Bydureon NDA is lacking a 2-year carcinogenicity study in mice, I believe the findings from the rat study has already shown that this formulation has a different carcinogenicity profile from the immediate-release formulation in that the latter only had C-cell adenoma findings. In addition, other studies of long-acting GLP-1 receptor agonists appear to suggest similar effects on rodent thyroid C-cells. As such, the current available evidence would warrant a similar regulatory approach to labeling and required studies for Bydureon as was done for liraglutide. This was conveyed to the applicant in the initial complete response letter requiring submission of a REMS including MedGuide and a follow-up teleconference with the firm that labeling resulting from nonclinical signal of MTC will be identical to what was done with liraglutide. The applicant has made these changes during labeling negotiations for first complete response.

5. Clinical Pharmacology/Biopharmaceutics

Please see reviews from Drs. Jaya Vaidyanathan and Sally Choe. The key issues to highlight from their review include:

- Failure to establish BE between the investigational product used in the pivotal clinical trial 105 and the commercial product
- Differences in PK profile between Bydureon and Byetta

Failure to Establish BE Between the Investigational Product and the Commercial Product
As stated in the *Introduction*, the applicant was required to bridge between its investigational product and the commercial product. According to the Clinical Pharmacology review, the commercial product ([redacted] (b) (4) manufacturing scale product) was 25-32% less bioavailable as compared to the investigational product [redacted] (b) (4) manufacturing scale product) which was used in the pivotal comparative efficacy and safety trial, 2993LAR-105. Clinical pharmacology has concluded that bioequivalence was not established between these two drug products but did provide several caveats including a statement that non-inferiority between the two drug products was established based on the upper limit of the 95% CI of the treatment difference falling below the 0.4% margin. I do not concur with this statement as the FDA did not agree with the applicant that this NI margin would be acceptable for the clinical efficacy bridging between the two products. Furthermore, the review of the clinical bridging substudy, as discussed under Section 7, suggests the possibility that the commercial product is *inferior* to the investigational product.

Differences in PK Profile Between Bydureon and Byetta
In the dose-response study LAR-104, a 15-week study comparing exenatide once-weekly 0.8 mg or 2 mg, the mean Cmax at steady state was 477.21 pg/mL. In the Phase 3 trial, LAR-105, a similar mean concentration was observed at Week 30 of 300 pg/mL, with 145 pg/mL and 702 pg/mL representing the 10th and 90th percentile of the observations. For Byetta, the mean Cmax is labeled as 211 pg/mL. Consequently, the Cmax for Bydureon may be two-fold higher than Byetta.

There was no dedicated study in patients with renal impairment in this NDA; however, population PK analysis was performed in Study LAR-105 in a subset of patients with mild to moderate renal impairment. The following figure from Dr. Vaidyanathan's review shows an increase in exenatide concentrations with decreasing creatinine clearance. Although the sample size for the moderate renal impairment is much lower than the normal and mild renal impairment patient population, the fact that exenatide is primarily cleared via the kidney would also support the concern of increased drug exposure in patients with moderate to severe renal impairment that may be as high as 2-fold.

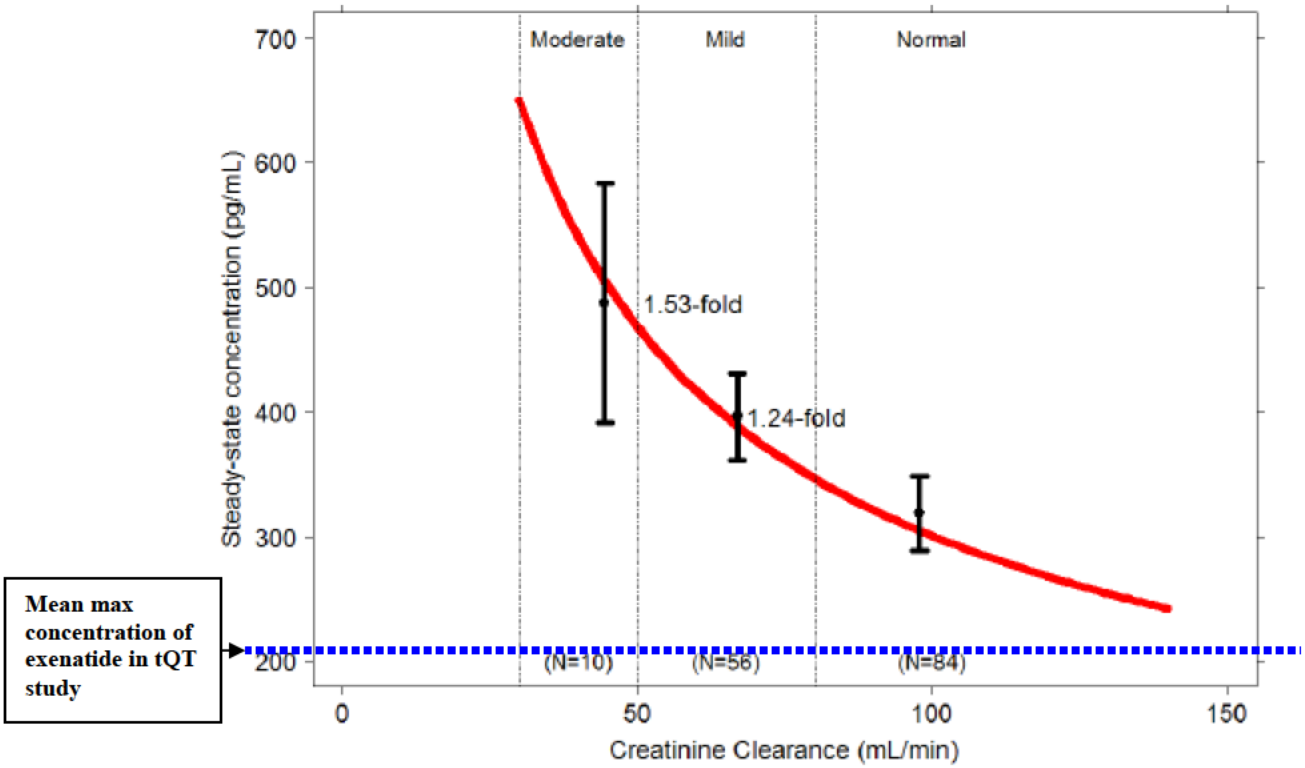


Figure 1. Significant increase in exenatide steady-state concentrations in patients with renal impairment (from Dr. Jaya Vaidyanathan's review)

It should be noted from the figure above that the mean maximum exenatide concentration achieved in the Byetta tQT study was 208 pg/mL (blue dashed line), highlighting the inability to extrapolate the findings from this study to anticipated exposures with Bydureon, especially in patients with renal impairment.

6. Clinical Microbiology

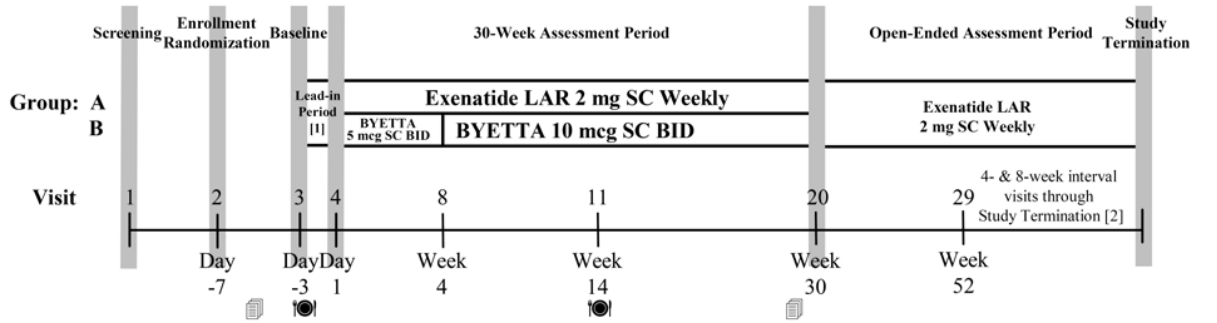
Not applicable. See Dr. Robert Mello's review for CMC microbiology issues.

7. Clinical/Statistical-Efficacy

The complete response submission did not include any additional efficacy study so I will refer to Dr. Janice Derr's FDA statistical review in the original NDA that was finalized on January 5, 2010.

Efficacy data were derived primarily from one controlled study, Study 2993LAR-105, which compared exenatide 2 mg SC once weekly with Byetta 10 mcg SC bid. As the PK profile between the two products was known to not be bioequivalent, this trial was designed to compare glycemic efficacy between these two products. The drug product used in this study

was from a different manufacturing source than the commercial product. As noted under Section 5, these two products failed to establish bioequivalence so the efficacy results in this trial cannot be directly applied to the commercial product. To address this, the applicant conducted a substudy (Study 105c) during the open-ended assessment period of Study 105 which compared the investigational source to the commercial source, also on glycemic efficacy parameters. The following schematic illustrates the trial design:



Abbreviations: BID, twice daily; LAR, long-acting release; SC, subcutaneous.

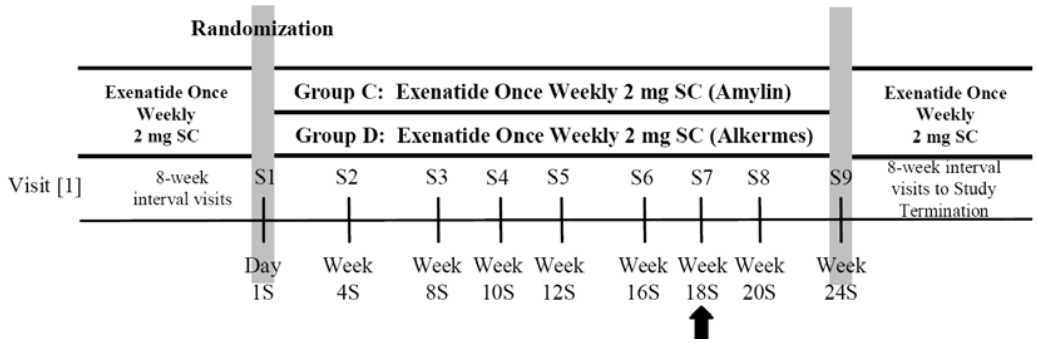
Indicates meal test and postprandial assessments for a subset of subjects at select sites.

Indicates 7-point self-monitored blood glucose profiles performed on any three days in week prior to subsequent visit.

[1] Subjects received BYETTA 5 mcg SC BID during the lead-in period.

[2] Visit 30 (Week 56) through Visits 35 (Week 76) occur at 4-week intervals. Thereafter, all study site visits occur at 8-week intervals.

Efficacy of the investigational exenatide once weekly product was compared to Byetta at Week 30 whereas assessment of clinical bioequivalence between the investigational and commercial exenatide once-weekly product was done in the Substudy illustrated in the following schematic:



As noted by Dr. Derr, the investigational exenatide once-weekly was superior to Byetta bid as summarized in the table below, adapted from Dr. Derr's table 8:

	N	Baseline mean HbA1c±SE	Adj Mean Chg from Baseline at Wk 30 ± SE	Investigational-Byetta diff in adj mean chg (95% CI)	p-value
All patients (ITT/LOCF)					
Investigational exenatide once-wkly	148	8.3 ± 0.1	-1.9±0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5±0.1		

However, Dr. Derr identified two limitations to this study in her review, one of which impacts our conclusion of superiority of Bydureon over Byetta. The first was the open-label design with a dose-adjustment in background SU allowed by study investigators. Dr. Derr carefully evaluated the impact of concomitant SU use including a review of differences in dose adjustments between the two treatment groups and comparison of efficacy between the concomitant SU group versus the non-SU group. These additional assessments did not support a conclusion that the unblinded dose-adjustments of SU favored efficacy in the investigational exenatide once-weekly treatment group and would unlikely impact the overall efficacy conclusions.

The second limitation was based on the findings from the substudy intended to provide a clinical bridge between the investigational and commercial drug product. There was extensive discussion with the applicant prior to NDA submission on this bridging substudy. Although the applicant intended to establish bioequivalence based on a non-inferiority margin of 0.4%, this was not accepted by the FDA and it was conveyed that determination of bioequivalence would be a review issue.

In her review of this substudy, Dr. Derr noted the increasing HbA1c in both the investigational and commercial treatment groups. This may not be an unexpected finding as these patients had been receiving treatment for 30 weeks prior, and deteriorating glycemic control has been noted in other diabetes trials which might reflect the progressive nature of the disease. However, the deterioration was greater with the commercial source than the investigational with the difference in the adjusted mean change and 95% CI being 0.2 (0.0, 0.3). The applicant might argue that the upper bound of the 95% CI was below the commonly accepted NI margin of 0.4; however, the following points need to be considered:

- The baseline HbA1c for both treatment groups was fairly low (6.7 and 6.8) and in this range, showing a difference in glycemic control may be difficult which might lead one to conclude non-inferiority.
- The lower bound of the 95% CI is at 0.0 which is bordering on demonstrating inferiority of the commercial product to the investigational product.

I agree with Dr. Derr that this substudy would, at a minimum, not support a conclusion that the commercial product is superior to Byetta based on the 30 wk efficacy data from Study 105. However, the inability to conclude that Bydureon provides superior efficacy to Byetta must be weighed against any safety concerns identified in this review cycle which I will discussed under Section 8 below.

I note that a study that is identical to Study 105 in which the commercial product of Bydureon is compared to Byetta has been completed. This study (Study 108) should be reviewed by the agency to enable accurate labeling on efficacy of the commercial product.

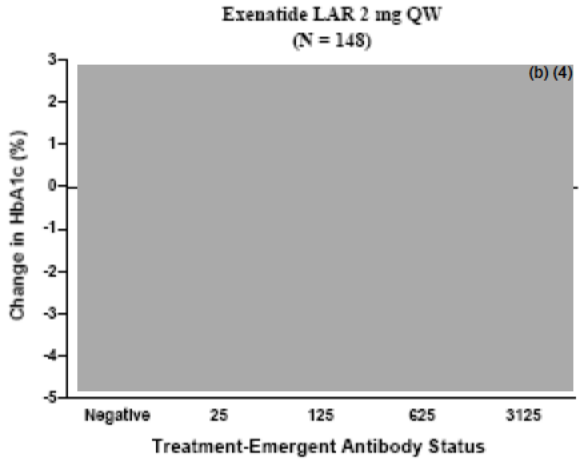
8. Safety

This application is relying on the safety findings for the approved product, Byetta. According to Dr. Pratt, there have been approximately 230 patients exposed to the once-weekly formulations for ≥ 1 year and 115 for ≥ 18 months, which is less than the recommended exposures from the February 2008 draft guidance (300-500 ≥ 18 months). In general, this is

acceptable for a new formulation relying on safety experience of the approved product, provided that differences in the PK profile that might raise relevant clinical concerns are addressed through additional studies. As I have already summarized under Section 5, there is at least a 2-fold greater exposure with Bydureon over Byetta. This exposure may be even greater in patients with renal impairment.

When there are higher drug exposures in the investigational product versus the referenced product, additional clinical studies are necessary to determine if known safety concerns of the active ingredient are exaggerated or if there are additional concerns resulting from the higher exposure or modified formulation. Please see reviews of both Drs. Pratt and Irony for a detailed summary of safety for Bydureon and Byetta. From the 30-wk, controlled portion of LAR-105, the incidence of adverse events was slightly higher with the once-weekly formulation (87.2%) vs Byetta (81.4%) with 5.4% of these being serious in the extended-release product vs 3.4% in Byetta. Notable findings were a lower incidence of nausea and vomiting with the extended release formulation (25.3% and 11%, respectively) vs Byetta (34.5% and 18.6%, respectively) but a higher incidence of developing anti-exenatide antibodies (74.3% vs 49.0%). The majority of patients who developed antibodies had low-titer Abs (< 25 to 125). There were 9 patients who had high-titer Abs (>325) and as illustrated in the figure from the applicant's submission, there is a trend towards lower efficacy with higher anti-exenatide Abs.

Figure 31. Change in HbA1c (%) at Week 30 by Anti-Exenatide Antibody Titer at Last Visit on or Prior to Week 30 (Study 2993LAR-105; Intent-to-Treat Population [N = 295])



In addition to a diminution in efficacy with very high Abs, there was a higher incidence of injection-site reactions in these patients versus those who were antibody-negative. Mild-to-moderate pruritus occurred in 21.8% of Ab+ patients versus 7.9% in Ab- patients. Injection site erythema occurred in 9.1% vs 2.6% of the Ab+ and Ab- patients, respectively. Overall, these findings can be included in labeling and would not be a basis for non-approval.

Other safety concerns related to GLP-1 agonists including pancreatitis and thyroid cancer have been summarized in Dr. Pratt's review. Overall, this NDA is limited in patient exposure and duration to assess these safety concerns and the REMS/PMR will continue to evaluate these concerns when the NDA is approved.

With the original NDA submission for Bydureon and its complete response, Amylin did not include the results of a tQT study it had conducted and submitted to HealthCanada. The Division requested these study results on April 13, 2010 after being notified by HealthCanada that concerns of a QT effect of Byetta precluded its approval in Canada. This report was submitted not to the NDA, but to the IND on April 15, 2010, and reviewed by the IRT. Please see their reviewed finalized August 16, 2010.

The IRT conclusion for this study was that it was sufficient to conclude no significant QT prolongation effect with the use of Byetta. However, IRT stated that no definitive conclusion on the QT effect of Bydureon could be drawn from this study because the mean maximum concentration achieved was approximately half the expected maximum concentration at steady state for Bydureon in patients with normal renal function. Furthermore, the IRT review noted that Bydureon may potentially cause QT prolongation based on the concentration-effect modeling illustrated in the following figure. This potential formed the basis for Byetta's non-approval in Canada and the IRT's recommendation for a tQT study conducted as a PMR.

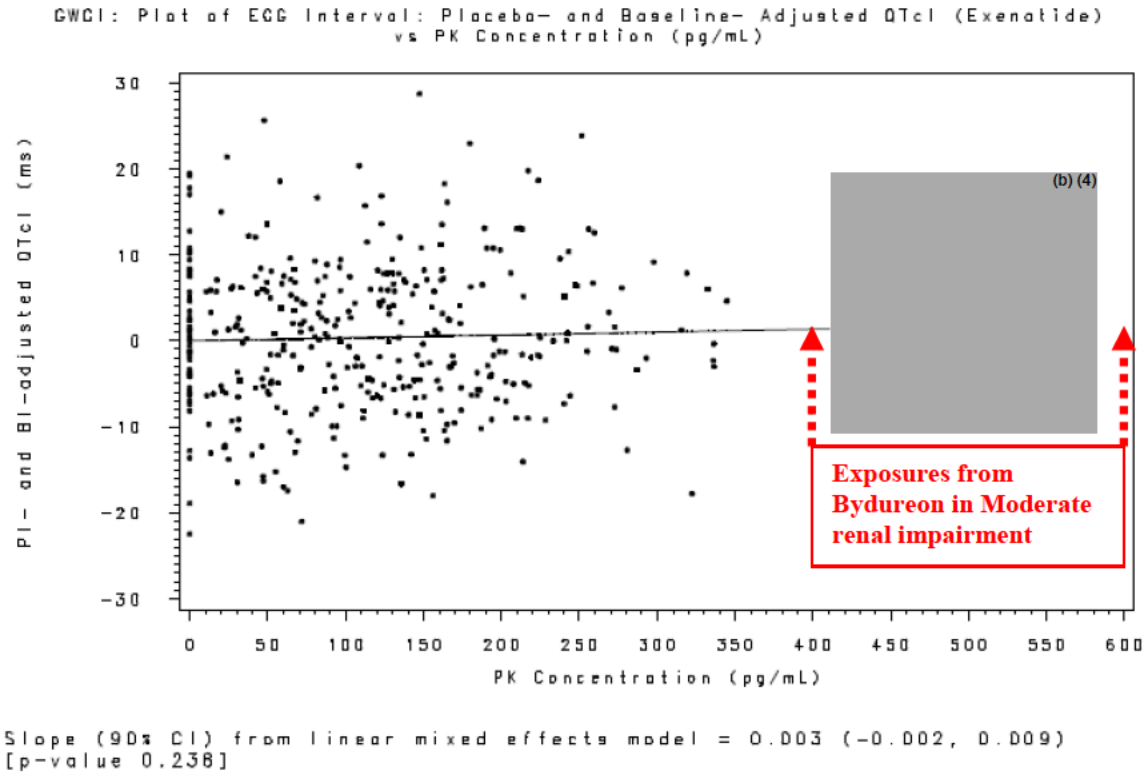


Figure 2. Relationship of ΔΔQTcI and exenatide plasma concentration

The applicant submitted by email an expert opinion from Dr. (b) (4) with emphasis on his conclusion that, "despite the lack of supratherapeutic does, it seems reasonable to conclude, based on concentration effect modeling, that the risk of QTc prolongation exceeding any level of safety concern in patients with impaired clearance of the drug is small." However,

preceding his conclusions, Dr. (b) (4) did note the limitations of the modeling at concentrations exceeding 350 pg/mL, which have a small number of observations. This is particularly relevant in the population with moderate renal impairment exposed to Bydureon.

I acknowledge the arguments put forth by the applicant that ECG assessments in the NDA did not identify a similar positive correlation between plasma exenatide concentrations and changes in QTc over a wide range of drug levels (maximum 1908.7 pg/mL); however, these data are also limited by the sample size in the population of most concern (only 10 patients with moderate renal impairment).

These data are not entirely conclusive of an absent QT prolonging effect of Bydureon to obviate the need for a second tQT study. I considered the timing of such a study and should this be a required postmarketing trial, the labeling would require more extensive warnings against use of this product in patients with moderate renal impairment than currently proposed by the applicant. There was also internal discussion as to the benefit of making this product available while awaiting the tQT study, and whether any benefit existed over Byetta to justify this action should such the required tQT study be positive. The efficacy results from LAR-105 could not support any claim of superior efficacy of Bydureon over Byetta. Consequently, I have concluded that a tQT study should be conducted prior to marketing. These results should also be reviewed with the completed results of LAR-108, a clinical efficacy study involving the actual commercial product. These data would provide a more complete picture of the benefits-risks of Bydureon to enable accurate labeling of its safety and effectiveness.

9. Advisory Committee Meeting

This is not an NME. The efficacy and safety issues related to the application are not novel to the class of GLP-1 receptor agonists and the recently identified concern regarding the QT effects may be readily addressed with another tQT study which would not warrant an advisory committee meeting.

10. Pediatrics

Please see Dr. Irony's CDTL memo summarizing the pediatric issues concerning the long-acting GLP-1 receptor agonists. I concur with his recommendations.

11. Other Relevant Regulatory Issues

None identified at this time.

12. Labeling

The review team has provided a near-complete labeling review and comments. This will need to be update once the results of the tQT study and LAR-108 are reviewed.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

Given the observation that Bydureon administration does have a higher exposure than Byetta; there is a potential for a QT effect at these higher exposures based on modeling of data from the Byetta tQT study; and there is insufficient evidence to conclude superior efficacy over Bydureon over Byetta to justify dismissing the potential for QT prolongation, it is difficult to ignore the uncertainty of CV safety raised by currently available data and not require a tQT study of this NDA as a premarketing trial.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Please see the memo from Dr. Amy Egan dated February 16, 2010. Bydureon would have a similar program to that of Novo Nordisks' Liraglutide.

- Recommendation for other Postmarketing Requirements and Commitments

A cardiovascular safety trial will be required.

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/s/

MARY H PARKS
10/18/2010

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	22-200 SDN 23
Priority or Standard	Standard
Submit Date(s)	04-22-10
Received Date(s)	04-22-10
PDUFA Goal Date	10-22-10
Division / Office	DMEP / ODE II
Reviewer Name(s)	Valerie S. W. Pratt, M.D.
Review Completion Date	09-14-10
Established Name	Exenatide LAR
(Proposed) Trade Name	Bydureon
Therapeutic Class	GLP-1 agonist
Applicant	Amylin Pharmaceuticals Inc.
Formulation(s)	Injection
Dosing Regimen	2 mg SC once weekly
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adult type 2 diabetics

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a complete response to this new drug application for exenatide for extended-release injectable suspension (Bydureon). The proposed indication was as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). However, study GWCI demonstrated a concentration-dependent increase in QTc interval with exenatide. I recommend the sponsor conduct a thorough QT (TQT) study which covers the steady state maximum concentration of Bydureon and high clinical exposure scenario prior to approval. As the potential approval of this NDA at the time of resubmission will depend on the risk: benefit analysis, I also recommend the sponsor submit study report BCB108, which compared the safety and efficacy of the to-be-marketed Bydureon product to Byetta.

1.2 Risk Benefit Assessment

Based on my review of the clinical data, I believe the benefits of Bydureon include convenient once weekly dosing and fewer gastrointestinal adverse events (specifically, nausea and vomiting). In supportive trial 105, the LS mean (SE) change in HbA1c from baseline to week 30 in the Bydureon (non-commercial source) group was -1.9% (0.08), a statistically significant change when compared to the -1.5% (0.08) change with Byetta (p=0.0023). However, study 105 used an investigational Alkermes source that was different from the commercial Amylin ((b) (4) scale) source. Substudy 105c was conducted to compare the two sources. The differences in the exposure resulting from the different manufacturing scale were in the maximal response region of the exposure-response relationship for Bydureon. However, the commercial Amylin source resulted in a less favorable average change in HbA1c by 0.2 when compared to the investigational Alkermes source (95% CI: 0.0, 0.3). The proximity of the lower bound of the CI to zero leads the division to question whether or not the to-be-marketed (b) (4) scale Bydureon product is noninferior to Byetta. (Please refer to Drs. Jayabharathi Vaidyanathan's and Janice Derr's reviews of the original NDA submission for full details.)

The risks of Bydureon include the following:

- Potential for QTc Prolongation: Although thorough QT (TQT) study GWCI demonstrated no significant QT prolongation with Byetta, when a single 10 microgram dose (non supra-therapeutic) is used, no definitive conclusion could be drawn for Bydureon, because of the higher exposures predicted with 2 mg weekly. Modeling of the QT interval data suggests an exposure proportional increase in QT interval. I recommend a premarketing TQT study of exenatide,

which covers the stead state maximum concentration of Bydureon and high clinical exposure scenario to cover potential risks in diabetic patients with moderate renal insufficiency. As the TQT may be conducted with Byetta, I recommend Bydureon cardiovascular (CV) safety study BCB109 include electrocardiogram (ECG) and pharmacokinetic (PK) assessments in a subset of the population. Depending on the outcome of the TQT study, a Warning and Precaution may be needed in the label.

- Thyroid tumors: Like another approved long acting GLP-1 agonist, nonclinical studies suggest that Bydureon may increase the risk of thyroid tumors. However, no thyroid cancers have been identified in Bydureon subjects. Mean calcitonin values remained within the normal range (up to 84 weeks). If this product was approved, I would recommend a risk mitigation strategy similar to that of liraglutide. The product should not be used as first-line therapy, and it should be contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2. I would also recommend a five-year prospective epidemiological study and an MTC case series registry of at least 15 years duration as described below. I would also recommend that the sponsor continue to analyze thyroid neoplasms events as adverse events (AEs) of special interest in PSURs. Long term cardiovascular (CV) safety study BCB109 will analyze thyroid carcinoma as an AE of special interest and should include screening, annual, and endpoint calcitonin measurements as well as safeguards to protect subjects from unnecessary thyroidectomies, such as having an expert group of thyroidologists review calcitonin data.
- Injection site nodules and reactions: Bydureon is (b) (4) exenatide, (b) (4) sucrose, and (b) (4) polymer (poly-D,L-lactide-coglycolide or PLG) microspheres. PLG and its degredation products are associated with local inflammatory reactions. To further to assess this safety issue after approval, I recommend the periodic safety update reports (PSURs) and cardiovascular (CV) safety study BCB109 analyze injection site reactions, including nodules, as AEs of special interest.
- Cardiovascular: Exenatide, like other long acting GLP-1 agonists, is associated with a small increase in heart rate. A postmarketing trial of Bydureon is necessary to definitively show that the upper bound of the two-sided 95% CI for the estimated risk ratio is <1.3. Although the sponsor acknowledged in its June 11, 2010 submission to IND 67,092 that negotiations on CV study protocol BCB109 were not complete, it initiated CV study BCB109 in June 2010. This study should include ECG and PK sampling in a subset of subjects, as described above. The sponsor should also analyze cardiovascular events in the PSURs and five-year epidemiological study.
- Pancreatitis: Although the incidence of pancreatitis in T2DM patients is debated in the literature, exenatide is associated with pancreatitis, including hemorrhagic and necrotizing forms. If Bydureon was approved, I would recommend a Warning and Precaution in the label and continued vigilance via the

postmarketing requirements described below and summaries in the Periodic Safety Update Reports (PSURs) to mitigate this risk.

- Hypersensitivity: Like Byetta, subjects using Bydureon are at risk of serious hypersensitivity reactions. Antibody-positive Bydureon subjects were nearly twice as likely to experience potentially immune-related AEs than antibody-negative Bydureon subjects and antibody positive and negative Byetta subjects. To mitigate this risk, the label will include a Warning and Precaution. To monitor this risk post approval, I recommend the sponsor analyze hypersensitivity events as an event of special interest in PSURs and CV study BCB109.
- Hypoglycemia: Like Byetta, there is a risk of hypoglycemia when Bydureon is used in combination with a sulfonylurea (SU). This is described in the Warnings and Precautions section of the label. Serious hypoglycemia will be analyzed in CV trial BCB109 and the five-year epidemiological study.
- Renal impairment: Subjects with moderate renal impairment have increased exenatide exposure, which may prolong the QT interval. Bydureon should be contraindicated in subjects with severe renal impairment and end stage renal disease. It should be used with caution in patients with moderate renal impairment or renal transplantation. Renal disorders will be analyzed as an AE of special interest in CV study BCB109.
- Gastrointestinal (GI) AEs: GLP-1 agonists, including exenatide, are associated with gastrointestinal AEs. However, the frequency of withdrawals in this system organ class (SOC) and incidence of nausea and vomiting were less with Bydureon when compared to Byetta. The Bydureon label will contain a Warning and Precaution regarding use in patients with severe GI disease and Adverse Reactions language.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Because of 1) the risk of thyroid tumors associated with glucagon-like-peptide-1 (GLP-1) analogues identified in preclinical studies, including exenatide LAR Study REST060229 ([redacted] (b) (4) #840-040), 2) post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide, and 3) the potential for QTc prolongation based on extrapolated data from TQT study GWCI and in order to ensure that the benefits of exenatide continue to outweigh this serious risk, I recommend a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide (MG), communication plan, and timetable for assessments.

1.4 Recommendations for Postmarket Requirements and Commitments

If the NDA was approved during this review cycle, I would recommend the following required postmarketing studies (PMRs). Please note that these are preliminary PMRs at the time of filing the review, pending additional internal discussion and negotiations with the sponsor.

- A deferred phase 1 pharmacokinetic (PK) pediatric study that will be conducted under Pediatric Research Equity Act (PREA). This study should investigate multiple doses of Bydureon and may be conducted independently or as a substudy of the safety and efficacy study described below (population PK).
- A deferred randomized, double-blind, adequately controlled pediatric study under PREA to evaluate the efficacy and safety of Bydureon for the treatment of T2DM in pediatric patients ages 10 to 16 years 11 months. This study should not be initiated until at least 1 month after the completed study report for the rodent study to determine if exenatide LAR-induced c-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation has been submitted to FDA and found to conclude no likely effects on human thyroid.
- A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of medullary thyroid cancer (MTC) among patients with type 2 diabetes exposed to Bydureon and patients with type 2 diabetes not exposed to Bydureon, as well as the incidence of cancer (in particular, thyroid [MTC and other forms] and pancreatic malignancies), pancreatitis (in particular, hemorrhagic and/or necrotizing forms with amylase levels and validation of the medical record), cardiovascular events, and serious hypoglycemia.
- Medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of MTC in the United States and to identify any increase related to the introduction of Bydureon into the marketplace. This study will also establish a registry of incident cases of MTC and characterize their medical histories related to diabetes and use of Bydureon.
- A randomized, double-blind, controlled trial evaluating the effect of Bydureon on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of Bydureon on potential biomarkers of medullary thyroid carcinoma (e.g. serum calcitonin) as well as the long-term effects on thyroid and pancreatic malignancies, pancreatitis (including hemorrhagic and/or necrotizing forms), injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders. The study should include ECG and PK sampling in a subset of subjects.

If the NDA was approved this cycle, I would also recommend the sponsor continue to analyze the following as AEs of special interest in the PSURs: cardiovascular events, thyroid neoplasms, injection site reactions (including nodules), allergic/hypersensitivity events, and pancreatitis events

2 Introduction and Regulatory Background

2.1 Product Information

Amylin Pharmaceuticals, Inc. has submitted a new drug application (NDA) for the use of exenatide for extended-release injectable suspension as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). The drug product is also referred to exenatide once weekly or long-acting release (LAR) injection. The proposed trade name is Bydureon.

Bydureon contains the same active ingredient as the commercial product exenatide (Byetta) injection (NDAs 21-773 and 21-919). Exenatide injection, an incretin mimetic (specifically, glucagon-like-peptide-1 [GLP-1] agonist), is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, the original Bydureon NDA submission referenced the safety and efficacy information in the Byetta NDA.

Bydureon was produced using drug substance from (b) (4) different suppliers during its development: (b) (4) Mallinckrodt, Inc. and Lonza, SA. It was also manufactured at (b) (4) different scales ((b) (4)) and at 2 different manufacturing sites (Alkermes, Inc. in Wilmington, Ohio and Amylin Ohio, LLC in West Chester, Ohio. Please refer to the CMC review and my previous NDA review for full details.

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of type 2 diabetes mellitus include the following:

- Sulfonylureas
  - Tolazamide (Tolinase)
  - Chlopropramide (Diabinese)
  - Glyburide (Micronase)
  - Glipizide (Glucotrol and Glucotrol XL)
  - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones
  - Rosiglitazone (Avandia)
  - Pioglitazone (Actos)

- α-Glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)
- Incretin-mimetics
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
- Amylinomimetics
  - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
- Bile acid sequestrants
  - Colesevelam (WelChol)
- Dopamine receptor agonists
  - Bromocriptine mesylate (Cycloset)

2.3 Availability of Proposed Active Ingredient in the United States

Bydureon is not currently approved for use in the United States, although exenatide has been approved in the United States since March 2005 and is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Exenatide is currently being studied under (b) (4) INDs:

1) IND 57,725 Exenatide injection for the treatment of T2DM
2) IND 67,092 Exenatide LAR injection for the treatment of T2DM

(b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

Exenatide is used to improve glycemic control in T2DM patients. Labeled safety concerns with exenatide include:

1. Acute pancreatitis
2. Gastrointestinal side effects
3. Hypoglycemia, especially when used in combination with a sulfonylurea
4. Hypersensitivity reactions as a result of anti-exenatide antibodies
5. Renal failure

The division recently approved NDA 22-341 for liraglutide, another GLP-1receptor agonist. Liraglutide causes thyroid c-cell tumors in rats and mice. Please refer to my review of the original NDA submission for more details.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Bydureon was developed for the treatment of T2DM under IND 67,092, which was opened March 17, 2003. As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, NDA 22-200 references the safety and efficacy information in Byetta NDA 21-773.

This is a Class 2 resubmission to the original Bydureon NDA, following a complete response letter issued March 12, 2010 related to the lack of REMS and CMC and microbiology deficiencies. The resubmission consists of draft labeling, a safety update, and minor clarifying information.

Please refer to my review of the original NDA submission for a summary of regulatory activities up until March 12, 2010. The following is a summary of presubmission regulator activity related to this submission:

- April 8, 2010: An End of Review (EOR) teleconference was held with the sponsor. The agency emphasized that the REMS and Post-Marketing Requirements (PMRs) should be modeled after Victoza (liraglutide) rather than Byetta. Clarification of the microbiology deficiencies was also provided.
- April 12, 2010: A teleconference was held with Health Canada regarding electrophysiology data they received, demonstrating effects of exenatide on the QT interval.
- April 13, 2010: Under Byetta NDA 21-773, a consult was placed to the Office of Surveillance and Epidemiology (OSE) to search the AERS database for arrhythmia-related standardized MedDRA queries (SMQs) reported in association with the use of Byetta, including but not limited to Conduction Defects, Tachyarrhythmias, and Torsade de Pointes/QT Prolongation. This review was completed June 28, 2010.
- April 15, 2010: The sponsor submitted clinical study report H8O-EW-GWCI (GWCI), “A placebo- and positive-controlled study of the electrophysiological effect of a single 10 mcg dose of exenatide on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects”, to exenatide IND 57,725.
- May 13, 2010: The sponsor submitted study GWCI’s datasets to exenatide IND 57,725, as well as cardiac arrhythmia and conduction-related safety results for Byetta and Bydureon and spontaneous Byetta postmarketing reports of cardiac arrhythmia and potential conduction-related events. The April 15 and May 13, 2010 submissions were consulted to the QT Interdisciplinary Review Team (IRT). The QT IRT completed its review on August 16, 2010.
- May 25, 2010: A teleconference was held to discuss the medullary thyroid carcinoma (MTC) registry.

- June 2, 2010: As requested, the sponsor submitted relevant information supporting the analysis of exenatide subjects with mild and moderate renal impairment, which indicated a 23% and 74% increase in exposure compared to subjects with normal renal function.
- June 21, 2010: The sponsor submitted a draft study design plan for the MTC registry, (b) (4)
- July 21, 2010: As requested, the sponsor submitted all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Bydureon as well as analyses of those data.
- August 25, 2010: As requested, the sponsor submitted all calcitonin data obtained in ongoing, terminated, and completed clinical trials of Bydureon as well as analyses of those data.
- August 27, 2010: The sponsor clarified the drug product scales, drug substance lot numbers, and manufacturers used in each of the phase 3 studies.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of appropriate quality. As discussed at the EOR teleconference, the sponsor submitted the following:

- Draft labeling including revised carton and container labeling, prescribing information, and a REMS consisting of a medication guide (MG) and communication plan, which were modeled after Victoza (liraglutide) labeling and REMS
- A safety update
- Clarifying information regarding product quality

3.2 Compliance with Good Clinical Practices

The original NDA submission and safety update cutoff dates were November 15, 2008 and March 31, 2009, respectively. This submission's cutoff date was December 31, 2009. In the 9-month period between cutoff dates for the safety update and the complete response, study BCB108 was completed and H8O-MC-GWBR (GWBR) and M8O-MC-GWDC (GWDC) were completed through week 26. Studies BCB108, GWBR,

and GWDC were conducted in compliance with Good Clinical Practices and the Code of Federal Regulations (CFT) Title 21 Part 56 relating to institutional review boards.

As the resubmission mostly included product quality and REMS-related information, the Division of Scientific Investigations (DSI) was not consulted for clinical site inspections.

3.3 Financial Disclosures

Not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Olen Stephens' CMC reviews of the NDA submission and resubmission for full details.

4.2 Clinical Microbiology

The original NDA submission had the following product quality deficiencies:

(b) (4)

Dr. Robert J. Mello's microbiology review indicated that Amylin's responses to the deficient items were acceptable. Please refer to his review for full details.

4.3 Preclinical Pharmacology/Toxicology

Please refer to B. Timothy Hummer's nonclinical review of the original NDA submission for a description of the thyroid c-cell tumor findings associated with GLP-1 agonists. No new nonclinical study reports were included in the resubmission.

4.4 Clinical Pharmacology

Please refer to Dr. Jaya Vaidynathan's clinical pharmacology review of the original NDA submission for full details.

4.4.1 Mechanism of Action

Exenatide is a GLP-1 receptor agonist that improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. It does this through the following mechanisms of action:

- Enhances glucose-dependent insulin secretion
- Restores first-phase insulin response
- Suppresses inappropriately elevated glucagon secretion
- Slows gastric emptying
- Reduces food intake

Bydureon is (b) (4) exenatide and (b) (4) sucrose encapsulated within (b) (4) biodegradable (b) (4) polymer (poly-D,L-lactide-coglycolide or PLG) microspheres that are designed to release therapeutic concentrations of exenatide over an extended period of time. PLG is a common, biodegradable medical polymer that has been previously used in human sutures, bone plates, and extended release pharmaceuticals, such as Vivitrol and Risperdal Consta ((b) (4) fold versus Bydureon, respectively). Please refer to section 2.6.6.8 of Dr. B. Timothy Hummer's nonclinical review for more information regarding the safety of PLG microspheres.

In short, the pharmaceutical industry has used polymer microspheres for sustained release formulations for over 20 years. The microspheres are suspected in an aqueous diluent prior to injection. Once in the body, the PLG degrades over time to lactic and glycolic acid and releases exenatide by a combination of drug diffusion and polymer erosion. PLG and its degredation products do not cause systemic toxicity, reproductive or developmental effects, genotoxicity, or carcinogenicity at clinically relevant doses, although local inflammatory reactions can occur. Please refer to section 7.3.3 Dropouts and/or Discontinuations for more details.

4.4.2 Pharmacodynamics

Phase 2 study 104 evaluated 0.8 and 2 mg Bydureon once weekly for 15 weeks in 43 T2DM subjects (12 placebo, 16 Bydureon 0.8 mg, 15 Bydureon 2 mg). Reductions in FPG were observed in both Bydureon groups throughout the treatment period. At week 15, the 0.8 mg and 2 mg Bydureon groups had mean reductions of 42.7 mg/dl and 39.0 mg/dl, respectively, whereas the placebo group's FPG concentrations increased by 18.2 mg/dl at week 15. The mean overall daily average self-monitored blood glucose concentration was also reduced for both the 0.8 mg (164.6 mg/dl) and 2 mg (149.1 mg/dl) Bydureon groups compared to baseline and to the placebo group (220.5 mg/dl).

Please refer to section 6.1.4 Analysis of Primary Endpoint of my original NDA review for a discussion of Bydureon's (Alkermes and Amylin) effect on HbA1c.

4.4.3 Pharmacokinetics

A single dose of Bydureon exhibits multiphasic release over approximately 10 weeks with complex release characteristics:

- Phase 1: Initial release of surface-bound exenatide
- Phases 2 and 3: Subsequent release peaks representing hydration and erosion, respectively, in weeks 2 and 6

Repeated once weekly injection of 2 mg Bydureon results in overlap of the single-dose release profiles and a gradual increase in the average plasma exenatide concentration, until steady state is achieved after approximately 7 weeks. At weeks 14-15, the average steady state concentration ($C_{ss\ ave}$) of the 2 and 0.8 mg doses are 289 and 118 pg/ml, respectively. There is a concentration-dependent decrease in HbA1c from baseline with maximal response at exenatide concentrations > 200 pg/ml. I therefore agree with the proposed 2 mg dose (EC_{50} ~83 pg/ml).

Age, gender, race, and body mass index (BMI) do not influence the PK. No dosage adjustment is proposed by the sponsor in patients with mild to moderate renal impairment. However, there was a 53% increase in exenatide exposure in the subjects with moderate renal impairment (n=10) in study 105 (versus 24% increase in subjects with mild renal impairment). As the increase in exenatide exposure seen in subjects with moderate renal impairment may put these subjects at risk for prolonged QT interval, I recommend a premarketing TQT study. (See section 7.4.4 Electrocardiograms.) Given our understanding of the product to date, I also support labeling that 1) recommends caution when using Bydureon in patients with moderate renal impairment and 2) contraindicates Bydureon in patients with severe renal or end-stage renal disease.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. NDA 22-200 SDN 23: Tabular listing of completed clinical studies in the complete response safety update

Study No. No. Centers-Country	Study Design Primary Objective	Population No. and Type	Treatment Duration	Outcomes
2993LAR-104 (104)	Phase 2, randomized, double blind, placebo controlled, multiple dose Safety and PK	45 T2DM subjects 31 Bydureon	3 day Byetta 5 mcg BID or placebo lead in followed by 0.8 or 2 mg exenatide (F17) or placebo once weekly x 15 wks	The 2 mg dose was selected for further development.
H8O-JE-GWBW (GWBW)	Phase 1, randomized, double blind, placebo controlled, multiple dose Safety in T2DM Japanese subjects	30 T2DM Japanese subjects 20 Bydureon	0.8 or 2 mg Bydureon (F17) or placebo once weekly x 10 wks	Weekly injections with no Byetta BID lead-in appeared safe in Japanese subjects.
2993LAR-105 (105)	Phase 3, randomized, open label, comparator controlled, multiple dose Safety and efficacy	295 T2DM subjects 148 Bydureon 147 Byetta	3 day Byetta 5 mcg BID lead in followed by 2 mg Bydureon or Byetta x 30 wks and ongoing Bydureon open ended assessment period	HbA1c and FPG were statistically significantly superior with Bydureon compared to Byetta. The safety profiles of Bydureon and Byetta were similar. Bydureon subjects had less nausea/vomiting but more injection site reactions and antibodies.

Study No. No. Centers-Country	**Study Design Primary Objective**	**Population No. and Type**	**Treatment Duration**	**Outcomes**
BCB106	Phase 3, randomized, double blind, comparator controlled, parallel group study	491 T2DM subjects 160 Bydureon + Met 166 sitagliptin + Met 165 pioglitazone + Met	2 mg exenatide LAR weekly, sitagliptin 100 mg daily, or pioglitazone 45 mg daily x 26 weeks followed by ongoing open-ended assessment period	Results were submitted with 4-month safety update of the original NDA. Weekly injections without Byetta BID lead-in.
BCB108*	Phase 3, randomized, open label, Byetta-controlled	252 T2DM subjects on stable oral meds or diet and exercise 129 Bydureon	Bydureon or Byetta x 24 wk	
H8O-MC-GWBR (GWBR)*	Phase 3, randomized, open label, glargine-controlled	456 T2DM subjects on Met or Met+SU 233 Bydureon	26 weeks followed by ongoing, controlled open-ended assessment period	
H8O-MC-GWDC (GWDC)*	Phase 3, open label, single arm	134 T2DM subjects on TZD or TZD + Met	26 weeks followed by ongoing 52 week assessment period	
H8O-EW-GWCI (GWCI)**	Phase 1, randomized, double blind, placebo controlled, double dummy, 3 period crossover QTc interval	Part A: 70 healthy M & F Part B: 62 healthy M & F	Part A: Exenatide 10 µg QD x 3d Part B: Single dose exenatide 10 µg, moxifloxacin 400 mg, and placebo	No subject had absolute QTcF >450 ms or change from baseline in QTc >30 ms. Slight positive correlation between exenatide concentration and change from baseline in QTcF.

*In the period between the cutoff dates for the 4-month safety update and the complete response resubmission, study BCB108 was completed and studies H8O-MC-GWBR and H8O-MC-GWDC were completed through Week 26.
**Study GWCI was submitted separately to exenatide IND 57,725 and not included in the safety update.

5.2 Review Strategy

My review focused on the controlled data in the complete response safety update, clinical study report GWCI, related OSE and QT IRT consults, and the requested amylase, lipase, and calcitonin data from ongoing and completed Bydureon clinical trials (BCB106, BCB108, GWBR, GWCH, and GWDC). Note, only amylase, lipase and calcitonin data were reviewed from studies BCB106, BCB108, GWBR, GWCH, as the study reports were not submitted at the time of NDA filing.

In the 9-month period between the cutoff dates for the 4-month safety update (31 March 2009) in the original NDA submission and this complete response Class 2 resubmission (December 31, 2009), Study BCB108 was completed and Studies H8O-MC-GWBR and H8O-MC-GWDC were completed through Week 26 and, thus, included in the complete response safety update. Studies 105, BCB106, GWBR, GWDC, and GWCH remain ongoing.

On April 12, 2010 Health Canada informed the FDA about a negative decision for exenatide based on cardiac electrophysiology data. Clinical study report GWCI, "A placebo- and positive-controlled study of the electrophysiological effect of a single 10 mcg dose of exenatide on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects", was submitted to exenatide IND 57,725 on April 15, 2010, in response to a FDA request. The study report and its related materials were consulted to the QT IRT. OSE was also consulted to search the AERS database for arrhythmia-related Standardized MedDRA Queries reported in association with the use of Byetta, including but not limited to Conduction Defects, Tachyarrhythmias, and Torsade de Pointes/QT Prolongation. Please refer to section 7.4.4 Electrocardiograms for more information.

5.3 Discussion of Individual Studies/Clinical Trials

Please refer to my review of the original NDA for a discussion of the pivotal studies. Please refer to Table 1 above for a summary of studies BCB108, GWBR, and GWDC which were included in the safety update. TQT study GWCI is described below.

1) GWCI: A placebo and positive-controlled study of the electrophysiological effects of a single 10 µg dose of exenatide on the 12 lead ECG QT interval in healthy subjects (Version approved March 28, 2008)

Study phase and dates conducted: Phase 1 study conducted April 23 – July 21, 2008

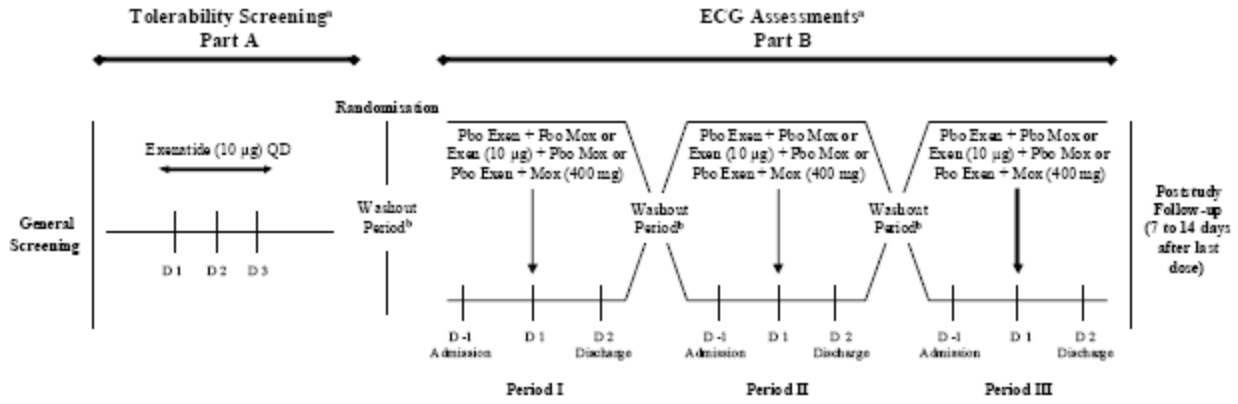
Objectives:
Primary: To determine, in healthy subjects, that a single 10 µg dose of exenatide does not differ from placebo in the mean change from predose in 12-lead ECG correct QTc

interval (QT interval corrected for heart rate) measurements (such that the upper bound of the one sided 95% confidence interval [CI] of the difference between exenatide and placebo was <10 msec).
Secondary:

- To evaluate the relationship between plasma exenatide concentrations and QTc interval in healthy subjects
- To explore the influence of potential physiological covariates such as plasma insulin, plasma glucose, and potassium on QTc interval in healthy subjects.

Study design: This was a randomized, placebo-controlled, double-dummy, double-blinded, three-period crossover study. In Part A (tolerability assessment), subjects received 10 µg exenatide once-daily for 3 days. Subjects who tolerated exenatide in Part A received single doses of 10 µg exenatide, 400 mg moxifloxacin, and placebo, on three separate occasions in Part B.

Figure 1. Study GWCI: Design



Abbreviations: D = Day in treatment period; Exen = exenatide; Mox = moxifloxacin; Pbo = placebo; QD = once-daily.
[a] Subjects who withdrew due to nausea or vomiting during Part A (tolerability screening phase), or who experienced severe nausea (inability to eat a meal), or more than one episode of vomiting, were not permitted to continue to Part B (ECG assessment phase).
[b] Washout following tolerability screening and each period of the ECG assessment phase was approximately 5 days.

Inclusion criteria:

1) Are overtly healthy males or females, as determined by medical history and physical examination.
2) If females, are not of child-bearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or menopause. Women with an intact uterus are deemed postmenopausal if they have had cessation of menses for at least 1 year or 6 to 12 months of spontaneous amenorrhea with follicle stimulating hormone >40 IU/mL; age ≥45 years; not taking oral contraceptives for at least 1 year; and otherwise healthy.
3) Are between the ages of 18 and 65 years, inclusive.
4) Have body mass index (BMI) between 19 and 35 kg/m2, inclusive.

5) Have clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant (NCS) by the investigator.
6) Normal blood pressure and heart rate (supine), as determined by the investigator.
7) Serum magnesium and potassium within the normal reference range at screening.
8) Subjects receiving hormone replacement therapy (HRT) or thyroxine as replacement therapy may participate in the study. Subjects receiving thyroxine as replacement therapy may participate providing they have been on stable therapy for at least 3 months and have a normal thyroid stimulating hormone (TSH) value.

Exclusion criteria:

1) Within 30 days of the initial dose of study drug, have received treatment with a drug that has not received regulatory approval for any indication.
2) Known allergies to exenatide or excipients.
3) Known allergies to moxifloxacin or related compounds or a history of multiple adverse drug allergies of any origin.
4) Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risk of participating in the study, such as a Bazett's corrected QT (QTcB) interval >450 msec. The following conduction abnormalities may confound QTc analysis and should be avoided: PR>220 msec, 2nd or 3rd degree Atrioventricular block, Intraventricular Conduction Delay with QRS>120 msec, complete Left Bundle Branch Block, Left Anterior Fascicular Block, Left Posterior Fascicular Block, Right Bundle Branch Block, or Wolffe-Parkinson- White Syndrome, defined as PR<120 msec, P axis from 1 to 90, QRS complex 120 msec, Delta wave present). In addition, the screening ECG should have QT intervals that are measurable by the central reader.
5) Current or history of recent (within 2 weeks) clinically significant infection or inflammatory process, at the discretion of the investigator.
6) Family history of sudden death.
7) Personal history of unexplained syncope within last year.
8) History or presence of cardiovascular (myocardial infarction, cerebrovascular accident, venous thromboembolism), respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; or constituting a risk when taking the study medication; or of interfering with the interpretation of data.
9) Evidence or history of Long QT Syndrome or significant active cardiac disease (e.g., arrhythmia, hypertension, congestive heart failure, hypokalemia, mitral valve regurgitation, endocarditis, coronary artery heart disease), or symptoms of angina pectoris or transient ischemic attacks within the previous 6 months.
10) Sinus arrhythmia where the range of beat to beat heart rate from lowest to highest on standard 12-lead ECG is >5 bpm.

11) Females who are lactating.
12) Have previously completed or withdrawn from this study or any other study investigating exenatide.
13) Regular use of known drugs of abuse and/or positive findings on urinary drug screening.
14) Evidence of human immunodeficiency virus (HIV) and/or positive human HIV antibodies.
15) Evidence of hepatitis C and/or positive hepatitis C antibody.
16) Evidence of hepatitis B and/or positive hepatitis B surface antigen.
17) Intended use of over-the-counter or prescription medication (other than, for example, thyroid replacement, occasional intake of paracetamol, or vitamin or mineral supplements) 7 and 14 days, respectively, before dosing and throughout the study. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator and sponsor.
18) Cumulative blood donation of more than 500 mL within the last 3 months.
19) Subjects who have an average weekly alcohol intake that exceeds 28 units per week (males) and 21 units per week (females), or subjects unwilling to stop alcohol consumption for the duration of the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
20) Subjects who smoke or have smoked within 28 days of their screening visit and who are unable to abide by the study restrictions.
21) Any other condition, which in the opinion of the investigator would preclude participation in the study.

Treatments and management: Please refer to Table 2 below.

Table 2. Study GWCI: Treatment Sequences

Sequence Group	3-Day Tolerability Screening (Part A)	ECG Assessments[a] (Part B)		
		Period I	Period II	Period III
1	Exenatide (10 μg) QD	Pbo exenatide, Pbo moxifloxacin	Exenatide, Pbo moxifloxacin	Pbo exenatide, Moxifloxacin
2	Exenatide (10 μg) QD	Exenatide, Pbo moxifloxacin	Pbo exenatide, Moxifloxacin	Pbo exenatide, Pbo moxifloxacin
3	Exenatide (10 μg) QD	Pbo exenatide, Moxifloxacin	Pbo exenatide, Pbo moxifloxacin	Exenatide, Pbo moxifloxacin
4	Exenatide (10 μg) QD	Pbo exenatide, Moxifloxacin	Exenatide, Pbo moxifloxacin	Pbo exenatide, Pbo moxifloxacin
5	Exenatide (10 μg) QD	Pbo exenatide, Pbo moxifloxacin	Pbo exenatide, Moxifloxacin	Exenatide, Pbo moxifloxacin
6	Exenatide (10 μg) QD	Exenatide, Pbo moxifloxacin	Pbo exenatide, Pbo moxifloxacin	Pbo exenatide, Moxifloxacin

Abbreviations: ECG = electrocardiogram; Pbo= placebo; QD = once daily.
Note: Washout following each treatment period should be approximately 5 days.
a Electrocardiograms should be performed at the same relative time on treatment days.

Study sites including enrollment: The study was conducted at 2 study sites (Leeds and Plymouth, UK) in 70 healthy subjects (Part A 70; Part B 62).

Efficacy (exposure/response) assessments:
Pharmacokinetic: AUC, Cmax, Tmax
Pharmacodynamic: Plasma glucose and insulin concentration, AUC, Cmax, Cmin, Tmax, Tmin

Safety assessments: Physical examination, vital signs, body weight and height, ECGs, QT measurement, laboratory testing, adverse events (AEs)

Please refer to section 7.4.4 Electrocardiograms for a discussion of study GWCI's results.

6 Review of Efficacy

Efficacy Summary

The NDA resubmission included CMC data, a safety update, and a proposed REMS. Therefore, most of the review sections below are not applicable. However, during this review cycle a new safety signal arose, specifically the potential for QT prolongation with Bydureon. To better demonstrate the efficacy of Bydureon in light of this potential new safety concern, the sponsor should submit results of study BCB108 to the NDA. BCB108 was an open label, randomized, comparator-controlled study of Bydureon ([redacted] (b) (4) Amylin scale) and Byetta over 24 weeks.

The sponsor should submit this additional efficacy information because bridging data provided for the [redacted] (b) (4) to [redacted] (b) (4) scale showed no bioequivalence. Supportive trial 105 demonstrated the LS mean change in HbA1c from baseline to week 30 in the Bydureon (non-commercial source) group was -1.9%, a statistically significant change when compared to -1.5% with Byetta. However, clinical comparability study 105c did not provide convincing evidence that the products are bioequivalent, due to the proximity of the lower bound of the confidence interval to zero. Please refer to the clinical pharmacology, clinical, and statistical reviews of the original NDA submission for full details.

6.1 Indication

The sponsor proposes 2 mg Bydureon subcutaneously weekly as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Like Victoza, Bydureon is a long-acting GLP-1 agonist. Based on nonclinical studies, it is thought that these agents may increase the risk of thyroid tumors. I therefore recommend that the product labeling include the important limitation of use "not

recommended as first-line therapy for patients inadequately controlled on diet and exercise". In addition, I recommend Bydureon be contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2.

As discussed in section 7.4.4 Electrocardiograms, I recommend that Bydureon be contraindicated in subjects with severe and end stage renal impairment and the potential risk for QT prolongation be clarified.

6.1.1 Methods

Not applicable.

6.1.2 Demographics

Not applicable.

6.1.3 Subject Disposition

In comparator-controlled studies summarized in the complete response resubmission, the withdrawal rate by treatment group ranged from 6.3% (insulin) to 20.6% (pioglitazone). The withdrawal rates for Bydureon and Byetta were 15.2% and 16.0%, respectively. Withdrawal of consent was highest in the pioglitazone group (9.1%; range 2.4-9.1%). Withdrawal due to AEs was highest in the Bydureon group (5.7%; range 0.9-5.7%). Loss of glucose control as defined in the protocol occurred most often in the Byetta group (1.5%; range 0.0-1.5%).

The withdrawal rates in comparator-controlled studies in the complete response safety update are similar to those in the four month safety update (Bydureon 17.2%, Byetta 10.3%, sitagliptin 13.3%, pioglitazone 20.6%).

Table 3. Subject disposition by study and treatment

	Efficacy and Safety Studies							
	Controlled							
	Placebo-Controlled		Comparator-Controlled					Uncontrolled [1]
Disposition	Exenatide Once Weekly (N = 51)	Placebo (N = 23)	Exenatide Once Weekly (N = 670)	BYETTA (N = 268)	Sitagliptin (N = 166)	Pioglitazone (N = 165)	Insulin (N = 223)	Exenatide Once Weekly (N = 392)
Completed [2]	49 (96.1)	22 (95.7)	568 (84.8)	225 (84.0)	144 (86.7)	131 (79.4)	209 (93.7)	338 (86.2)
Withdrawn	2 (3.9)	1 (4.3)	102 (15.2)	43 (16.0)	22 (13.3)	34 (20.6)	14 (6.3)	54 (13.8)
Reason for Withdrawal								
Withdrawal of Consent	0 (0.0)	0 (0.0)	30 (4.5)	11 (4.1)	4 (2.4)	15 (9.1)	8 (3.6)	24 (6.1)
Adverse Event	0 (0.0)	0 (0.0)	38 (5.7)	13 (4.9)	5 (3.0)	6 (3.6)	2 (0.9)	8 (2.0)
Investigator Decision	1 (2.0)	0 (0.0)	4 (0.6)	4 (1.5)	3 (1.8)	1 (0.6)	1 (0.4)	6 (1.5)
Protocol Violation	1 (2.0)	0 (0.0)	6 (0.9)	2 (0.7)	2 (1.2)	0 (0.0)	0 (0.0)	4 (1.0)
Lost to Follow-up	0 (0.0)	0 (0.0)	17 (2.5)	9 (3.4)	7 (4.2)	11 (6.7)	1 (0.4)	8 (2.0)
Administrative	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)
Loss of Glucose Control as Defined in the Protocol	0 (0.0)	1 (4.3)	4 (0.6)	4 (1.5)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Note: Subject 5001 from Study GWDC died due to colon cancer 12 weeks after his last injection of study medication (22 weeks after his first injection of study medication). The termination reason was recorded as "Entry Criteria Not Met" in the database and was coded as "Protocol Violation" in this table.
[1] Includes subjects from GWDC and subjects who completed LAR105 controlled period and enrolled in the uncontrolled period.
[2] Subjects who did not terminate from study at the time of analysis were counted in the completed category.

6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

My review focused on the controlled data in the complete response resubmission, clinical study report GWCI, related OSE and QT IRT consults, and the requested amylase, lipase, and calcitonin data from ongoing and completed Bydureon clinical trials (BCB106, BCB108, GWBR, GWCH, and GWDC). Note, only amylase, lipase, and calcitonin data were reviewed from studies BCB106, BCB108, GWBR, GWCH, and GWDC, as the study reports were not submitted at the time of NDA filing.

The complete response included safety data from completed clinical safety and efficacy studies through December 31, 2009 and data from ongoing clinical studies from the 4-month safety update cutoff data (March 31, 2009) through December 31, 2009. The four-month safety update included integrated data from 990 subjects from seven studies (102, 103, 104, 105, BCB106, BCB107, and GWBW). The complete response resubmission also included data from completed study BCB108 and the first 26 weeks of studies GWBR and GWDC.

As of the December 31, 2009 cutoff date for the complete response, ~1,900 subjects had been exposed to Bydureon in completed and ongoing trials. The complete response describes 1,700 subjects in 7 completed safety and efficacy studies, including 985 subjects treated with Bydureon and 845 subjects treated with comparator (placebo, Byetta, insulin, sitagliptin, or pioglitazone). Of the 985 subjects, 682 have been exposed to Bydureon for ≥26 weeks but <52 weeks. A total of 110 subjects were exposed for ≥96 weeks. The total exposure of Bydureon subjects is less than the 2,500 exposed subjects recommended in the draft February 2008 diabetes mellitus guidance. However, the Bydureon NDA references Byetta NDA 21-773 for a different formulation with the same active ingredient (exenatide). Taken together, exposure is adequate.

Bydureon does not appear to be associated with an increase in death or serious adverse events (SAEs), but the safety database and exposure are insufficient to be conclusive. Five deaths (2 Bydureon) occurred in the Bydureon development program. The most common system organ classes (SOCs) that SAEs occurred in were Cardiac Disorders and Infections and Infestations (both n=11, 1.1%). The second most common SOCs that SAEs occurred in were Gastrointestinal Disorders and Neoplasms (both 6, 0.6%). However, in long term (i.e. ≥10 weeks) controlled trials, all Bydureon SAEs occurred as single events, except for viral pericarditis and calculus ureteric which occurred twice. In long term comparator-controlled trials, SAEs occurred less commonly in the Bydureon arm than pioglitazone and insulin arms (3.9% vs. 6.1% and 4.5%, respectively).

The SOCs with the most adverse events (AEs) leading to withdrawal was Gastrointestinal Disorders (n=10, 1.0%), Investigations (n=6, 0.6%), and General

Disorders (n=4, 0.4%). In these SOCs, diarrhea, nausea, and injection site mass/nodule/pruritis occurred more than once (n=3, 0.3% each). In long term controlled trials, the frequency of withdrawals due to Bydureon was less than that with Byetta in the Gastrointestinal Disorders SOC (n=9 [1.3%] for Bydureon vs. n=11 [4.1%] for Byetta).

With regards to significant adverse events:

- No thyroid cancers have been identified in Bydureon subjects. When the available calcitonin data were reviewed, mean calcitonin values remained within the normal range (up to 84 weeks). Approximately 3% of subjects had elevated postbaseline calcitonin levels, although the change seen with Bydureon was small (~0.3 pg/ml). Calcitonin measurements >20 pg/ml were more common in men, but they also had a higher normal range (up to 18.2 pg/ml). Byetta nonclinical and clinical trial and postmarketing data do not suggest an increased risk of thyroid tumors.
- There have been 6 cases of pancreatitis in the Bydureon development program (3 Bydureon). With regards to the available laboratory measurements, the mean change in amylase and lipase concentrations from baseline to week 24 or 26 in Bydureon subjects ranged from 6.5 to 13.1 IU/L and 16.1 to 19.8 U/L, respectively. The amylase and lipase changes are likely not clinically significant, as we consider an increase in enzymes ≥3x ULN to be consistent with the diagnosis of pancreatitis. However, I agree with the April 7, 2010 OSE review of 2 Byetta postmarketing observational studies that concern is still warranted.
- Bydureon should be contraindicated in patients with severe renal impairment or end-stage renal disease. It should be used with caution in patients with moderate renal impairment or renal transplantation.

The most common AEs were mild to moderate gastrointestinal (GI) events, infections (specifically nasopharyngitis and upper respiratory infection), and injection site related AEs. The incidence of nausea and vomiting was lower in Bydureon (n=670) than Byetta (n=268) subjects (18.2% vs. 34.7% and 8.1% vs. 14.2%, respectively) in pooled, comparator-controlled studies. Injection-site related AEs such as pruritis and erythema were more common with Bydureon than Byetta (6.8% vs. 1.1% and 4.1% vs. 1.1%) in comparator-controlled studies.

Consistent with my original NDA review, a small mean increase (2.7 beats per minute) in heart rate (HR) and decrease in blood pressure (BP) (-3.3/1.1 mm Hg) were observed in completed controlled studies of Bydureon. A mean increase in the HR of Byetta and sitagliptin subjects was also observed (1.0 and 0.7 bpm, respectively). Although the etiology of these changes is unclear, the central GLP-1 system may be a regulator of sympathetic outflow. This potential association deserves additional study. A cardiovascular safety trial of Bydureon has been initiated and will be required of the sponsor.

During the first review cycle, the QT IRT concluded there are no apparent QT-prolonging effects of exenatide when administered as extended or immediate release formulations. However, as discussed in section 2.5 on April 12, 2010, Health Canada informed the agency of Byetta electrophysiology data that they received. At our request, the sponsor submitted study report H8O-EW-GWCI (GWCI), "A placebo- and positive-controlled study of the electrophysiological effect of a single 10 mcg dose of exenatide on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects", and related safety information.

Although thorough QT (TQT) study GWCI demonstrated no significant QT prolongation with Byetta, no definitive conclusion can be drawn for Bydureon. This is because the QTc interval appears to increase in a concentration-dependent manner. The projected upper bound of 90% CI for QTc interval following steady state Cmax of exenatide using Bydureon (in subjects with moderate renal impairment) may exceed 10 ms, given the caveat that the model predictions are mainly based on extrapolation. I therefore recommend 1) the sponsor conduct a thorough QT (TQT) study which covers the steady state maximum concentration of Bydureon and high clinical exposure scenario prior to approval, 2) CV safety study BCB109 include ECG and PK assessments in a subset of subjects, and 3) Bydureon be contraindicated in subjects with severe and end stage renal disease. As the potential approval of this NDA at the time of resubmission will depend on the risk:benefit analysis, I also recommend the sponsor submit study report BCB108, which compared the safety and efficacy of the to-be-marketed Bydureon product to Byetta.

Please also refer to section 7 Review of Safety in my original NDA review.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The complete response resubmission included safety data for completed clinical safety and efficacy studies through December 31, 2009 and data for ongoing clinical studies from the 4-month safety update cutoff data (March 31, 2009) through December 31, 2009. In the nine month period between the cutoff dates for the four-month safety update and the complete response resubmission, study BCB108 was completed and studies GWBR and GWDC were completed through week 26. Four new studies were initiated during this time and are ongoing: GWCK, GWCL, GWDL, and GWBX. Studies 105, BCB106, GWBR, GWDC, and GWCH remain ongoing.

The four-month safety update included integrated data from 990 subjects from seven studies (102, 103, 104, 105, BCB106, BCB107, and GWBW). The complete response safety update also included data from study BCB108 and the first 26 weeks of studies

GWBR and GWDC. Data from efficacy and safety studies with similar designs were pooled as shown in Table 4. Only subjects who received the proposed commercial formulation of Bydureon (F17 formulation with aqueous diluent) and the appropriate control subjects were included in the complete response resubmission.

On April 15, 2010, the sponsor submitted clinical study report GWCI, "A placebo- and positive-controlled study of the electrophysiological effect of a single 10 mcg dose of exenatide on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects", to exenatide IND 57,725.

My review focused on the controlled data in the complete response, clinical study report GWCI, related OSE and QT IRT consults, and the requested amylase, lipase, and calcitonin data.

Table 4. NDA 22-200 Complete Response: Overview of safety data for Bydureon

Source of data	Details
Complete response safety update	Controlled studies (repeat dose over 15-30 wks treatment): • Placebo controlled: 104 and GWBW • Comparator controlled: 105 (through week 30), BCB106 (through week 26), BCB108, GWBR (through week 26) Uncontrolled Bydureon exposure: 105 open label assessment (week 30-2 years) and GWDC (through week 26)
QT study report GWCI	Placebo and positive controlled ECG study

7.1.2 Categorization of Adverse Events

The sponsor's coding and categorization of adverse events was adequate. The studies submitted used MedDRA version 12.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Please refer to section 7.1.1 above for a description of the studies pooled.

I generally agree with the pooled study groups. However, it must be noted that studies GWBW, BCB106, BCB108, GWBR, and GWDC did not include a Byetta twice daily lead-in and study GWBW was a non-IND study conducted in 30 Japanese subjects.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of the November 15, 2008 cutoff for the original NDA, 860 subjects had been exposed to Bydureon in 9 ongoing and completed studies. The NDA'S integrated summary of safety described 366 subjects exposed to Bydureon.

As of the December 31, 2009 cutoff date for the complete response, ~1,900 subjects had been exposed to Bydureon in completed and ongoing trials (see Table 5). The complete response describes ~1,100 subjects in 7 completed studies treated with Bydureon (this includes 130 subjects in study 105 randomized to Byetta who received open label Bydureon during the open ended assessment period) (see Table 6). When appropriate, I also include data from the ongoing uncontrolled extension study 105 through 2 years of treatment, although the lack of a control group limits any meaningful interpretation. Approximately 800 additional subjects were exposed to Bydureon in ongoing studies as of December 31, 2009.

Table 5. Number of subjects in completed and ongoing studies who received at least one dose of Bydureon as of December 31, 2009

Study	Subjects in Completed Studies	Additional Subjects in Ongoing Studies	Total Exenatide Once Weekly Subjects
2993LAR102 [1]	10	—	10
BCB107 [1]	60	—	60
2993LAR103	47	—	47
2993LAR104	**31**	—	31
H8O-JE-GWBW	**20**	—	20
2993LAR-105	**278** [2]	—	278
BCB106	**160**	245 [3]	405
BCB108	**129**	—	129
H8O-MC-GWBR	**233**	—	233
H8O-MC-GWCH [4]	—	248	248
H8O-MC-GWCK	—	204	204
H8O-FW-GWCL	—	3	3
H8O-MC-GWDC	**134**	—	134
H8O-FW-GWDL	—	7	7
H8O-JE-GWBX	—	95	95
Total	1102	802	1904

Notes: -Due to ongoing enrollment of some of the studies, the numbers of subjects treated as of the cutoff date are approximate.
-Studies and subject numbers indicated in **bold font** are included in the integrated analysis in this safety update.

[1] Includes only those subjects who received the F17 formulation of exenatide once weekly.
[2] Includes 130 subjects in Study 2993LAR-105 randomized to BYETTA comparator who received open-label exenatide once weekly during open-ended assessment period.
[3] Includes subjects randomized to sitagliptin and pioglitazone comparator who received open-label exenatide once weekly during open-ended assessment period.
[4] Study H8O-MC-GWCH is a blinded study; the number of subjects that received exenatide once weekly is an estimate.

Table 6. NDA 22-200 Complete Response: Cumulative number of subjects exposed to Bydureon as of December 31, 2009 (ITT, n=1102).

Study Subgroup	Any Duration	Cumulative Duration (wks)				
		≥12 wk	≥26 wk	≥52 wk	≥78 wk	≥96
Clin Pharm Subtotal	117					
Efficacy & Safety						
Placebo controlled						
LAR104	31	31				
GWBW	20					
Subtotal	51	31				
Comparator controlled						
LAR105	278	268	251	-	-	-
BCB106	160	140	124			
GWBR	233	218	195			
BCB108	129	118	18			
Subtotal	800	744	588			
Controlled Subtotal	851	775	588			
Uncontrolled						
LAR105	-	-	-	233	115	110
GWDC	134	126	94			
Efficacy & Safety Subtotal	985	901	682	233	115	110
Grand Total	**1102**	**901**	**682**	**233**	**115**	**110**

Source: Complete response table 3

The total exposure of Bydureon subjects (n=1,102) is less than the 2,500 exposed subjects recommended in the draft February 2008 diabetes mellitus guidance. However, the Bydureon NDA references Byetta NDA 21-773 for a different formulation with the same active ingredient (exenatide). As of September 30, 2009, over (b) (4) patients have been exposed to exenatide in the United States. More than 6,000 subjects and healthy volunteers have been exposed to exenatide in clinical trials. Thus, the exposure is adequate.

The demographic and baseline characteristics of subjects in controlled trials are shown below. Approximately half of subjects were male. The mean age ranged from 53.0 - 57.3 years; the majority of subjects were < 65 years. The distribution of races varied by study but, overall, was diverse. The mean BMI ranged from 31.80 - 34.72. The mean HbA1c and duration of diabetes ranged from 7.92 - 8.49% and 4.9 – 7.2 years, respectively. The majority of subjects were on background antidiabetic medication in addition to diet and exercise. The majority of subjects had normal renal function or mild renal insufficiency.

Table 7. NDA 22-200 Complete Response: Demographic and baseline characteristics treatment by controlled study and treatment (ITT)

	Placebo Controlled		Comparator Controlled				
	Bydureon (n=51)	Placebo (n=23)	Bydureon (n=670)	Byetta (n=268)	Sitagliptin (n=165)	Pioglitazone (n=165)	Insulin (n=223)
Male	35 (68.6)	9 (39.1)	368 (54.9)	142 (53.0)	86 (51.8)	79 (47.9)	123 (55.2)
Mean age (y)	54.3	57.3	55.5	55.0	52.2	53.0	58.3
Age							
≥18-65	40 (78.4)	17 (73.9)	549 (81.9)	224 (83.6)	149 (89.8)	143 (86.7)	167 (74.9)
≥65	11 (21.6)	6 (26.1)	121 (18.1)	44 (16.4)	17 (10.2)	22 (13.3)	56 (25.1)
Race							
Caucasian	18 (35.3)	9 (39.1)	447 (66.7)	173 (64.6)	50 (30.1)	65 (39.4)	189 (84.8)
Black	5 (9.8)	1 (4.3)	36 (5.4)	28 (10.4)	20 (12.0)	13 (7.9)	1 (0.4)
Asian	21 (41.2)	10 (43.5)	55 (8.2)	6 (2.2)	42 (25.3)	40 (24.2)	14 (6.3)
Native Am	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)
Hispanic	6 (11.8)	3 (13.0)	131 (19.6)	61 (22.8)	49 (29.5)	44 (26.7)	19 (8.5)
Other	1 (2.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (1.2)	3 (1.8)	0 (0.0)
Mean BMI	31.95	31. 89	33.04	34.12	31.80	32.47	32.27
Mean HbA1c (%)	8.0	8.1	8.4	8.3	8.5	8.5	8.3
Mean T2DM duration (y)	4.9	5.2	7.2	6.7	5.4	5.8	8.0
Background diet & exercise only	22 (43.1)	6 (26.1)	42 (6.3)	49 (18.3)	0 (0.0)	0 (0.0)	0 (0.0)
Renal function							
Normal	35 (68.6)	13 (56.5)	404 (60.3)	142 (53.0)	83 (50.0)	72 (43.6)	171 (76.7)
Mild	16 (31.4)	9 (39.1)	234 (34.9)	107 (39.9)	69 (41.6)	79 (47.9)	51 (22.9)
Moderate	0 (0.0)	0 (0.0)	30 (4.5)	19 (7.1)	11 (6.6)	13 (7.9)	1 (0.4)
Severe	0 (0.0)	1 (4.3)	1 (0.1)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)

Source: Complete response safety update SDS 2.

Byetta (exenatide) should not be used in patients with severe renal impairment or end-stage renal disease (ESRD). It should be used with caution in patients with renal transplantation. Caution should be applied when initiating exenatide or escalating the dose in patients with moderate renal failure.

The sponsor proposes not recommending Bydureon in subjects with severe and end stage renal impairment, whereas I propose contraindicating it in these subjects due to the concentration-dependent increase in QT interval observed in study GWCI (see section 7.4.4). In addition, studies of Bydureon excluded subjects with renal failure as follows:

- Studies 104, 105, 105c: Included male and female subjects with serum creatinine ≤ 1.6 and 1.4 mg/dl, respectively. Excluded subjects with creatinine clearance (CrCl) ≤ 30 mg/dl
- Study GWBW: Excluded subjects with a history of renal transplantation, currently receiving dialysis, or serum creatinine ≥ 1.5 or 1.4 mg/dl for males or females, respectively

- Study BCB106: Excluded subjects with serum creatinine level > 1.5 or 1.4 mg/dl in men and women, respectively
- Study BCB108: Excluded subjects with clinically significant, as judged by the investigator, renal disease
- Study GWBR: Excluded subjects with a history of renal transplantation or are currently receiving renal dialysis or have serum creatinine ≥1.5 mg/dL (132 µmol/L) for males and ≥1.2 mg/dL (110 µmol/L) for females
- Study GWDC: Excluded subjects with a history of renal transplantation or are currently receiving dialysis or have serum creatinine ≥135 µmol/L (≥1.5 mg/dl) for males and ≥110 µmol/L (1.25 mg/dl) for females

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide. The proposed Bydureon label also states these points. However, studies of Bydureon excluded subjects with hepatic impairment as follows:

- Studies 104, 105, 105c, BCB106: Hepatic disease or an ALT or AST >3x ULN
- Studies GWBW and GWDC: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or ALT or AST ≥ 2.5x ULN
- Study BCB108: Excluded subjects with clinically significant, as judged by the investigator, hepatic disease
- Study GWBR: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, ALT or AST >3x ULN

7.2.2 Explorations for Dose Response

Please refer my review of the original NDA submission.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to section 4.3 Preclinical Pharmacology/Toxicology of my original NDA review for a discussion of the relevant animal thyroid data with Bydureon and related products, exenatide and liraglutide. An epidemiological study to assess the relative risk of thyroid neoplasm with exenatide is required from the sponsor.

Although the incidence of pancreatitis in T2DM patients is debated in the literature, exenatide is associated with pancreatitis, including hemorrhagic and necrotizing pancreatitis. The sponsor did not conduct special animal or in vitro studies of pancreatitis with Bydureon. However, an adequately powered epidemiological study to determine the incidence rate, severity, and risk factors for pancreatitis with Byetta (exenatide) and a 3 month pancreatic safety study in a diabetic rodent model treated with exenatide will be required from the sponsor.

A thorough QT study was not submitted with NDA 22-200, but to determine whether continuous exposure to therapeutic plasma exenatide concentrations affected overall ECG findings or QT intervals, ECG recordings were performed for subjects treated with Bydureon at baseline and weeks 14 and 30 in study 105, after steady state concentrations were achieved. Please refer to section 7.4.4 Electrocardiograms of my original NDA review and this complete response review. Please also refer to the QT IRT and OSE reviews.

7.2.4 Routine Clinical Testing

The sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. Limitations of this testing included the following:

- Serum amylase and lipase was not drawn in key studies 105 or 105c nor in studies 104 or GWBW which were included in the safety review. However, as the clinical significance of routine amylase and lipase monitoring is not clear, this is acceptable. The incidence of pancreatitis was summarized again in the complete response safety update. Serum lipase and amylase were monitored in other studies. Data were submitted, in response to our request.
    - BCB106 and BCB108: Screening, baseline, and weeks 14 and 26
    - GWBR: Weeks -2 and 26
    - GWBC: Week 0
- As there were no concerns about medullary thyroid cancer when the majority of studies were planned, calcitonin was not measured in studies submitted to the original NDA. However, the incidence of thyroid neoplasms was discussed in the complete response resubmission. After a request was made, the sponsor submitted calcitonin data that was obtained in later studies.
    - BCB108: Screening and week 26
    - GWBR: Weeks 14 and 26
    - GWDC: Weeks 0, 12, and 26

Please refer to section 7.4.2 Laboratory Findings for an analysis of the data submitted.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to my review of the original NDA submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As discussed in section 2.4 Important Safety Issues with Consideration to Related Drugs, GLP-1 mimetics currently approved in the United States include exenatide and liraglutide. Labeled safety concerns with exenatide include:

- Acute pancreatitis

- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions as a result of anti-exenatide antibodies
- Renal failure

Liraglutide and other longer acting GLP-1 receptor agonists are associated with thyroid c-cell tumors in rats and mice.

7.3 Major Safety Results

7.3.1 Deaths

Five deaths occurred in the Bydureon once weekly development program.

- BCB106-161030 (sitagliptin): Died of "hypertension" after 119 days of study medication
- 2993LAR-105-10802 (Bydureon): Died of a fatal myocardial infarction after approximately 198 days of study medication. The subject was a 67 year old American male with a history of T2DM (8 years) and hyperlipidemia who was overweight.
- BCB108-147005 (Byetta): Died of an MI
- H8O-MC-GWDC-5001 (Bydureon): The subject was diagnosed with stage II descending colon adenocarcinoma <1 month after the first dose of Bydureon. The subject was subsequently diagnosed with stage 2 right lung adenocarcinoma and died.
- H8O-MC-GWCH-1043 (blinded treatment): The subject discontinued blinded injectable and oral study medication after ~5 months due to abdominal pain, which remained ongoing. Approximately 1 month later, the subject was hospitalized for severe abdominal pain and distension and was diagnosed with gastric adenocarcinoma with carcinomatosis ascites. The subject died of multiple organ failure ~1 month later (after the December 31, 2009 cutoff for the complete response safety update).

Bydureon was not associated with an increased risk of death in the clinical development program.

7.3.2 Nonfatal Serious Adverse Events

The SAEs which occurred in the completed studies in the pooled analysis are shown below. In the total Bydureon population (n=985), the most common SOCs in which SAEs occurred in were Cardiac Disorders and Infections and Infestations (both n=11, 1.1%). The second most common SOCs that SAEs occurred in were Gastrointestinal

Disorders and Neoplasms (both 6, 0.6%). In these SOCs, all events occurred once, except for angina pectoris, MI, urinary tract infection, pancreatitis (1 edematous), and bladder cancer which occurred twice. There was one case of injection site nodule.

In long term controlled trials, all Bydureon SAEs occurred as single events, except for viral pericarditis and calculus ureteric which occurred twice. In long term comparator-controlled trials, SAEs occurred less commonly in the Bydureon arm than pioglitazone and insulin arms (3.9% vs. 6.1% and 4.5%, respectively).

Bydureon does not appear to be associated with an increase in SAEs.

Table 8. NDA 22-200 Complete Response: Serious adverse events by system organ class and treatment in completed placebo- and comparator-controlled and uncontrolled safety and efficacy studies

	Long-Term Placebo-Controlled		Long-Term Comparator-Controlled					Uncontrolled	Total
System Organ Class [1]	EQW (N = 51) n (%)	Placebo (N = 23) n (%)	EQW (N = 670) n (%)	BYETTA (N = 268) n (%)	Sitagliptin (N = 166) n (%)	Pioglitazone (N = 165) n (%)	Insulin (N = 223) n (%)	EQW (N = 392) n (%)	EQW (N = 985) n (%)
All Serious Treatment-Emergent Adverse Events	2 (3.9)	0 (0.0)	26 (3.9)	10 (3.7)	5 (3.0)	10 (6.1)	10 (4.5)	29 (7.4)	56 (5.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (2.0)	0 (0.0)	4 (0.6)	3 (1.1)	0 (0.0)	3 (1.8)	1 (0.4)	6 (1.5)	11 (1.1)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.5)	2 (0.2)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	3 (0.4)	1 (0.4)	0 (0.0)	2 (1.2)	0 (0.0)	3 (0.8)	6 (0.6)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.4)	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.5)	4 (0.4)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.7)	0 (0.0)	1 (0.6)	1 (0.4)	3 (0.8)	4 (0.4)
Infections and infestations	0 (0.0)	0 (0.0)	6 (0.9)	0 (0.0)	1 (0.6)	4 (2.4)	0 (0.0)	6 (1.5)	11 (1.1)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	5 (0.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	4 (1.0)	6 (0.6)
Nervous system disorders	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.4)	1 (0.6)	1 (0.6)	2 (0.9)	2 (0.5)	4 (0.4)
Renal and urinary disorders	1 (2.0)	0 (0.0)	2 (0.3)	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	4 (0.4)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.3)
Surgical and medical procedures	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.2)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

EQW = exenatide once weekly.

Notes: Subjects experiencing multiple episodes of a given adverse event are counted once. For 2993LAR-105, subjects with multiple episodes of a given adverse event are counted once in each period (comparator-controlled or uncontrolled) in which the event occurred.

- Placebo-controlled studies include Studies 2993LAR-104 and H8O-JE-GWBW; comparator-controlled studies include Studies 2993LAR-105 (through Week 30), BCB106 (through Week 26), BCB108, and H8O-MC-GWBR (through Week 26); uncontrolled studies include Studies 2993LAR-105 (Week 30 through 2 years) and H8O MC-GWDC (through Week 26).
- Sitagliptin and pioglitazone comparator treatment groups received placebo once weekly injections.

7.3.3 Dropouts and/or Discontinuations

The AEs leading to withdrawal in completed studies in the pooled analysis are shown below by SOC. In the total Bydureon population (n=985), the SOC with the most AEs leading to withdrawal was Gastrointestinal Disorders (10, 1.0%), followed by Investigations (6, 0.6%) and General disorders (4, 0.4%). In these SOCs, diarrhea, nausea, and injection site mass/nodule/pruritis occurred more than once (3, 0.3% each).

In long term comparator-controlled trials, the frequency of withdrawals due to Bydureon was less than that with Byetta in the Gastrointestinal Disorders SOC (n=9 [1.3%] for Bydureon vs. n=11 [4.1%] for Byetta). Only diarrhea (n=3) and nausea (n=2) occurred more than once in the Bydureon group. The SOC with the second most events was Investigations (n=5, 0.7%). These were all single events (decreased weight and increased ALT, blood creatinine, blood potassium, and lipase). The SOC with the third most common events was General disorders (n=4, 0.6%). These events included three injection site reactions, specifically a mass, nodule, and pruritis. No Byetta subject was withdrawn due to an injection site reaction.

The sponsor-proposed labeling includes the following injection site language:

(b) (4)

COMMENT: As described in section 4.4.1 Mechanism of Action, Bydureon contains PLG which is associated with local inflammatory reactions. Although one PLG-containing approved product (Vivitrol, NDA 21-897) contains an injection site Warning and Precaution, that product is administered through a different route and the microsphere dose (mg/injection) significantly exceeds that of Bydureon (b) (4) fold). The labeling of most products containing PLG includes Adverse Reactions language regarding possible injection site reactions.

I recommend the following regarding injection site reactions:

- **Revising the proposed Adverse Reactions language to include the exact incidence of injection site reactions, percentage of subjects withdrawn due to this AE, and mean event duration**
- **The Periodic Safety Update Reports (PSURs) analyze injection site reactions (including nodules)**

Table 9. NDA 22-200 Complete Response: Adverse events leading to withdrawal by system organ class and treatment in completed placebo- and comparator-controlled and uncontrolled safety and efficacy studies

	Long-Term Placebo-Controlled		Long-Term Comparator-Controlled					Uncontrolled	Total
System Organ Class [1]	EQW (N = 51) n (%)	Placebo (N = 23) n (%)	EQW (N = 670) n (%)	BYETTA (N = 268) n (%)	Sitagliptin (N = 166) n (%)	Pioglitazone (N = 165) n (%)	Insulin (N = 223) n (%)	EQW (N = 392) n (%)	EQW (N = 985) n (%)
All Treatment-Emergent Adverse Events Leading to Withdrawal	0 (0.0)	0 (0.0)	26 (3.9)	13 (4.9)	5 (3.0)	7 (4.2)	0 (0.0)	5 (1.3)	31 (3.1)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	9 (1.3)	11 (4.1)	3 (1.8)	3 (1.8)	0 (0.0)	1 (0.3)	10 (1.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Infections and infestations	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Investigations	0 (0.0)	0 (0.0)	5 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	6 (0.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Nervous system disorders	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

EQW = exenatide once weekly.

Notes: Placebo-controlled studies include Studies 2993LAR-104 and H8O-JE-GWBW; comparator-controlled studies include Studies 2993LAR-105 (through Week 30), BCB106 (through Week 26), BCB108, and H8O-MC-GWBR (through Week 26); uncontrolled studies include Studies 2993LAR-105 (Week 30 through 2 years) and H8O MC-GWDC (through Week 26).

- Sitagliptin and pioglitazone comparator treatment groups received placebo once weekly injections.

7.3.4 Significant Adverse Events

As described in section 2.4, thyroid tumors are an adverse event of special interest with regard to long acting GLP-1 analogues. The exenatide label contains the following safety concerns:

- Acute pancreatitis
- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions as a result of anti-exenatide antibodies
- Renal failure

Thyroid tumors: There have been no events of thyroid carcinoma with Bydureon. No new AEs of thyroid neoplasm were identified in completed or ongoing studies of Bydureon between March 31 – December 31, 2009.

- Subject BCB108-150001 completed 24 weeks of Bydureon treatment. Although no AEs occurred in this subject, his screening calcitonin concentration of 59 pg/ml increased to 91 pg/mol at week 24 (normal 0-8.4 pg/ml). Approximately 11 weeks after study termination, the subject's calcitonin was 121 pg/ml (normal 0-7.5 pg/ml). Thyroid ultrasound revealed a heterogenous thyroid with complex nodules. Fifteen weeks after study termination, his calcitonin concentration was 80.5 pg/ml. Eighteen weeks after study termination, a thyroid uptake and scan was unremarkable, with no focal areas of increased or decreased uptake. An ultrasound-guided thyroid fine needle aspiration revealed no evidence of malignancy.
- An event of benign thyroid mass occurred in a Bydureon subject in study 105. Please refer to my review of the original NDA submission for this information as well as my review of the pre- and postmarketing Byetta data.

On August 25, 2010, the sponsor submitted an analysis of calcitonin data, which is described in section 7.4.2 Laboratory Findings. With regards to thyroid tumors, the submission described the following:

- Bydureon subject BCB108-150001 had a peak calcitonin value of 121 pg/ml 11 weeks after study termination. He has a heterogeneous thyroid with complex nodules but benign fine needle aspiration.
- Glargine subject GWBR-5053 had a planned thryoidectomy for pre-existing goiter.
- Pioglitazone subject GWCH-0500 had a pre-existing thyroid neoplasm.
- Byetta subject GWCK-4307 had a peak calcitonin concentration of 29 pg/ml and three 5 mm nodules in the right thyroid. (She received one Bydureon dose.) Fine needle aspirate was consistent with papillary thyroid microcarcinoma. Surgery is planned.

- Bydureon subject GWCK-1624 had a peak calcitonin concentration of 26.1 pg/ml at week 26. One month later, thyroid ultrasound revealed a small right-sided thyroid nodule. No additional information was available at the time of the report.

NOTE: As the human relevance of the animal thyroid c-cell tumors is unknown and (b) (4) described adverse exocrine pancreatic effects expressed as necrotizing pancreatitis, the sponsor was asked to conduct an epidemiologic study of thyroid neoplasms and pancreatic cancer under exenatide (Byetta) monotherapy NDA PMR 1559-3.[1] (b) (4), (b) (5)

In summary, no thyroid cancers have been identified in Bydureon subjects. When the available calcitonin data were reviewed, mean calcitonin values remained within the normal range (up to 84 weeks). Approximately 3% of subjects had elevated postbaseline calcitonin levels, although the change seen with Bydureon was small (~0.3 pg/ml). Calcitonin measurements >20 pg/ml were more common in men, but they also had a higher normal range (up to 18.2 pg/ml). In addition, Byetta nonclinical and clinical trial and postmarketing data do not suggest an increased risk of thyroid tumors. Yet, due to the nonclinical findings associated with Bydureon and other GLP-1 agonists, I recommend the following:

- The label clearly state that Bydureon is contraindicated in subjects with a person or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2
- Bydureon not be used as a first-line antidiabetic therapy for patients inadequately controlled on diet and exercise
- A five-year prospective epidemiological study as described in section 1.4 Requirements for Postmarketing Requirements and Commitments
- A MTC case series registry of at least 15 years duration as described in section 1.4
- The sponsor analyze thyroid tumors as an AE of special interest in the PSURs

1 Matveyenko, AV et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes. Diabetes 2009, 58:1604-1615.

Acute pancreatitis: In the Bydureon clinical development program, the following 6 cases of acute pancreatitis or elevated amylase/lipase were reported in the complete response resubmission (cutoff data December 31, 2009) and Bydureon IND 67,092 (SDN 201 June 3, 2010): (Note: All but subject 152006 and report DK201005005637 were previously described.)

1) 170002 (BCB106, pioglitazone): Necrotizing pancreatitis which resulted in withdrawal
2) 125013 (BCB106, pioglitazone): Pancreatitis
3) 5802 (GWBR, Bydureon): Moderate edematous pancreatitis which led to withdrawal but resolved within 3 days.
4) 3181 (GWCH, blinded): Chronic pancreatitis 9 days after starting blinded study medication which lead to withdrawal
5) 152006 (BCB108, Bydureon): The subject presented to the emergency room approximately 61 days after starting Bydureon with moderate perumbilical pain. Amylase and lipase were 160 and 324, respectively (units not provided). The subject had a history of dyslipidemia but did not experience nausea or vomiting. CT scan showed no acute inflammatory abnormality. The pancreatitis resolved in 3 days, while the subject was receiving study mediation. However, the subject was subsequently withdrawn due to the pancreatitis.
6) Report DK2010050056372957 (GWBR, Bydureon): On June 3, 2010, the sponsor submitted to Bydureon IND 67,092 an initial report of gastroenteritis and pancreatitis. The subject is a 47 year old male with history of obesity and T2DM, who started Bydureon 2 mg weekly on an unknown date. Although the drug was held on May 10, 2010, the report also stated that the last dose of drug before the event is unknown. On May 17, 2010, the subject had nausea, vomiting, and diarrhea. On (b) (6), the subject was hospitalized for abdominal pain, vomiting, and diarrhea. The admitting diagnosis was gastroenteritis versus pancreatitis. On (b) (6) amylase was 432 u/L (normal 25-120 u/L) and C-reactive protein was 112 mg/L (normal 0-8 mg/L). On (b) (6) amylase was 200 u/L and C-reactive protein was 70 mg/L. Treatment was not reported. An ultrasound was ordered but was not yet completed. Other family members also had gastroenteritis symptoms. The subject had not recovered. It is not known if Bydureon was restarted. **COMMENT: While gastroenteritis cannot be excluded due to the family members' symptoms, a study drug effect must also be considered.**

There have been 6 cases of pancreatitis in the Bydureon development program (3 Bydureon). The symptoms of pancreatitis in the Bydureon subjects 5802 and 152006 resolved within 3 days while exenatide was still in circulation at therapeutic concentrations. However, the subject described in report DK201005005637 had not yet recovered.

Please also refer to section 7.4.2 Laboratory Findings for a discussion of the amylase and lipase data submitted on July 21, 2010.

On April 7, 2010, OSE completed a review of two completed postmarketing observational studies (the I3 Drug Safety and IMS studies) that evaluated the risk of acute pancreatitis among exenatide twice daily (Byetta) users. The results across studies were not consistent. The I3 Drug Safety cohort study noted an increased risk among recent and past users of exenatide when compared with other antidiabetic drug initiators as a group and by individual drug class, but the I3 nested case-control study and the IMS study noted no increased risk among recent or past exenatide users. None of the studies noted an increased risk among current users of exenatide, but the "observed increased risk still warrants concern" given the limitations of the studies. Please refer to Dr. Angelika Manthripragada's review for full details.

I therefore agree with the sponsor's proposal to include pancreatitis-related Warnings and Precautions language that is similar to Byetta's in the Bydureon label. I also recommend that the Bydureon cardiovascular trial (BCB109), the five-year prospective epidemiological study, and PSURs include an assessment of pancreatitis events.

Gastrointestinal side effects: Please refer to my review of the initial NDA submission.

Hypoglycemia: There were no events of major hypoglycemia, defined as loss of consciousness, seizure, or severe impairment in consciousness or behavior. In comparator-controlled trials, 16.5% of Bydureon subjects using a concomitant SU experienced minor hypoglycemia, compared to 0.5-3% of Bydureon subjects not using a SU. The planned labeling includes a Warning and Precaution about the increased risk of hypoglycemia when used in combination with a SU.

Hypersensitivity reactions as a result of anti-exenatide antibodies: Please refer to section 7.4.6 Immunogenicity.

Renal failure: No acute renal failure events were reported between March 31 – December 31, 2009. Please refer my previous NDA 22-200 review and section 7.4.4 Electrocardiograms.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The data contained in the complete response safety update are generally consistent with those presented in the previous safety update. Table 10, below, displays the common AEs (≥2%) in pooled, completed, placebo- and comparator-controlled efficacy and safety studies of Bydureon. The most common AEs were mild to moderate gastrointestinal (GI) events, infections (specifically nasopharyngitis and upper respiratory infection), and injection site related AEs. The incidence of nausea and vomiting was lower in Bydureon (n=670) than Byetta (n=268) subjects (18.2% vs. 34.7% and 8.1% vs. 14.2%, respectively) in pooled, comparator-controlled studies. Injection-site related AEs such as pruritis and erythema were more common with Bydureon than Byetta (6.8% vs. 1.1% and 4.1% vs. 1.1%) in comparator-controlled studies.

Table 10. NDA 22-200 Complete Response: Common AEs (≥ 2% in the placebo- or comparator-controlled Bydureon group) in completed, placebo- and comparator-controlled efficacy and safety studies of Bydureon

Preferred Term	Placebo controlled		Comparator controlled				
	Bydureon (n=51)	Placebo (n=23)	Bydureon (n=670)	Byetta (n=145)	Sitaglip (n=166)	Pioglit (n=165)	Insulin (n=223)
Nausea	10 (19.6)	2 (8.7)	126 (18.8)	93 (34.7)	16 (9.6)	8 (4.8)	3 (1.3)
Diarrhea	5 (9.8)	1 (4.3)	83 (12.4)	24 (9.0)	16 (9.6)	12 (7.3)	8 (3.6)
Nasopharyngitis	4 (7.8)	2 (8.7)	51 (7.6)	9 (3.4)	4 (2.4)	5 (3.0)	39 (9.9)
Upper respiratory tract infection	0 (0.0)	1 (4.3)	31 (4.6)	30 (11.2)	15 (9.0)	17 (10.3)	3 (1.3)
Vomiting	1 (2.0)	0 (0.0)	50 (7.5)	38 (14.2)	4 (2.4)	5 (3.0)	3 (1.3)
Headache	1 (2.0)	0 (0.0)	53 (7.9)	17 (6.3)	15 (9.0)	7 (4.2)	16 (7.2)
Injection site pruritis	10 (19.6)	4 (17.4)	43 (6.4)	3 (1.1)	8 (4.8)	2 (1.2)	1 (0.4)
Constipation	2 (3.9)	1 (4.3)	33 (4.9)	14 (5.2)	3 (1.8)	2 (1.2)	4 (1.8)
Urinary tract infection	2 (3.9)	1 (4.3)	32 (4.8)	16 (6.0)	9 (5.4)	6 (3.6)	1 (0.4)
Sinusitis	2 (3.9)	0 (0.0)	15 (2.2)	10 (3.7)	2 (1.2)	11 (6.7)	5 (2.2)
Back pain	1 (2.0	0 (0.0)	25 (3.7)	7 (2.6)	7 (4.2)	5 (3.0)	5 (2.2)
Arthralgia	0 (0.0)	1 (4.3)	24 (3.6)	8 (3.0)	8 (4.8)	3 (1.8)	6 (2.7)
Dyspepsia	0 (0.0)	0 (0.0)	28 (4.2)	6 (2.2)	6 (3.6)	4 (2.4)	2 (0.9)
Injection site erythema	5 (9.8)	0 (0.0)	26 (3.9)	3 (1.1)	4 (2.4)	0 (0.0)	1 (0.4)
Injection site nodule	0 (0.0)	0 (0.0)	23 (3.4)	0 (0.0)	2 (1.2)	1 (0.6)	0 (0.0)
Gastroenteritis viral	1 (2.0)	0 (0.0)	18 (2.7)	8 (3.0)	2 (1.2)	0 (0.0)	1 (0.4)
Fatigue	0 (0.0)	0 (0.0)	26 (3.9)	7 (2.6)	0 (0.0)	5 (3.0)	1 (0.4)
Gastroesophageal reflux	1 (2.0)	0 (0.0)	20 (3.0)	7 (2.6)	2 (1.2)	2 (1.2)	2 (0.9)
Influenza	2 (3.9)	0 (0.0)	12 (1.8)	7 (2.6)	2 (1.2)	5 (3.0)	8 (3.6)
Injection site hematoma	2 (3.9)	0 (0.0)	17 (2.5)	22 (8.2)	2 (1.2)	4 (2.4)	2 (0.9)
Dizziness	2 (3.9)	0 (0.0)	15 (2.2)	17 (6.3)	8 (4.8)	6 (3.6)	3 (1.3)
Pain in extremity	2 (3.9)	0 (0.0)	12 (1.8)	2 (0.7)	4 (2.4)	2 (1.2)	2 (0.9)
Hypertension	2 (3.9)	0 (0.0)	16 (2.4)	4 (1.5)	5 (3.0)	2 (1.2)	7 (3.1)
Cough	0 (0.0)	0 (0.0)	14 (2.1)	3 (1.1)	2 (1.2)	5 (3.0)	8 (3.6)
Bronchitis	1 (2.0)	1 (4.3)	13 (1.9)	7 (2.6)	3 (1.8)	1 (0.06)	7 (3.1)
Injection site induration	16 (31.4)	6 (26.1)	7 (1.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)
Anorexia	5 (9.8)	0 (0.0)	7 (1.0)	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)

Musculoskeletal pain	3 95.9)	0 (0.0)	8 (1.2)	0 (0.0)	2 (1.2)	3 (1.8)	7 (3.1)
Decreased appetite	0 (0.0)	0 (0.0)	18 (2.7)	5 (1.9)	2 (1.2)	0 (0.0)	0 (0.0)
Abdominal distension	2 (3.9)	0 (0.0)	10 (1.5)	3 (1.1)	2 (1.2)	1 (0.6)	1 (0.4)
Abdominal discomfort	0 (0.0)	0 (0.0)	13 (1.9)	3 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)
Abdominal pain	1 (2.0)	0 (0.0)	13 (1.9)	6 (2.2)	6 (3.6)	2 (1.2)	2 (0.9)
Oropharyngeal pain	0 (0.0)	1 (4.3)	11 (1.6)	3 (1.1)	1 (0.6)	1 (0.6)	7 (3.1)
Contusion	0 (0.0)	0 (0.0)	9 (1.3)	3 91.1)	0 (0.0)	1 (0.6)	5 (2.2)
Gastroenteritis	6 (11.8)	0 (0.0)	10 (1.5)	1 (0.4)	3 (1.8)	1 (0.6)	4 (1.8)
Nephrolithiasis	1 (2.0)	0 (0.0)	6 (0.9)	2 (0.7)	0 (0.0)	2 (1.2)	1 (0.4)
Depression	2 (3.9)	0 (0.0)	5 (0.7)	4 (1.5)	3 (1.8)	0 (0.0)	1 (0.4)
Myalgia	1 (2.0)	0 (0.0)	10 (1.5)	4 (1.5)	2 (1.2)	3 (1.8)	2 (0.9)
Tooth abscess	2 (3.9)	0 (0.0)	6 (0.9)	1 (0.4)	0 (0.0)	1 (1.2)	2 (0.9)
Injection site pain	1 (2.0)	0 (0.0)	7 (1.0)	3 (1.1)	2 (1.2)	0 (0.0)	1 (0.4)
Arthritis	1 (2.0)	0 (0.0)	3 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)
Injection site hemorrhage	1 (2.0)	0 (0.0)	5 (0.7)	2 (0.7)	2 (1.2)	2 (1.2)	0 (0.0)
Neck pain	1 (2.0)	0 (0.0)	3 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)	2 (0.9)
Pharyngitis	3 (5.9)	0 (0.0)	6 (0.9)	0 (0.0)	4 (2.4)	3 (1.8)	5 (2.2)
Pruritis	1 (2.0)	0 (0.0)	4 (0.6)	1 (0.4)	0 (0.0)	1 (0.6)	4 (1.8)
Anxiety	2 (3.9)	0 (0.0)	4 (0.6)	4 (1.5)	2 (1.2)	1 (0.6)	3 (1.3)
Otitis media	1 (2.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis contact	2 (3.9)	0 (0.0)	3 (0.4)	1 (0.4)	2 (1.2)	1 (0.6)	1 (0.4)
Road traffic accident	1 (2.0)	0 (0.0)	3 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	1 (2.0)	0 (0.0)	6 (0.9)	3 (1.1)	2 (1.2)	4 (2.4)	4 (1.8)
Rash	1 (2.0)	2 (8.7)	2 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)
Joint sprain	1 (2.0)	1 (4.3)	4 (0.6)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site rash	3 (5.9)	1 (4.3)	4 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster	1 (2.0)	0 (0.0)	3 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	1 (2.0)	0 (0.0)	3 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)	0 (0.0)
Hypoaesthesia	1 (2.0)	0 (0.0)	4 (0.6)	1 (0.4)	2 (1.2)	1 (0.6)	0 (0.0)
Dysmenorrhea**	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus congestion	1 (2.0)	0 (0.0)	1 (0.1)	2 (0.7)	0 (0.0)	1 (0.6)	1 (0.4)
Ear infection	1 (2.0)	0 (0.0)	1 (0.1)	2 (0.7)	1 (0.6)	1 (0.6)	0 (0.0)
Angina pectoris	1 (2.0)	1 (4.3)	1 (0.1)	1 (0.4)	0 (0.0)	1 (0.6)	2 (0.9)
Vision blurred	1 (2.0)	1 (4.3)	2 (0.3)	1 (0.4)	2 (1.2)	1 (0.6)	0 (0.0)
Wound	1 (2.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Blood amylase increased	2 (3.9)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Blood glucose decreased	3 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gingivitis	1 (2.0)	1 (4.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hypogeusia	2 (3.9)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calculus ureteric	1 (2.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	1 (2.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Fibromyalgia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Furuncle	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)
Nocturia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Periarthritis	1 (2.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)
Upper respiratory tract inflammation	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal discomfort	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parosmia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract congestion	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Urine ketone body present	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urobilin urine present	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Included studies: 104, GWBW, 105, BCB106, BCB108, GWBR*							
Source: Complete response safety update SDS 5.2							
*The majority of subjects in placebo-controlled study GWBW in Japan had injection site induration.							
** Term is only observed in the female population.							

When Supporting Data Summary 5.2 of frequent AEs (incidence rate ≥1% in any arm) was reviewed for uncontrolled Bydureon trials up to 2 years (n=392) and compared to the incidence rate in shorter duration (~26 week), comparator-controlled Bydureon trials, notable differences included an increase in infectious events (e.g. upper respiratory tract infection, nasopharyngitis, sinusitis, influenza) as one would expect with a longer duration of observation. Events of injection site pruritis, erythema, induration, nodule, pain, reaction, and irritation occurred at a similar or less incidence to that in comparator-controlled trials. However, numeric comparisons are not possible due to different exposures.

On July 7, 2010, nonclinical team leader Dr. Karen Davis-Bruno was informed during the monthly European Medicines Agency Pediatric Committee (PDCO) nonclinical working group teleconference that clinical reports suggest there may be an association between Byetta and alopecia. As the April 9, 2010 Byetta (IND 57,725) annual report did not describe alopecia events, an information request was sent to the sponsor asking them to submit the “relevant information with respect to this adverse reaction”.

The Bydureon complete response safety update was searched for events of alopecia. Two mild events occurred in the comparator-controlled Byetta population (n=268, 0.7%). One mild event occurred in the comparator-controlled Bydureon population (n=670, 0.1%). There were no reports in the sitagliptin (n=166), pioglitazone (n=165), and insulin (n=233) groups.

7.4.2 Laboratory Findings

Please refer to section 7.4.2 in my original NDA 22-200 review. I review newly submitted laboratory data below, specifically calcitonin, amylase, and lipase data.

Calcitonin: On August 25, 2010 as requested by the agency, the sponsor submitted an analysis of all calcitonin data obtained in ongoing, terminated, and completed clinical trials of Bydureon. The submission included data from 4 completed or ongoing clinical trials for which an interim data cut (July 5, 2010) was available. Please refer to Table 11 below.

Table 11. Studies include in the calcitonin analysis (July 5, 2010 cutoff)

Study	Calcitonin time points	Data duration	ITT Subjects		
			Bydureon	Byetta	Comparator

BCB108	Baseline & wk 24 (or early termination)	24 wk	129	123	-
GWBR	Wks 14, 26, 36, 48, 60, 72, & 84; every 12 wk thereafter; & follow up	84 wk	233	-	223
GWCH*	Baseline & wks 12, 26, & 36 (10 wk follow up)	26 wk; 10 wk follow up	248	-	572
GWDC	Baseline; wks 12, 26, 40, & 52; every 3 mo thereafter; & 10 wk follow up	52 wk	134	-	-
*GWCH is a phase 3b, comparator-controlled, randomized, double-blind, parallel-design study to compare the effects of Bydureon on glycemic control, safety, and tolerability, to those of sitagliptin, pioglitazone, and metformin in T2DM subjects. (Please refer to Table 1 for a description of the other studies.)					

A total of 1,662 ITT subjects participated in these studies (744 Bydureon, 123 Byetta, 795 non-exenatide comparator [sitagliptin, pioglitazone, metformin, or glargine]). However, as calcitonin assessments were introduced into studies GWBR, GWCH, and GWDC after these studies began, complete calcitonin profiles were not available for all ITT subjects. Change from baseline was described when baseline information was available (i.e. studies BCB108 and GWCH). Due to differences in study duration and calcitonin assay and sampling times, data was not pooled but presented by study.

Preliminary data (through August 16, 2010) was also provided in the form of line listings for ongoing studies GWBX, GWCK, GWDE, and GWDL. However, as this data are preliminary and not final, they were not reviewed here.

Table 12. Normal calcitonin ranges

Study	Males (pg/ml)	Females (pg/ml)
BCB108	0-8.4	0-5
GWBR, GWBX, GWCH, GWCK, GWDC, GWDE, GWDL	0-18.2	0-11.5

In studies BCB108 and GWCH, Bydureon was associated with a slight increase in mean calcitonin concentrations from baseline to last visit, when compared to comparators, including Byetta. However, the mean change (0.35 and 0.31 pg/ml, respectively) is likely not clinically significant. The mean calcitonin levels remained in the normal range.

Table 13. Mean change in calcitonin (pg/ml) from baseline to last visit in studies BCB108 and GWCH

Study	Bydureon	Byetta	Sitagliptin	Pioglitazone	Metformin
BCB108	N=112	N=111	-	-	-
Screening (mean, SD)	4.0 (6.9)	4.4 (5.6)	-	-	-
Δ screening to wk 24 (or ET)	0.35 (5.5)	-0.02 (4.4)	-	-	-
GWCH	N=93→91	-	N=68→66	N=66→63	N=103→101
Baseline	3.0 (3.8)	-	2.2 (2.5)	3.2 (4.8)	2.9 (3.7)
Δ baseline to last visit	0.31 (1.5)	-	0.06 (1.3)	-0.22 (1.3)	-0.22 (1.4)

When mean calcitonin data were reviewed for studies GWBR and GWDC to weeks 84 and 52, respectively, the values remained within the normal range. No significant difference was observed between the Bydureon and glargine values in study GWBR.

Table 14. Mean calcitonin concentrations (pg/ml) in study GWBR

	Treatment	
Time Point	Exenatide Once Weekly 2 mg (N = 233)	Insulin Glargine (N = 223) [1]
Week 26		
n	15	22
Mean (SD)	3.5 (4.1)	2.4 (2.7)
Week 36		
n	56	56
Mean (SD)	2.2 (2.9)	2.7 (3.1)
Week 48		
n	127	135
Mean (SD)	3.1 (3.7)	3.0 (4.3)
Week 60		
n	129	132
Mean (SD)	3.3 (4.0)	3.0 (3.6)
Week 72		
n	130	131
Mean (SD)	2.9 (3.1)	3.2 (4.2)
Week 84		
n	118	116
Mean (SD)	2.8 (3.0)	3.3 (4.1)

Table 15. Mean calcitonin concentrations (pg/ml) in study GWDC

Time point (n)	Bydureon
Week 26 (n=84)	3.3 (4.8)
Week 40 (n=65)	3.4 (4.7)
Week 52 (n=73)	3.4 (5.5)

Of the 612 subjects in BCB108 and GWCH who had baseline calcitonin assessments, 24 (3.9%) had concentrations > ULN at baseline. Of these 24, 7 subjects had postbaseline calcitonin concentrations within the normal range and 17 continued to have abnormal concentrations. An additional 14 subjects (6 Bydureon, 1 Byetta, 7 non-exenatide comparator) had normal baseline and abnormal postbaseline concentrations. In total, 31 (3.3%) of the 935 subjects with postbaseline calcitonin assessments in studies BC108 and GWCH had abnormal calcitonin concentrations.

Table 16. Summary of baseline and postbaseline abnormal calcitonin concentrations by treatment in studies BCb108 and GWCH

	Treatment				
Abnormal Calcitonin Category	Exenatide Once Weekly 2 mg n / N (%)	BYETTA 10 mcg BID n / N (%)	Sitagliptin 100 mg/day n / N (%)	Pioglitazone ≤45 mg/day n / N (%)	Metformin ≤2500 mg/day n / N (%)
Baseline Only	3 / 229 (1.3)	4 / 122 (3.3)	0 / 73 (0.0)	0 / 74 (0.0)	0 / 114 (0.0)
Baseline and Postbaseline	6 / 205 (2.9)	9 / 111 (8.1)	0 / 68 (0.0)	1 / 66 (1.5)	1 / 103 (1.0)
Postbaseline Only	6 / 330 (1.8)	1 / 112 (0.9)	4 / 138 (2.9)	1 / 136 (0.7)	2 / 219 (0.9)
Postbaseline Total	12 / 330 (3.6)	10 / 112 (8.9)	4 / 138 (2.9)	2 / 136 (1.5)	3 / 219 (1.4)

BID = twice daily
Notes: -n = number of subjects who fulfill specified criteria; N = number of subjects with non-missing results; % = n×100/N.
-Postbaseline summary does not include assessments at Week 36 (off-drug safety assessment) of Study GWCH.

When the calcitonin data in studies GWBR and GWDC were reviewed to weeks 84 and 52, respectively, 12 of 451 (2.7%) subjects had an abnormal calcitonin level at one or more postbaseline assessment (2.2% Bydureon, 1.7% glargine).

Most subjects with abnormal postbaseline calcitonin had values ≤2x ULN. Only 7 of 1,386 (0.5%) subjects had values >2x ULN. These 7 subjects were in study BCB108 (2 Bydureon, 5 Byetta).

When data were analyzed for calcitonin concentrations >20 pg/ml, 23 (<2%) subjects on various treatments met this criteria (see below). The majority (91.3%) of these subjects were male. This may have to do with the male normal range being higher than the female normal range in all studies and the male normal range being 0-18.2 pg/ml in 3 of the 4 studies analyzed.

Nine of the 23 subjects with values >20 pg/ml had baseline measurements. Seven of these subjects (3 Bydureon, 2 Byetta, 1 pioglitazone, and 1 metformin) had baseline values >20 pg/ml. Two of these 7 subjects (1 Bydureon, 1 Byetta) had normal levels at week 24.

Table 17. Subjects with calcitonin >20 pg/ml during BCB108

Subject	Treatment	Gender	Calcitonin (pg/ml)		Relevant history
			Screening	Week 24	
121009	Bydureon	M	48	<5.0	History of elevated calcitonin
145001	Bydureon	M	22	NA	-
150001	Bydureon	M	59	91	Nodules identified after study completion
105007	Byetta	M	40	5.5	-
109005	Byetta	M	17	24	Used Prilosec
148004	Byetta	M	9.6	34	-
156016	Byetta	M	30	28	-

Bydureon subject BCB108-150001 had a screening and week 24 calcitonin levels of 59 and 91 pg/ml, respectively. The subject experienced no AEs during the study, but 11 weeks after termination, his calcitonin level was 121 pg/ml (nl 0-7.5 pg/ml). A thyroid ultrasound showed a heterogenous thyroid with complex nodules. Fifteen weeks after termination, the calcitonin level was 80.5 pg/ml. Eighteen weeks after termination, a thyroid scan and uptake were unremarkable. A fine needle aspiration revealed no evidence of malignancy.

Glargine subject GWBR-50523 had a planned thyroidectomy for a pre-existing goiter. Pioglitazone subject BWCH-0500 had a pre-existing thyroid neoplasm.

Table 18. Subjects with calcitonin >20 pg/ml through week 26 in study GWCH

Subject	Treatment	Gender	Calcitonin (pg/ml)			Relevant history
			Wk 0	Wk 12	Wk 26	
3026	Bydureon	F	NA	37.0	35.3	-
6058	Bydureon	M	NA	17.1	20.2 & 26.6	23.1 (wk 36)
0590	Sitagliptin	M	NA	22.0	16.8	-
0661	Sitagliptin	M	NA	20.8	18.8	-
5562	Sitagliptin	F	NA	99.5	NA	-
6501	Sitagliptin	M	NA	28.4	26.1	28.9 (wk 36)
5141	Pioglitazone	M	35.1	43.2	36.3	24.7 (wk 16), 44.2 (wk 36)
0556	Metformin	M	NA	14.5	20.0	18.4 (wk 36)
1043	Metformin	M	25.3	25.0	NA	Withdrew & died of gastric adenocarcinoma

Table 19. Subjects with calcitonin >20 pg/ml during study GWBR

Subject	Treatment	Gender	Calcitonin (pg/ml)				
			Wk 26	Wk 48	Wk 60	Wk 72	Wk 84
007852	Bydureon	M	NA	21.3	17.6	NA	NA
004953	Glargine	M	NA	14.7	18.7	22.6	NA
005803	Glargine	M	NA	23.4	14.0	18.3	18.0
007000	Glargine	M	NA	24.6	20.9	28.8	24.8

Table 20. Subjects with calcitonin concentrations >20 pg/ml during GWDC

Study	Treatment	Gender	Calcitonin (pg/ml)			Relevant history
			Wk 26	Wk 40	Wk 52	
1003	Bydureon	M	31.4	26.8	31.2	-
5003	Bydureon	M	26.1	19.5	15.6	-
5114	Bydureon	M	NA	NA	31.1	Used proton pump inhibitor

In summary, the sponsor submitted final calcitonin data from 4 studies (BCB108, GWBR, GWCH, and GWDC), which used different assessment time points and assays (Bydureon n=744). Mean calcitonin levels increased from baseline slightly in studies BCB108 and GWCH (0.35 and 0.31 pg/ml, respectively), although mean values remained in the normal range in the 4 studies. Approximately 3.3% of subjects with postbaseline calcitonin assessments in 24- and 26-week studies BCB108 and GWCH had abnormal values. When the calcitonin data in studies GWBR and GWDC were reviewed to weeks 84 and 52, respectively, 12 of 451 (2.7%) subjects had an abnormal calcitonin level at one or more postbaseline assessment (2.2% Bydureon). Less than 2% of subjects (all treatment groups) had calcitonin levels >20 pg/ml. Approximately 91% of these subjects were male; this may be related to the higher male normal range (up to 18.2 pg/ml). There were no AEs of thyroid neoplasm, thyroid nodule, or thyroid malignancy in the 4 studies analyzed.

Amylase and lipase: On July 21, 2010, as requested by the agency, the sponsor submitted an analysis of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Bydureon. Using a June 30, 2010 cutoff, the sponsor included data from 2,153 subjects in 5 trials (1 completed, 4 ongoing). Of these subjects, 904 were treated with Bydureon, 123 were treated with Byetta, and 1,126 were treated with non-exenatide comparators (sitagliptin, pioglitazone, metformin, or insulin glargine). Of the 1,126 non-exenatide comparators, 245 later received Bydureon in the open-label, uncontrolled treatment period of study BCB106. Ninety of the 134 subjects who received Bydureon in study GWDC had been previously treated with Byetta either commercially or in GWCG.

Because of differences in the laboratory assays, study duration, and design, amylase and lipase data were not pooled but presented separately. Serum amylase concentration increases almost immediately with the onset of pancreatitis, peaks within several hours, and remains elevated 3-5 days before returning to normal. There is no significant correlation between the magnitude of serum amylase elevation and the severity of pancreatitis. Please note that studies BCB106, BCB108, and GWBR measured pancreatic amylase (p-amylase), while studies GWCH and GWDC measured total amylase (t-amylase). Because hyperamylasemia can be observed in many extrapancreatic diseases, measuring p-amylase rather than t-amylase (which also includes salivary amylase) makes the diagnosis more specific (~90%). Serum lipase,

on the other hand, remains elevated for several days after amylase has returned to baseline and has a sensitivity >90%.

Table 21. Summary of Bydureon studies and subjects included in the amylase and lipase analyses

Study	Status	Sampling/Amylase*	Dose (mg)	ITT subjects		
				Bydureon	Byetta	Comparator
BCB106	Ongoing but wk 26 completed & wk 52 summarized	Screen, day 1, and wks 14, 26, 40 & 52 (P)	Bydureon 2 Sitagliptin 100 Pioglitazone 45	160	-	331
BCB108	Completed 24 wks	Screen, day 1, and wks 14 & 24 (P)	Bydureon 2 Byetta 10 mcg	129	123	-
GWBR	Ongoing but wk 26 completed	Screen & wk 26 (P)	Bydureon 2 Glargine	233	-	223
GWCH	Ongoing	Screen, day 1, and wk 12 & 26 (T)	Bydureon 2 Metformin up to 2500 Sitagliptin 100 Pioglitazone up to 45	248	-	572
GWDC	Ongoing	Day 1 & wk 52 (T)	Bydureon 2	134		
*Amylase sampled was either pancreatic (P) or total (T).						

For study BCB106, analyses of the 52 week data included subjects who received at least 1 dose of exenatide once weekly in the open-label treatment period. Data for study BCB106 were summarized separately for the double-bind controlled period (through week 26, ITT population) and for the combined double-blind/open-label uncontrolled period (through week 52, OLE ITT population).

Table 22. Normal ranges of amylase and lipase concentrations

Study	Pancreatic or total amylase (IU/L)	Lipase (U/L)
BCB106, BCB108, GWBR	13-53; pancreatic	0-60
GWCH, GWDC	20-112; total	0-60

Five additional studies of Bydureon, in which amylase and lipase data are being collected are ongoing, and could not be included in the sponsor's response (H8O-MC-GWCK, H8O-FW-GWCL, H8O-FW-GWDL, H8O-JE-GWBX, and H8O-MC-GWDE).

The demographic and baseline characteristics for studies included in the analysis were similar when analyzed by study and treatment group, except for race/ethnicity (which varied slightly) and the mean duration of diabetes (2.6-8.0 years).

Mean t-amylase or p-amylase concentrations were within the normal range at baseline and remained within the normal range throughout the 24- or 26-week treatment periods

in subjects treated with Bydureon, Byetta, and comparators. Small mean increases from baseline in amylase were observed. In Bydureon subjects, mean changes in amylase concentrations from baseline to week 24 or 26 ranged from 6.5 to 13.1 IU/L. Small increases were also observed with Byetta and non-exenatide comparator treatment (1-7.4 IU/L).

Mean lipase concentrations were within normal limits at baseline in all treatment groups (range 36.0-47.8 U/L). In Bydureon subjects, mean changes in lipase concentrations from baseline to week 24 or 26 ranged from 16.1 to 19.8 U/L. In 3 of the 4 comparator-controlled studies (BCB106, BCB108, and GWBR), mean lipase concentrations were 0.8-5.1 U/L above the upper limit of normal after 24 or 26 weeks of treatment. Changes from baseline to week 12 or 14 were similar in magnitude to those observed at week 24 or 26.

Subjects treated with Byetta (study BCB108), sitagliptin (studies GWCH and BCB106), and metformin (study GWCH) also had mean increases in lipase from baseline to weeks 24 or 26 of 8.8, 4.5, 8.5, and 2.2 U/L, respectively. However, treatment with glargine (study GWBR) and pioglitazone (studies BCB016, GWCH) resulted in a mean decrease in lipase when compared to baseline (range -5.0 to -2.9 U/L).

In study GWDC, 134 ITT subjects were treated with Bydureon for 52 weeks. The mean changes in t-amylase and lipase from baseline to week 52 were 6.3 U/L and 9.7 U/L, respectively. The mean lipase value at week 52 exceeded the upper limit of normal by 2.4 U/L.

In study BCB106, 364 ITT subjects were treated with Bydureon 2 mg, sitagliptin 100 mg, or pioglitazone 45 mg for 26 weeks and then continued on or switched to Bydureon 2 mg for an additional 26 weeks. At week 14, the Bydureon group had a greater increase in mean p-amylase and lipase than the sitagliptin and pioglitazone groups. At week 26, the pioglitazone group had a negligible change from baseline in mean p-amylase and lipase improved (-5.3 U/L), whereas both the Bydureon and sitagliptin groups experienced an increase in mean p-amylase and lipase.

Table 23. Mean p-amylase (IU/L) and lipase (U/L) concentrations and change from baseline in study BCB106 (open-label extension ITT population, n=364)

	P-Amylase (IU/L)			Lipase (U/L)		
Time Point	EQW 2 mg (N = 119)	Sitagliptin 100 mg→ EQW 2 mg (N = 130)	Pioglitazone 45 mg→ EQW 2 mg (N = 115)	EQW 2 mg (N = 119)	Sitagliptin 100 mg→ EQW 2 mg (N = 130)	Pioglitazone 45 mg→ EQW 2 mg (N = 115)
Screening						
n	125	131	115	125	131	115
Mean (SD)	26.6 (13.0)	27.0 (14.9)	31.6 (32.3)	42.4 (32.6)	38.8 (20.1)	48.1 (38.5)
Baseline						
n	119	130	115	119	130	115
Mean (SD)	26.9 (12.8)	27.4 (15.0)	29.8 (23.4)	43.6 (26.4)	38.9 (18.5)	49.4 (55.1)
Change from Baseline to Week 14						
n	116	125	114	117	125	114
Mean (SD)	9.4 (16.8)	2.5 (12.1)	2.3 (10.6)	19.7 (41.7)	5.7 (23.2)	-1.9 (20.6)
Change from Baseline to Week 26						
n	114	129	112	114	129	112
Mean (SD)	6.3 (13.8)	4.1 (11.4)	0.5 (16.2)	16.4 (33.3)	9.6 (24.3)	-5.3 (49.9)
Change from Baseline to Week 40						
n	109	119	101	109	119	101
Mean (SD)	6.3 (13.5)	8.1 (14.2)	5.3 (21.6)	12.9 (31.5)	17.9 (27.7)	10.4 (46.3)
Change from Baseline to Week 52						
n	102	117	99	102	117	99
Mean (SD)	9.8 (20.0)	5.0 (12.4)	6.0 (17.4)	28.0 (70.5)	13.8 (23.1)	13.4 (36.8)

EQW = exenatide once weekly; p-amylase = pancreatic amylase; SD = standard deviation.
Notes: -Normal range for p-amylase is 13 to 53 IU/L; normal range for lipase is 0 to 60 U/L.
-Subjects randomized to receive sitagliptin and pioglitazone in the double-blind period of the study (baseline to Week 26) received exenatide once weekly in the uncontrolled period of the study (Week 26 to Week 52).

When pioglitazone subjects were switched to Bydureon at week 26, the mean lipase level not only normalized but increased (Δ13.4 U/L at week 52); the mean amylase level also increased (Δ6.0 U/L at week 52). Subjects who were switched from sitagliptin to Bydureon or continued on Bydureon at week 26 also experienced increases in mean p-amylase and lipase. At week 52, mean lipase concentrations were 10.1 U/L above the upper limit of normal in subjects treated continuously with Bydureon.

Abnormal pancreatic enzyme concentrations were observed in subjects both prior to and after study drug administration. Of the 2,153 subject analyzed, 246 (11.4%) had lipase concentrations >ULN at baseline. Of the 1,199 subjects in which p-amylase was evaluated in BCB106, BCB108, and GWBR, 58 (4.8%) had levels >ULN at baseline. Twenty-four of 954 (2.5%) of subjects in GWCH and GWDC had t-amylase levels >ULN at baseline. Baseline elevations appeared to be transient elevations and not predictive of continued or worsened enzyme elevation following therapy.

During the controlled treatment periods, 541 (25.1%) had abnormal lipase concentrations, 126 (10.5%) had abnormal p-amylase, and 65 (6.8%) had abnormal t-amylase at one or more postbaseline assessments. When the proportion of subjects

with amylase or lipase levels >3x ULN at any time point were examined, the proportion of subjects with elevated enzymes was small. Elevations in lipase were more common than elevations in amylase; this is consistent with changes in mean concentrations described above. Although enzyme elevations were seen with all therapies, slightly more Bydureon subjects appeared to have elevated lipase than subjects on comparators. However, given the small number of subjects studied, it is not clear if these differences are clinically significant.

Table 24. Summary of t-amylase, p-amylase, and lipase concentrations >3x ULN at baseline or at any postbaseline visit (ITT, n=2153)

Study Time Point Treatment	Lipase			Total Amylase or P-Amylase [2]		
	>3×ULN and ≤5×ULN	>5×ULN and ≤10×ULN	>10×ULN	>3×ULN and ≤5×ULN	>5×ULN and ≤10×ULN	>10×ULN
BCB106 (Baseline through Week 26)						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	1/160 (0.6)	0/160 (0.0)	0/160 (0.0)	0/160 (0.0)	0/160 (0.0)	0/160 (0.0)
SIT n/N (%) [3]	0/166 (0.0)	0/166 (0.0)	0/166 (0.0)	0/166 (0.0)	0/166 (0.0)	0/166 (0.0)
PIO n/N (%) [3]	0/165 (0.0)	1/165 (0.6)	0/165 (0.0)	2/165 (1.2)	0/165 (0.0)	0/165 (0.0)
Any Postbaseline Time Point						
EQW n/N (%) [3]	4/155 (2.6)	1/155 (0.6)	0/155 (0.0)	0/154 (0.0)	0/154 (0.0)	0/154 (0.0)
SIT n/N (%) [3]	3/157 (1.9)	0/157 (0.0)	0/157 (0.0)	0/157 (0.0)	0/157 (0.0)	0/157 (0.0)
PIO n/N (%) [3]	2/149 (0.7)	0/149 (0.0)	1/149 (0.7)	1/149 (0.7)	0/149 (0.0)	0/149 (0.0)
BCB108						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	2/129 (1.6)	0/129 (0.0)	0/129 (0.0)	1/129 (0.8)	0/129 (0.0)	0/129 (0.0)
BYETTA n/N (%) [3]	0/123 (0.0)	0/123 (0.0)	0/123 (0.0)	0/123 (0.0)	0/123 (0.0)	0/123 (0.0)
Any Postbaseline Time Point						
Exenatide Once Weekly n/N (%) [3]	4/125 (3.2)	2/125 (1.6)	1/125 (0.8)	1/125 (0.8)	1/125 (0.8)	0/125 (0.0)
BYETTA n/N (%) [3]	0/113 (0.0)	1/113 (0.9)	0/113 (0.0)	1/113 (0.9)	0/113 (0.0)	0/113 (0.0)
H8O-MC-GWBR						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	2/233 (0.9)	0/233 (0.0)	0/233 (0.0)	0/233 (0.0)	0/233 (0.0)	0/233 (0.0)
Insulin glargine n/N (%) [3]	1/223 (0.4)	1/223 (0.4)	0/223 (0.0)	0/223 (0.0)	0/223 (0.0)	0/223 (0.0)
Any Postbaseline Time Point						
Exenatide Once Weekly n/N (%) [3]	4/219 (1.8)	0/219 (0.0)	0/219 (0.0)	2/219 (0.9)	0/219 (0.0)	0/219 (0.0)
Insulin glargine n/N (%) [3]	0/217 (0.0)	0/217 (0.0)	0/217 (0.0)	0/217 (0.0)	0/217 (0.0)	0/217 (0.0)

Study Time Point Treatment	Lipase			Total Amylase or P-Amylase [2]		
	>3×ULN and ≤5×ULN	>5×ULN and ≤10×ULN	>10×ULN	>3×ULN and ≤5×ULN	>5×ULN and ≤10×ULN	>10×ULN
H8O-MC-GWCH						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	0/248 (0.0)	0/248 (0.0)	0/248 (0.0)	0/248 (0.0)	0/248 (0.0)	0/248 (0.0)
SIT n/N (%) [3]	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)
PIO n/N (%) [3]	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)	0/163 (0.0)
Metformin n/N (%) [3]	0/246 (0.0)	0/246 (0.0)	0/246 (0.0)	0/246 (0.0)	0/246 (0.0)	0/246 (0.0)
Any Postbaseline Time Point						
EQW n/N (%) [3]	2/241 (0.8)	2/241 (0.8)	0/241 (0.0)	0/241 (0.0)	0/241 (0.0)	0/241 (0.0)
SIT n/N (%) [3]	0/152 (0.0)	0/152 (0.0)	0/152 (0.0)	0/152 (0.0)	0/152 (0.0)	0/152 (0.0)
PIO n/N (%) [3]	1/153 (0.7)	1/153 (0.7)	0/153 (0.0)	0/153 (0.0)	0/153 (0.0)	0/153 (0.0)
Metformin n/N (%) [3]	2/245(0.8)	0/245 (0.0)	0/245 (0.0)	0/245 (0.0)	0/245 (0.0)	0/245 (0.0)
BCB106 (Week 26 through Week 52) [4]						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	1/119 (0.8)	0/119 (0.0)	0 119 (0.0)	0/119 (0.0)	0/119 (0.0)	0/119 (0.0)
SIT →EQW n/N (%) [3]	0/130 (0.0)	0/130 (0.0)	0 130 (0.0)	0/130 (0.0)	0/130 (0.0)	0/130 (0.0)
PIO →EQW n/N (%) [3]	0/115 (0.0)	1/115 (0.9)	0/115 (0.0)	2/115 (1.7)	0/115 (0.0)	0/115 (0.0)
Any Postbaseline Time Point in Uncontrolled Period						
EQW n/N (%) [3]	4/117 (3.4)	3/117 (2.6)	1/117 (0.9)	1/117 (0.9)	0/117 (0.0)	0/117 (0.0)
SIT →EQW n/N (%) [3]	1/126 (0.8)	0/126 (0.0)	0 126 (0.0)	0/126 (0.0)	0/126 (0.0)	0/126 (0.0)
PIO →EQW n/N (%) [3]	5/112 (4.5)	1/112 (0.9)	1/112 (0.9)	1/112 (0.9)	1/112 (0.9)	0/112 (0.0)
H8O-MC-GWDC						
Baseline (Prior to First Injection of Study Medication)						
EQW n/N (%) [3]	2/129 (1.6)	0/129 (0.0)	1/129 (0.8)	0/129 (0.0)	0/129 (0.0)	0/129 (0.0)
Any Postbaseline Time Point						
Exenatide Once Weekly n/N (%) [3]	3/127 (2.4)	1/127 (0.8)	0/127 (0.0)	0/127 (0.0)	0/127 (0.0)	0/127 (0.0)

EQW = exenatide once weekly; ITT = intent-to-treat; OLE = open-label extension; p-amylase = pancreatic amylase; PIO = pioglitazone; SIT = sitagliptin.

Notes: -Subjects randomized to BYETTA received BYETTA 5 mcg SC BID for 4 weeks followed by BYETTA 10 mcg SC BID for the remainder of the treatment period. Subjects randomized to SIT or PIO in Study BCB106 received SIT or PIO through Week 26 and EQW from Week 26 through Week 52.
- For the "Any Postbaseline Time Points," if subjects had elevated lipase or amylase at more than one postbaseline visit, they are counted only once in the highest relevant enzyme category. BCB106 subjects may be counted once in the controlled period and once in the uncontrolled period, if they had elevated enzymes in both periods.

[1] The upper limit of normal range is 53 IU/L for p-amylase, 112 IU/L for total amylase, and 60 U/L for lipase.

[2] Pancreatic amylase was assayed in Studies BCB106, BCB108, and H8O-MC-GWBR; total amylase was assayed in Studies H8O-MC-GWCH and H8O-MC-GWDC.

[3] n = number of subjects that fulfill specified criteria; N = number of subjects with non-missing results; % = n * 100 / N.

[4] BCB106 OLE ITT Population used for analysis from Week 26 through Week 52. Subjects 147006, 164006 (EQW), 108016, and 117001 (PIO→EQW) had elevated lipase concentrations during both the double-blind and uncontrolled periods of Study BCB106; Subject 108016 (PIO→EQW) had elevated p-amylase concentrations during both the double-blind and uncontrolled periods of study BCB106 (see Table 12).

When abnormal amylase or lipase concentrations were analyzed by the presence or absence of abdominal pain, nausea, and vomiting in studies BCB106, BCB108, GWBR, GWCH, and GWDC, no clear association was seen. Furthermore, when a subgroup of 6 Bydureon subjects in study BCB106 with elevated enzyme concentrations and sometimes gastrointestinal symptoms (e.g. nausea, reflux) was evaluated with noninvasive abdominal imaging, gallstones were a common finding but pancreatic inflammation was not. (Please refer to section 7.3.4 Significant Adverse Events in my initial review of NDA 22-200.)

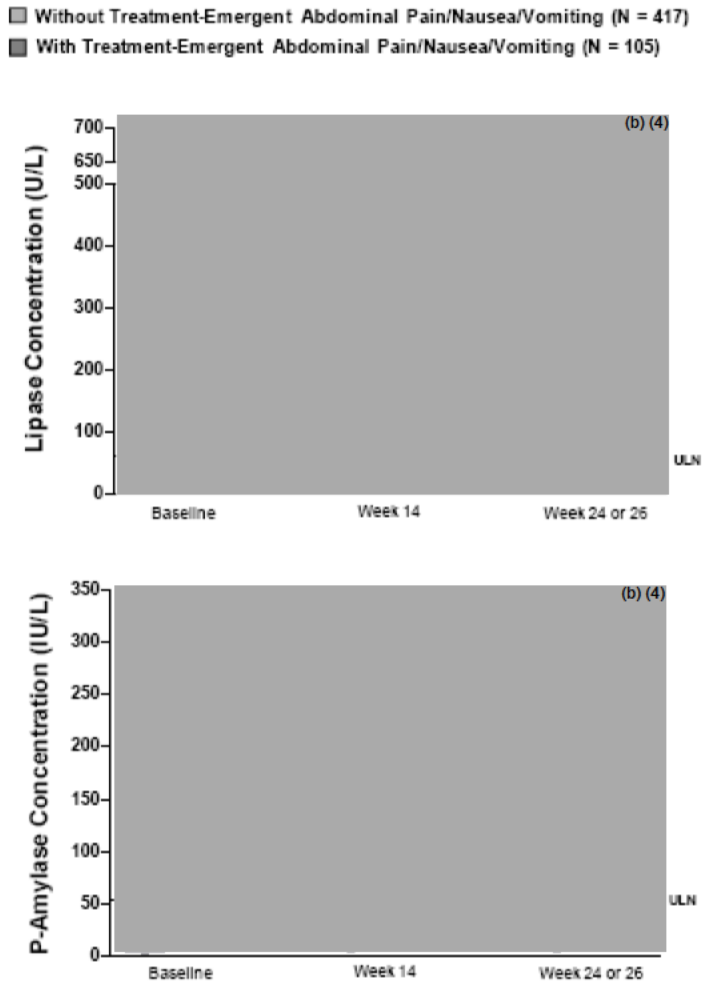


Figure 2. Scatterplot of p-amylase (IU/L) and lipase (U/L) concentrations by adverse event status and time point in studies BCB106, BCB108, GWBR (ITT receiving Bydureon, n=522)

When the incidence of gastrointestinal AEs (specifically, abdominal pain, abdominal pain upper/lower, nausea, and vomiting) were analyzed by postbaseline amylase and lipase levels, no clear association was observed (see Table 25). Adverse events

occurred similarly in subjects with normal and abnormal enzyme levels, except for abdominal pain upper which occurred in 0.9% subjects with normal enzymes and 2.0-2.2% subjects with abnormal enzymes. However, when the abdominal pain, abdominal pain lower, and abdominal pain upper groups were tallied, the percentage of subjects with normal (3.1%) and abnormal (4.4%) enzymes was similar.

Table 25. Incidence of gastrointestinal adverse events among subjects treated with Bydureon by postbaseline amylase and lipase status in studies BCB106, BCB108, GWBR, GWCH, and GWDC (n=1149)

	Postbaseline Enzyme Status [2]		
System Organ Class/ Preferred Term(s) [3]	Normal P-Amylase and Lipase (N = 651) n (%)	Abnormal P-Amylase or Lipase (N = 454) n (%)	Abnormal P-Amylase and Lipase (N = 136) n (%)
Gastrointestinal disorders	222 (34.1)	159 (35.0)	52 (38.2)
Nausea, vomiting, abdominal pain, abdominal pain upper, abdominal pain lower	116 (17.8)	85 (18.7)	29 (21.3)
Abdominal pain, abdominal pain upper, abdominal pain lower	20 (3.1)	20 (4.4)	6 (4.4)
Abdominal pain	13 (2.0)	11 (2.4)	3 (2.2)
Abdominal pain lower	1 (0.2)	0 (0.0)	0 (0.0)
Abdominal pain upper	6 (0.9)	9 (2.0)	3 (2.2)
Nausea	96 (14.7)	65 (14.3)	21 (15.4)
Vomiting	37 (5.7)	29 (6.4)	7 (5.1)

P-amylase = pancreatic amylase; SD = standard deviation.
Notes: Seven subjects who received exenatide once weekly in the uncontrolled period of Study BCB106 did not have p-amylase or lipase assessments in the uncontrolled period and are not summarized.
[1] Subjects who received exenatide once weekly in both the double-blind treatment period and the uncontrolled treatment period in Study BCB106 are counted once. For subjects who only received exenatide once weekly in the uncontrolled treatment period of Study BCB106, enzyme status is based upon the uncontrolled period and only adverse events with onset during the uncontrolled period are included.
[2] Normal amylase and lipase = amylase and lipase ≤ULN at all postbaseline visits; abnormal (amylase and lipase) = amylase and lipase >ULN at any postbaseline visit; abnormal (amylase or lipase) = amylase or lipase >ULN at any postbaseline visit.
[3] MedDRA terms.

Note: The sponsor's July 21, 2010 amylase/lipase submission (cutoff June 30, 2010) describes 5 events of pancreatitis in the Bydureon development program (2 Bydureon [5802 and 152006], 2 pioglitazone [170002 and 125013], and 1 sitagliptin [3181]). I agree with the cases described but also (as described in section 7.3.4 above) include initial report DK2010050056372957 of a Bydureon subject in study GWBR which was submitted to the IND on June 3, 2010.

In summary:

- The measurement of p-amylase in studies BCB106, BCB108, and GWBR provided a more specific assessment of amylase than the use of t-amylase in studies GWCH and GWDC.
- Although mean t-amylase or p-amylase concentrations were within the normal range at baseline and remained within the normal range throughout the 24- or 26-week treatment periods, the mean changes in amylase concentrations from baseline to week 24 or 26 in Bydureon subjects ranged from 6.5 to 13.1 IU/L. Small increases were also observed with Byetta and non-exenatide comparator treatment (1-7.4 IU/L).
- In Bydureon subjects, mean changes in lipase concentrations from baseline to week 24 or 26 ranged from 16.1 to 19.8 U/L. In 3 of the 4 comparator-controlled studies (BCB106, BCB108, and GWBR), mean lipase concentrations were 0.8-5.1 U/L above the upper limit of normal after 24 or 26 weeks of treatment. Subjects treated with Byetta, sitagliptin, and metformin also had mean increases in lipase from baseline to weeks 24 or 26, although subjects treated with glargine and pioglitazone experienced a mean decrease.
- When subjects were switched from pioglitazone or sitagliptin to Bydureon at week 26 in study BCB106, pancreatic enzyme levels tended to increase slightly.
- Abnormal pancreatic enzyme concentrations were observed both prior to and after study drug administration.
    - Baseline elevations appeared to be transient elevations and not predictive of continued or worsened enzyme elevation following therapy.
    - The proportion of subjects with pancreatic enzymes >3xULN at any time point was small. Consistent with the changes in mean concentrations described above, elevations in lipase were more common than elevations in amylase. Although enzyme elevations were seen with all therapies, slightly more Bydureon subjects appeared to have elevated lipase than subjects on comparators. However, given the small number of subjects studied, it is not clear if these differences are clinically significant.
- When amylase and lipase levels were analyzed based on the presence or absence of GI symptoms, no predictable pattern was observed.
- Similarly, when the incidence of gastrointestinal AEs (specifically, abdominal pain, abdominal pain upper/lower, nausea, and vomiting) was analyzed by postbaseline amylase and lipase levels, no clear association was observed.
- Six cases of pancreatitis have been reported in the Bydureon development program (3 Bydureon, 2 pioglitazone, 1 sitagliptin)

7.4.3 Vital Signs

Consistent with my original NDA review, a small mean increase (2.7 beats per minute) in heart rate (HR) and decrease in blood pressure (BP) (-3.3/1.1 mm Hg) were observed in completed controlled studies of Bydureon. A similar trend was observed in Byetta

subjects (change in HR and BP 1.0 bpm and -1.3/2.2 mmHg, respectively). Sitagliptin was also associated with a small increase in HR (0.7 bpm).

The etiology of these changes is unclear. The slight decrease in BP and increase in HR could result from volumetric changes, since GLP-1 agonists are associated with nausea and diarrhea. However, Bydureon is associated with less GI effects than Byetta and the changes in HR and BP were similar. A more likely explanation is that the central GLP-1 system is a regulator of sympathetic outflow.[2] This potential association deserves additional study. A cardiovascular safety trial of Bydureon has been initiated and will be required of the sponsor. However, as described in my initial review of NDA 22-200, Bydureon is not a new molecular entity but a reformulation of exenatide which has been on the market since April 2005 without a signal for increased CV risk. Thus, the overall risk-benefit analysis supports approval with a required postmarketing CV trial.

Table 26. NDA 22-200 Complete Response: Mean values at baseline and mean change from baseline to last visit (ITT, n=1700)

	Controlled						Uncontrolled
Vital Sign (Unit)/ Parameter	Exenatide Once Weekly (N = 721)	Placebo (N = 23)	BYETTA (N = 268)	Sitagliptin (N = 166)	Pioglitazone (N = 165)	Insulin (N = 223)	Exenatide Once Weekly [2] (N = 392)
Heart Rate (beats/min)							
n	713	23	257	163	165	222	392
Baseline	73.9	70.1	73.8	72.6	74.1	74.5	73.2
Change	2.7	-2.0	1.0	0.7	-0.6	-0.7	2.9
Sitting DBP (mmHg)							
n	713	23	257	163	165	222	392
Baseline	79.3	78.0	78.5	78.9	79.5	80.0	77.8
Change	-1.1	-2.0	-1.3	-0.2	-2.6	-0.7	-0.8
Sitting SBP (mmHg)							
n	713	23	257	163	165	222	392
Baseline	130.7	128.6	128.6	125.8	126.7	133.5	128.6
Change	-3.3	-2.1	-2.2	0.8	-1.4	-0.6	-2.3

[1] Baseline = Day -3 for LAR104 and LAR105, Day 1 for BCB106 and BCB108, and Week 0 for GWBW, GWBR, and GWDC. If unavailable, a value from an earlier visit is used. Change = value at the last visit - value at the baseline.
[2] Includes subjects from GWDC and subjects who completed LAR105 controlled period and enrolled in the uncontrolled period.

NOTE: Reproduced from the sponsor (SDS 6).

7.4.4 Electrocardiograms (ECGs)

Repeat-dose toxicity studies showed no adverse effects on the CV system in rodents (mice and rat histopathology) and monkeys (ECGs including QT/QTc, histopathology) after administration of various exenatide formulations up to 2 years in rodents and 9 months in monkeys.

A thorough QT study was not FDA-required for approval for all new molecular entities in March 2005, when exenatide was approved. During the first review cycle of Bydureon,

2 Yamamoto, H et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. Journal of Clinical Investigation 2002, 110:43-52.

we consulted the QT Interdisciplinary Review Team (IRT). In pivotal study 105, replicate 12 lead ECGs were obtained at baseline and weeks 14 and 30. Although small increases in QTc interval (< 10 ms) could not be ruled out, the average exenatide exposures achieved with the Bydureon formulation were lower (relative bioavailability is 25%) than with approved Byetta. The QT IRT thought that a dedicated TQT was not needed unless there were CV AEs such as syncope, seizure, ventricular arrhythmias, or sudden death in the clinical development program and postmarketing reports, which was not the case. Thus, the QT IRT concluded there are no apparent QT-prolonging effects of exenatide when administered as extended or immediate release formulations.

However, as discussed in section 2.5 on April 12, 2010, Health Canada informed the agency of Byetta electrophysiology data that they received. At our request, the sponsor submitted study report H8O-EW-GWCI (GWCI), "A placebo- and positive-controlled study of the electrophysiological effect of a single 10 mcg dose of exenatide on the 12-lead electrocardiogram (ECG) QT interval in healthy subjects", and related datasets to exenatide IND 57,725, as well as cardiac arrhythmia and conduction-related safety results for Byetta and Bydureon and spontaneous Byetta postmarketing reports of cardiac arrhythmia and potential conduction-related events. These documents were consulted to the QT IRT. An OSE consult was also placed to the AERS database for arrhythmia-related standardized MedDRA queries (SMQs) reported in association with the use of Byetta, including but not limited to Conduction Defects, Tachyarrhythmias, and Torsade de Pointes/QT Prolongation.

After a search of the AERS database and literature, OSE identified no postmarketing reports that met the definition of Torsades de Points (TdP) or QT prolongation. However, noting the limitations of its search, OSE stated the risk would be better evaluated clinically.

As requested, the sponsor searched its Bydureon and Byetta databases for arrhythmia and conduction-related AEs. The Bydureon database included the 7 long-term, controlled and uncontrolled studies included in the complete response resubmission (1,700 subjects: 985 Bydureon, 845 comparator). The Byetta dataset included the 17 studies included in the CV meta-analysis provided in the original Bydureon NDA (4,117 subjects: 2,919 exenatide, 1,629 placebo or insulin). The incidence of arrhythmia and conduction-related AEs in controlled studies of Bydureon was low in all treatment groups. Although the Bydureon group had the highest incidence, it was similar to other non-insulin comparators (range 1.1-1.5%). The incidence in the Byetta development program was similar to placebo/insulin (1.5% vs. 1.4%, respectively).

Table 27. Incidence of arrhythmia and conduction-related AEs in Bydureon development program

SOC/PT	Controlled							Uncontrolled
	Placebo-controlled		Comparator-controlled					
	Bydureon (n=51)	Placebo (n=23)	Bydureon (n=670)	Byetta (n=268)	Sitaglip (n=166)	Pioglit (n=165)	Insulin (n=223)	Bydureon (n=392)
All events	**-**	**-**	**10 (1.5)**	**3 (1.1)**	**2 (1.2)**	**2 (1.2)**	**1 (0.4)**	**10 (2.6)**
Cardiac disorder	**-**	**-**	**7 (1.0)**	**2 (0.7)**	**2 (1.2)**	**2 (1.2)**	**1 (0.4)**	**6 (1.5)**
Atr fibrillation	-	-	-	-	-	-	1 (0.4)	2 (0.5)
Atr flutter	-	-	2 (0.3)	-	-	1 (0.6)	-	-
AV block	-	-	1 (0.1)	-	-	-	-	-
AV block 1st deg	-	-	-	-	1 (0.6_	-	-	-
Cardiac arrest	-	-	1 (0.1)	1 (0.4)	-	-	-	-
Cardiac flutter	-	-	1 (0.1)	-	-	-	-	-
Conduct disorder	-	-	-	-	-	-	-	1 (0.3)
Palpitation	-	-	-	1 (0.4)	1 (0.6)	1 (0.6)	-	1 (0.3)
Sinus tachycardia	-	-	2 (0.3)	-	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	1 (0.3)
Vent extrasystole	-	-	1 ().1)	-	-	-	-	1 (0.3)
Vent tachycardia	-	-	-	-	-	-	-	1 (0.3)
Investigation	**-**	**-**	**1 (0.1)**	**1 ().4)**	**-**	**-**	**-**	**3 (0.8)**
ECG QT prolongn	-	-	-	1 (0.4)	-	-	-	-
HR increased	-	-	-	-	-	-	-	1 (0.3)
HR irregular	-	-	1 ().1)	-	-	-	-	2 (0.5)
Nervous disord	**-**	**-**	**2 (0.3)**	**-**	**-**	**-**	**-**	**2 (0.5)**
Syncope	-	-	2 (0.3)	-	-	-	-	2 (0.5)

In Byetta PSUR 8 (March 2009), the sponsor conducted a review of cardiac-related events and concluded the following:

- The reporting rate of atrial fibrillation in Byetta patients is ~0.08 per 1,000 person-years, which is below the estimated incidence in the general population of 3.68 per 1,000 person-years
- The reporting rate of cardiac arrest, cardio-respirator arrest, sudden cardiac death, sudden death, ventricular fibrillation, and ventricular tachycardia in Byetta patients is ~0.03 per 1,000 patient-years, which is below the estimated incidence reported in the general population of 1 per 1,000 person-years

Thus, the pre and postmarketing Bydureon and Byetta data as analyzed by OSE and the sponsor do not support an arrhythmia or conduction-related signal. However, the QT IRT review of Byetta TQT study GWCI concluded that, although no significant QT prolongation was seen with Byetta (mean Cmax 208 pg/ml), no definitive conclusion can be drawn for Bydureon. This is because the mean maximum concentration (Cmax) of exenatide observed in the TQT study is 208 pg/mL, which is half the steady state concentration following the therapeutic dose of Bydureon. The TQT study indicated that exenatide appears to increase the QTc interval in a concentration-dependent manner (P = 0.003). Based on the concentration-response relationship, for each 100 pg/ml

concentration of exenatide, the predicted increase is ~2 ms. Following treatment with Bydureon, the clinical exposure of exenatide in patients with moderate renal impairment is 50-60% higher (~500 pg/ml) compared to that in patients with normal renal function. Therefore, Bydureon may potentially cause QTc prolongation. The projected upper bound of 90% CI for QTc interval following steady state Cmax of exenatide using Bydureon may exceed 10 ms, given the caveat that the model predictions are mainly based on extrapolation.

Recognizing that the Bydureon assessment is based on extrapolation (which is associated with some uncertainty) and the clinical exenatide data do not suggest a signal, the QT IRT recommended a required postmarketing TQT study and the following Warning and Precaution: *Bydureon may potentially cause QTc prolongation. Avoid Bydureon in patient with congential long QT syndrome. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, moderate to severe renal impairment, bradyarrhythmias, drugs known to prolong the QTc interval including Class Ia and III antiarrhythmics and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating Bydureon and monitor these electrolytes periodically during therapy.*

The IRT recommended the required postmarketing TQT study characterize the QTc and other ECG interval changes following treatment with Bydureon. Due to the long half-life and delayed second peak of Bydureon, the study could be conducted with Byetta so long as it covers the steady state maximum concentration of Bydureon (Cmax = 433 pg/ml) and high clinical exposure scenario (estimated moderate renal impairment Cmax = 600 pg/ml). The IRT and clinical pharmacology estimate that a 20-40 mcg Byetta dose will cover the exposure expected with Bydureon 2 mg in patients with moderate renal impairment. (Previous dose finding studies of exenatide have used up to 0.4 mcg/kg or 28 mcg in a 70 kg person.) The TQT study may be conducted in healthy or diabetic subjects.

I disagree with the proposed timing of the TQT trial. I propose this study be conducted premarketing. My rationale is that, based on the results of TQT study GWCI, exenatide is associated concentration-dependent increase in QTc interval. Although the Food and Drug Administration Amendments Act (FDAAA) of 2007 permits the agency to require certain postmarketing trials, it has been CDER's policy since October 2005, when a related guidance was issued, that sponsors test the effects of new agents on the QT/QTc interval *prior* to approval. As a question about the effects of Bydureon on the QT interval has arisen, I recommend a complete response to this NDA resubmission and a preapproval TQT be required. Furthermore, as the potential approval of this NDA at the time of resubmission will depend on the risk:benefit analysis, I also recommend the sponsor submit study report BCB108, which compared the safety and efficacy of the to-be-marketed Bydureon product to Byetta.

As the TQT study may not be conducted with Bydureon but with Byetta, I recommend that Bydureon CV study BCB109 include robust ECG and PK monitoring in a subset of subjects.

Until this safety issue is better understood, I also recommend the labeling encourage weekly administration in the case of a missed dose or changed dosing day. Administration of 2 doses on consecutive days is not expected to change the average steady state concentration significantly. However, I cannot rule out an initial increase in peak concentration, and a relationship between Cmax and QT has been established.

7.4.5 Special Safety Studies/Clinical Trials

Cardiac disorder AEs occurred in 2.3% of Bydureon subjects in the pooled analysis of completed studies and in 2.7% of Bydureon subjects included in the original NDA submission. Bydureon subjects experiencing cardiac disorder SAEs in the complete response and original NDAs were 1.1% versus 1.4%, respectively.

Please also refer to Dr. Fiona Callaghan's statistical review of the sponsor's MACE analysis.

7.4.6 Immunogenicity

In active-controlled studies 105, BCB106, BCB108, and GWBR, 464 of 670 (69%) subjects were positive for antibodies to exenatide at some point during the study, with 142 (21%) having higher titer (≥625) and 322 (48%) having low titer (<625). These data are similar to those described in my original NDA review.

Potentially immune-related AEs were also identified in the complete response safety update and are shown below. Antibody-positive (Ab+) Bydureon subjects were nearly twice as likely to experience potentially immune-related AEs than antibody-negative (Ab-) Bydureon subjects and antibody positive and negative Byetta subjects (22.4% Bydureon Ab+ vs. 12.2% Bydureon Ab- and 10.2% Byetta). The increase in overall AEs is mostly attributed to the significant increase in General Disorders and Administration Site Conditions AEs in antibody-positive Bydureon subjects. This is expected; as discussed in my review of the original NDA submission, the incidence of injection site reactions (i.e. erythema, pruritis, rash, and urticaria) is higher in high titer, antibody-positive Bydureon subjects than low titer, antibody-positive and antibody-negative Bydureon subjects (21.8% vs. 7.5% and 2.6%). However, less than 1% of subjects withdrew due to injection site AEs.

Table 28. NDA 22-200 Complete Response: Potentially immune-related AEs by antibody status in comparator-controlled studies 105, BCB106, BCB108, and GWBR (ITT, n=1492)

System Organ Class [1]	Exenatide Once Weekly (N = 670)		BYETTA (N = 268)		Sitagliptin	Pioglitazone	Insulin
	TEAB Positive (N = 464)	TEAB Negative (N = 189)	TEAB Positive (N = 128)	TEAB Negative (N = 129)	All Subjects (N = 166)	All Subjects (N = 165)	All Subjects (N = 223)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Treatment-Emergent Potentially Immune-Related Adverse Events	104 (22.4)	23 (12.2)	13 (10.2)	13 (10.1)	24 (14.5)	13 (7.9)	17 (7.6)
Blood and Lymphatic System Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions	77 (16.6)	9 (4.8)	3 (2.3)	4 (3.1)	12 (7.2)	3 (1.8)	2 (0.9)
Immune System Disorders	3 (0.6)	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.2)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	20 (4.3)	10 (5.3)	7 (5.5)	4 (3.1)	9 (5.4)	3 (1.8)	9 (4.0)
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.2)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	2 (1.2)	1 (0.4)
Skin and Subcutaneous Tissue Disorders	13 (2.8)	4 (2.1)	2 (1.6)	3 (2.3)	5 (3.0)	6 (3.6)	6 (2.7)

TEAB = treatment-emergent antibody.
Note: Positive status for treatment-emergent antibodies to exenatide is defined as an antibody titer that is observed at any time following a negative or missing titer at baseline, or a positive titer that has increased by at least 3 dilutions at any time from a detectable baseline titer.
[1] MedDRA Version 12.0 terms.

A total of 142 subjects with antibodies to exenatide in Byetta and Bydureon clinical studies were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No cross-reactive antibodies were observed across the range of titers.

COMMENT: I recommend that labeling section 6.1 Adverse Reactions include the number of subjects tested for antibodies, how often crossreacting antibodies occurred, and a description of adverse events in subjects with and without antibodies.

Please also refer to section 7.3 above for my recommendations pertaining to injection site reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please refer to my review of the original NDA submission.

7.5.2 Time Dependency for Adverse Events

Please refer to my review of the original NDA submission.

7.5.3 Drug-Demographic Interactions

Please refer to my review of the original NDA submission.

7.5.4 Drug-Disease Interactions

Please refer to my review of the original NDA submission.

7.5.5 Drug-Drug Interactions

Please refer to my review of the original NDA submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to my review of the original NDA submission.

7.6.2 Human Reproduction and Pregnancy Data

In most clinical studies of Bydureon pregnancy or lactation were exclusion criteria, and pregnancy during the study was cause for withdrawal. As of December 31, 2009, six pregnancies were reported in Bydureon studies. Two of these reports (one each in studies BCB107 and GWBR) were described in my review of the original NDA submission. The four new reports are as follows:

- BCB106:
    - Pregnancy ended in a spontaneous abortion at approximately 10 weeks
    - Pregnancy ended with an elective abortion due to personal reasons
- BCB108: Pregnancy was progressing without complications as of December 31, 2009
- GWBR: Pregnancy ended in a spontaneous abortion after an unknown duration

Bydureon will be labeled pregnancy category C. There are no adequate and well-controlled studies of Bydureon use in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please refer to my review of the original NDA submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to my review of the original NDA submission.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Bydureon is not marketed in any country.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to my review of the original NDA submission and the following sections of this review for my proposed changes and the rationale underlying those changes.

- 6.1 Indication
- 7.3.3 Dropouts and/or Discontinuations
- 7.3.4 Significant Adverse Events
- 7.4.4 Electrocardiograms
- 7.4.6 Immunogenicity

9.3 Advisory Committee Meeting

Not applicable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S PRATT
09/14/2010

ILAN IRONY
09/15/2010
I concur with Dr. Pratt's conclusions and recommended action for this Class 2 Resubmission. See also CDTL review.

Cross-Discipline Team Leader Review

Date	9/10/2010
From	Ilan Irony
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22200/ Class 2 Resubmission
Applicant	Amylin
Date of Submission	4/22/2010
PDUFA Goal Date	10/22/2010
Proprietary Name / Established (USAN) names	Bydureon / Exenatide LAR
Dosage forms / Strength	SC injection / 2 mg once weekly
Proposed Indication(s)	Improve glycemic control in Type 2 diabetes mellitus
Recommended:	Complete Response

1. Introduction

This is the Cross Discipline Team Leader (CDTL) review of exenatide LAR Class 2 Resubmission. Exenatide LAR is a new, once weekly formulation of exenatide, a glucagon-like peptide (GLP-1) receptor agonist approved in the US since March of 2005, indicated for improvement in glycemic control in patients with type 2 diabetes mellitus (T2DM). Exenatide is used as a twice daily (bid) subcutaneous (SC) injection, so that exenatide LAR was developed to improve convenience of administration and, possibly, compliance.
The original New Drug Application (NDA) relied on the findings of safety and efficacy of exenatide, and contains mainly two bridging clinical studies: one to demonstrate non-inferiority of exenatide LAR to exenatide bid and the second to demonstrate non-inferiority of the commercial product to the product formulated for the pivotal Phase 3 study. The application received a complete response (CR) action on March 12, 2010, due to the lack of Risk Evaluation and Mitigation Strategies (REMS) and Post-marketing requirements to address safety issues and for several unresolved Microbiology issues.
This review will touch upon the main issues noted in the Clinical review and the Interdisciplinary Review Team for QT studies (IRT) consultation memorandum, noting in particular the reason I again recommend a CR action, due to the potential for exenatide to prolong the cardiac QT interval in certain populations, and the lack of beneficial data obtained with the commercial exenatide LAR formulation to weigh against the new negative cardiac evidence.

2. Background

Exenatide is the first drug in the class of GLP-1 receptor agonists, and was approved in the US in March 2005 for improvement in glycemic control in patients with T2DM. The effect is

derived from a serum glucose-dependent exenatide stimulation of insulin secretion (thus reducing the risk of hypoglycemia and severe hypoglycemia), suppression of endogenous glucagon, slowing the rate of gastric emptying and effects on appetite, with consequent mild reductions in body weight. Significant post-marketing findings which resulted in label changes and required studies include the risk of pancreatitis, including severe forms of pancreatitis (hemorrhagic and necrotizing, sometimes fatal), renal dysfunction, attributed mostly to GI effects causing dehydration and pre-renal damage, and hypoglycemia when combined with a sulfonylurea. High titers of anti-exenatide antibody may also reduce its efficacy.
Exenatide needs to be administered as a sc bid injection, so pharmaceutical companies are looking to reproduce or enhance the effects of exenatide or other GLP-1 receptor agonists with a more convenient regimen.
Liraglutide was approved in January 2010 as a once daily GLP-1 receptor agonist, the second drug in the class. In addition to the concerns related to pancreatitis, known from the exenatide experience, a new concern arose from the review of the liraglutide NDA regarding the potential risk of medullary cancer of thyroid, based on rodent findings (two species, both genders) at low multiples of clinical exposure. In a rat carcinogenicity study conducted with exenatide LAR, a statistically significant increase thyroid c-cell tumors (adenomas plus carcinomas) was observed at clinically relevant doses. As mentioned in my prior review of the original NDA, I view exenatide LAR as carrying a similar potential risk of medullary cancer of the thyroid as liraglutide, and recommend imposing PMRs to assess this risk in humans similar to those listed in the liraglutide approval letter.

2.1 Different manufacturing scales of exenatide LAR and efficacy concerns

In the original NDA submission, Amylin proposed to reference the larger efficacy and safety experience with exenatide bid in support of the LAR application. To bridge that experience, Amylin conducted study 105 to compare effects of exenatide LAR (manufactured at Alkermes at the (b) (4) scale, investigational product) to exenatide bid (Byetta) in a randomized 30-week trial in 295 subjects that were either treatment naïve, or treated with stable regimen of metformin, sulfonylurea (SU), thiazolidinediones (TZD) or a combination of SU and TZD for a minimum of two months prior to screening, with HbA1c between 7.1 and 11.1% at the time of screening.
Table 1 shows the primary efficacy analysis of that trial.

Table 1. Change in HbA1c from baseline at week 30 in Study 105, ITT population

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE[1]	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI)[1]	P-value
All patients (ITT/LOCF)					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		

Amylin implemented a scale up manufacturing change, from the (b) (4) scale manufactured at Alkermes to a (b) (4) scale manufactured at Amylin. Typically, manufacturing changes are bridged by PK bioequivalence. FDA did not agree to grant a biowaiver based on an in vitro – in vivo correlation strategy proposed by the applicant.

The applicant then proposed to compare the two manufacturing scales ((b) (4) versus (b) (4)) in a 18-week, open label extension to Study 105 named Study 105c. The comparability between the two formulations was assessed via efficacy (glycemic markers), PK (AUC at steady state, $AUC_{0\text{-}168h}$, concentration at steady state) and safety endpoints. The primary analysis for this comparison of clinical efficacy in Study 105c was a non-inferiority assessment of the change in HbA1c at Week 18 of the comparability assessment for the evaluable population, using a predefined margin of 0.4%. The non-inferiority margin selected is commonly used in active-controlled efficacy trials of antidiabetics and accepted by FDA, but it has not been agreed upon the margin for the purpose of demonstration of comparability between the two products at the pre-NDA meeting held June 28, 2008.

Table 2 shows the changes in HbA1c between the investigational and the commercial scale products after an 18-week treatment period, in subjects who had already been treated with exenatide LAR during and after Study 105, with a mean HbA1c at baseline of approximately 6.8%.

Table 2. Comparability of the 2 sources of exenatide LAR in Study 105c: Change in HbA1c after 18 weeks

	N	Day 1S baseline HbA1c ± SE	Adjusted mean change from Day 1S to Week 18S ± SE[1]	Amylin - Alkermes Difference in adjusted mean change (95% CI)[1]	P-value
All patients (ITT/LOCF with respect to the comparability sub-study[2])					
investigational Alkermes source	109	6.8 ± 0.1	0.3 ± 0.1	0.2 (0.0, 0.3)	0.062
commercial Amylin source	108	6.7 ± 0.1	0.4 ± 0.16		

Notes:
[1] The comparability study is described in Part 3.1.4 of this review
[2] The adjusted mean change from baseline 1S at week 18S and the difference in the adjusted mean change were estimated from an analysis of variance model with treatment and baseline 1S HbA1c stratum.
Sources: Study 2993 LAR-105c comparability assessment, Table 6

The bridging study 105c had failed to demonstrate PK bioequivalence between the investigational and the commercial formulation of exenatide LAR (32% less with the commercial formulation). However, from the Clinical Pharmacology perspective:

1. The concentration range resulting from the two products were similar and greater than the EC_{50} (approximately 83 pg/mL).
2. Differences in the exposure resulting from different manufacturing scales are in the maximal response region of the exposure-response relationship for exenatide LAR (approximately 200 pg/mL).

Therefore, Clinical Pharmacology concluded the investigational and commercial products are comparable.

From the clinical perspective, the applicant met a commonly agreed NI margin, but barely so (since the upper bound of the 95% CI of the difference in HbA1c is 0.3%). In addition, we were somewhat reassured by the following evidence:

1. Investigational exenatide LAR was borderline superior to exenatide bid in Study 105 (95% CI does excludes “0”), so even if there was a drop in efficacy in transitioning to the commercial exenatide LAR, the overall ability to reduce HbA1c would probably be at least equivalent to that of exenatide bid;

2. A previously manufactured version of exenatide LAR, manufactured at a (b) (4) scale, was tested in Study 104, a dose-finding, 15-week Phase 2 study in 45 subjects. The population PK analysis demonstrated a 36% lower mean exenatide plasma steady-state concentration at the (b) (4) manufacturing scale as compared to that of the (b) (4) scale. Despite this, the mean (SE) reduction in HbA1c from baseline to week 15 was -1.3% (0.3) compared to a mean increase of 0.4% (0.3) among the placebo group. Despite a 36 % lower bioavailability with the (b) (4) scale product compared to the investigational product, a clinically meaningful reduction in HbA1c was reported with the (b) (4) scale product. It is noteworthy that the increase in bioavailability going from the (b) (4) scale product to the investigational product is similar to the decrease in bioavailability going from the investigational product to the commercial product.
3. Study 106 was only submitted with the 4-month safety update. It was a randomized, double-blind, parallel group (3-arm), active-controlled, multicenter study to compare the effect of exenatide LAR (investigational product) to sitagliptin 100 mg qd and to pioglitazone 45 mg qd during a 26-week treatment period in 491 subjects treated with metformin at stable doses. The primary endpoint was the change in HbA1c from baseline at week 26. In the ITT Population at Week 26, the LS mean change (SE) in HbA1c from baseline in the exenatide LAR group was -1.5 (0.1) %, a statistically significantly greater decrease than that observed with sitagliptin (-0.9 [0.1] %; adjusted $p < 0.0001$) or pioglitazone (-1.2 [0.1] %; adjusted $p = 0.0165$). While these findings were not used in the original regulatory decision for exenatide LAR, they are nonetheless supportive of the relative efficacy of this product.
4. Study 108 (BCB108 or DURATION-5) is being conducted since the first quarter of 2009, testing the safety and glycemic efficacy of exenatide LAR manufactured at the (b) (4) scale (commercial product) against exenatide bid for 26 weeks in a non-inferior design. This is similar to Study 105, except that the commercial product is being assessed, instead of the investigational ((b) (4) scale) product.

The observations above have to be interpreted with caution, for the following reasons:

1. One cannot compare the results of Study 105 (randomized, with high baseline HbA1c) to Study 105c (different randomized subpopulation of Study 105, with lower baseline HbA1c);
2. Similarly one cannot establish any direct comparisons between the bioavailability of the (b) (4) scale product to the commercial (b) (4) scale product, through their comparisons to the intermediary, investigational (b) (4) scale product;
3. Study 106 had a strong double-blind design, but the study has not been fully reviewed;
4. Study 108 has not been completed.

2.2 Cardiovascular safety assessment of exenatide bid and exenatide LAR

At the time of exenatide approval in the US, new drugs (particularly peptides, such as exenatide) were not required to undergo clinical testing for their effects in the QT interval. Similarly, there was no requirement that a new drug indicated for the treatment of T2DM be shown to exclude a cardiovascular risk in excess of 1.8 prior to approval (this requirement came about in December 2008). Regarding cardiovascular risks of exenatide and / or exenatide LAR, the Division of Biometrics 7 conducted a review of the applicant's metanalysis of 12 exenatide studies during the review cycle of the original NDA submission. There were two

endpoints of primary interest: “SMQ MACE” and “Custom MACE”. The first endpoint (SMQ MACE) included all the preferred terms in the standardized MedDRA queries for “Myocardial Infarction” and “Central nervous system haemorrhages and cerebrovascular accidents”. The Custom MACE endpoint is based on a narrower definition of cardiovascular events and is comprised of a list of preferred terms that focus on myocardial infarction and stroke events. The definition of the Custom MACE endpoint was provided by the FDA. The risk ratios and confidence intervals were 0.9 (0.5, 1.5) and 0.9 (0.3, 2.3) for the SMQ MACE and Custom MACE endpoints respectively.

During the review cycle of the original NDA review, IRT also conducted an analysis of effects of exenatide LAR and exenatide bid on QT interval in Study 105. ITR conducted a parallel metanalysis of exenatide bid in three studies supporting exenatide bid approval. IRT concluded, in its consultation memo to our division, that “there are no apparent QT-prolonging effects of exenatide when administered as the extended release (BYDUREON) or immediate release (BYETTA) formulations. However, we cannot rule out small increases in the QTc interval (<10 ms) because a dedicated TQT study with positive and placebo controls was not conducted. Our conclusions are based on the following data:

• In study 2993LAR-105, replicate 12-lead ECGs were obtained at baseline, at Week 14, once steady-state plasma concentrations were achieved, and at Week 30. No individual subject post-baseline QTcF measurements ≥ 450 ms. The mean change from baseline QTcF was < 5ms.

• In a meta-analysis of studies 2993-112, 2993-113 and 2993-115, there were no apparent QTc-prolonging effects of exenatide immediate release. No subjects had change from baseline > 60 ms. The mean change from baseline QTcF at week 30 on treatment were similar to placebo. There was no apparent relationship between exenatide concentrations and change in QTcF intervals.

The average exenatide exposures achieved with the extended-release formulation are lower (relative bioavailability is 25%) than the approved formulation (BYETTA). A dedicated TQT is not needed unless there are cardiovascular AEs such as syncope, seizures, ventricular arrhythmias or sudden death in the clinical development program and post-marketing reports, for which a more accurate and precise assessment of the effects of exenatide on QTc is desired.”

2.3 Action taken on the exenatide LAR NDA original submission

The initial review of exenatide LAR resulted in a CR action mainly because the applicant needed to propose REMS (Medication Guide, Communication Plan and Timetable of Assessments) and PMRs to allow for the potential glycemic benefits to outweigh the risks, particularly for the remote but serious medullary cancer of thyroid and for serious forms of pancreatitis. These have been under discussion with the applicant during the review cycle of this resubmission and were nearing final agreement between FDA and the applicant. The labeling changes we recommended have been substantially accepted by the applicant.

3. CMC/Device

The Microbiology review team had noted three deficiencies in the original NDA submission:

(b) (4)

These deficiencies were addressed in the Class 2 Resubmission, and Microbiology now recommends approval based on this review.
The development of exenatide LAR was characterized by multiple changes in formulation and scale production. The changes in scale were covered in the biopharmacology and clinical reviews of the original NDA submission as well as in the respective sections of the CDTL review of the original NDA submission.

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical data relevant to this review.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review and conclusions regarding a new TQT study are summarized and discussed in Section 8, below.

6. Clinical Microbiology

Not applicable. The product is not an anti-microbial.

7. Clinical/Statistical- Efficacy

Not applicable. There are no new efficacy data for review in this Class 2 resubmission.

8. Safety

Health Canada required a Thorough QT Study (TQT) for exenatide, as recommended in ICH E14[1]. The applicant conducted the study outside of the IND. FDA was not aware of its existence or results until April of 2010, when we were contacted by Health Canada to discuss the study results and its implications. Health Canada reviewers were concerned about the potential for QT prolongation based on the results, taking into account that dose of exenatide used in the TQT study was lower than the marketed dose. Health Canada also was concerned about the increase in PR interval and heart rate.
To address the concern, FDA requested the applicant to submit the report for the TQT study (Study GWCI), and the associated datasets and ECG waveforms for our independent review.

[1] Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005

The applicant notes that there were no nonclinical data suggesting an exenatide effect on the QT interval (in vitro hERG and chronic studies in mice, rats and monkeys).

Thorough QT Study

"A Placebo- and Positive-Controlled Study of the Electrophysiological Effects of a Single 10 µg Dose of Exenatide on the 12-Lead Electrocardiogram QT Interval in Healthy Subjects"

The TQT study was conducted between April 2008 and February 2009.
Protocol

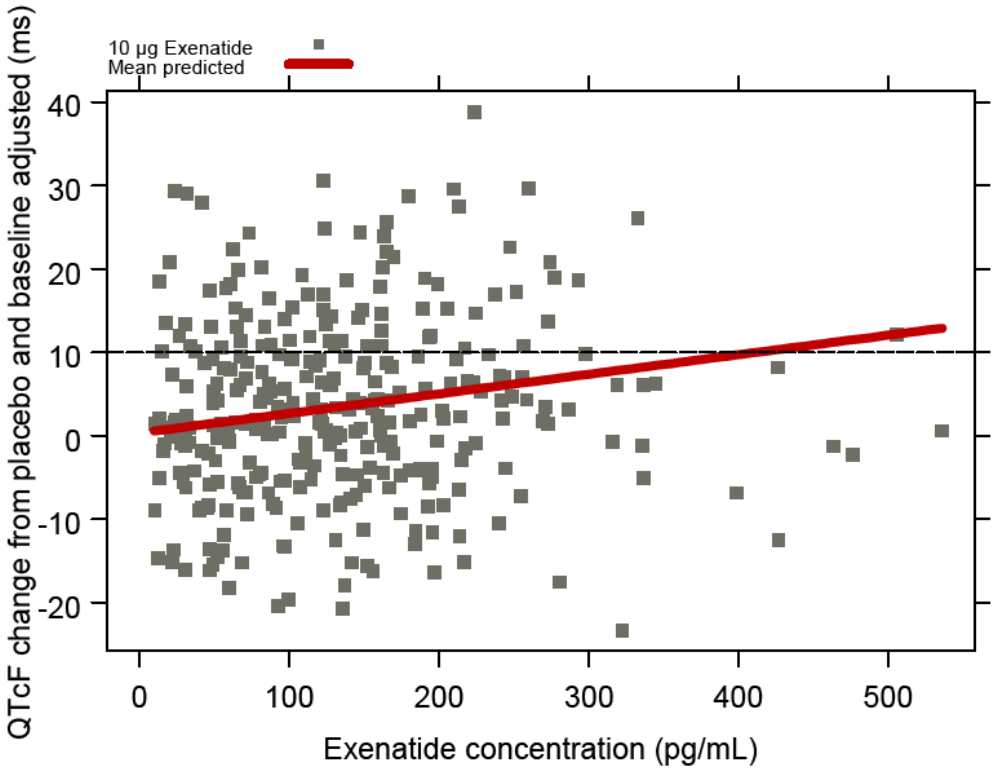
Amylin screened healthy volunteers by administering 10 µg of exenatide daily for 3 days: subjects who tolerated the dose were deemed eligible to participate. Eligible subjects were to be randomized to one of six possible sequences of exenatide 10 µg, moxifloxacin 400 mg or placebo. The primary method to correct the QT interval in both the applicant's and IRT's analysis was the Fridericia (QTcF).

Summary of Results

Of the 70 subjects screened, 62 tolerated the dose received for 3 days and were dosed in the randomized sequence of exenatide 10 µg, moxifloxacin 400 mg or placebo. The timing of samples and ECGs collected covered adequately T_{max} of exenatide. The assay sensitivity was adequate, as shown by increase in QTcF interval detected following administration of moxifloxacin 400 mg.
For the primary endpoint, QTcF, the upper limit of the two-sided 90% CI (equivalent to one-sided 95% CI) for the mean difference between exenatide and placebo was less than 10 ms at all time points, and thus, within the limits sets for clinical relevance in regulatory guidelines. The largest upper bound was 8.0 ms.
The secondary QT corrections, QTcP (population-specified correction), QTcI, and model based QTc, support the primary analysis, with the upper limit of the two-sided 90% CI for the mean difference between exenatide and placebo being less than 10 ms at all time points.
No subject had a QTc interval > 450 ms following the administration of 10 µg exenatide. A few individual subjects showed QTc values > 450 ms following administration of placebo and moxifloxacin, although none of these subjects had QTc values > 480 ms.
No subject showed an increase from pre-dose in QTc interval of > 30 ms following administration of 10 µg exenatide or placebo. A few individual subjects showed increases in QTc interval > 30 ms following administration of moxifloxacin, but none of these increases was > 60 ms.
There was a mean increase in the PR interval from 1-3 hours post-treatment with exenatide 10 µg with the largest upper bound of the 90% CI being 9.5 ms. However this finding may not be clinically significant because most subject with post-treatment PR over 200 ms had an elevated PR interval at baseline. The maximum increase in PR interval compared to baseline was < 15%.
There were no clinically relevant effects on the QRS interval. No subject with a post-treatment QRS of over 110 ms had more than a 5% change from baseline.

Heart rate was increased from baseline for 1-4 hours post-dosing. The maximum placebo-adjusted heart rate increase was 10.2 beats per minute at hour 2 post-dose.
The conclusion of the TQT study is that exenatide dosed at 10 µg bid does not prolong the QT interval in a clinically meaningful way. Due to the relatively short half life and lack of accumulation in patients with mild or moderate renal insufficiency, exenatide bid can be considered similarly safe for this special population. These conclusions are based on a C_{max} of 208 pg/mL following dosing with 10 µg exenatide.
Exposure to exenatide LAR at 2 mg is about twice of that noted with exenatide 10 µg bid in subjects with normal renal function. In subjects with mild to moderate renal impairment, exposure may four times higher.
The linear regression analysis (Figure 1) suggested a significantly positive slope of the exposure-response relationship (slope: 0.023 with p-value: 0.0003). At the mean C_{max} of 208 pg/mL with the 10 µg exenatide, the predicted ΔΔQTcF (90% CI) is 4.92 ms (2.64, 7.20), which is below the clinical threshold per ICH E-14, 10 ms. However, the predicted values (90% CI) of ΔΔQTcF are 9.58 (5.63, 13.53) and 14.07 (8.16, 19.99) at the geometric mean of steady-state $C_{max\ ss}$ of 433 pg/mL obtained with the 2 mg of exenatide LAR and the clinical exposure $C_{max\ ss}$ of 650 pg/mL in patients with moderate renal impairment (assuming 50% increase in $C_{max\ ss}$) respectively.
The modeling based on these results suggests a potential effect of exenatide on QT prolongation for exposures resulting from exenatide LAR 2 mg weekly in the general diabetic population and a stronger effect for diabetic patients with mild or moderate renal insufficiency. However, prediction (especially at 650 pg/mL) from the linear regression model should be taken with caution, due to extrapolation.

Figure 1. ΔΔ QTcF vs. Exenatide Concentration



From the IRT review, Figure 5.

Postmarketing Requirements and Risk Evaluation and Mitigation Strategy (REMS) Requirements

Of more important consequences for the approvability and labeling of exenatide LAR, four particular issues need to be emphasized:

1. Pancreatitis is now considered a risk for this class of antidiabetic drugs, and labeling for exenatide LAR will reflect FDA's view of the risk, including a Boxed Warning for serious cases of pancreatitis.
2. Although FDA has not traditionally made recommendations about specific antidiabetic treatments being first line (use in treatment naïve) or second line (use as add-on or to replace a drug upon secondary failure) therapies, FDA approved liraglutide specifically as a second line therapy due to the uncertainty regarding the nonclinical findings of c cell carcinoma in rodents at clinical exposures and the lack of data to assure us that those findings cannot be extrapolated to humans. A similar approach is expected to be used for exenatide LAR and other GLP-1 agonists in the future.
3. Cardiovascular events are common in the diabetic population. Although FDA considers a beneficial effect on glycemic control sufficient to provide evidence of efficacy, a guidance published in December 2008 notified sponsors that new products will be approved if they demonstrate that the risk of MACE events with the use of their drugs do not exceed a risk ratio of 1.8 and, once approved, may remain on the market if the risk ratio against a control treatment does not exceed 1.3 (upper bound of the 95% confidence interval). A metanalysis of events reported in the exenatide development program has not ruled out the unacceptable risks needed to demonstrate the CV safety of exenatide. In anticipation of this requirement, the applicant submitted in October 2009 a protocol for Study BCB109, a dedicated CV trial of exenatide LAR. The protocol has been amended in April 2010 and, according to ClinicalTrials.gov, has been open for enrollment since June 2010. Nonetheless, I recommend we formalize this as a Postmarketing requirement.
4. A 5-year epidemiology study and a Registry (preferably combined with other applicants of GLP-1 receptor agonist products) to assess the long term risk of MTC.

Similarly to liraglutide, REMS for exenatide LAR will include a Medication Guide, a Communication Plan and a Timetable of Assessments.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

A pediatric trial to investigate the safety and efficacy of exenatide BID is currently ongoing, as part of PREA requirements and under a Written Request (BPCA). The Division is considering a common approach to liraglutide and exenatide LAR with regard to pediatric studies. Approval of liraglutide in adults with T2DM was accompanied by the PREA PMR to conduct studies in pediatric patients age 10 -1 6 years. However, due to the potential risk of MTC

based on the rodent data, FDA prefers than additional nonclinical studies elucidating the mechanisms of GLP-1 induced c cell hyperplasia and MTC (namely, thyroid GLP-1 receptor binding and rearranged-during-transfection [RET] proto-oncogene activation) be conducted and reviewed before any recommendation that pediatric studies are conducted.
These points were presented to the Pediatric Research Committee and accepted by the committee.
The applicant will need to submit a pediatric plan with timelines to be included in the approval letter, but the actual execution of pediatric trials will be contingent upon the findings of the additional nonclinical studies.
Even the single dose PK study in a pediatric population, typically conducted in order to define the best dose(s) to evaluate in a subsequent safety and efficacy study, will not be conducted prior to the nonclinical study results: a single dose of exenatide LAR yields detectable exenatide levels for up to 10 weeks, making the exposure prolonged enough to be of concern. In addition, specifically for exenatide LAR, single dose PK may not accurately reflect exposure and predict PD effects as multidose PK do. So, if the nonclinical findings do not raise additional concerns for children, it is likely that a single safety and efficacy study will be required and conducted in pediatric age subjects, to also include population PK assessments.

11. Other Relevant Regulatory Issues

None.

12. Labeling

FDA and the applicant had reached agreement regarding most substantive issues in labeling and the Medication Guide, **prior** to the review of the Thorough QT Study, which modified our conclusion regarding the risk / benefit assessment of exenatide LAR at this time.

13. Recommendations/Risk Benefit Assessment

My assessment of the risks and benefits of exenatide LAR has changed after receipt and review of the Thorough QT Study results and analyses conducted by the IRT. I was ready to recommend approval during this review cycle (as noted in my original CDTL review of the original NDA), based on reaching agreement on labeling, REMS and PMRs.
Exenatide is approved without dose reduction for diabetic patients with mild or moderate renal insufficiency. Many of these patients may transition to a once weekly formulation despite a Warning and Precaution related to the potential risk of QT prolongation. Similarly other diabetic patients at high risk groups for QT prolongation (those under treatment with neuroleptic drugs or anti-arrhythmia drugs that prolong QT interval, or patients with long QTc syndrome) may also be exposed to exenatide LAR and its potential associated risk.
Therefore, I recommend a Complete Response action at this time.
To address the deficiencies identified, the applicant will need to conduct a new Thorough QT study in healthy volunteers or diabetics, with an effort to reproduce the exenatide exposure noted in patients with moderate renal insufficiency, to inform our decision on this risk without resorting to extrapolation. In addition, submission of the report and datasets for Study BCB108, a study conducted entirely with the commercial formulation ([redacted] (b) (4) scale) against

exenatide bid, may allow FDA to determine the efficacy of the to-be-marketed exenatide LAR, without "second guessing" beneficial effects on glycemia based on the investigational formulation ([redacted] scale).

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/s/

ILAN IRONY
09/16/2010

MARY H PARKS
09/17/2010
please see Division Director's memo

Medical Officer Postmarketing Requirement Review
Division of Metabolism and Endocrinology Products

NDA 21-773 SDN 215

Name of Drug: Byetta (exenatide injection)

Sponsor: Amylin

Relevant IND: 57,725

Relevant NDAs:
- 21-773 Byetta (exenatide twice daily)
- 22-200 Bydureon (exenatide once weekly)

Relevant Tracked Safety Issue (TSI): 892 GLP-1 and pancreatitis

Indication: Type 2 diabetes mellitus (T2DM)

Date of Submission: March 25, 2010

Medical Reviewer: Valerie Pratt, M.D.

Medical Team Leader: Ilan Irony, M.D.

Background: Exenatide injection (Byetta, NDA 21-773) was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in 2005. Although the incidence of pancreatitis in patients with T2DM is not well characterized in the published literature, postmarketing reports suggest that patients using exenatide may be at increased risk for pancreatitis, including the severe hemorrhagic and necrotizing forms. Therefore, when exenatide was approved for monotherapy use (NDA 21-919) on October 30, 2009, pancreatitis was included in the Warnings and Precautions section of the label and the following pancreatitis-related postmarking studies were required (PMRs):
- 1559-2: An adequately powered epidemiological study to determine the incidence rate, severity and risk factors for the development of acute pancreatitis, including the more severe forms of hemorrhagic and necrotizing pancreatitis, in exenatide-exposed versus unexposed patients.
- 1559-3: Epidemiologic queries using i3 Aperio to assess the relative risk of pancreatic cancer and thyroid neoplasm among patients using Byetta and those using metformin or glyburide. Thyroid neoplasm assessment will also include benign and malignant diagnosis event stratification.
- 1559-4: A 3-month pancreatic safety study in a diabetic rodent model treated with Byetta

- *1559-5: Submission of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Byetta, as well as analyses of those data. Also provide a systematic analysis of amylase and lipase data from those patients who presented with abdominal pain or nausea, with or without vomiting, during the treatment phase of those trials.*
- 1559-6: A clinical trial investigating the effects of exenatide on CCK (cerulitide) - stimulated gallbladder emptying (as an indirect measure of a potential impact on the sphincter of Oddi) to assess any non-physiologic effects of exenatide on biliary emptying.

The sponsor now submits final report, "Clinical analysis of amylase and lipase concentrations", (b) (4).

Summary of Submission: On August 27, 2009, the agency requested the sponsor collect amylase and lipase data in new and ongoing clinical trials of exenatide. As the October 30, 2009 exenatide (Byetta) monotherapy NDA 21-919 approval defined the PMR 1559-5 study completion date as October 27, 2009, this cutoff was used for the pancreatic enzyme analysis. Thus, the analysis included four clinical trials for which a complete adverse event (AE), amylase, and/or lipase could be assessed. Please refer to the table below for a summary of studies BCB108, GWCV, GWAV, and GWBB, which were included in the analysis.

NDA 21-773. Summary of Byetta studies and subjects included in the amylase and lipase analysis

Study	Study Design	Amylase/Lipase Sampled/Collection Time Points	Dose(s)/ Duration [1]	Number of ITT Subjects Included in Analyses		
				Placebo	Sitagliptin	BYETTA [1]
BCB108	Phase 3, comparator-controlled, randomized, open-label, parallel-design study to compare the effects of exenatide once weekly on glycemic control, safety, and tolerability to those of BYETTA in subjects with type 2 diabetes	P-amylase and lipase/ Screening, Day 1, Week 14, Week 24	**BYETTA** 10 mcg/ 24 Weeks	--	--	123
H8O-US-GWCV	Phase 4, comparator-controlled, randomized, double-blind, crossover study to compare the effects of BYETTA on 24-hour time-averaged serum glucose to those of sitagliptin in subjects with type 2 diabetes	Total amylase and lipase/ Week 0, Week 4, Week 8	**BYETTA** 10 mcg **Sitagliptin** 100 mg/ 8 Weeks [2]	--	49 [3]	48 [3]
H8O-JE-GWAV	Phase 2, placebo-controlled, randomized, double-blind, parallel-design study of BYETTA in Japanese subjects with type 2 diabetes	Total amylase/ Week 0, Week 4, Week 8, Week 12	**BYETTA** 2.5, 5, or 10 mcg **Placebo**/ 12 Weeks	40	--	111
H8O-JE-GWBB	Phase 3, placebo-controlled, randomized, double-blind, parallel-design study of BYETTA in Japanese patients with type 2 diabetes (included a 28 week open-label extension)	Total amylase/ Screening, Week 0, followed by 4 to 8-week intervals	**BYETTA** 5 or 10 mcg **Placebo**/ 52 Weeks [4]	35 [5]	--	144 [5]

ITT = intent-to-treat; p-amylase = pancreatic amylase.
[1] Depending on the study design, includes treatment with BYETTA 2.5 mcg BID or 5 mcg BID for duration of study, or 1 to 4 weeks of BYETTA 5 mcg BID followed by BYETTA 10 mcg BID for remainder of BYETTA treatment period.
[2] Crossover study with 4 weeks of BYETTA therapy and 4 weeks of sitagliptin therapy.
[3] A total of 83 subjects were randomized and received at least one dose of study medication in Study H8O-US-GWCV, however, baseline total amylase and lipase concentration data were only available for 52 subjects (total amylase and lipase assessments added with a protocol amendment following initiation of study conduct). Of these 52 subjects, 49 received BYETTA and 48 received sitagliptin (45 subjects received both BYETTA and sitagliptin).
[4] Duration of the double-blind period of the study was 24 weeks; duration of the open-label period of the study was 28 weeks.
[5] In addition to 144 subjects receiving BYETTA in the 24-week double-blind period, 33 placebo subjects received BYETTA in the 28-week open-label extension.

Notes:

- In study GWBB, amylase data was collected during the double blind, open label, and combined (52 week) periods.

- In crossover study GWCV, a total of 31 subjects had missing baseline total amylase and lipase data, because the enzyme assessments were added with a protocol amendment after the study was initiated. These subjects were excluded from the data summaries due to incomplete information, but all subjects with available data were included in the data listings.

Three additional Byetta studies, in which amylase and lipase data are being collected, are ongoing. However, according to the sponsor, final laboratory results and adverse event data were not yet available.

(b) (4)

[redacted]

Note: The sponsor did not submit amylase and lipase data for exenatide once weekly (Bydureon) subjects in studies BCB108, BCB106, GWBR, and GWDC. The sponsor could have included an analysis of Bydureon subjects' data in studies BCB108 and BCB106, as it reported Byetta subjects' data in study BCB108 and already submitted complete study report BCB106.

Studies GWBR and GWDC are ongoing but have been completed through week 26. It is not known to me if the sponsor could have submitted Bydureon data for these studies, as it did for study BCB108 prior to submission of the complete report.

Comment: Please submit all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Bydureon, as well as analyses of those data. Also provide a systematic analysis of amylase and lipase data from those patients who presented with abdominal pain or nausea, with or without vomiting, during the treatment phase of those trials.

Using the study population defined above (i.e. studies BCB108, GWCV, GWAV, and GWBB), 505 subjects were included in the analysis (426 Byetta, 75 placebo, 4 sitagliptin only). Of the 426 Byetta subjects, 45 received both sitagliptin and Byetta in crossover study GWCV and are therefore included in both treatment groups. Of the 75 placebo subjects, 33 received Byetta in the open label period of study GWBB; thus their

laboratory values are included among the Byetta subjects in summaries of the open label period of study GWBB.

Demographic and baseline characteristics were similar between treatments. With the exception of differences in race/ethnicity between studies and a lower mean body weight and BMI in studies conducted in Japan (GWAV and GWBB) compared to those conducted in the United States (BCB108 and GWCV), demographic and baseline characteristics were also similar between studies.

Note: Despite the similarity in most demographic and baseline characteristics, one must question whether or not the results from studies GWAV and GWBB, which were conducted in Japan, are applicable to the American population.

Due to differences in the laboratory assays and study designs, amylase and lipase data for studies BCB108, GWCV, GWAV, and GWBB were not pooled but presented separately. Data was collected in the studies as follows:

- BCB108: pancreatic amylase and lipase were assessed at screening, day 1, week 14, and week 24
- GWCV: total amylase and lipase were assessed at week 0 and at the end of the sitagliptin and Byetta treatment periods
- GWAV: total amylase was assessed at weeks 0, 4, 8, and 12
- GWBB: total amylase was assessed at screening, week 0, and 4- to 8- week intervals during the double blind (through week 24) and open label (weeks 24-54) periods

NDA 21-773. Normal ranges

Study	Pancreatic or Total Amylase [1]	Lipase (U/L)
BCB108	13-53 IU/L	0-60
H8O-US-GWCV	20-112 IU/L	0-60
H8O-JE-GWAV	60-190 U/L	N/A
H8O-JE-GWBB	39-134 U/L	N/A

N/A = not applicable.
[1] Pancreatic amylase was assayed in Study BCB108; total amylase was assayed in Studies GWCV, GWAV, and GWBB.

Change in amylase and lipase concentrations: When the baseline and change from baseline amylase and lipase values were reviewed in studies BCB108 and GWCV, a small, likely not clinically significant increase was seen. However, mean pancreatic amylase (p-amylase), total amylase (t-amylase), and lipase concentrations remained with the normal range throughout the treatment periods in both studies. The largest increase (Δ lipase 11.3 U/L) was seen in Byetta subjects in study GWCV.

NDA 21-773. Mean (SD) amylase and lipase values for Byetta 10 mcg (B) and sitagliptin 100 mg (S) subjects in studies BCB108 and GWCV. Note: Subjects had 24 weeks exposure to study drug in BCB108 and 4 weeks exposure in study GWCV.

Study - Lab	**Screening**	**Baseline**	**Change from baseline to**		
			Week 14	**Week 24**	**Last visit**
BCB108 (n=122)					
P-amylase (IU/L)	25.0 (9.7)	26.0 (12.9)	2.0 (11.1)	2.8 (18.5)	1.5 (12.3)
Lipase (U/L)	38.3 (15.5)	41.1 (20.1)	6.1 (24.9)	8.8 (42.4)	5.4 (22.8)
GWCV (S n=49; B n=48)					
T-amylase (IU/L)		S: 45.4 (15.3) B: 44.7 (15.2)			S: 4.8 (14.6) B: 5.8 (11.2)
Lipase (U/L)		S: 34.0 (14.7) B: 33.5 (16.5)			S: 5.8 (26.8) B: 11.3 (22.2)

Mean total amylase concentrations remained within the normal range throughout the treatment period in studies GWAV and GWBB. However, in study GWBB, there were small increases in amylase from baseline at most time points in the Byetta groups when compared to the placebo group, which often experienced decreases in amylase values from baseline. Yet, the magnitude of change was small and probably not clinically significant. At 52 weeks in the open label period, Byetta 5 mcg was associated with a slightly greater change from the open label baseline than Byetta 10 mcg (2.5 vs. 0.7 U/L).

NDA 21-773. Mean (SD) total amylase concentrations (U/L) and change from baseline in studies GWAV and GWBB. Note: Please see above for the different normal ranges for the 2 studies.

Time point	**Study GWAV**				**Study GWBB**		
	Placebo (n=40)	**Byetta 2.5 (n=37)**	**Byetta 5 (n=40)**	**Byetta 10 (n=37)**	**Placebo (n=35)**	**Byetta 5 (n=72)**	**Byetta 10 (N=72)**
Screening					73.3 (28.0)	79.0 (46.4)	70.3 (26.1)
Double blind baseline	96.4 (31.3)	103.1 (28.3)	99.7 (42.6)	94.5 (37.9)	71.9 (26.7)	73.2 (26.2)	70.6 (28.1)
Change from baseline to							
Week 4	7.3 (10.0)	6.5 (14.9)	12.9 (31.5)	15.9 (24.4)	1.2 (16.9)	5.3 (18.1)	6.9 (15.7)
Week 8	6.5 (18.3)	8.3 (26.5)	7.9 (25.9)	10.3 (23.4)	-1.1 (14.3)	9.5 (23.2)	5.4 (15.3)
Week 12	4.9 (22.4)	6.6 (19.9)	4.1 (12.6)	7.1 (22.7)	-0.4 (21.3)	4.9 (21.3)	4.3 (17.2)
Week 16					0.6 (23.0)	3.4 (16.3)	5.1 (15.4)
Week 20					-2.1 (14.0)	4.5 (20.4)	5.1 (23.1)
Week 24					-1.1 (13.6)	24.4 (171.5)*	7.6 (14.3)
Last Visit	5.0 (22.1)	6.9 (19.4)	3.3 (12.3)	5.9 (21.7)	-0.9 (13.5)	5.1 (26.5)	6.4 (13.0)
Open label baseline (Byetta 5 mcg n=80; 10 mcg n=69)						75.5 (26.2)	76.3 (26.5)
Change from open label baseline to week 52						2.5 (18.9)	0.7 (17.0)
Change from open label baseline to last visit						1.8 (16.9)	0.2 (18.7)

*Large increase in mean total amylase at week 24 in the Byetta 5 mcg group resulted from the increased concentration in 1 subject (#1005, 1432 U/L), who was diagnosed with pancreatitis. Excluding the 1432 U/L value at week 24 resulted in a mean (SD) change from baseline of 3.2 (15.6) U/L.

Study GWBB permitted the evaluation of total amylase concentrations over 52 weeks of Byetta therapy and following the switch from placebo to Byetta at week 24. Although mean concentrations remained within the normal range through 52 weeks, the mean total amylase values in the placebo groups tended to be less than those in Byetta groups

through week 24. Following the switch to Byetta at week 24, placebo subjects had increases from baseline in total amylase concentration (1.8-16.3 U/L).

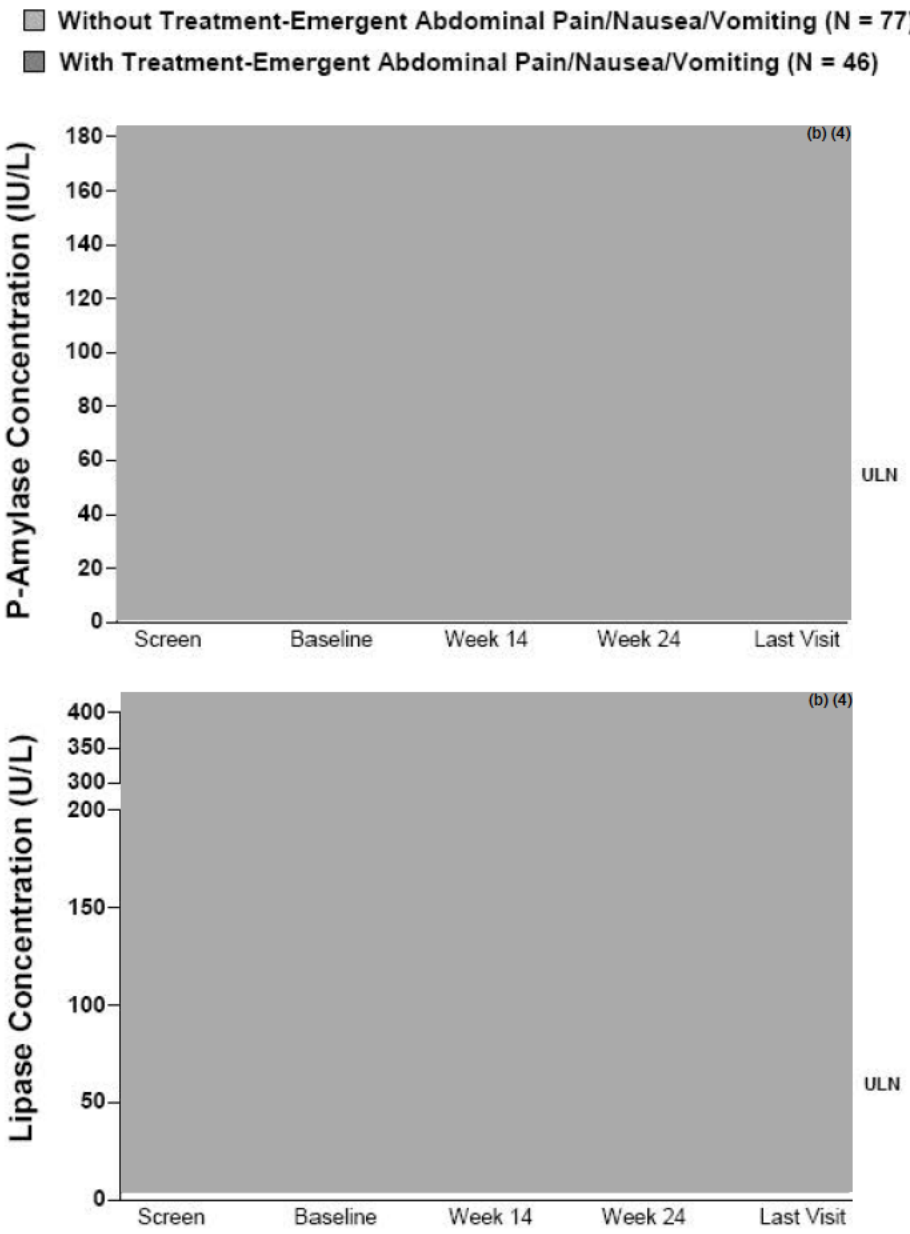
NDA 21-773. Mean (SD) total amylase (U/L) concentrations and change from baseline in study GWBB				
Time point	**Placebo/Byetta 5 (n=18)**	**Placebo/Byetta 10 (n=17)**	**Byetta 5 (n=72)**	**Byetta 10 (n=72)**
Screening	77.2 (32.6)	69.1 (22.3)	79.0 (46.4)	70.3 (26.1)
Baseline	73.4 (29.2)	70.3 (24.6)	73.2 (26.2)	70.6 928.1)
Change from baseline to				
Week 4	3.8 (22.2)	-1.4 (9.1)	5.3 (18.1)	6.9 (15.7)
Week 8	-1.6 (17.1)	-0.5 (11.3)	9.5 (23.2)	5.4 (15.3)
Week 12	-4.8 (17.4)	3.9 (24.3)	4.9 (21.3)	4.3 (17.2)
Week 16	-4.0 (13.5)	5.2 (29.4)	3.4 (16.3)	5.1 (15.4)
Week 20	-3.4 (14.7)	-0.8 (13.6)	4.5 (20.4)	5.1 (23.1)
Week 24	-3.5 (13.6)	1.2 (13.7)	24.4 (171.5)*	7.6 (14.3)
Week 28	10.5 (23.6)	7.9 (13.9)	5.6 (20.7)	7.8 (14.3)
Week 36	1.8 (13.1)	16.3 (27.1)	6.2 (16.7)	7.7 (15.0)
Week 44	1.8 (19.7)	8.5 (15.5)	3.9 (17.1)	10.5 (24.7)
Week 52	5.0 (16.4)	8.0 (22.0)	3.7 (23.9)	6.7 (12.9)
Last visit	2.9 (11.7)	2.1 (23.6)	5.7 (31.0)	6.4 (11.9)
*Large increase in mean total amylase at week 24 in the Byetta 5 mcg group resulted from the increased concentration in 1 subject (#1005, 1432 U/L), who was diagnosed with pancreatitis. Excluding the 1432 U/L value at week 24 resulted in a mean (SD) change from baseline of 3.2 (15.6) U/L.				

Change in amylase and lipase concentrations by adverse event status: Mean p-amylase, total amylase, and lipase concentrations were also evaluated by the sponsor based on the presence or absence of the gastrointestinal adverse events (AEs), specifically abdominal pain, abdominal pain upper/lower, nausea, and vomiting. Enzyme concentrations did not correlate with the presence or absence of the selected gastrointestinal adverse events.

Note: The sponsor did not include pancreatitis (any form) in the list of selected gastrointestinal events. However, the agency recognizes that pancreatic enzyme levels >3xULN with symptoms or positive imaging are consistent with pancreatitis. Two cases of pancreatitis and two cases, which may have developed into pancreatitis if study drug was not stopped, are described below.

NDA 22-773. Change in pancreatic enzyme level from baseline to endpoint in subjects on Byetta 10 mcg in studies BCB108, GWCV, GWAV, and GWBB		
	Byetta 10 mcg	
BCB108 (week 24)	**Symptoms present**	**Symptoms absent**
P-amylase	1.8 (14.2)	3.3 (20.2)
Lipase	3.9 (30.4)	10.9 (46.8)
GWCV (week 4)		
T-Amylase	5.4 (12.6)	6.1 (10.4)
Lipase	9.0 (21.3)	13.0 (23.1)
GWAV (week 12)		
T-Amylase	1.0 (10.9)	4.7 (13.0)
GWBB (week 24)		
T-amylase	9.7 (15.7)	6.8 (13.8)
Open label GWBB (week 52)		
T-amylase	3.7 (14.7)	0.0 (17.6)

Figure 1. Scatterplot of P-Amylase (IU/L) and Lipase (U/L) Concentrations by Treatment-Emergent Adverse Event Status and Time Point (Study BCB108; Intent-to-Treat Subjects Receiving BYETTA [N = 123])



Notes: -Abdominal pain/nausea/vomiting included the Preferred terms (MedDRA version 12.0) of abdominal pain, abdominal pain upper, abdominal pain lower, nausea, or vomiting. Subjects without treatment-emergent abdominal pain/nausea/vomiting had no events during the study. Subjects with treatment-emergent abdominal pain/nausea/vomiting had at least one event at any point during the study.

-Subject 113008 had high p-amylase and lipase values at Week 24 that had decreased 7 days following the Week 24 assessment. The decreased values are reflected in the "last visit" column.

-Dashed lines indicate the upper limit of the normal range. Normal range for P-amylase is 13 to 53 IU/L; normal range for lipase is 0 to 60 U/L.

-Solid lines indicate median values.

Incidence of abnormal amylase and lipase levels: Two of the 505 subjects (0.4%) evaluated experienced an elevated pancreatic enzyme level >3xULN during study-related laboratory assessments. One subject (#2103 in study GWBB) experienced elevated pancreatic enzyme concentrations at an unscheduled laboratory assessment.

- Subject ID 113008 (study BCB108; Byetta 10 mcg): 60 year old Caucasian male who had a lipase concentration >5×ULN and a p-amylase concentration >3×ULN at Week 24. The subject had a lipase concentration of 51 U/L at screening (normal 0-60 U/L), 46 U/L on Day 1, 108 U/L at week 14, and 393 U/L at week 24. Study medication was discontinued at week 24. Seven days after the week 24 assessment, the subject's lipase concentration was 46 U/L. The subject's p-amylase concentrations were 39 IU/L at screening and on Day 1 (normal 13-53 IU/L). At week 14, the p-amylase concentration was 69 IU/L and at week 24, the p-amylase concentration was 169 IU/L, with a drop to 39 IU/L after 7 days. No gastrointestinal adverse events were reported for this subject during the study. **Note: As study drug was discontinued at week 24 when amylase and lipase values were >3x ULN, it is not known if the subject, had he continued on study drug, would have presented with gastrointestinal symptoms and, thus, the diagnosis of pancreatitis.**
- Subject ID 1005 (study GWBB; Byetta 5 mcg): 62 year old Japanese male who had a total amylase concentration >10×ULN at Week 24 of therapy. The subject had a medical history of cholelithiasis, hypercholesterolemia, and hyperlipidemia. The subject's total amylase concentration was 60 U/L at screening, 52 U/L on day 1, and ranged from 53 U/L to 56 U/L from week 4 through week 12 (normal 39-134 U/L). At week 16 and week 20, the amylase concentration was 75 U/L and 78 U/L, respectively. On the day prior to the week 24 study-site visit, the subject experienced epigastric pain after a large lunch. The following day, the subject experienced vomiting and visited the emergency room, where treatment included metoclopramide and famotidine. On the same day, at the week 24 visit, the subject's total amylase concentration was 1432 U/L, and the investigator diagnosed pancreatitis based on the enzyme concentration, although the subject was asymptomatic at that time. Study medication was discontinued and the subject was withdrawn from the study, hospitalized, and treated with intravenous imipenum/cilastatin sodium, ulinastatin, and famotidine. An abdominal ultrasound revealed an enlarged gallbladder and a gallstone. Two days later, computed tomography (CT) of the abdomen revealed an enlarged pancreas, density of the peripheral adipose tissue, a gallstone, and an enlarged adrenal gland. On the same day, the total amylase concentration was 239 U/L. Acute pancreatitis and possible cholelithiasis were diagnosed. The acute pancreatitis resolved 4 days later. A cholecystectomy was performed 19 days after the week 24 visit and the subject was discharged from the hospital 10 days later. **Note: Pancreatitis may have been due to Byetta and/or gallstone.**
- Subject ID 2103 (study GWBB, Placebo/Byetta 10 mcg): 33 year old Japanese male who was randomized to receive placebo. From week 0 through week 24, the subject's total amylase concentration ranged from 86 U/L to 196 U/L. The subject received the first dose of open-label BYETTA at week 24. Approximately 2.5 months later, the subject experienced stomach pain, pyrexia,

and vomiting. Two days later, the subject visited the study site with ongoing stomach pain. Total amylase concentration was 327 IU/L (normal 38 to 137 IU/L), p-amylase concentration was 223 IU/L (normal range 19 to 53 IU/L), and lipase concentration was 1330 IU/L (normal range 14 to 51 IU/L). Hepatic function was normal. Byetta therapy was discontinued. The following day, the subject had an abdominal CT scan, revealing fatty liver, mild hepatomegaly, no space occupying lesion, no enlargement of biliary tract or gallbladder, calculus at the end of common bile duct (12 mm), normal size pancreas, mild enlargement of the pancreatic duct, normal absorption around the pancreas, and no effusion. The subject was diagnosed with fatty liver, common bile duct stone, and acute pancreatitis due to the common bile duct stone. The subject was treated with nafamostat mesilate, normal saline, vitamins, scopolamine buthylate, famotidine, glimepiride, and telmisartan. Three days later (7 days since initial symptoms), the subject was nearly asymptomatic at a visit to the study site and total amylase concentration was 42 U/L. A CT scan performed 2 days later was normal (ongoing common bile duct stone not mentioned). Approximately 1.5 months after the initial symptoms, the common bile duct stone, which had decreased in size, was removed by endoscopic sphincterotomy and the subject subsequently recovered. **Note: It is not clear if Byetta may have help precipitate the event of pancreatitis which was caused by a common bile duct stone.**

An adverse event of elevated lipase was also reported for BCB108 subject 122003 (Byetta 10 mcg), a 56 year old Asian female, although the lipase concentration did not reach 3×ULN. Lipase concentrations were 72 U/L at screening, 82 U/L at week 14, and 83 U/L at early termination. The subject had experienced nausea, vomiting, and diarrhea during the study and was withdrawn from the study due to investigator decision. **Note: The sponsor did not report the amylase value, which should have also been measured in study BCB108. If this value was >3xULN, the subject would have met criteria for the diagnosis of pancreatitis. In addition, as study drug was discontinued, it is not known if the subject, had she continued on study drug, would have presented with pancreatitis.**

No subjects in studies GWCV or GWAV had pancreatic enzyme levels >3xULN.

Incidence of gastrointestinal AEs by postbaseline amylase and lipase: The table below summarizes the incidence of AEs in the system organ class "gastrointestinal disorders" by the selected preferred terms listed above and postbaseline enzyme level for Byetta 10 mcg subjects. No clear association was seen between abnormal amylase and/or lipase levels and gastrointestinal disorders. This was in part due to the small number of subjects studied (e.g. abnormal amylase and lipase n=9).

NDA 21-773. Incidence of gastrointestinal AEs among subjects treated with Byetta 10 mcg by postbaseline amylase and lipase status

System Organ Class/ Preferred Term(s) [2]	Postbaseline Enzyme Status [1]		
	Normal Amylase and Lipase (N =231) n (%)	Abnormal Amylase and Lipase (N = 9) n (%)	Abnormal Amylase or Lipase (N = 51) n (%)
Gastrointestinal disorders	131 (56.7)	5 (55.6)	23 (45.1)
Nausea, vomiting, abdominal pain, abdominal pain upper, abdominal pain lower	99 (42.9)	5 (55.6)	20 (39.2)
Abdominal pain, abdominal pain upper, abdominal pain lower	12 (5.2)	1 (11.1)	3 (5.9)
Abdominal pain	2 (0.9)	1 (11.1)	3 (5.9)
Abdominal pain lower	3 (1.3)	0 (0.0)	0 (0.0)
Abdominal pain upper	8 (3.5)	0 (0.0)	0 (0.0)
Nausea	89 (38.5)	5 (55.6)	15 (29.4)
Vomiting	31 (13.4)	2 (22.2)	9 (17.6)

SD = standard deviation.

[1] Normal amylase and lipase = amylase and lipase (when lipase measured) ≤ULN at all postbaseline visits; abnormal (amylase and lipase) = amylase and lipase >ULN at any postbaseline visit; abnormal (amylase or lipase) = amylase or lipase >ULN at any postbaseline visit.

[2] MedDRA terms.

Concomitant medications: No differences in the use of concomitant medications among subjects with different enzyme levels or the presence/absence of gastrointestinal symptoms were seen.

Summary: The sponsor submitted an acceptable final report, "Clinical analysis of amylase and lipase concentrations", (b) (4)

According to the data presented above, which included 2 of 4 studies conducted in Japan,

- Byetta may increase amylase/lipase levels, as seen in study GWBB. This change is not clinically significant in most patients. Mean pancreatic enzyme levels remained in the normal range in studies BCB108, GWCV, GWAV, and GWBB. However, two of the 505 subjects analyzed (ID# 1005 and 2103) were diagnosed with pancreatitis. If study drug had not been discontinued in subjects #113008 and 122003, they too may have presented with pancreatitis; in this case, the event rate would have been 0.8%.
- Postbaseline pancreatic enzyme levels and the change in pancreatic enzyme level from baseline to endpoint do not correlate with the presence of selected gastrointestinal adverse events, specifically abdominal pain, abdominal pain upper/lower, nausea, and vomiting. Arguably, the sponsor could have included pancreatitis (e.g. acute, chronic, necrotizing, hemorrhagic, idiopathic) in this analysis. However, the agency already recognizes that pancreatic enzyme levels >3xULN with symptoms or positive imaging are consistent with pancreatitis.
- Drawing random amylase/lipase levels does not appear to be clinically useful for most subjects. Only three of 505 subjects (0.6%) experienced pancreatic enzymes >3xULN (although amylase data were not presented for a fourth). Subject 2103 in study GWBB experienced pancreatitis (partly or fully precipitated by a common bile duct stone) at an unscheduled laboratory assessment.

The following comment will be conveyed to the sponsor under exenatide once weekly (Bydureon) NDA 22-200: Please submit all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Bydureon, as well as analyses of those data. Also provide a systematic analysis of amylase and lipase data from those patients who presented with abdominal pain or nausea, with or without vomiting, during the treatment phase of those trials.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)
NDA-21773	PMR/PMC-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
SAFETY-892	ORIG-1	FOOD AND DRUG ADMINISTRATION	GLUCAGON-LIKE-PEPTIDE I (GLP-1)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S PRATT
07/01/2010

ILAN IRONY
07/01/2010
I concur with Dr. Pratt that the applicant [redacted] (b) (4).

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 10, 2010

FROM: John Bishai

SUBJECT: Inclusion of data from Safety Update in the NDA resubmission

APPLICATION/DRUG: NDA 022200 Amylin Pharmaceuticals, Inc.

On May 10, 2010, Amylin was informed via a phone conversation that the data from Study BCB106 which was included in their April 22, 2010 resubmission and not included in the original submission will not be reviewed for efficacy. The data from the trial was originally submitted as a safety update and will only be reviewed for safety. If the sponsor wants the information to be considered for efficacy, the sponsor has one of two options: (1) submit data from Study 106 as a stand-alone NDA or (2) wait until the resubmission is approved and then submit BCB 106 as a supplement.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN M BISHAI
05/12/2010

Cross-Discipline Team Leader Review

Date	2/12/2010
From	Ilan Irony
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22200/ Original
Applicant	Amylin
Date of Submission	5/4/2009
PDUFA Goal Date	3/5/2010
Proprietary Name / Established (USAN) names	Bydureon / Exenatide LAR
Dosage forms / Strength	SC injection / 2 mg once weekly
Proposed Indication(s)	Improve glycemic control in Type 2 diabetes mellitus
Recommended:	Complete Response

1. Introduction

This is the Cross Discipline Team Leader (CDTL) review of exenatide LAR, a new, once weekly formulation of exenatide, a glucagon-like peptide (GLP-1) receptor agonist approved in the US since March of 2005, indicated for improvement in glycemic control in patients with type 2 diabetes mellitus (T2DM). Exenatide is used as a twice daily (bid) subcutaneous (SC) injection, so that exenatide LAR was developed to improve convenience of administration and, possibly, compliance.

The New Drug Application (NDA) relies on the findings of safety and efficacy of exenatide, and contains mainly two bridging clinical studies: one to demonstrate non-inferiority of exenatide LAR to exenatide bid and the second to demonstrate non-inferiority of the commercial product to the product formulated for the pivotal Phase 3 study.

This review will touch upon the main issues noted in the Chemistry, Pharmacology / Toxicology, Clinical Pharmacology, Statistical and Clinical reviews, as well as a brief comparison to the review of a similar product recently approved, liraglutide. Finally, the CDTL review will briefly touch upon data submitted to support the cardiovascular safety of exenatide bid and exenatide LAR (as part of this application) to fulfill a FDA requirement to demonstrate that new products intended for the treatment of T2DM do not incur in unacceptably increased risks of major cardiovascular adverse events.

2. Background

Exenatide is the first in class GLP-1 receptor agonist, approved in the US in March 2005 for improvement in glycemic control in patients with T2DM. The effect is derived from a serum glucose-dependent exenatide stimulation of insulin secretion (thus reducing the risk of hypoglycemia and severe hypoglycemia), suppression of endogenous glucagon, slowing the

rate of gastric emptying and effects on appetite, with consequent mild reductions in body weight. Significant post-marketing findings which resulted in label changes and required studies include the risk of pancreatitis, including severe forms of pancreatitis (hemorrhagic and necrotizing, sometimes fatal), renal dysfunction, attributed mostly to GI effects causing dehydration and pre-renal damage, and hypoglycemia when combined with a sulfonylurea. High titers of anti-exenatide antibody may also reduce its efficacy.
Exenatide needs to be administered as a sc bid injection, so pharmaceutical companies are looking to reproduce or enhance the effects of exenatide with a more convenient regimen. Liraglutide was approved in January 2010 as a once daily GLP-1 receptor agonist, the second drug in the class. In addition to the concerns related to pancreatitis, known from the exenatide experience, a new concern arose from the review of the liraglutide NDA regarding the potential risk of medullary cancer of thyroid, based on rodent findings (two species, both genders) at low multiples of clinical exposure.

3. CMC/Device

Exenatide is a 39-amino acid peptide produced by [redacted] (b) (4). The drug product in exenatide LAR consists of exenatide ([redacted] (b) (4) w/w) and sucrose [redacted] (b) (4) % w/w) encapsulated within biodegradable poly-(D,L-lactide-co-glycolide) (PLG) microspheres designed for controlled released of the active drug over an extended period of time. Exenatide LAR is intended for patient self-administration: the single-dose kit contains one vial of 2 mg exenatide in PLG microspheres, one vial connector, one pre-filled diluent syringe and two needles. Exenatide LAR must be injected immediately after reconstitution.
The two CMC issues initially identified related to characterization and specification of impurities and [redacted] (b) (4) have been resolved during the review cycle.
The applicant was granted categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31b.
There were no issues consulted to CDRH, as drug administration requires only a standard syringe.
The Office of Compliance report regarding GMP facility inspection is pending at this time.
The review from the New Drug Microbiology review team on the Sterility Assurance is also pending.
The expiration dating period grantable for the exenatide LAR injectable suspension is [redacted] (b) (4) months or limited by the expiration of the exenatide microspheres or diluent.
The CMC team recommended approval, pending the final recommendation from the Office of Compliance.

- The Microbiology review team recommended communication of three deficiencies:
  [redacted] (b) (4)
- [redacted]
- [redacted]

The development of exenatide LAR was characterized by multiple changes in formulation and scale production. The changes in scale will be covered in the biopharmacology and clinical

sections of this review, as FDA required from the applicant bridging studies to demonstrate similar therapeutic benefits.

4. Nonclinical Pharmacology/Toxicology

The nonclinical team recommends a Complete Response (Not Approvable) action on the NDA. The reason for this decision is the statistically significant finding of thyroid c-cell tumors in a 2-year carcinogenicity study in rats, at clinically relevant exposures based on area under the curve drug levels in animals that were anti-exenatide antibody negative. In addition, there is insufficient evidence at this time to conclude that induction of c-cell hyperplasia or tumors mediated by exenatide LAR is not relevant to patients.
The Pharmacology / Toxicology team decision is consistent with that taken for another GLP-1 receptor agonist, liraglutide. Liraglutide is dosed once daily due to an effect on GLP-1 receptors more prolonged than that observed for exenatide. Unlike exenatide, liraglutide and exenatide LAR were shown to induce c-cell tumors (adenomas and carcinomas) and more commonly c-cell hyperplasia in male and female rats treated with these drugs for 2 years. The liraglutide carcinogenicity program also demonstrated a similar effect in mice, although at exposures higher than those approximating therapeutic human exposures.
When the rodent carcinogenicity experience with exenatide (bid use), liraglutide and exenatide LAR are combined, FDA concludes that longer acting GLP-1 agonists are more prone to stimulation of thyroid receptors, with induction of hyperplasia and tumors, compared to the absence of such signal in the nonclinical carcinogenicity experiments with exenatide (bid use).
The following key findings from the exenatide LAR rat carcinogenicity study are reproduced here (in *italics* type) from Dr. Timothy Hummer's review:

***Key study findings**:*

- *The overall mortality for exenatide QW-treated groups was similar to controls. There were no meaningful differences in the number of deaths due to tumors between treated and control groups.*
- *Treated groups weighed less than both diluent and microsphere control groups at the end of the treatment period, with the difference being greater for females. For the 0.3, 1, and 3 mg/kg dose groups, males weighed 8%, 13%, and 11% less and females weighed 17%, 21%, and 21% less than diluent controls, respectively. The effects on body weight correlated with decreased food consumption, a known pharmacological effect of GLP-1 receptor agonists.*
- *There were no hematologic or gross pathology findings attributed to the test article.*
- *Non-neoplastic microscopic findings included an increase in **foreign body granulomas at the injection sites** in all male and female groups receiving PLG microsphere; a slight increase in **acinar cell atrophy of the pancreas** (minimal to moderate) for high-dose males and low-dose and high-dose females; a slight increase in **adipose tissue depletion** (mild to severe) in all exenatide-treated males, especially those that were found dead or sacrificed moribund; and an increase in **pelvic mineralization of the kidney** (minimal to moderate) for all exenatide-treated males.*
- *<u>Neoplastic findings</u>*

- *The key neoplastic finding was **thyroid c-cell adenomas**, which was statistically significant for males for dose response and for pair-wise comparison vs. Control 1 and Control 2 at the MD and HD. For females the number c-cell adenomas were statistically significant for all dose groups for pair-wise comparison vs. Control 1 but not Control 2. Also, there was not a statistically significant increase when assessed for dose response vs. Control 1 or Control 2. The mean number of animals with c-cell adenomas for all exenatide-treated groups exceeded the high end of the historical control range (15.4% for males and 11.4% for females).*
- *The number of **thyroid c-cell carcinomas** was only statistically significant for MD males when compared with Control 1, although the number of tumors was outside the background control range (0% to 1.7%) for that laboratory for the LD (2.9%), MD (7.1%), and HD (4.3%). For females, the number of c-cell carcinomas was statistically significant for dose response when compared with Control 1; only the HD group had a value (5.7%) that was outside the historical control range (0% to 4.0%), but was not statistically significantly different from either control group.*
- *The number of **total thyroid c-cell tumors** (adenomas plus carcinomas) was statistically significantly increased for males for dose response and at MD and HD for pair-wise comparison versus Control 1 and Control 2. The p value for LD males was just slightly higher than the 0.01 threshold for significance. For females c-cell tumors were increased for dose response versus Control 1 only and at all doses versus Control 1 and at HD versus Control 2 for pair-wise comparison.*
- ***Fibromas of the skin**, subcutis, were found to be statistically significantly increased for males when assessed for dose response vs. Control 1 and increased in HD males when analyzed for pair-wise comparison vs. Control 1. The LD and HD groups (but not MD) had values (5.7% and 11%, respectively) greater than the historical control range (0% to 5%). Because the PLG microspheres probably contributed to the increase in fibromas due to foreign body response, a comparison to Control 2 does not seem as relevant as Control 1 for this particular tumor type.*
- *A potential increase in schwannomas (all tissues combined) was observed in males and an increase in kidney tubular cell carcinomas was observed in females. However, these tumors were likely not related to exenatide because of a lack of statistical significance at any dose level when compared to either control by pair-wise comparison.*
- *A potential increase in parathyroid benign adenomas and pancreatic islet cell adenomas were noted in males and females, respectively; however, these findings were not shown to be statistically significantly different from either control group when using trend analysis or pair-wise comparison.*

- *Approximately one third of exenatide-treated males had anti-exenatide antibodies at the 6-, 12-, and 18-month time points. The number of anti-exenatide antibody positive females ranged from 41% (low dose at 6 months) to 24% (high dose at 18 months). The number of females testing positive for antibodies tended to be inversely related to dose level. Generally, the percentage of animals with anti-exenatide antibodies was lower at 24 months, which could have been due to a smaller sample size because of decreased survival at two years.*
- *TK data show that exposure was slightly less than dose proportional between 0.3 and 1.0 mg/kg and 0.3 and 3.0 mg/kg; exposure was approximately dose proportional between*

1.0 and 3.0 mg/kg. C_{max} increased in a less than dose proportional manner. Both C_{max} and AUC were increased by the presence of anti-exenatide antibodies.

- *In conclusion, an increase in thyroid c-cell tumors (adenomas plus carcinomas) was observed at all doses for males and females, although the increase for low-dose males was not statistically significant. Based on TK data in antibody negative animals on Day 183, the mean exposure at the low dose is approximately 1.3 fold the maximum anticipated clinical exposure. An increase in skin fibromas was observed in males treated with 3 mg/kg, which is approximately 20-fold higher than the maximum clinical dose based on exposure.*

To better illustrate the incidence of thyroid abnormalities reported, please refer to Table 1 and Table 2, adapted from Dr. Hummer's review.

Table 1. Summary of incidence of thyroid hyperplasia or tumors in Rat Carcinogenicity Study

	Males					Females				
Dose (mg/kg)	**DC**	**MC**	**0.3**	**1.0**	**3.0**	**DC**	**MC**	**0.3**	**1.0**	**3.0**
Thyroid, c-cell										
Hyperplasia, focal	(15)	(10)	**(23)**	**(19)**	**(23)**	(13)	(12)	**(31)**	**(29)**	**(40)**
-minimal	13	8	19	15	18	11	9	28	16	23
-mild	2	2	4	4	5	2	3	3	13	16
-moderate	-	-	-	-	-	-	-	-	-	1
Adenoma	9	9	**20**	**32**	**33**	5	9	**22**	**19**	**21**
Carcinoma	-	1	2	**5**	**3**	-	1	1	1	**4**
Adenoma + carcinoma†	9	10	**22**	**34**	**35**	5	10	**23**	**20**	**25**
Carcinoma, secondary										
-thoracic cavity	-	-	-	1	-	-	-	-	-	-
-parathyroid	-	-	-	-	-	-	-	1	1	-

DC = diluent control; MC = microsphere control.
†animals having both an adenoma and carcinoma for the same tumor type (e.g., c-cell tumor) were only counted once for the combined (e.g., adenoma + carcinoma) tumor incidence.

Table 2. Percent incidence of thyroid tumors compared to study controls and historical controls - Rat Carcinogenicity Study

	Males (%)						Females (%)					
Dose (mg/kg)	**DC**	**MC**	**0.3**	**1.0**	**3.0**	**HIS**	**DC**	**MC**	**0.3**	**1.0**	**3.0**	**HIS**
Thyroid, c-cell												
Adenoma	14	14	29	46	47	8.8 (1.9-15.4)	7.1	13	31	27	30	8.1 (2-11.4)
Carcinoma	0	1.4	2.9	7.1	4.3	0.6 (0-1.7)	0	1.4	1.4	1.4	5.7	0.6 (0-4.0)

DC = diluent control; HIS = historical control data from 11 studies; MC = microsphere control; NP = not provided.

It is important to emphasize that no clinical cases of medullary thyroid cancer (MTC) were reported from either the liraglutide or the exenatide development LAR programs. But the incidence of MTC in the United States is approximately 600 cases per year, so one would not expect to see any reports of MTC from the relatively limited exposure in these

programs, or at least, not enough reports to provide stable and conclusive estimates of the true incidence rates and association with study drug.
Drs. Parks and Rosebraugh (DMEP Division Director and ODE II Director, respectively) weighed these risks of liraglutide and the process considered in the approval of this drug[1]. The NEJM article reflects on countless hours of discussions (internal to the Division, as well as external with thyroid and epidemiology experts) entertained in order to arrive at the regulatory action taken in approving liraglutide.
I believe an approach similar to that taken for liraglutide can be taken for exenatide LAR. We have less carcinogenicity data with exenatide LAR, but the data we have are sufficient to raise a concern of a class effect for "longer acting GLP-1 agonists". On the other hand, as discussed in section 7 of my review, exenatide LAR offers glycemic efficacy at least as comparable to that of exenatide, and perhaps with less gastrointestinal ill effects and certainly with increased convenience of administration.

5. Clinical Pharmacology/Biopharmaceutics

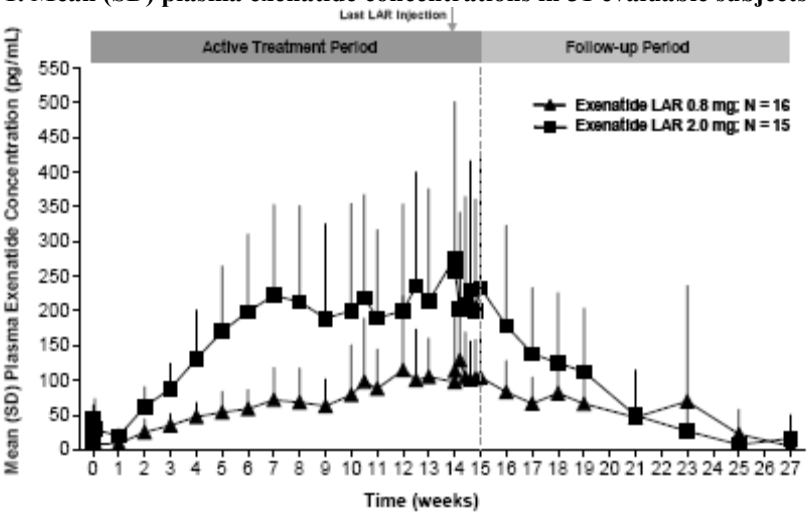
The Division of Clinical Pharmacology II and Office of Clinical Pharmacology recommend approval of Bydureon, pending labeling discussions. Please refer to Drs. Jayabharathi Vaidyanathan and Manoj Khurana primary reviews for details of the discipline review, including a review of Pharmacometrics, led by Dr. Tornoe.
The active product ingredient is exenatide with PK characteristics modified by the PLG microspheres. After injection into the SC space, the polymer biodegrades over time, resulting in an extended duration of peptide release.
Prior to submission of NDA 22200, the applicant has tested several formulations for exenatide LAR during early clinical trials, and finally selected a formulation coded F17. Phase 2 and Phase 3 trials were conducted with the F17 formulation. In addition, over the course of premarketing development, Amylin has manufactured exenatide LAR drug product at (b) (4) different scales ((b) (4)) in two different manufacturing sites (Alkermes, Inc. in Wilmington OH and Amylin Ohio, LLC in West Chester OH).
The Clinical Pharmacology review briefly covered the single dose PK findings in healthy volunteers and in subjects with T2DM, but focused on the PK and PD (exposure / dose response relationship) characteristics of exenatide LAR demonstrated in a dose ranging (two dose strengths) Phase 2 study and in two sequential Phase 3 studies.
The Phase 2 study 2993LAR-104 (referred henceforth as Study 104 in this review) was conducted using only the (b) (4) manufacturing scale product. The pivotal Phase 3 clinical trial 2993LAR-105 (referred henceforth as Study 105 in this review) used product that was manufactured in (b) (4) and (b) (4) scales. These products were manufactured at the Alkermes site. The commercial formulation is manufactured at the Amylin site at (b) (4) manufacturing scale, and was used in an extension of Study 105 for the purpose of bridging to the (b) (4) scale product.

[1] Parks M and Rosebraugh C. Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy. NEJM 362(9):774-777, 2010

Key PK findings

Following a single exenatide LAR injection in subjects with T2DM (after a 2-week lead-in period of exenatide to improve tolerability), mean plasma exenatide concentrations generally return to pre-injection values after approximately 10 weeks for all dose groups tested (2.5 mg, 5.0 mg, 7.0 mg, and 10.0 mg). Overall exposure to exenatide LAR progressively increased with dose for each of the four treatment groups as determined by the PK parameters.
The multiple-dose PK of exenatide LAR was evaluated in Study 104 and subsequently in Study 105. In Study 104, two doses (0.8 mg and 2 mg) of exenatide LAR were evaluated. Dose-dependent increases in mean plasma exenatide were observed following the two doses. From Week 7 through the remainder of the treatment period, mean plasma exenatide concentrations remained relatively constant for both LAR dose groups, indicating that steady-state concentrations are achieved in approximately 7 weeks. At Week 14-15, mean (SD) plasma exenatide steady-state concentrations for the 0.8 mg and 2 mg exenatide LAR groups were 117.86 (59.05) pg/mL and 288.8 (134.02) pg/mL, respectively (Figure 1). Similar steady-state concentrations were achieved in the Phase 3 study.

Figure 1. Mean (SD) plasma exenatide concentrations in 31 evaluable subjects in Study 104



Adapted from Dr. Vaidyanathan's review

Baseline creatinine clearance (CrCL) was determined to be the most significant predictor of steady-state concentration of exenatide following once weekly dosing based on population PK analysis. There was a 53% increase in the observed average steady-state concentrations in subjects with moderate renal impairment (CrCL = 30-50 mL/min) and 24% in subjects with mild renal impairment (CrCL = 50-80 ml/min) as compared to subjects with normal creatinine clearance. No major adverse events were observed in any patients including the renal impaired subjects in the Phase 3 trial (Study 105). No dose adjustment is proposed for mild and moderate renal impairment. It is contraindicated in severe and end stage renal impairment. Due to the very limited experience with moderate renal impairment (10 subjects) in the pivotal Phase 3 trial and the possibility of increased exposure (up to 2 fold when approaching CrCL of 30 mL/min), the clinical pharmacology

reviewer recommends caution when initiating Bydureon in patients with moderate renal impairment.
Based on the results of the population PK analysis, the sponsor's proposal of no dose adjustment based on age, gender, race and body weight is justified. These covariates do not affect exenatide pharmacokinetics in a clinically meaningful manner.

Key findings from Exposure (Dose)-Response Relationship

The exposure-response relationship for effectiveness is based on in studies 104 (dose ranging study) and 105 (pivotal efficacy trial). The clinical pharmacology review notes a concentration-dependent decrease in HbA1c from baseline with maximal response at exenatide concentrations greater than 200 pg/mL. There was some overlap of exenatide concentrations following the 0.8 mg and 2 mg dose. However, the median concentrations achieved following 0.8 mg was about 60 pg/mL which is less than the EC_{50} value (83.5 pg/mL) indicating sub-optimal exposures are achieved following 0.8 mg exenatide LAR dose whereas the majority of patients receiving 2 mg exenatide LAR dose had exposures above EC_{50} (median ~290 pg/mL).
The data are insufficient to determine the effect of immunogenicity. There was a considerable interference with the ability to quantify exenatide in samples with higher titer antibodies (data from those samples with anti-exenatide titers ≥ 625 were excluded).
The population PK analysis demonstrated a 36% higher mean exenatide plasma steady-state concentration at the (b) (4) manufacturing scale as compared to the (b) (4) scale. The exposure resulting from the (b) (4) manufacturing scale product (intended for market) was 32% less as compared to the (b) (4) manufacturing scale product and did not meet the bioequivalence criteria for AUC (refer to bioequivalence below).
Although higher concentrations were achieved from the (b) (4) scale, the majority of the steady-state concentration distribution for the (b) (4) manufacturing scale is encompassed within the range of the (b) (4) manufacturing scale. Also, the concentrations are in the proximity of the maximal HbA1c response indicating that the 36% difference may not be lead to differences in efficacy.

Bioequivalence

The to-be-marketed formulation is manufactured at the Amylin site at a different manufacturing scale ((b) (4) as compared to the clinical investigational product (manufactured at Alkermes at (b) (4) scale) used in the Phase 3 study 105. An open-label extension of the study 105 intended to provide comparability between the investigational and the commercial products. The comparability between the two formulations was assessed via efficacy (glycemic markers), PK (AUC at steady state, $AUC_{0\text{-}168h}$, concentration at steady state) and safety endpoints. The primary analysis for this comparison of clinical efficacy was a non-inferiority assessment of the change in HbA1c at Week 18 of the comparability assessment for the evaluable population, using a predefined margin of 0.4%. The non-inferiority margin selected is commonly used in active-controlled efficacy trials of antidiabetics and accepted by FDA.

The exenatide exposure ($AUC_{0\text{-}168h}$ and AUC_{ss}) from the (b) (4) scale product was 25-32% lower as compared to that of the (b) (4) scale product and the C_{ss} for the was also 25% lower. The bioequivalence between the two products thus has not been established. Despite failed to formally show bioequivalence, the range of concentration values for (b) (4) scale product was within the range of concentration values observed with (b) (4) scale product and they were greater than the EC50 (~83 pg/mL) and the differences in the exposure resulting from different manufacturing scale were in the maximal response region of the exposure-response relationship for exenatide LAR (~200 pg/mL).
In addition, the HbA1c values and fasting plasma glucose concentration demonstrated substantial overlap, indicating the ranges of exposure and response are similar between the 2 treatment groups. Non-inferiority between the (b) (4) and (b) (4) scale products was demonstrated based on the upper limit of the 95% CI of the difference between the treatment groups (0.34%) being below the predefined 0.4% margin for the change in HbA1c at week 18 (please refer to the clinical review).

Drug-Drug Interactions (DDI)

Exenatide has the potential to alter the absorption of concomitantly administered oral drugs due to its pharmacological effect of delay of gastric emptying as indicated in Byetta labeling. Assessment of the effects on gastric emptying occurred at Week 14, when steady-state concentrations of exenatide had been achieved with exenatide LAR treatment. This was compared to the effect of exenatide administered BID. Exenatide reduced the absorption as seen from a 21% decrease in acetaminophen C_{max} (under fed conditions). The magnitude of the decrease in acetaminophen C_{max} was less with the exenatide LAR, 16% and 5% under fasting and fed conditions, respectively. On the other hand, exenatide BID had a similar effect on the AUC of acetaminophen, with a 20% decrease, while acetaminophen AUC was not altered by exenatide LAR. The sponsor did not conduct additional DDI studies. Although there is no effect on the AUC of acetaminophen, exenatide LAR causes a decrease in the $C_{max,}$ especially under fasting conditions. Therefore, the label for exenatide LAR should contain similar language regarding DDI as present in the exenatide BID label.

6. Clinical Microbiology

Not applicable. The product is not an anti-microbial.

7. Clinical/Statistical- Efficacy

The CDTL review of the efficacy of exenatide LAR is based on:

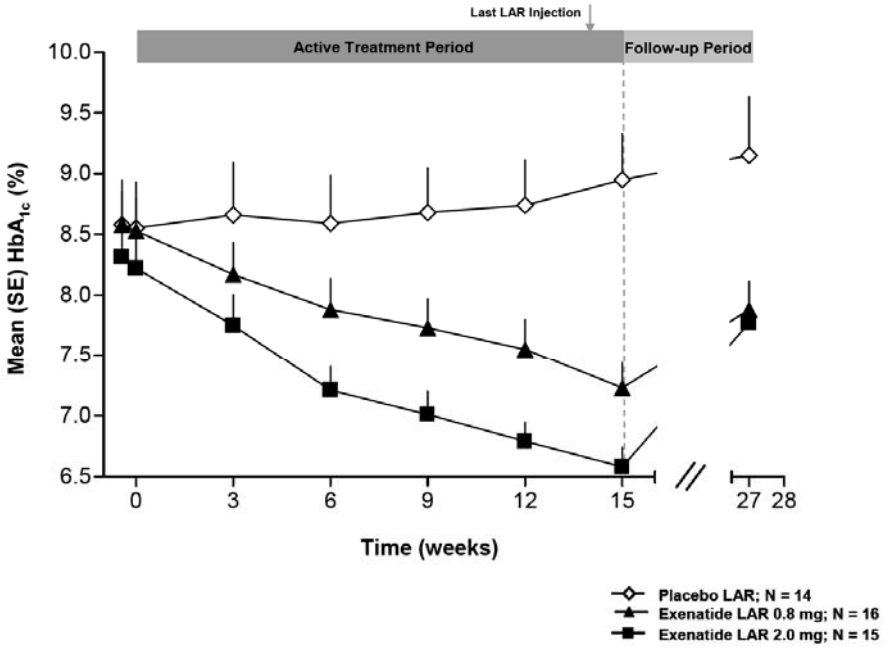
- The Phase 2 dose-ranging study 104
- On Dr. Pratt's and Dr. Derr's reviews of the Phase 3 study 105 (and its extension 105c to demonstrate comparability to the to-be-marketed product), and
- A brief review of the efficacy of exenatide LAR demonstrated in Study 106; a study report from the latter was submitted with the 4-Month Safety Update.

Please refer to Dr. Valerie Pratt's review for details of the clinical review and to Dr. Janice Derr's review for a more detailed discussion of statistical issues related to Study 105. Both disciplines recommend approval of exenatide LAR 2 mg SC weekly for the treatment of T2DM.

Study 104

The first important clinical study in the exenatide LAR development program was the dose ranging Study 104, a Phase 2, randomized, double-blind, placebo-controlled, safety and PK study of 2 doses of exenatide LAR. Forty five subjects with T2DM, either treatment naïve (n = 18) or not controlled with metformin (n=27), were randomized 1:1:1 to exenatide LAR 0.8 mg SC qw, 2 mg SC qw or placebo SC qw for 15 weeks, after a lead-in 3-day period of treatment with exenatide BID. The lead-in period with exenatide was incorporated into the design in order to improve gastrointestinal tolerability.
Dose-dependent increases in mean plasma exenatide were observed following the two doses. From Week 7 through the remainder of the treatment period, mean plasma exenatide concentrations remained relatively constant for both LAR groups, indicating that steady-state concentrations are achieved in approximately 7 weeks. At Week 14-15, mean (SD) plasma exenatide steady-state concentrations for the 0.8 mg and 2 mg exenatide LAR groups were 117.86 (59.05) pg/mL and 288.8 (134.02) pg/mL, respectively (see Figure 1, above). Similar steady-state concentrations were achieved in the Phase 3 study.
The pharmacodynamic endpoint in Study 104 was the change in HbA1c from baseline to week 15 (Figure 2).

Figure 2. Mean (SE) HbA1c changes in Study 104 in the ITT population)



Abbreviations: HbA1c, glycosylated hemoglobin-specific A_{1c} fraction; ITT, intent-to-treat; LAR, long-acting release; SE, standard error.
Copied from the applicant's Exenatide LAR Clinical Study Report 2993LAR104, Figure 4

Safety and tolerability were similar between the two doses of exenatide LAR examined. The applicant selected the 2 mg dose to move forward to the phase 3 study due to the slightly greater mean reduction in HbA1c compared to the lower dose, and the reduction in mean body weight, not observed with the lower dose. In addition, average steady-state concentrations of plasma exenatide for the 2 mg dose (288.8 pg/mL) exceeded the 200 pg/mL concentration shown to result in a consistent reduction in postprandial glucose and were similar to the exenatide concentrations seen with exenatide 10 mcg BID at steady state. Steady-state concentrations of plasma exenatide for the 0.8 mg dose were below that threshold.

Study 105

This is the pivotal Phase 3 study to provide evidence of efficacy and safety of exenatide LAR, as submitted with the initial NDA filing.

Study Protocol

Study 105 was a Phase 3, randomized, open label, multicenter, active comparator (exenatide BID) trial. The active-controlled treatment period lasted for 30 weeks, followed by an open ended extension lasting at least another 22 weeks, for which data were included in the clinical study report. Starting at the baseline visit, all subjects received exenatide 5 mcg SC bid for 3 days (lead in period). After the lead in period, subjects were randomized 1:1 to exenatide BID or to exenatide LAR. Subjects randomized to the exenatide BID arm continued to receive the same dose (5 mcg BID) for 4 weeks, and the dose was then increased to 10 mcg bid until week 30. Subjects randomized to exenatide LAR 2 mg started on that treatment immediately after the 3 days lead in period with exenatide BID. The source of exenatide LAR was the Alkermes (b) (4) scale product. Stratification factors were baseline HbA1c stratum (<9% or ≥ 9%) and concomitant sulfonylurea (SU) use at screening (yes, no). Eligible subjects were patients with T2DM, 16 years of age or older, treatment naïve or on a stable regimen of metformin, SU, thiazolidinedione (TZD), a combination of metformin + SU or metformin + TZD, with HbA1c between 7 and 11 %. For subjects treated with SU or metformin + SU as background antidiabetic therapy at screening, the protocol called for a decrease in the SU dose to the minimum recommended dose at the start of the lead in exenatide BID in order to prevent SU-induced hypoglycemia. Between weeks 10 and 22, the dose of SU would be uptitrated, as needed, to keep fasting plasma glucose (FPG) at ≤ 110 mg/dL. As noted in Dr. Derr's review, power calculation yielding a total of 300 subjects was adequate. The primary endpoint was the change in HbA1c from baseline at week 30 in the ITT population, using LOCF for imputation of missing Week 30 data in an analysis of variance model that includes treatment and the stratification variables (HbA1c strata and use of SU). The main aim of the study was to demonstrate the non-inferiority of exenatide LAR to exenatide BID, by a margin of 0.4%. The non-inferiority margin selected in commonly used in active controlled studies in diabetes, and is particularly appropriate to preserve the placebo-subtracted effect of exenatide BID from 3 studies (please refer to Table 2 of Dr. Derr's review).

Dr. Derr's statistical review points 2 weaknesses in study design. After discussion of the study results, my CDTL review addresses her comments regarding the study weaknesses.

Study Results

The study was conducted in 29 sites, being 28 in the US and one in Canada. The first subject was dosed on April 15, 2005 and the last subject's week 52 visit was on February 20, 2008.
Four hundred and seventy subjects were screened, 303 subjects were enrolled, and eight withdrew prior to dosing. The remaining 295 subjects were included in the ITT population for analysis of efficacy at week 30; two of these withdrew during the lead in period, so 293 subjects were randomized. Thirty five subjects (11.9%) withdrew during the assessment period, with about half due to adverse events (AEs) with similar proportions in both treatment arms. The vast majority of the subjects were patients in the US, with background use of medications consistent with commonly prescribed medications (antidiabetic and other concomitant medications) in the US, so the trial data is applicable to the US population of T2DM.

The primary efficacy analysis is shown in Table 3.

Table 3. Change in HbA1c from baseline at week 30 in Study 105, ITT population

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE[1]	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) [1]	P-value
All patients (ITT/LOCF)					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		

Copied from Table 1 in Dr. Derr's review.

I will not discuss here other supportive or exploratory analyses of the change in HbA1c, except to state they were consistent with the primary analysis. Analyses of efficacy in different subgroups based on demographic, baseline characteristics or baseline use of concomitant medications also demonstrated consistency of glycemic effect.

More subjects on exenatide LAR developed anti-exenatide antibodies than subjects treated with exenatide BID (74.3 % versus 49%), but the mean magnitude of the attenuating effect on the efficacy of exenatide was either similar or perhaps even smaller than the anti-exenatide antibody effect on the efficacy of exenatide BID.

The other glycemic supportive endpoint, FPG, was also favorable to exenatide LAR with a between-group adjusted mean difference (exenatide LAR – exenatide BID) of – 17 mg/dL with a 95% CI between -24 and – 9 mg/dL ($p < 0.001$).
The other secondary endpoint was body weight, with an almost complete overlap between the two treatments in the magnitude of effect on that parameter (mean weight loss of 3.7 kg at week 30).

A question regarding study integrity arose from the Dr. Pratt's clinical review related to DSI findings in one of the high enrollment sites (site 108). Dr. Eric Klein from Olympia, Washington enrolled 39 subjects (of the total 295) (b) (6) Dr. Klein received a Voluntary Action Indicated due to irregularities in the reporting of adverse events, but also about subject complaints of problems with administration of exenatide BID. A sensitivity analysis executed by Dr. Derr at my request yielded similar efficacy results:
When all sites were included: Mean -0.348 +/- 0.10 (SEM), with 95% CI (-0.55 to -0.15)
When Site 108 was excluded: Mean -0.313 +/- 0.12 (SEM) with 95% CI (-0.54 to -0.08)

Dr. Derr's review points to two weaknesses in the design of Study 105, for consideration when weighing the evidence of exenatide LAR efficacy:

1. The study was open label, and the investigators, with the knowledge of treatment assignment, were able to adjust the dose of SU during the treatment period and before ascertainment of the efficacy endpoint (HbA1c at week 30). Dr. Derr suggests that a potential bias to favorably increase the estimated effect of exenatide LAR on HbA1c could be minimized by a double-blind design or by use of a firewall to keep personnel responsible for managing the SU dose (in response to fasting hyperglycemia) blinded to treatment assignment.
   The point raised in Dr. Derr's review merits careful consideration: it is clear that the open label design was implemented to facilitate recruitment and study conduct: a double blind study would have required subjects randomized to exenatide LAR to receive BID sham SC injections for the duration of the study.
   The idea of a firewall is also valid in principle. But in reality the SU-treated subject would know his / her daily blood glucose reportable via IVRS; would be aware of the need to have the SU dose adjusted, and would also know his / her treatment assignment, due to the open label nature of the study.
   The applicant fortunately designed the randomization to be stratified by the presence or absence of SU treatment at screening, thus ensuring balance between the treatment arms with respect to this variable. Thirty seven percent of subjects (109 subjects) were treated with SU alone or SU + metformin at screening. Again fortunately, from the standpoint of the applicant, a larger proportion of SU-treated subjects on exenatide BID required uptitration than SU-treated subjects on exenatide LAR (50% versus 30.6%, respectively) and fewer SU-treated subjects on exenatide BID had their SU dose decreased compared to SU-treated subjects on exenatide LAR (30 % for BID versus 45% for LAR). Dr. Derr also points out that fewer subjects on exenatide LAR had their SU dose increased to the maximum-labeled dose, compared to subjects on exenatide BID. Therefore, in my view, for subjects starting on a low dose of SU and facing FPG criterion that is objective, predefined and applicable to both groups, these facts suggest that exenatide LAR had a greater effect on FPG than exenatide BID, thus supporting the efficacy of exenatide LAR among SU-treated patients.
   Finally, Dr. Derr points out that another ongoing study, GWBR, has a design similar to Study 105 (comparing an exenatide LAR arm to an insulin glargine arm, with background therapy of metformin or metformin + SU), but two other Phase 3 studies comparing exenatide LAR to oral antidiabetic therapies were designed as double blind studies. While Study GWCH is still ongoing, Study BCB106 was completed, and a

final study report was submitted to the exenatide LAR NDA at the 4-month safety update. Dr. Pratt had reviewed the latter study for safety. My brief review of Study BCB106 indicates that exenatide LAR is effective under the more rigorous conditions of a double blind study, without post randomization titration of concomitant medications with the potential to confound and bias efficacy findings (see below).

2. Change in manufacturing source: Although the Phase 3 program was conducted with the (b) (4) scale product manufactured at Alkermes, the applicant plans to market the (b) (4) scale product. Typically, manufacturing changes are bridged by PK bioequivalence. Exenatide LAR failed the IVIVC and the PK bioequivalence tests, although the Clinical Pharmacology team was comfortable with the range of exposures obtained with exenatide LAR manufactured at the (b) (4) scale being at the maximal exenatide exposure-glycemic response. The failure to establish bioequivalence triggered a clinical comparability study, with a non-inferiority design (Study 105c, described below). Rather than a study intent on comparing the effect of the exenatide LAR manufactured at the two different scales in diabetic subjects inadequately controlled, the applicant elected to evaluate the effect of each of these scale products on glycemic control <u>after</u> a period of time on treatment with exenatide LAR at the (b) (4) scale, therefore with mean HbA1c close to glycemic target. Although no agreement had been reached between the applicant and FDA on the non-inferiority margin to demonstrate comparability between the two manufacturing scale products (b) (4) versus (b) (4) Study 105c data showed great overlap on the maintenance of glycemic effect after 18 weeks of that trial. Therefore, in my view, marketing of the (b) (4) scale product based on demonstration of efficacy for the (b) (4) product is not problematic, due to the combination of the PK and the limited clinical evidence presented at Study 105c. In response to a FDA request for information, the applicant informed us that only one clinical study was conducted using the (b) (4) scale product <u>exclusively</u>: Study BCB108, completed in December 2009, for which we have no data or study reports.

<u>Study 105c</u>

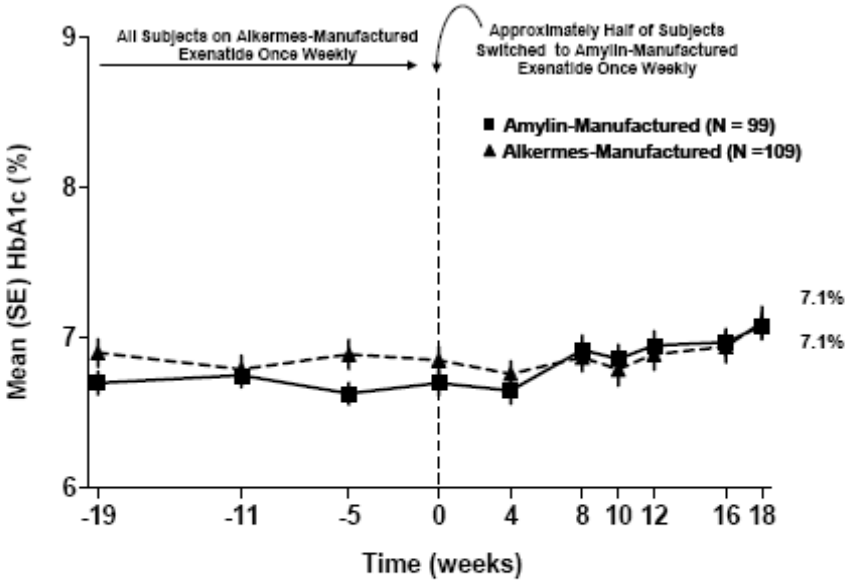
This is the study conducted to demonstrate the clinical comparability between the exenatide LAR manufactured at Alkermes at the (b) (4) scale and exenatide LAR manufactured at Amylin at the (b) (4) scale. This is a substudy of Study 105, conducted during the open ended extension of that Study.
Of 258 subjects in Study 105 who entered the open ended assessment period, 217 agreed to participate in the substudy 105c. These subjects, with a mean HbA1c of 6.8%, were randomized 1:1 to receive exenatide LAR from Alkermes (b) (4) scale product) or from Amylin (b) (4) scale product) SC QW. On day 1 of Study 105c, subjects had been exposed to exenatide LAR (b) (4) scale for a variable duration of time, ranging from almost 1 year to almost 2 years. The primary endpoint was the change in HbA1c from baseline (average of 3 assessments during the open ended period of Study 105) to week 18. Randomization was stratified by the average HbA1c being < 6.5% or ≥ 6.5 %. FDA did not commit in accepting 0.4% as the non-inferiority margin to demonstrate the comparability, preferring instead to examine the totality of data submitted with the NDA.
The results of Study 105c are shown in Table 4 and Figure 3.

Table 4. Comparability of the 2 sources of exenatide LAR in Study 105c: Change in HbA1c after 18 weeks of treatment

	N	Day 1S baseline HbA1c ± SE	Adjusted mean change from Day 1S to Week 18S ± SE[1]	Amylin - Alkermes Difference in adjusted mean change (95% CI)[1]	P-value
All patients (ITT/LOCF with respect to the comparability sub-study[2])					
investigational Alkermes source	109	6.8 ± 0.1	0.3 ± 0.1	0.2 (0.0, 0.3)	0.062
commercial Amylin source	108	6.7 ± 0.1	0.4 ± 0.16		

Notes:
[1] The comparability study is described in Part 3.1.4 of this review
[2] The adjusted mean change from baseline 1S at week 18S and the difference in the adjusted mean change were estimated from an analysis of variance model with treatment and baseline 1S HbA1c stratum.
Sources: Study 2993 LAR-105c comparability assessment, Table 6

Figure 3. Mean change in HbA1c from baseline (mean of 3 assessments) to week 18



Abbreviations: SE, standard error.
Notes: Mean baseline HbA1c at the 3 observations prior to Day 1S (time = 0) and at Day 1S was 6.8% for the Alkermes-manufactured and 6.7% for the Amylin-manufactured exenatide once weekly drug product.
-For evaluable subjects who did not complete the Week 18S visit, nonmissing data at Week 16S was carried forward to Week 18S.
-The time points at the 3 observations prior to Day 1S (time = 0) are median time points based on observations in the Pharmacokinetic Evaluable Population (N = 196).

The results were similar in a supportive analysis in the evaluable population.
Study 105c is not optimal to demonstrate the efficacy of the Amylin (b) (4) scale product. Conceivably, it may be more difficult to lower HbA1c in treatment-naïve patients with inadequate glycemic control than maintain an adequate control in subjects already shown to tolerate and to have tolerated and responded to a very similar product (i.e., the exenatide

LAR manufactured at Alkermes at the (b) (4) scale). On the other hand, it is reasonable to expect that diabetics who had a mean HbA1c close to 9% at the baseline for Study 105 treated with a less effective product for 18 weeks would experience deterioration of glycemic control. The very close results with nearly overlapping range of HbA1c provide some assurance that the 2 sources of exenatide LAR are equally effective. In addition, the PK dose/ exposure – response data obtained in Study 105c provides additional evidence of the comparability of the 2 sources of exenatide LAR.

Study 106

The report for Study BCB106, referred to as Study 106 in this review, was only submitted with the 4-Month safety update. Therefore, the study data were reviewed to supplement and update the overall safety of exenatide LAR. As seen in Dr. Pratt's review of exenatide LAR safety, both Study 104 and Study 105 were designed with a 3-day lead in period of exenatide BID, prior to any treatment with exenatide LAR. There had been no other study shown to evaluate the safety or the tolerability of exenatide LAR without prior exenatide BID treatment. Based on that experience alone, the label of exenatide LAR would have to necessarily reflect that patients prescribed exenatide LAR would need to be treated with a lead in period with exenatide BID. Dr. Pratt's review of Study 106 was very useful to shed light on the use of exenatide LAR without prior lead in exenatide BID treatment. The safety and tolerability of exenatide LAR without the lead in period with exenatide BID were similar to the same treatment preceded by exenatide BID.
I took the initiative to briefly review the efficacy data in Study 106 to alley the concern raised by Dr. Derr regarding one weakness in the sole source of efficacy in the NDA: the open label study 105 with post-baseline glycemic manipulation potentially incurring bias in the estimate of treatment effect.

Protocol

Study 106 was a randomized, double-blind, parallel group (3-arm), active-controlled, multicenter study to compare the effect of exenatide LAR QW to sitagliptin and to pioglitazone during a 26-week treatment period. The primary endpoint was the change in HbA1c from baseline at week 26, but the study intended to compare changes in weight, other glycemic secondary endpoints and patient-reported outcomes as well. Eligible subjects were randomized to 1 of 3 treatment groups, the exenatide LAR 2 mg SC QW plus placebo PO QAM, sitagliptin 100 mg PO QAM plus placebo QW SC, or pioglitazone 45 mg PO QAM plus placebo QW SC.
Adults with T2DM treated with a stable regimen of metformin for a minimum of 2 months prior to screening were eligible to participate. Additional eligibility criteria included screening HbA1c of 7.1% to 11.0% and body mass index (BMI) of 25 kg/m^2 to 45 kg/m^2.
The primary study endpoint was change in HbA1c from baseline to Week 26. Superiority of exenatide LAR to sitagliptin or pioglitazone was demonstrated if the Hochberg adjusted p-value for the pairwise comparison (exenatide LAR vs. sitagliptin or exenatide LAR vs. pioglitazone) was < 0.05 based on a general linear model which included factors for treatment group, country, and baseline HbA1c stratum ($< 9.0\%$ or $\geq 9.0\%$). The primary analysis was based on the ITT Population using imputed data.

Results

The study was initiated on 2/11/2008 (first subject dosed) and ended on 3/9/09 (last subject's Week 26 visit). The study was conducted in 72 sites: 57 in the US, eight in India and seven in Mexico. Of 514 subjects randomized, 491 received ≥ 1 dose of study medication and were included in the ITT Population. Of these subjects, 89 withdrew during the 26-week assessment period. A total of 79% of exenatide LAR, 87% of sitagliptin, and 79% of pioglitazone subjects in the ITT Population completed the 26-week assessment period. Withdrawals during this period were due to withdrawal of consent (6.5%), lost to follow-up (4.7%), adverse events (4.5%), investigator decision (0.8%), protocol violation (0.6%), loss of glucose control (0.6%), and administrative reasons (0.4%).

Approximately half (51.7%, 254 subjects) of subjects were male. The majority of subjects were distributed fairly equally across 3 races/ethnicities: Caucasian, Hispanic and Asian. At screening, mean age was 52.5 years and mean duration of diabetes was 5.7 years. At baseline, mean body weight was 88 kg, mean BMI was 32 kg/m^2, mean HbA1c was 8.5%, and mean fasting plasma glucose concentration was 164 mg/dL. Demographic and baseline characteristics were generally evenly distributed among the treatment groups. Similar demographic and baseline characteristics were observed across the 3 treatment groups within each country.

In the ITT Population at Week 26, the LS mean change (SE) in HbA1c from baseline in the exenatide LAR group was -1.5 (0.1) %, a statistically significantly greater decrease than that observed with sitagliptin (-0.9 [0.1] %; adjusted $p < 0.0001$) or pioglitazone (-1.2 [0.1] %; adjusted $p = 0.0165$). Similar improvements were observed in the 26-Week Evaluable Population. These results demonstrate that statistically superior glycemic control, as measured by change in HbA1c, was achieved with exenatide once weekly compared to sitagliptin or pioglitazone treatment (Table 5 and Figure 4).

Table 5. Change in HbA1c from baseline to week 26 in the ITT and evaluable population in Study 106

HbA1c (%)	Treatment [2]		
	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.

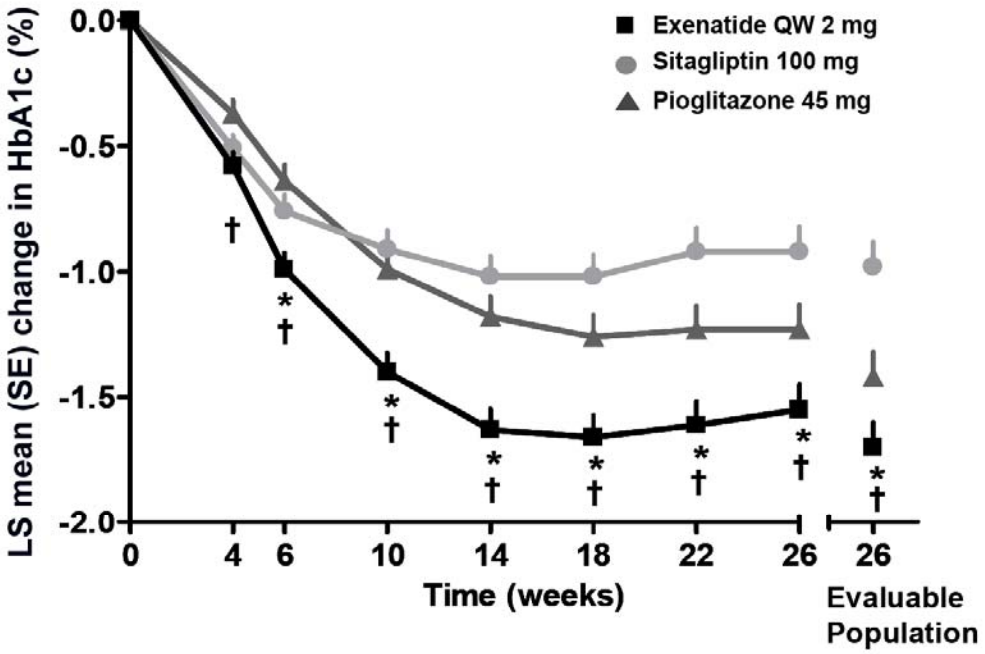
[2] Treatment: Exenatide QW 2 mg = Exenatide QW 2 mg SC weekly plus placebo PO QAM; Sitagliptin 100 mg = Sitagliptin 100 mg PO QAM plus placebo QW SC weekly; Pioglitazone 45 mg = Pioglitazone 45 mg PO QAM plus placebo QW SC weekly.

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

[4] Based on the Hochberg procedure.

Copied from Table 7 of the applicant's bcb106-study –report-body.pdf

Figure 4. Change in HbA1c over the 26 weeks of Study 106 in the ITT and Evaluable Populations



Evaluable Population = 26-Week Evaluable Population; 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.

- 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.
- Mean baseline HbA1c values for the ITT Population were 8.57% for the exenatide QW group, 8.49% for the sitagliptin group, and 8.47% for the pioglitazone group. For the 26-Week Evaluable Population, mean baseline HbA1c values were 8.62% for the exenatide QW group, 8.45% for the sitagliptin group, and 8.41% for the pioglitazone group.

*p <0.05 exenatide QW vs. sitagliptin (Hochberg adjustment).

†p <0.05 exenatide QW vs. pioglitazone (Hochberg adjustment).

Copied from Figure 3 of the applicant's bcb106-study –report-body.pdf

The efficacy was consistent across subgroups based on demographic or baseline characteristics.
Exenatide LAR was also effective in lowering FPG and other glycemic parameters examined, and caused more weight loss than sitagliptin and pioglitazone.

Thus, exenatide LAR shows robust evidence of efficacy against commonly used antidiabetic medications at effective or maximally effective doses: sitagliptin and pioglitazone, in the context of a double-blind study without the potential bias generated by the design of Study 105.

8. Safety

At the cutoff date for the original NDA submission, 366 subjects had been exposed to exenatide LAR in its final formulation (F17). At the cutoff date for the 4-Month Safety Update, 606 subjects had been exposed to exenatide LAR. At the 4-Month safety update the exposure was 233 subjects with ≥ 1 year of treatment, and 115 subjects with ≥ 18 months of treatment. The vast majority of subjects were treated with the 2 mg SC QW dose, the dose proposed for marketing.
For a more comprehensive review of the safety of exenatide LAR, please refer to Dr. Pratt's clinical review.
In summary, one death was reported in a subject treated with exenatide LAR, who suffered a myocardial infarction 198 days after initial participation in Study 105.
No specific pattern of SAEs or AEs leading to discontinuation can be seen, either in analyses of SOCs or specific events.
I will specifically highlight a few safety issues of interest for the class of GLP-1 receptor agonists:

Acute pancreatitis

Pancreatitis, including severe cases (necrotizing and / or hemorrhagic) has been initially identified post-approval of exenatide. FDA has required applicants of the approved GLP-1 agonists (exenatide BID and liraglutide) to place pancreatitis (including the severe cases) under the Warnings and Precautions section of the label and issued several health alerts related to the risk of pancreatitis associated with the use of exenatide. Other GLP-1 receptor agonists in development and the recently approved liraglutide have also been associated with pancreatitis. The mechanism by which exenatide may cause pancreatitis is not understood, and mechanistic studies with exenatide and other GLP-1 agonists in humans and in animals are underway.
In the completed studies of exenatide LAR, there were 3 reports of pancreatitis in the exenatide groups, in subjects treated with exenatide BID (0.1%) compared to 3 reports in subjects treated with comparator drugs (0.3%). No cases of pancreatitis were reported in subjects treated with exenatide LAR.

Gastrointestinal AEs

Gastrointestinal AEs predominate among subjects treated with exenatide LAR, particularly nausea, diarrhea and vomiting. Interestingly, these AEs were less frequently reported with exenatide LAR than with exenatide BID, when these treatments were compared side by side in Study 105.
Table 6 shows the incidence of frequent GI AEs in the integrated analysis of safety at the 4-Month Safety Update.

Table 6. Gastrointestinal adverse events (n/%) with incidence ≥ 5% in exenatide LAR subjects in Studies 104, 105, 106 and GWBW) (n=858)

PT	Comparator controlled				Placebo controlled	
	LAR (n=308)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)	LAR (n=51)	Placebo (n=23)
Nausea	78 (25.3)	50 (34.5)	16 (9.6)	8 (4.8)	10 (19.6)	2 (15.4)
Diarrhea	51 (16.6)	19 (13.1)	16 (9.6)	12 (7.3)	5 (9.8)	1 (7.7)
Vomiting	34 (11.0)	27 (18.6)	4 (2.4)	5 (3.0)	1 (2.0)	0 (0.0)
Constipation	25 (8.1)	9 (6.2)	3 (1.8)	2 (1.2)	2 (3.9)	1 (7.7)
Dyspepsia	18 (5.8)	4 (2.8)	6 (3.6)	4 (2.4)	0 (0.0)	0 (0.0)
Anorexia	4 (1.3)	1 (0.7)	1 (0.6)	0 (0.0)	5 (9.8)	0 (0.0)
Gastroenteritis	1 (0.3)	0 (0.0)	3 (1.8)	1 (0.6)	6 (11.8)	0 (0.0)

Copied from the 4-Month Safety Update Table 7

Six subjects on exenatide LAR (0.1%) withdrew due to GI AEs: three subjects in Study 105 (impaired gastric emptying, nausea and vomiting) and three subjects in Study 106 (diarrhea).

Immunogenicity and hypersensitivity (local and systemic)

Exenatide LAR proved to be more immunogenic than exenatide BID (74.3% versus 49% in Study 105), although no clinical consequences appear evident, in terms of hypersensitivity reactions or neutralization of glycemic effects. With regard to the latter, it is worth stating that anti-exenatide antibody attenuation of glycemic effects is more evident with exenatide BID than with exenatide LAR in Study 105 (Table 7).

Table 7. Change in HbA1c from baseline at week 30 by antibody status in Study 105

Study group	Low titer positive antibodies	Negative antibodies
Exenatide LAR	-1.8	-2.1
Exenatide	-1.1	-1.7

Adapted from Table 5 in Dr. Pratt's clinical review.

Nine subjects in Study 105 had high anti-exenatide antibody titers, defined by the applicant as greater than a 1/625 dilution, and the mean HbA1c change in that small group was lessened compared to the entire exenatide LAR group, suggesting some greater attenuation of effect with high titers of anti-exenatide antibodies. Importantly, the applicant did not find cross-reacting antibodies directed against endogenous GLP-1.
Local injection site reactions (pruritus, erythema, rash or swelling) were more common with exenatide LAR than with exenatide BID, but they were well tolerated and not a reason for discontinuation. These reactions were also more common among anti-exenatide antibody positive subjects (18.3%) than in anti-exenatide antibody negative subjects (4.9%). There were no reports of SAEs related to hypersensitivity. There were no reports of fibromas or other injection site-related neoplastic AE, even in subjects with the longer exposures to exenatide LAR.

Thyroid tumors

Thyroid tumors, in particular medullary cancer of the thyroid, have been of concern with GLP-1 receptor agonists with duration of effect longer than that of exenatide BID. The

concern relates to the rodent findings at clinically relevant exposures. Medullary cancer of the thyroid is a rare occurrence, and persuasive evidence through adequately powered controlled clinical trials is not possible. Liraglutide was approved with required postmarketing animal studies to further explore the mechanism of disease and required case registries of medullary cancer (with duration of at least 15 years) to better estimate the association to GLP-1 treatment in humans.

No thyroid cancer was reported in the exenatide LAR development program, although the exposure was too low to allow for a reliable assessment of the risk. One subject treated with exenatide LAR in Study 105 had a benign thyroid mass. In the ongoing Study BCB108, serum calcitonin levels are being monitored. Please refer to Dr. Pratt's clinical review for additional relevant information regarding thyroid tumors and calcitonin monitoring.

Cardiovascular Events

All antidiabetic drugs except for insulins for parenteral administration are subject to a requirement to demonstrate that they do not exceed an unacceptable rate of cardiovascular (CV) events, compared to a control group. Exenatide was approved in 2005 prior to the implementation of the CV guidance that describes this requirement. For drugs approved prior to the guidance (including exenatide), the applicant needs to demonstrate that the risk ratio of major CV adverse events in patients treated with that drug does not exceed 1.3 (or 30 % greater than a control group).

Drs. Marciniak and Stockbridge, from the Division of Cardiorenal Products / Office of New Drugs and Drs. Fiona Callaghan and Mark Levenson, from the Office of Biostatistics, were consulted regarding a metanalysis of CV events in patients treated with exenatide (combined exenatide BID and exenatide LAR), which was prepared by the applicant and submitted under the exenatide LAR NDA.

The applicant's meta-analysis of the 12 exenatide trials used the intent-to-treat population, which was defined as all randomized subjects that received at least one dose of study medication. There were 2 endpoints of interest. The first endpoint (Standardized MedDRA Query of Major Adverse CV Events, or SMQ MACE) included all the preferred terms in the SMQs for "Myocardial Infarction" and "Central nervous system haemorrhages and cerebrovascular accidents". The second endpoint ("Custom MACE") is based on a narrower definition of CV events and is comprised of a list of preferred terms that focus on myocardial infarction and stroke events. The definition of the Custom MACE endpoint was provided by the FDA.

The statisticians calculated a Mantel-Haenszel risk ratio of 0.915 with 95% confidence intervals of 0.555 and 1.511 for the SMQ MACE, and a risk ratio of 0.875 with confidence intervals between 0.332 and 2.306 for the Custom MACE.

They recommended "that Bydureon be approved on the condition that at least one further post-marketing study is completed in order to ascertain whether the cardiovascular risk ratio is below 1.3 or not. It is also recommended that a subgroup analysis on race, gender and age be included in the post-marketing study, as per the guidance."

The cardiologists emphasized the primary endpoint being the traditionally defined MACE as CV death, non-fatal myocardial infarction and nonfatal stroke and recalculated the risk ratios and 95 % confidence intervals. In addition, they recalculated the risk ratio with an

expanded definition of events, to include coronary artery disease, unstable angina, and angina; heart failure; and transient ischemic attack. They excluded arrhythmia and intervention-related events.
The summary of their metanalysis is shown in Table 8.

Table 8. DCRP Metanalysis of CV events

	CV death/MI/stroke		+angina/CAD/HF/TIA	
	EX	P-C	EX	P-C
Patients at risk (N)	2316	1629	2316	1629
Patients with events (n)	9	7	28	18
Percentage (n/N x 100)	0.4%	0.4%	1.2%	1.1%
Mantel-Haenszel RR*	0.84 (0.33 - 2.17)		0.98 (0.56-1.71)	
I-squared	0		0.24	
Dersimonian-Laird RR*	0.79 (0.28-2.19)		0.98 (0.45-2.13)	

* RR = relative risk (95% confidence interval)
Copied from Dr. Marciniak's review Table 3

The QT-IRT consultants, Dr. Christine Garnett and Norman Stockbridge, reported that there are no apparent QT-prolonging effects of exenatide when administered as the LAR or BID formulations. However, they cannot rule out small increases in the QTc interval (<10 ms) because a dedicated TQT study with positive and placebo controls was not conducted. Their conclusions are based on the following data:
• In study 2993LAR-105, replicate 12-lead ECGs were obtained at baseline, at Week 14, once steady-state plasma concentrations were achieved, and at Week 30. No individual subject post-baseline QTcF measurements ≥ 450 ms. The mean change from baseline QTcF was < 5ms.
• In a meta-analysis of studies 2993-112, 2993-113 and 2993-115, there were no apparent QTc-prolonging effects of exenatide immediate release. No subjects had change from baseline > 60 ms. The mean change from baseline QTcF at week 30 on treatment were similar to placebo. There was no apparent relationship between exenatide concentrations and change in QTcF intervals.
The average exenatide exposures achieved with the LAR formulation are lower than the approved BID formulation. A dedicated TQT is not needed unless there are cardiovascular AEs such as syncope, seizures, ventricular arrhythmias or sudden death in the clinical development program and post-marketing reports, for which a more accurate and precise assessment of the effects of exenatide on QTc is desired.

Due to the paucity of events in the entire exenatide program and the wide confidence intervals exceeding the CV guidance goalposts, the applicant has proposed and the FDA consultants agree that a dedicated cardiovascular safety trial be conducted, with rigorous event adjudication, following the FDA CV guidance.

Postmarketing Requirements and Risk Evaluation and Mitigation Strategy (REMS) Requirements

Of more important consequences for the approvability and labeling of exenatide LAR, three particular issues need to be emphasized:

1. Pancreatitis is now considered a risk for this class of antidiabetic drugs, and labeling for exenatide LAR will reflect FDA's view of the risk, including placement in the Warnings and Precaution section of the label, due to serious cases of pancreatitis.
2. Although FDA has not traditionally made recommendations about specific antidiabetic treatments being first line (use in treatment naïve) or second line (use as add-on or to replace a drug upon secondary failure) therapies, FDA approved liraglutide specifically as a second line therapy due to the uncertainty regarding the nonclinical findings of c cell carcinoma in rodents at clinical exposures and the lack of data to assure us that those findings cannot be extrapolated to humans. A similar approach is expected to be used for exenatide LAR and other GLP-1 agonists in the future.
3. Cardiovascular events are common in the diabetic population. Although FDA considers a beneficial effect on glycemic control sufficient to provide evidence of efficacy, a new guidance published in December 2008 notified sponsors that new products will be approved if they demonstrate that the risk of MACE events with the use of their drugs do not exceed a risk ratio of 1.8 and, once approved, may remain on the market if the risk ratio against a control treatment does not exceed 1.3 (upper bound of the 95% confidence interval). A metanalysis of events reported in the exenatide development program has not ruled out the unacceptable risks needed to demonstrate the CV safety of exenatide. FDA will not require that exenatide LAR per se is subject to the guidance requirements, as we view exenatide LAR as a different formulation of exenatide. FDA may accept CV evidence gathered from the combined experience of exenatide BID and exenatide LAR, through a more robust metanalysis or, preferably, through a dedicated CV safety study. In practical terms, however, we foresee that once exenatide LAR is approved, it will be difficult to recruit sufficient number of subjects to be treated with exenatide BID for years, for the minimal exposure required to yield enough MACE events to rule out a risk ratio of 1.3. So, the applicant will likely propose that a dedicated CV safety study be conducted exclusively with exenatide LAR, and not exenatide BID. My view is that such proposal is acceptable, as most new exenatide prescriptions will be for exenatide LAR. In addition, a substantial proportion of patients currently on exenatide BID will like to convert to exenatide LAR, due to the greater convenience.

Similarly to liraglutide, REMS for exenatide LAR will include a Medication Guide, a Communication Plan and a Timetable of Assessments.

9. Advisory Committee Meeting

This NDA was not presented at an Advisory Committee Meeting. It is an extended formulation of exenatide, an approved drug for the same indication.

10. Pediatrics

A pediatric trial to investigate the safety and efficacy of exenatide BID is currently ongoing, as part of PREA requirements and under a Written Request (BPCA). The Division is considering a common approach to liraglutide and exenatide LAR with regard to pediatric studies. Approval of liraglutide in adults with T2DM was accompanied by the PREA PMR to conduct studies in pediatric patients age 10 -1 6 years. However, due to the potential risk of MTC based on the rodent data, FDA prefers than additional nonclinical studies elucidating the mechanisms of GLP-1 induced c cell hyperplasia and MTC (namely, thyroid GLP-1 receptor binding and rearranged-during-transfection [RET] proto-oncogene activation) be conducted and reviewed before any recommendation that pediatric studies are conducted.

These points were presented to the Pediatric Research Committee and accepted by the committee.

The applicant will need to submit a pediatric plan with timelines to be included in the approval letter, but the actual execution of pediatric trials will be contingent upon the findings of the additional nonclinical studies.

Even the single dose PK study in a pediatric population, typically conducted in order to define the best dose(s) to evaluate in a subsequent safety and efficacy study, will not be conducted prior to the nonclinical study results: a single dose of exenatide LAR yields detectable exenatide levels for up to 10 weeks, making the exposure prolonged enough to be of concern. In addition, specifically for exenatide LAR, single dose PK may not accurately reflect exposure and predict PD effects as multidose PK do. So, if the nonclinical findings do not raise additional concerns for children, it is likely that a single safety and efficacy study will be required and conducted in pediatric age subjects, to also include population PK assessments.

11. Other Relevant Regulatory Issues

None.

12. Labeling

The Division of Medication Error Prevention and Analysis found the proprietary name Bydureon acceptable. Other labeling issues are discussed throughout this review, where applicable. At the time of this writing, labeling negotiations with the applicant have not been initiated, with the exception of a notification that a REMS will be required, to include a Medication Guide, a Communication Plan and a Timetable for Assessments.

13. Recommendations/Risk Benefit Assessment

For this review cycle, I recommend a Complete Response action, so that we can discuss and fine tune with the applicant the REMS proposal and the necessary PMRs.

Once these are agreed upon and submitted to FDA for final review, in the next cycle, I foresee we will be able to approve exenatide LAR as second line treatment for adults with T2DM, a restriction similar to that imposed for liraglutide. Overall the risk benefit profile

is favorable, as efficacy in lowering glucose and controlling hyperglycemia has been demonstrated, and the risks of exenatide are well known through 5 years of postmarketing experience. Two potential risks will not be defined by the time exenatide LAR is approved: the risk of MTC in humans associated with this or other GLP-1 agonists of duration more prolonged than exenatide BID, and the CV risks associated with both exenatide BID and exenatide LAR. We expect the MTC risk to be gradually informed by the 15-year plus registries being established for that purpose, and the CV risks to be elucidated through the results of a well designed CV safety trial.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	Bydureon (exenatide LAR)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ILAN IRONY
03/12/2010

MARY H PARKS
03/12/2010
I concur with Dr. Ilrony's recommendations that a complete response letter be issued. His memo will also serve as the decisional memo for the division.

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	22-200
Priority or Standard	Standard
Submit Date(s)	05-04-09
Received Date(s)	05-05-09
PDUFA Goal Date	03-05-10
Division / Office	DMEP / ODE II
Reviewer Name(s)	Valerie S. W. Pratt, M.D.
Review Completion Date	February 22, 2010
Established Name	Exenatide LAR
(Proposed) Trade Name	Bydureon
Therapeutic Class	GLP-1 agonist
Applicant	Amylin Pharmaceuticals Inc.
Formulation(s)	Injection
Dosing Regimen	2 mg SC once weekly
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adult type 2 diabetics

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a complete response to this new drug application due to the lack of an agreed upon Risk Evaluation and Mitigation Strategy (REMS) at this time.

1.2 Risk Benefit Assessment

Based on my review of the clinical data, I believe that without a REMS the potential benefits of exenatide LAR 2 mg subcutaneously once weekly for the treatment of type 2 diabetes mellitus (T2DM) do not outweigh the potential risks. Risks include pancreatitis and nonclinical thyroid tumors which have been associated with other currently marketed or soon-to-be approved GLP-1 analogues as well as injection site reactions which are specific to exenatide LAR. The sponsor has been unable to rule out an excessive cardiovascular risk through a meta-analysis of combined exenatide and exenatide LAR studies. Therefore a cardiovascular outcomes study should be required as a Postmarketing Requirement.

Benefits of exenatide LAR include efficacy in glucose lowering, convenient dosing, and fewer gastrointestinal adverse events. In the single supportive trial (Study 105) the LS mean (SE) change in HbA1c from baseline to week 30 in the exenatide LAR group in pivotal study 105 was -1.9% (0.08), a statistically significant change when compared to the -1.5% (0.08) change in HbA1c with exenatide (p=0.0023). Furthermore, exenatide LAR is conveniently dosed with weekly administration. Study 105 also demonstrated reduced incidence of gastrointestinal adverse events, specifically nausea and vomiting, which are associated with exenatide.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Because of 1) the risk of thyroid tumors associated with glucagon-like-peptide-1 (GLP-1) analogues and identified in preclinical study REST060229 ((b) (4) #840-040) and 2) post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide and in order to ensure that the benefits of exenatide continue to outweigh this serious risk, I recommend a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide (MG), communication plan, and timetable for assessments. The sponsor should also continue to submit 15-day reports for cases of thyroid tumors and suspected pancreatitis, so that

we may continue to assess these evolving issues. I also recommend the postmarket requirements (PMRs) described in section 1.4.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the following required postmarketing studies (PMRs). However, please note that these are preliminary PMRs at the time of filing the review, pending additional internal discussion and negotiations with the sponsor.

- A deferred phase 1 pharmacokinetic (PK) pediatric study that will be conducted under Pediatric Research Equity Act (PREA). This study should investigate multiple doses of exenatide LAR and may be conducted independently or as a substudy of the safety and efficacy study described below (population PK).
- A deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of exenatide LAR for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years 11 months. This study should not be initiated until at least 1 month after the completed study report for the rodent study to determine if exenatide LAR-induced c-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation has been submitted to FDA and found to conclude no likely effects on human thyroid. Note, protocol(s) for the pediatric studies should be submitted with the NDA with clear timelines (i.e. dates) for completion.
- A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to exenatide LAR and patients with type 2 diabetes not exposed to exenatide LAR, as well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, injection site reactions, and neoplasms.
- Medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of exenatide LAR into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of exenatide LAR.
- A randomized, double-blind, controlled trial evaluating the effect of exenatide and/or exenatide LAR on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This trial must also assess adverse events of interest including the long-term effects of exenatide/LAR on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects on serious hypoglycemia, pancreatitis, immunogenic potential, hypersensitivity, injection site reactions, neoplasms, and renal safety.

2 Introduction and Regulatory Background

2.1 Product Information

Amylin Pharmaceuticals, Inc. has submitted this new drug application (NDA) for the use of exenatide long-acting release (LAR) injection (proposed trade name Bydureon) as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

Exenatide LAR contains the same active ingredient as the commercial product exenatide (Byetta) injection (NDAs 21-773 and 21-919). Exenatide injection, an incretin mimetic (specifically, glucagon-like-peptide-1 [GLP-1] agonist), is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, this NDA references the safety and efficacy information in the Byetta NDA.

Exenatide LAR had been produced using drug substance from (b) (4) different suppliers during its development: (b) (4) Mallinckrodt, Inc. and Lonza, SA. It had also been manufactured at (b) (4) different scales ((b) (4)) and at 2 different manufacturing sites (Alkermes, Inc. in Wilmington, Ohio and Amylin Ohio, LLC in West Chester, Ohio. The phase 2 study 2993LAR-104 (study 104) and all prior studies were conducted using the (b) (4) scale. Phase 3 studies used material from all (b) (4) scales. The phase 3 study 2993LAR-105 (study 105) started with material from the (b) (4) scale, although (b) (4) scale product was later introduced. Comparability of the Amylin drug product intended for commercial use and Alkermes drug product used during clinical development was assessed via glycemic, pharmacokinetic, and safety endpoints in extension study 105c. Please refer to the CMC review for full details.

2.2 Tables of Currently Available Treatments for Proposed Indications

Medications currently approved for the treatment of type 2 diabetes mellitus include the following:

- Sulfonylureas
  - Tolazamide (Tolinase)
  - Chlopropramide (Diabinese)
  - Glyburide (Micronase)
  - Glipizide (Glucotrol and Glucotrol XL)
  - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)

- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones
  - Rosigitazone (Avandia)
  - Pioglitazone (Actos)
- α-Glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)
- Incretin-mimetics
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
- Amylinomimetics
  - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
- Bile acid sequestrants
  - Colesevelam (WelChol)
- Dopamine receptor agonists
  - Bromocriptine mesylate (Cycloset)

2.3 Availability of Proposed Active Ingredient in the United States

Exenatide LAR is not currently approved for use in the United States, although exenatide has been approved in the United States since March 2005 and is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Exenatide is currently being studied under (b) (4) INDs:

1) IND 57,725 Exenatide injection for the treatment of T2DM
2) IND 67,092 Exenatide LAR injection for the treatment of T2DM

(b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

Exenatide is used to improve glycemic control in T2DM patients. Labeled safety concerns with exenatide include:

1. **Acute pancreatitis**
2. **Gastrointestinal side effects**
3. **Hypoglycemia, especially when used in combination with a sulfonylurea**
4. **Hypersensitivity reactions as a result of anti-exenatide antibodies**

5. **Renal failure**

The division recently approved NDA 22-341 for liraglutide, another GLP-1receptor agonist. Liraglutide causes thyroid c-cell tumors in rats and mice.

- Thyroid c-cell tumors occurred at all doses tested in males and females in a 104-week repeat subcutaneous dose study of 0.075, 0.25, or 0.75 mg/kg/day liraglutide in Sprague Dawley rats, but survival was unaffected by treatment. The No Observed Adverse Effect Level (NOAEL) for thyroid c-cell tumors was < 0.075 mg/kg/day liraglutide, below the lowest dose tested. The rodent tumors occurred at exposures equivalent to the human exposure based on plasma AUC0-24 comparison across species. Malignant c-cell carcinomas increased with dose in males at 0.75 mg/kg and the incidence was above the historical control group range at > 0.075 mg/kg in males and at > 0.75 mg/kg in females.
- The sponsor also conducted a 104-week lifetime-exposure carcinogenicity study of 0.03, 0.2, 1, or 3 mg/kg/day liraglutide injected subcutaneously once a day in CD-1 mice. The NOAEL for thyroid c-cell tumors in mice was 0.2 mg/kg/day liraglutide (1.8x human exposure) and the NOAEL for fibrosarcomas on the dorsal skin and subcutis was 1 mg/kg/day (10x human exposure). Benign c-cell adenomas dose-dependently increased compared to concurrent controls and above the historical control group range at > 1 mg/kg liraglutide in males and females. Malignant c-cell carcinoma occurred in 2 high dose females, and the incidence of combined c-cell carcinoma and adenomas dose-dependently increased at > 1 mg/kg in females. The data are consistent with dose-related progression of focal hyperplasia to adenomas in males and females with further progression to carcinomas in high dose females.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Exenatide LAR was developed for the treatment of T2DM under IND 67,092, which was opened March 17, 2003. As Bydureon and Byetta share the same active ingredient and the Bydureon application proposes the same indication, NDA 22-200 references the safety and efficacy information in Byetta NDA 21-773.

Key agreements and developments related to the exenatide LAR development program are as follows:

- March 9, 2006: Written responses were conveyed to the sponsor, as a guidance meeting request was denied.
    - Study 105 should be a non-inferiority (NI) trial. Exenatide may be used as an active control, but no NI margin was proposed or discussed. The protocol should be submitted to the agency prior to study initiation.
    - The impact of exenatide LAR on gastric emptying may not be the same as exenatide. Further evaluation of drug interactions depends on the outcome of the acetaminophen study.

  - Additional cardiovascular safety (CV) assessments, specific for the exenatide LAR product, may not be necessary, if there are no signals for QT prolongation.
- May 1, 2007: The End of Phase 2 (EOP2) meeting was held.
  - A bioequivalence (BE) study comparing the (b) (4) commercial product with either the (b) (4) or (b) (4) product was recommended, due to the Level 3 site change. Alternatively, a waiver for the BE study could be requested although a validated in vitro/in vivo correlation (IVIVC) would then be required and this is quite challenging. The sponsor chose to submit an IVIVC development plan.
- December 5, 2007: The agency responded to questions pertaining to the IVIVC.
  - Formulations outside of the proven acceptable ranges of commercial formulation (AC2993-F17) in terms of PLG polymer molecular weight and/or lactide:glycolide ratio could be used to establish an IVIVC.
  - Both Cmax and AUC must be assessed in the model validation. The IVIVC should cover exenatide LAR release phases 1, 2, and 3.
  - The agency recommended the IVIVC model be developed in humans, as rats appear less sensitive than humans and may not accurately predict human data. To prevent tolerability (e.g. nausea and vomiting) concerns with 10 mg exenatide when developing the IVIVC model in humans, a 2.5-10 mg dose was recommended.
- June 24, 2008: The pre-NDA meeting was held.
  - The agency agreed with the chemistry, manufacturing, and controls (CMC) proposals.
  - The sponsor should submit the IVIVC-based biowaiver prior to the NDA. If the waiver is not acceptable (which was later reported to be the case), the NDA must contain clinical trial results supporting similarity of the product used in the exenatide LAR development program and the commercial product.
  - The division did not accept the 12-week extension study proposed in the study 105 protocol amendment. It was felt that data from such a short extension study would not be reliable. The division recommended a separate randomized trial, which would take into account the HbA1c-time profile for exenatide LAR. Study results should be included in the NDA, unless the division previously accepted the IVIVC-based biowaiver.
  - The ongoing rat carcinogenicity study may be submitted as a postmarketing commitment, although this may be made a postmarketing requirement. The sponsor should submit as 15-day safety reports preliminary results which suggest exenatide LAR induces a greater increase in c-cell adenomas or increases in tumor types not previously observed with exenatide.
  - An additional QT study is not required, although the final decision regarding CV safety is a review issue.

  - The division strongly encouraged the sponsor to submit the results of clinical trials conducted without an exenatide lead-in. The final decision regarding whether patients may initiate exenatide LAR without prior exenatide exposure is a review issue.
  - Exenatide LAR may be presented in a separate label.
  - The sponsor should conduct failure modes and effects analysis (FMEA) to evaluate whether a new proprietary name or utilization of an extension of the Byetta name would be less error-prone.
  - Although a final decision regarding pediatric study deferral or waiver will be made after a discussion with the Pediatric Review Committee (PeRC), a waiver for studies in ages 0-11 years and deferral of studies in 12-16 years is reasonable.
  - An analysis of thyroid neoplasms in exenatide LAR and exenatide trials and postmarketing reports was requested as well as an analysis of immunogenicity in the exenatide LAR clinical trials.
- October 29, 2008: The IVIVC BE-waiver to support a proposed manufacturing site change from the clinical manufacturing site to the intended commercial site was denied because 1) the utilization of rats for BE studies is not acceptable and 2) the IVIVC poorly predicts Cmax.
- November 3, 2008: The sponsor was made aware that, due to the recommendations of the July 1-2, 2008 Endocrinologic and Metabolic Drugs Advisory Committee, additional evidence is needed to address concerns about CV risk. The sponsor must demonstrate that exenatide does not result in an unacceptable increase in CV risk. Recommendations included conducting a phase 2 and 3 meta-analysis, prospective CV event adjudication, and proper statistical analysis.
- November 12, 2008: The sponsor submitted draft study results from REST060229 ([redacted] (b) (4) #840-040), "104-week carcinogenicity study following every other week subcutaneous administration." Please refer to section 4.3 Preclinical Pharmacology/Toxicology for the report's details. As a result, the division recommended excluding subjects at risk for thyroid cancer from exenatide LAR studies, inclusion of study findings in the informed consent, as well as thyroid cancer monitoring.
- November 17, 2008: The sponsor was made aware that the extension to study 105 proposed on July 16, 2008 was generally acceptable.
  - Appropriate pharmacokinetic (PK) sampling to establish BE based on Cmax and area under the curve (AUC) between the investigational and commercial drug products was advised.
  - If the sponsor is unable to demonstrate BE based on AUC, the efficacy results from the extension study may not be sufficient for product approval.
  - If a decline in glycemic control is observed at the end of the extension, the division will not be able to discern whether this is a common phenomenon

observed with other diabetes drugs or if it is evidence of lower efficacy of the commercial product.

- March 3, 2009: The sponsor reported a case (manufacturer report #FR200901001446) of elevated amylase and lipase in an asymptomatic 49 year old female (patient identification #5651) who used exenatide LAR for 6 months.
    - Recommendations were conveyed regarding pancreatitis exclusion criteria, serum amylase/lipase monitoring, pancreatitis management and further study.
    - Recommendations were also conveyed regarding the risk of lactic acidosis in studies of a GLP-1 analogue and metformin coadministration, especially in the setting of nausea, vomiting, and decreased renal function.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of appropriate quality. As discussed at the pre-NDA meeting, the sponsor submitted a comparability assessment between the products manufactured at the (b) (4) scale and the (b) (4) scale (study 105c) and analysis of thyroid neoplasms and immunogenicity. The sponsor was also asked at the pre-NDA meeting to submit with the NDA results of clinical trials conducted without an exenatide lead-in, if it intended to pursue labeling which recommended the use of exenatide LAR without prior use of exenatide. Although the sponsor submitted such labeling, it only submitted data from a small Japanese study GWBW with the NDA. A larger study (BCB106) conducted in a more diverse population was submitted with the four month safety update.

The sponsor followed the December 2008 diabetes mellitus cardiovascular (CV) guidance, by providing a metanalysis of combined exenatide and exenatide LAR studies. However, on October 17, 2009, a request that the sponsor reanalyze the major adverse cardiovascular events (MACE) was made. The sponsor responded to this request and the clinical requests in the 74 day letter in a timely and appropriate manner. The information submitted was reasonably well organized.

3.2 Compliance with Good Clinical Practices

Pivotal studies 2993LAR-105 and 105c were conducted in compliance with Good Clinical Practices and the Code of Federal Regulations (CFT) Title 21 Part 56 relating to institutional review boards.

The Division of Scientific Investigations (DSI) was consulted for clinical site inspections of pivotal studies 105 and 105c. Two sites were recommended:

- 108 Eric J. Klein of Olympia, Washington due to his high enrollment (39 subjects in study 105 and 11 subjects in study 104) (b) (6)
- 405 Dean Kereiakes of Cincinnati, Ohio because he is (b) (4), (b) (6) and was last inspected in October 1996 when voluntary action was indicated (VAI).

DSI investigations found that no action was indicated at Dr. Kereiakes' site and voluntary action is indicated at Dr. Klein's site. A form FDA 483 was issued at Dr. Klein's site for the following reasons:

- There was no documentation of stable weight for subjects 10823, 10825, and 10833 prior to enrollment.
- There was not complete reporting of adverse events for Subject 10813. This included one instance of headache and one instance of vomiting that were recorded in the subject diary and one episode of vomiting that was recorded in response to a direct question from the Clinical Trial Research Pharmacist (CTRP). However, these were not reported in the case report form. In his reply of October 29, 2009, Dr. Klein stated that Subject 10813 had numerous adverse events, and he considered the headache part of an upper respiratory illness all ready reported. Dr. Klein did not consider the episode of bloating as a true adverse event because it was elicited by direct questioning by the CTRP.

The data from both sites were found to be adequate for use in support of the proposed indication.

An additional observation was that some subjects at the Klein site experienced difficulty with administration of study products, both test article and comparator, for example priming of the pens used for the comparator exenatide BID, clogging of needles, and leaking pens. During the study, the sponsor established a call center to handle product complaints and distributed example questions to be used for reporting complaints (e.g. date clog occurred, week or injection number, how much volume was injected prior to the clog). Please refer to section 7.7 Additional submissions/Safety Issues for more detail.

In key study 105, the rate of protocol deviations was generally less in the exenatide LAR than the exenatide BID group. (See table below.) In pivotal study 105's 30 week

assessment, 16 (5.4%) subjects had protocol deviations based on inclusion/exclusion criteria at screening. These deviations included excluded medications, duration of diabetes/treatment, clinically significant medical conditions (e.g. HIV and thyroid cancer within 5 years), and BMI and FPG above the allowable limit.

In addition to protocol deviations based on inclusion/exclusion criteria, other protocol deviations were reported by the Amylin investigator for 31 (10.5%) ITT subjects. The most common deviation was "restricted concomitant medication", which was reported for 18 (6.1%) subjects. Thirteen (4.4%) subjects had "other study drug deviation". Two subjects had a "study procedure" deviation.

Table 1. Study 105: Protocol deviations by treatment (Reproduced from study report table 7)

Type Category	Treatment BYETTA 10 mcg BID (N = 147) n (%) [1]	Exenatide LAR 2 mg QW (N = 148) n (%) [1]	All Subjects (N = 295) n (%) [1]
All Inclusion/Exclusion Criteria	10 (6.8)	6 (4.1)	16 (5.4)
Reported by the Investigator	20 (13.6)	11 (7.4)	31 (10.5)
Other Study Drug Deviation [2]	13 (8.8)	0 (0.0)	13 (4.4)
Restricted Concomitant Medication Change	7 (4.8)	11 (7.4)	18 (6.1)
Study Procedure	2 (1.4)	0 (0.0)	2 (0.7)

In key study 105c, only 4 (1.8%) protocol deviations were reported. Two included the addition of a restricted concomitant medication, 1 participated in another double blind investigational study, and 1 was dispensed the wrong medication kit on day 1. Subject 22411, who took a restricted concomitant medication, was withdrawn from the study. Subject 01715, who received the wrong study medication, was excluded from the evaluable population.

Protocol deviations did not likely affect data quality.

3.3 Financial Disclosures

Only 2 investigators disclosed a financial interest. [redacted] (b) (6) enrolled [redacted] (b) (6) subjects in [redacted] (b) (6)

[redacted] (b) (6) owns Amylin stock, valued at $50,000. [redacted] (b) (6) enrolled [redacted] (b) (6) subjects in [redacted] (b) (6). As the studies reviewed are [redacted] (b) (6)

[redacted] (b) (4) studies, the outcome of the trials was not likely influenced by the compensation received by either physician.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The commercial drug formulation of exenatide LAR is coded as AC2993-F17, which is [redacted] (b) (4) exenatide, [redacted] (b) (4) sucrose, and [redacted] (b) (4) polymer (poly-D,L-lactide-coglycolide [PLG], 50:50). The product is a powder in a [redacted] (b) (4) vial, co-packaged in a kit that includes a aqueous diluent in a syringe, injection needles, and a vial connector. Once reconstituted, exenatide LAR should be administered subcutaneously (SC) immediately.

The recommended storage temperature for the drug product in vials is 2-8ºC and allows for 4 weeks of storage at up to 25ºC for patient convenience. The product is light-sensitive. The sponsor proposes an expiration dating period of [redacted] (b) (4) months but may extend this with additional stability data if exenatide LAR is approved.

Exenatide LAR has been manufactured at [redacted] (b) (4) scales during development. The [redacted] (b) (4) and [redacted] (b) (4) scales products were manufactured at Alkermes, Inc. in Wilmington, Ohio. The proposed commercial [redacted] (b) (4) scale is manufactured at the proposed commercial site of Amylin Ohio, LLC in West Chester, Ohio. Prior to phase 3, all studies were conducted using drug product manufactured at the [redacted] (b) (4) scale. Phase 3 studies used material from all [redacted] (b) (4) scales. The phase 3 study 105 started with Alkermes material from the [redacted] (b) (4) scale, although [redacted] (b) (4) scale product was later introduced. Comparability of the Amylin drug product ([redacted] (b) (4) scale) intended for commercial use and the Alkermes drug product used during clinical development was assessed via glycemic, pharmacokinetic, and safety endpoints in extension study 105c. As the attempt to establish IVIVC failed, the drug release test was used for quality control only.

At the EOP2 meeting, the sponsor proposed establishing Lonza and Mallinckrodt as drug substance suppliers for the exenatide LAR drug product. However, in the NDA, the sponsor also proposed [redacted] (b) (4)

Please refer to Dr. Olen Stephens' CMC review for full details.

4.2 Clinical Microbiology

The product is packaged for single use and is not preserved.

Please refer to Dr. Robert J. Mello's microbiology review for full details.

4.3 Preclinical Pharmacology/Toxicology

To bridge to the Byetta nonclinical program, 2- and 4-month rat and 3- and 9-month monkey studies were conducted. In vitro genotoxicity studies and a carcinogenicity study in rats were also conducted.

GLP-1 agonists have been associated with thyroid c-cell tumors. Benign thyroid c-cell adenomas were observed in the 104-week exenatide carcinogenicity study in female rats at all exenatide doses (18 [5x], 70 [22x], or 250 [130x] mcg/kg/day SC), although there was no evidence of tumors at doses up to 250 mg/kg/day [95x] in mice.

Thyroid c-cell tumors occurred at all doses tested in males and females in the 104-week carcinogenicity study of 0.075, 0.25, and 0.75 mg/kg/day liraglutide in Sprague Dawley rats, but survival was unaffected by treatment. The No Observed Adverse Effect Level (NOAEL) for thyroid c-cell tumors was <0.075 mg/kg/day, below the lowest dose tested. In mice dosed with 0.03, 0.2, 1, or 3 mg/kg/day liraglutide, the NOAEL for thyroid c-cell tumors in mice was 0.2 mg/kg/day (1.8x human exposure). There was a dose-related progression of focal hyperplasia to adenomas in males and females with further progression to carcinomas in high dose females.

The estimated daily steady state for exenatide LAR is approximately 3.6x the daily exposure for exenatide twice daily, based on the exposure information presented in the label. Therefore, not only are the PK characteristics of exenatide twice daily and exenatide once weekly different, but the overall daily exposure is higher for the once weekly formulation.

In a draft report of study REST060229 ([(b) (4)] #840-040), "104-week carcinogenicity study following every other week subcutaneous administration", the administration of exenatide LAR 0.3-3.0 mg/kg every other week for 2 years to rats was associated with a statistically significant increase in thyroid c-cell tumor incidence in males and females. The incidence of c-cell adenomas was significantly increased at all doses (27-31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%) in males. Thus, the NOAEL for thyroid c-cell adenomas occurred at a clinically relevant exposure level (<1.3). The incidence of c-cell carcinomas also increased significantly in the high dose group females (6%), while nonstatistically significant increases were noted in the low, mid, and high dose males (3%, 7%, and 4%, respectively). However, the NOAEL was not established with regard to tumorigenic potential, because an increase in c-cell adenomas and hyperplasia was observed in both males and females at 0.3 mg/kg.

Although an agreement was reached at the pre-NDA meeting that the sponsor would submit the final rat carcinogenicity study report post-marketing, the sponsor was asked in the 74-day letter to submit the final report premarketing due to the increased incidence of c-cell adenomas and carcinomas. This information should be included in the exenatide LAR labeling if approved.

The sponsor has not evaluated the effects of exenatide LAR in a 104-week carcinogenicity study in mice, and the Executive Carcinogenicity Assessment Committee (ECAC) determined that this was not required.

On the basis of these nonclinical data, pharmacology/toxicology reviewer, Dr. B. Timothy Hummer, recommends a complete response. There is insufficient information to conclude that GLP-1 receptor agonist-induced c-cell tumors are not relevant to human risk. (Please refer to his review for full details.) However, he acknowledges that the ultimate decision for marketing approval is a clinical one, as the broader risk to benefit ratio must be considered. He recommends the following factors also be considered:

- Clinical benefit, including once weekly administration
- Labeling, including the use of a boxed warning
- PMRs, including nonclinical studies to determine the relevance of these findings in humans
- Regulatory precedence, liraglutide (Victoza) was recently approved in the United States for the treatment of T2DM with similar concerns and PMRs

4.4 Clinical Pharmacology

Please refer to Dr. Jaya Vaidynathan's clinical pharmacology review for full details.

4.4.1 Mechanism of Action

Exenatide is a GLP-1 receptor agonist that improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. It does this through the following mechanisms of action:

- Enhances glucose-dependent insulin secretion
- Restores first-phase insulin response
- Suppresses inappropriately elevated glucagon secretion
- Slows gastric emptying
- Reduces food intake

Exenatide LAR is (b) (4) exenatide and (b) (4) sucrose encapsulated within (b) (4) biodegradable (b) (4) polymer (poly-D,L-lactide-coglycolide or PLG) microspheres that are designed to release therapeutic concentrations of exenatide over

an extended period of time. PLG is a common, biodegradable medical polymer that has been previously used in human sutures, bone plates, and extended release pharmaceuticals, such as Vivitrol and Risperdal Consta. In the body, the PLG degrades over time to lactic and glycolic acid and releases exenatide by a combination of drug diffusion and polymer erosion. The microspheres are suspected in an aqueous diluent prior to injection. The formulation selected, AC2993-F17, has been studied in the clinical program starting with phase 2 studies 2993LAR-103 and 2993LAR-104 and including phase 3 study 2993LAR-105.

4.4.2 Pharmacodynamics

Phase 2 study 104 evaluated 0.8 and 2 mg exenatide LAR once weekly for 15 weeks in 43 T2DM subjects (12 placebo, 16 exenatide LAR 0.8 mg, 15 exenatide LAR 2 mg). Reductions in FPG were observed in both exenatide LAR groups throughout the treatment period. At week 15, the 0.8 mg and 2 mg exenatide LAR groups had mean reductions of 42.7 mg/dl and 39.0 mg/dl, respectively, whereas the placebo group's FPG concentrations increased by 18.2 mg/dl at week 15. The mean overall daily average SMBG concentration was also reduced for both the 0.8 mg (164.6 mg/dl) and 2 mg (149.1 mg/dl) exenatide LAR groups compared to baseline and to the placebo exenatide LAR group (220.5 mg/dl).

Please refer to section 6.1.4 Analysis of Primary Endpoint for a discussion of exenatide LAR's (Alkermes and Amylin) effect HbA1c.

4.4.3 Pharmacokinetics

A single dose of exenatide LAR exhibits multiphasic release over approximately 10 weeks with complex release characteristics:

- Phase 1: Initial release of surface-bound exenatide
- Phases 2 and 3: Subsequent release peaks representing hydration and erosion, respectively, in weeks 2 and 6

Repeated once weekly injection of 2 mg exenatide LAR results in overlap of the single-dose release profiles and a gradual increase in the average plasma exenatide concentration, until steady state is achieved after approximately 7 weeks. At weeks 14-15, the average steady state concentration ($C_{ss\ ave}$) of the 2 and 0.8 mg doses are 289 and 118 pg/ml, respectively. The proposed 2 mg dose is acceptable (EC50 ~83 pg/ml). However, there is 23% lower exposure to exenatide from the proposed commercial drug product marketing site (b) (4) scale Amylin drug product) when compared to the (b) (4) scale Alkermes drug product. (The 90% confidence interval for the geometric least squares ratio mean of AUC was 0.70, 0.85.) Thus, the sponsor failed to meet the terms for acceptability of the comparability assessment which were specified in the February 2, 2009 letter. In addition, steady state concentration was affected by the scale; the (b) (4) scale had a higher concentration than the (b) (4) scale. However, based on

exposure-response data and the variability associated with this drug product, the clinical pharmacology team accepts the difference in PK.

Age, gender, race, and body mass index (BMI) do not influence the PK. Similar to exenatide, Exenatide LAR is not recommended for use in patients with severe renal or end-stage renal disease. No dosage adjustment is proposed by the sponsor in patients with mild to moderate renal impairment. However, because there was a 53% increase in exenatide exposure in the subjects with moderate renal impairment (n=10) in study 105 (versus 24% increase in subjects with mild renal impairment), clinical pharmacology supports labeling which recommends caution when initiating exenatide LAR in patients with moderate renal impairment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. NDA 22-200: Tabular listing of completed clinical studies

Study No. No. Centers-Country	Study Design Primary Objective	Population No. and Type	Treatment Duration	Outcomes
ALK23-101	Phase 1, randomized, single blind, placebo controlled, dose escalation, single dose Safety of 3 formulations (F10, F11, F12)	30 healthy subjects	Single dose F10, F11, or F12, or placebo dose	The 3 formulations tested were not selected for further development due to low bioavailability.
2993LAR-101 (101)	Phase 2, randomized, single blind, placebo controlled, single dose Safety and PK of 2 formulations (F13 & F14)	48 T2DM subjects: 10 lifestyle 27 lifestyle, Met 4 lifestyle, TZD 6 lifestyle, Met, TZD 1 lifestyle, Met, TZD, SU	2 wk Byetta 5 mcg TID or placebo TID lead in followed by a single F13, F14, or placebo dose	Formulations tested were not selected for further development due to excessive exenatide release over first 24 h.
2993LAR-102 (102)	Phase 2, open label, single dose Safety and PK of 2 formulations (F16 & F17)	21 healthy subjects	2 wk Byetta 5 mcg TID lead in followed by a single F16 or F17 dose	F17 had safety and PK profile to support further development.
2993LAR-103 (103)	Phase 2, randomized, single blind, placebo controlled, single dose Safety and PK of F17	62 T2DM subjects: 16 lifestyle 46 lifestyle, Met	2 wk Byetta 5 mcg TID lead in followed by a single placebo or exenatide LAR (F17) 2.5, 5, 7, or 10 mg SC dose	Exposure increased with dose. 0.8 and 2 mg exenatide LAR (F17) were selected for study 104.
2993LAR-104 (104)	Phase 2, randomized, double blind, placebo controlled, multiple dose Safety and PK	45 T2DM subjects: 18 lifestyle 27 lifestyle, Met	3 day Byetta 5 mcg BID or placebo lead in followed by 0.8 or 2 mg exenatide (F17) or placebo once weekly x 15 wks	The 2 mg dose was selected for further development.
2993LAR-105 (105)	Phase 3, randomized, open label, comparator	295 T2DM subjects (subjects may be	3 day Byetta 5 mcg BID lead in followed by 2 mg	HbA1c and FPG were statistically significantly

Study No. **No. Centers-Country**	**Study Design** **Primary Objective**	**Population No. and Type**	**Treatment Duration**	**Outcomes**
	controlled, multiple dose Safety and efficacy	represented in ≥1 category): 44 Lifestyle 106 Met 9 TZD 16 SU 27 Met+TZD 82 Met+SU 10 TZD+SU 1 Met+TZD+SU	exenatide once weekly or Byetta BID x 30 wks and exenatide once weekly open ended assessment period	superior with exenatide LAR compared to Byetta. The safety profiles of exenatide LAR and Byetta were similar. LAR subjects had less nausea/vomiting but more injection site reactions and antibodies.
BCB107	Phase 1, open label, parallel group PK of F17 (2 lots), F28, or F30 to support IVIVC	120 healthy subjects	Byetta 10 mcg SC x 1 followed by a single dose of exenatide once weekly	The 3 exenatide once weekly formulations evaluated (commercial F17 [2 lots], fast release F28, and slow release F30) exhibited appropriate PK for IVIVC modeling. Tolerability was as expected, given the doses were 4-5x greater than the proposed commercial dose.
2993LAR-105 Comparability (105c)	Phase 3, randomized, open label, comparator controlled, multiple dose	217 T2DM subjects: 33 Lifestyle 159 Met alone or combo 83 SU alone or combo 34 TZD alone or combo	2 mg F17 Amylin (proposed commercial use) or Alkermes (clinical use) material with primary hbA1c assessment at 18 wks and PK measures at 20 wks	Amylin and Alkermes materials were comparable. HbA1c was noninferior. PK differences did not have clinically meaningful effect on glycemic control.
H8O-JE-GWBW (GWBW)	Phase 1, randomized, double blind, placebo controlled, multiple dose Safety in T2DM Japanese subjects	30 T2DM Japanese subjects 11 lifestyle 9 SU 9 Met alone or with SU 4 TZD alone or with SU	0.8 or 2 mg exenatide LAR (F17) or placebo once weekly x 10 wks	Weekly injections with no Byetta BID lead-in appeared safe in Japanese subjects.

Study No. **No. Centers-Country**	**Study Design** **Primary Objective**	**Population No. and Type**	**Treatment Duration**	**Outcomes**
BCB106	Phase 3, randomized, double blind, comparator controlled, parallel group study	491 T2DM subjects: 122 LAR + Met 137 sitagliptin + Met 128 pioglitazone + Met	2 mg exenatide LAR weekly, sitagliptin 100 mg daily, or pioglitazone 45 mg daily x 26 weeks followed by an open-ended assessment period	Results were submitted with 4-month safety update. Weekly injections without Byetta BID lead-in.

Note: Studies 105 and BCB106 have open-ended assessment periods. Results for these studies describe treatment through weeks 30 and 26, respectively, although comments on the uncontrolled, open-ended assessment portion of study 105 are made where appropriate.

5.2 Review Strategy

The efficacy review focuses on pivotal, phase 3 studies 2993LAR-105 (105) and 2993LAR-105 Comparability (105c), which evaluated multiple doses of the proposed exenatide LAR formulation in T2DM subjects. As study 104 evaluated 2 mg exenatide LAR in only 15 T2DM subjects and the drug product was manufactured in a different scale ([redacted] (b) (4) and by a different manufacturer (Alkermes) than the proposed commercial formulation, its efficacy results are not reviewed here.

With regards to the safety review, studies 102, 103, 104, and 105 were included in the original integrated summary of safety that was submitted with the NDA, as they used the commercial formulation. Studies 102, 103, and 104 used the Alkermes material from the [redacted] (b) (4) scale. Phase 3 study 105 started with Alkermes material from the [redacted] (b) (4) scale, although the [redacted] (b) (4) scale product was later introduced (see section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations). Safety data from studies BCB107, GWBW, and 105c were not included in the integrated summary of safety in the original NDA submission because these studies were designed with very specific goals and patient populations.

The four-month safety update's analysis included data from previously completed studies BCB107 and GWBW and recently completed study BCB106. It included 990 subjects (606 on exenatide LAR), whereas the integrated summary of safety included 409 subjects (366 on exenatide LAR). The four-month safety update pooled studies as follows:

- Clinical pharmacology studies (single-dose)
  - Healthy subjects: 102 and BCB107 (both placebo-controlled)
  - T2DM subjects: 103
- Efficacy and safety studies (repeat dose studies over 15-30 weeks)
  - Placebo-controlled: 104 and H8O-JE-GWBW
  - Comparator-controlled: 105 and BCB106
- Uncontrolled exenatide once weekly exposure: 105 open-label assessment (week 30 – 2 years)

The four-month safety update also included a response to the 74 day letter's request for an updated integrated analysis of safety of exenatide and exenatide LAR, which was described in this review where appropriate. However, my safety review focused on the controlled, repeat dose, efficacy and safety studies described in the four-month safety update, especially larger pivotal study 105.

Study BCB106 is a phase 3, randomized, double blind, comparator controlled, parallel group study in 491 T2DM subjects who received 2 mg exenatide LAR weekly (with no exenatide BID lead-in), sitagliptin 100 mg daily, or pioglitazone 45 mg daily for 26

weeks. As the study report was submitted in the 4 month safety update but not the original NDA, it was reviewed only with regards to safety, especially exenatide LAR tolerability without an exenatide BID lead-in. Study 106 has an extension beyond week 26, and the preliminary results for the extension have not been reviewed here.

The sponsor also included an exenatide LAR antibody summary that is reviewed in section 7.4.6 Immunogenicity.

NDAs under review must meet the cardiovascular (CV) safety standards recommended in the December 2008 final diabetes cardiovascular guidance. As exenatide LAR is bridging to exenatide NDA 21-773, it was decided that a meta-analysis of the cardiovascular events in exenatide (Byetta) studies was acceptable for review. Please refer to section 9.4 Exenatide Cardiovascular Safety Submission for full details.

As studies ALK23-101 and 2993LAR-101 used exenatide once weekly formulations different from the commercial formulation, they were not included in this review.

5.3 Discussion of Individual Studies/Clinical Trials

1) Study 105: A randomized, open label, multicenter, 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 oral antidiabetic medications

Study phase and dates conducted: Phase 3 study conducted April 15, 2006 – February 20, 2008.

Objectives:
Primary:
- To compare the effect on glucose control, as measured by HbA1c, of exenatide LAR SC weekly injection to that achieved by exenatide SC BID for 30 weeks in subjects with T2DM
- To examine the safety and tolerability of exenatide LAR SC weekly for 30 weeks in subjects with T2DM
- To examine glucose control during the transition from treatment with exenatide SC BID to exenatide LAR SC weekly in subjects with T2DM

Secondary:
- To examine the effects of exenatide LAR administered SC weekly for 30 weeks in subjects with T2DM on the following:
    - Body weight, fasting and postprandial glucose and insulin concentrations
    - Fasting glucagon, proinsulin, and lipid concentrations
    - Rate of gastric emptying as assessed by the appearance of circulating acetaminophen
    - Exenatide PK

  - Homeostatic model assessment (HOMA)
  - Patient reported outcomes (PRO) in terms of change in satisfaction with treatment (Diabetes Treatment Satisfaction Questionnaire [DTSQ] and the impact of weigh change on quality of life [IWQOL-Lite]
- To examine the incidence and rate of hypoglycemic events associated with the proactive approach to sulfonylurea (SU) management (reducing the SU dose upon initiation of exenatide LAR treatment) for subjects using a concomitant SU
- To examine the long term (at least 52 weeks of treatment) effect on glucose control (HbA1c) of exenatide LAR administered SC weekly in subjects with T2DM
- To assess the long term (at least 52 weeks of treatment) safety and tolerability of exenatide LAR administered SC weekly in subjects with T2DM

Study design: This phase 3 study compared the safety and effect on glucose control in T2DM subjects for at least 30 weeks of exenatide LAR to exenatide using an open-label, randomized, exenatide BID-controlled, two-arm design. The study was also designed to examine glucose control during the transition from exenatide to exenatide LAR after week 30. The long term safety and efficacy of exenatide LAR were monitored in the uncontrolled group during an open-ended assessment period for an additional 22 weeks to week 52.

The study was conducted at 29 study sites in 303 randomized (295 ITT) subjects with T2DM treated with diet and exercise alone or in combination with a stable regimen of metformin, SU, TZD, or combination of metformin and SU, metformin and TZD, or SU and TZD.

Subjects were randomized 1:1 to one of the following 2 treatment groups:
- exenatide LAR weekly
- exenatide SC BID for 30 weeks followed by exenatide LAR SC weekly for the remainder of the study

Randomization was stratified with respect to screening HbA1c (<9% or ≥9%) and whether or not a subject was taking a concomitant SU at screening

Study 105 is an open-ended study. It included a 30 week assessment period with a minimum of 20 study visits from screening (visit 1) to week 30 (visit 20). As of March 31, 2009, approximately 205 subjects had received more than 2 years treatment. On day -7 (visit 2), eligible subjects were enrolled and randomized. On day -3, subjects began a 3 day lead-in period, when they received exenatide 5 mcg BID The assessment period was comprised of 17 visits (day 1 [visit 4] through week 30 [visit 20]). Following visit 15, exenatide LAR subjects returned to the clinic on any 4 days (visits 16-19) prior to visit 20 (week 30), whereas exenatide subjects were contacted by telephone for visits 16-19. The open-ended assessment period was comprised of at least 9 visits (visits 21-29 [week 52]).

Subjects in both treatment groups who were treated with SU decreased their SU dose to the minimum recommended dose on at the start of lead in (day -3) to reduce the risk of hypoglycemia. These subjects recorded daily fingerstick blood glucose measurements after week 10 through week 22, when steady state concentrations of plasma exenatide were expected to be reached. The duration of the glucose monitoring could be modified by the investigator to optimize the SU dose. The daily glucose measurements were recorded in the interactive voice response system (IVRS) weekly and reviewed by the investigator weekly to determine if subjects on SU required optimization of the SU dose to reach the goal FBG ≤110 mg/dl. If FBG was >110 mg/dl on 3 consecutive days without severe hypoglycemia, the SU dose was doubled, up to the maximum labeled SU dose. Hypoglycemia could result in a reduction in the SU dose.

During the lead-in period (3 days), all subjects received exenatide 5 mcg SC BID. During the 30 week assessment period, subjects received either exenatide LAR 2 mg SC weekly or exenatide 5 mcg BID SC for 4 weeks followed by 10 mcg SC BID for 26 weeks.

Following 30 weeks of treatment with exenatide LAR 2 mg, exenatide LAR subjects continued to receive exenatide LAR 2 mg SC weekly during the open-ended assessment period. Exenatide subjects who completed 30 weeks of exenatide treatment switched to exenatide LAR 2 mg SC weekly during open-ended assessment period. Exenatide subjects receiving SU decreased their SU dose to the minimum recommended dose again at week 30. These subjects recorded daily fingerstick blood glucose measurements weeks 40-52, when, according to the sponsor, steady state concentrations of plasma exenatide were expected to be reached. Like previously, the duration of glucose monitoring could be modified by the investigator, and goal FBG was ≤110 mg/dl.

At select study sites, a subset of subjects was randomized to a gastric-emptying study. The first 60 exenatide LAR subjects were included in one of 2 arms (fed and fasting, 1:1). The first 60 exenatide subjects were randomized 1:1 to either the fed arm of the gastric emptying study or to be a nonparticipant of the gastric emptying study.

NOTE: Study 105 was also open label. Subjects and study administrators were cognizant of the medication used, which could have contributed to study bias. However, due to the significant difference in injection frequency and long duration of study (> 2 years), it was ethically acceptable to conduct an open label study and not subject half of the study population to prolonged placebo injections.

The concomitant anti-diabetic medications used in study 105 included diet and exercise alone (14.9%); metformin, SU, or TZD (44.4%); or a combination of metformin and SU, metformin and TZD, or SU and TZD (40.7%)

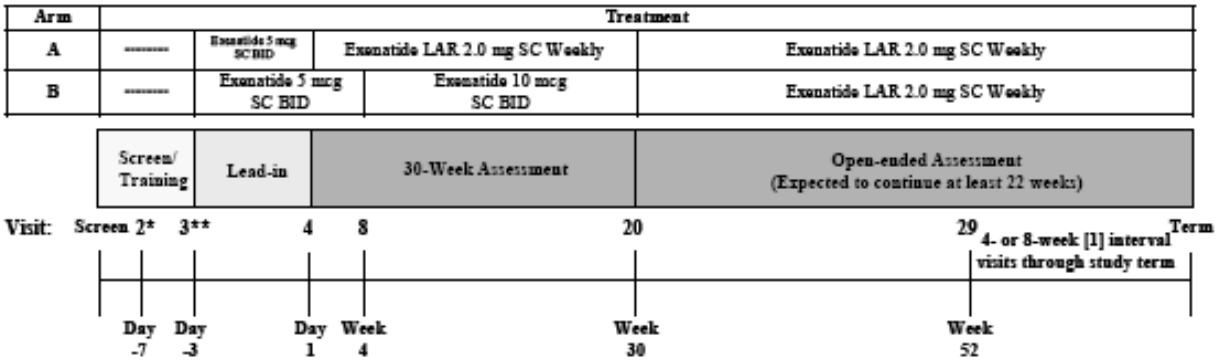
The use of SU in study 105 complicates its analysis for the following reasons:

- **Although SU doses were later optimized, subjects receiving exenatide LAR had their SU dose reduced once (i.e. day -3), whereas subjects receiving exenatide had their SU dose reduced twice (i.e. day -3 and week 30). However, due to my focus on the 30 week treatment period, the second SU dose adjustment did not affect key study results.**
- **There was no 26 week period free of SU interference for an adequate interpretation of HbA1c. However, after 12 weeks of SU dose titration, the remaining 18 weeks in this 30 week trial were sufficient to assess HbA1c after stabilization.**

During the open-ended assessment period, the clinical comparability of exenatide LAR manufactured at 2 different manufacturing sites was evaluated. (Please refer to the description of study 105c below.)

The investigator, sponsor, subjects, and all study personnel were unblinded to the identity of study medication. Sponsor personnel involved with data review and analysis were blinded to efficacy data (HbA1c and plasma glucose concentration) throughout the 30 week assessment period.

Figure 1. Study 105: Design



*Subjects are enrolled and randomized at Visit 2 (Day –7).
**Baseline efficacy and pharmacodynamic assessments will be conducted at Visit 3 (Day –3).
[1] Visit 30 (Week 56) through Visits 35 (Week 76) will occur at 4-week intervals. Thereafter, all study site visits will occur at 8-week intervals.

NOTE: Reproduced from the sponsor

Table 3. Study 105: Schedule

Appendix 1: Study Plan for Group A (Protocol 2993LAR-105)

	Screen	Train	Lead-In	Assessment Period [1]								Open-Ended Assessment Period [2, 3]				Term
	Visit 1 Screen	isit 2 Da -7	Visit 3 Day –3	Visit 4 Day 1	Visits 5-8 Wks 1-4	Visits 9, 10 Wks 6, 10	Visit 11 Wk 14	Visits 12, 13, 14 Wks 18, 22, 26	Visit 15 Wk 29	Visits 16-19 [4]	Visit 20 Wk 30	Visits 21-24 Wks 31-34	Visits 25–28 Wks 36–48	Visit 29 Wk 52	4- & 8-week interval visits	Study or Early Term
Consent Forms & Medical History [5]	X															
Pregnancy Test [6]	X			X	X	X	X	X	X		X	X	X	X	X	X
Vital Signs, Height, & Weight [7]	X	X	X	X	X [8]	X	X	X	X [8]		X	X [8]	X	X	X	X
Injection Site Examination				X	X	X	X	X	X		X	X	X	X	X	X
Adverse Event & Medication Review	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology, Urinalysis	X		X	X		X	X	X			X		X	X	X	X
HbA1c	X		X	X	X [10]	X	X	X			X	X [11]	X	X	X	X
Fasting Glucose	X		X	X	X	X	X	X			X	X	X	X	X	X
Physical Exam		X									X			X		X
12-Lead ECG		X					X				X [12]					X [12]
Randomization		X														
Study-Related Training		X [13]	X [14]	X [15]	X [15]											
Patient Reported Health Outcome Measures		X	X				X				X			X		X
Anthropometric Measures			X	X		X	X	X			X		X	X	X	X
7-Point Glucose Profiles [16]			X								X					
Dispense Exenatide			X [17]													
Standard Meal Tolerance Test [18]			X				X									
Acetaminophen Dosing [19]			X				X									
Fasting Insulin, Proinsulin, Glucagon, Lipids			X	X		X	X	X			X		X	X	X [23]	X [23]
Anti-Exenatide Antibodies			X	X		X	X	X			X		X	X	X	X
Additional Analytes (to archive)			X								X			X		X
Collect Returned Exenatide				X												
Dispense Exenatide LAR				X	X [20]	X	X	X			X	X [21]	X	X	X	
Plasma Exenatide [22]				X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Returned Exenatide LAR					X [20]	X	X	X			X	X [21]	X	X	X	X

[1] Phone calls with a CTRP to discuss issues related to study medication will be scheduled as follows: within one day of Visit 3 (Day –3), approximately 1 week following Visit 8 (Week 4), and weekly between Visit 9 (Week 6) to Visit 10 (Week 10).
[2] Expected to continue at least 22 weeks through Visit 29 (Week 52).
[3] Phone calls with a CTRP to discuss issues related to study medication will be scheduled as follows: approximately 1 week following Visit 24 (Week 34), and weekly between Visit 25 (Week 36), and Visit 26 (Week 40).
[4] Group A subjects will return to the clinic on any four days between Visit 15 (Week 29) and Visit 20 (Week 30) for Visit 16, Visit 17, Visit 18, and Visit 19.
[5] Informed consent and authorization to use and disclose protected health information.
[6] Serum pregnancy test at Visit 1 (Screening) and Study Termination/Early Termination. Urine pregnancy test for all other specified visits.
[7] Height will be measured at Visit 1 (Screening) only.
[8] Weight will not be collected at this visit.
[9] Adverse event data will not be collected at Visit 1 (Screening).
[10] Visit 7 (Week 3) only.
[11] Visit 23 (Week 33) only.
[12] 12-Lead ECG performed at Visit 20 (Week 30) and Early Termination only if subject completes visit prior to 02 July 2007. 12-Lead ECG not performed at Study Termination.
[13] Group A subjects will learn how to use a blood glucose meter, how to perform finger-stick glucose measurements associated with hypoglycemia or titration of SU, how to complete a 7-point SMBG profile, study medication injection compliance, how to use the IVRS to report glucose measurements with titration of SU, and how to call the CTRP to report hypoglycemia events and glucose measurements associated with hypoglycemia.
[14] Group A subjects will learn how to administer study medication (exenatide).
[15] Group A subjects will learn how to administer exenatide LAR at these visits. The first injection of exenatide LAR will be administered SC at the clinic by a medically qualified staff member at Visit 4 (Day 1). At Visit 5 (Week 1), Visit 6 (Week 2), Visit 7 (Week 3), and Visit 8 (Week 4), exenatide LAR injection will be self-administered under the supervision of a medically qualified staff member at the clinic. Subjects may opt to have the injection performed by study site personnel at these visits.
[16] Measurements recorded on 3 days between Visit 2 (Day –7) and Visit 3 (Day –3) and between Visit 15 (Week 29) and Visit 20 (Week 30).
[17] Group A subjects will receive their first dose of exenatide 5 mcg after Visit 3 (Day -3) study procedures are completed.
[18] Approximately 30 Group A subjects; Includes timed blood samples for postprandial glucose and insulin and at –15 min, 15 min, 30 min, 60 min, 90 min, 120 min, 3 h, and 5 h relative to the standard meal at time = 0 min.
[19] Approximately 60 Group A subjects; Includes timed blood samples at –15 min, 15 min, 30 min, 60 min, 90 min, 120 min, 3 h, and 5 h relative to acetaminophen administration at time = 0 min.
[20] Visit 6 (Week 2) only.
[21] Visit 22 (Week 32) only.
[22] Includes timed blood samples at –15 min, 30 min, 60 min, 90 min, 120 min, 4 h, and 6 h relative to exenatide LAR injection at time = 0 min at Visit 4 (Day 1) and Visit 15 (Week 29) for all Group A subjects and timed blood samples at –15 min, 15 min, 30 min, 60 min, 90 min, 2 h, 3 h, and 5 h relative to acetaminophen dosing at time = 0 min at Visit 11 (Week 14) for Group A subjects in the gastric emptying cohort; preinjection blood samples will be collected at all other applicable visits.
[23] Samples for proinsulin and glucagon not collected after 01 October 2008.

Appendix 2: Study Plan for Group B (Protocol 2993LAR-105)

	Screen	Train	Lead-In	Assessment Period [1]								Open-Ended Assessment Period [2, 3]				Term
	Visit 1 Screen	Visit 2 Day -7	Visit 3 Day –3	Visit 4 Day 1	Visits 5-8 Wks 1-4	Visits 9, 10 Wks 6, 10	Visit 11 Wk 14	Visits 12, 13, 14 Wks 18, 22, 26	Visit 15 Wk 29	Visits 16-19 [4]	Visit 20 Wk 30	Visits 21-24 Wks 31-34	Visits 25–28 Wks 36–48	Visit 29 Wk 52	4- & 8-week interval visits	Study or Early Term
Consent Forms & Medical History [5]	X															
Pregnancy Test[6]	X			X	X	X	X	X	X		X	X	X	X	X	X
Vital Signs, Height, & Weight [7]	X	X	X	X	X [8]	X	X	X	X [8]		X	X [8]	X	X	X	X
Injection Site Examination				X	X	X	X	X	X		X	X	X	X	X	X
Adverse Event & Medication Review	X [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology, Urinalysis	X		X	X		X	X	X			X		X	X	X	X
HbA1c	X		X	X	X[10]	X	X	X			X	X[11]	X	X	X	X
Fasting Glucose	X		X	X	X	X	X	X			X	X	X	X	X	X
Physical Exam		X									X			X		X
12-Lead ECG		X									X [12]					X [12]
Randomization		X														
Study-Related Training		X [13]	X [14]		X [15]						X [16]	X [16]				
Patient Reported Health Outcome Measures		X	X				X				X			X		X
Anthropometric Measures			X	X		X	X	X			X		X	X	X	X
7-Point Glucose Profiles [17]			X								X					
Dispense Exenatide			X [18]	X	X [19]	X	X	X								
Standard Meal Tolerance Test [20]			X				X									
Acetaminophen Dosing [21]			X				X									
Insulin, Proinsulin, Glucagon, Lipids			X	X		X	X	X			X		X	X	X [24]	X [24]
Anti-Exenatide Antibodies			X	X		X	X	X			X		X	X	X	X
Additional Analytes (to archive)			X								X			X		X
Collect Returned Exenatide				X	X [19]	X	X	X			X					
Dispense Exenatide LAR											X	X [22]	X	X	X	
Plasma Exenatide [23]							X				X	X	X	X	X	X
Collect Returned Exenatide LAR												X [22]	X	X	X	X

[1] Phone calls with a CTRP to discuss issues related to study medication will be scheduled as follows: within one day of Visit 3 (Day –3), approximately 1 week following Visit 8 (Week 4), and weekly between Visit 9 (Week 6) to Visit 10 (Week 10).
[2] Expected to continue at least 22 weeks through Visit 29 (Week 52).
[3] Phone calls with a CTRP to discuss issues related to study medication will be scheduled as follows: approximately 1 week following Visit 24 (Week 34), and weekly between Visit 25 (Week 36), and Visit 26 (Week 40).
[4] The study site coordinator will contact Group B subjects by phone for each visit.
[5] Informed consent and authorization to use and disclose protected health information.
[6] Serum pregnancy test at Visit 1 (Screening) and Study Termination/Early Termination. Urine pregnancy test for all other specified visits.
[7] Height will be measured at Visit 1 (Screening) only.
[8] Weight will not be collected at this visit.
[9] Adverse event data will not be collected at Visit 1 (Screening).
[10] Visit 7 (Week 3) only.
[11] Visit 23 (Week 33) only.
[12] 12-Lead ECG performed at Visit 20 (Week 30) and Early Termination only if subject completes visit prior to 02 July 2007. 12-Lead ECG not performed at Study Termination.
[13] Group B subjects will learn how to use a blood glucose meter, how to perform finger-stick glucose measurements associated with hypoglycemia or titration of SU, how to complete a 7-point SMBG profile, study medication injection compliance, how to use the IVRS to report glucose measurements associated with titration of SU, and how to call the CTRP to report hypoglycemia events and glucose measurements associated with hypoglycemia.
[14] Group B subjects will learn how to administer study medication (exenatide 5 mcg).
[15] Visit 8 (Week 4) only; Group B subjects will learn how to administer study medication (exenatide 10 mcg).
[16] Group B subjects will learn how to administer exenatide LAR at these visits. The first injection of exenatide LAR will be administered SC at the clinic by a medically qualified staff member at Visit 20 (Week 30). At Visit 21 (Week 31), Visit 22 (Week 32), Visit 23 (Week 33), and Visit 24 (Week 34), exenatide LAR injection will be self-administered under the supervision of a medically qualified staff member at the clinic. Subjects may opt to have the injection performed by study site personnel at these visits.
[17] Measurements recorded on 3 days between Visit 2 (Day –7) and Visit 3 (Day –3) and between Visit 15 (Week 29) and Visit 20 (Week 30).
[18] Group B subjects will receive their first dose of exenatide 5 mcg after Visit 3 (Day -3) study procedures are completed.
[19] Visit 6 (Week 2) only.
[20] Approximately 30 Group B subjects; Includes timed blood samples for postprandial glucose and insulin and at –15 min, 15 min, 30 min, 60 min, 90 min, 120 min, 3 h, and 5 h relative to the standard meal at time = 0 min.
[21] Approximately 30 Group B subjects; Includes timed blood samples at –15 min, 15 min, 30 min, 60 min, 90 min, 120 min, 3 h, and 5 h relative to acetaminophen administration at time = 0 min.
[22] Visit 22 (Week 32) only.
[23] Includes timed blood samples at –15 min, 15 min, 30 min, 60 min, 90 min, 2 h, 3 h, and 5 h relative to acetaminophen dosing at time = 0 min at Visit 11 (Week 14) for Group B subjects in the gastric emptying cohort; preinjection blood samples will be collected at all applicable visits.
[24] Samples for proinsulin and glucagon not collected after 01 October 2008.

NOTE: Reproduced from the sponsor

Inclusion criteria:

- Is at least 16 years of age at visit 1 (screening)
- Has T2DM 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 at visit 1
- Has an HbA1c of 7.1-11.0% inclusive at visit 1
- Has a fasting glucose concentration of <280 mg/dl at visit 1
- Has a BMI of 25-45 kg/m^2 inclusive at visit 1
- Has stable body weight, i.e. not varying by >10% for at least 6 months prior to visit 1 screening as documented by the investigator
- Is male or female, has a negative pregnancy test (human chorionic gonadotropin beta subunit) regardless of menopausal status. If female and of childbearing potential (including peri-menopausal women who have had a menstrual period within 1 year), must practice and be willing to continue to practice appropriate birth control (defined as a method which results in a failure rate <1% per year when used consistently and correctly, such as implants, injectables, oral contraceptives, some intrauterine contraceptive devices, sexual abstinences, tubal ligation, or a vasectomized partner) during the entire duration of the study
- Has a physical examination and ECG judged not to be clinical significant by the investigator at visit 2 (day -7)
- Has clinical laboratory test values (chemistry, hematology, or urinalysis) judged to not be clinical significant by the investigator at visit 1
    - ALT or AST concentration within 3x ULN at visit 1
    - Serum creatinine ≤1.6 mg/dl (males) or ≤1.4 mg/dl (females) at visit 1
    - Abnormalities of glucose, lipids, urinary glucose, and urinary protein consistent with T2D are acceptable without sponsor approval
- Is able to understand and to sign the informed consent and/or child assent forms and an Authorization to Use and Disclose Protected Health Information, answer the study questionnaires, communicate with the investigator, and understand and comply with protocol requirements and, if less than 18 years of age, has a parent or legal guardian to read and understand these forms, communicate with the investigator, and understand and comply with protocol requirements

Exclusion criteria:

- Has a clinical 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
    - Renal disease (including subjects with creatinine clearance ≤30 ml/min)
    - Seizure disorder
    - Gastrointestinal disease
    - Cardiovascular disease

  - Organ transplantation
  - Active or untreated malignancy or has been in remission from clinically significant malignancy for <5 years
  - Evidence of known or suspected HIV, HBV, or HCV
- Currently abuses drug or alcohol or has a history of abuse that in the investigator's opinion would cause the individual to be noncompliant with study procedures
- Has been previously exposed to exenatide, exenatide LAR, or any GLP-1 analog or dipeptidyl peptidase (DPP)-4 inhibitors.)
- Received any investigational drug or has participated in any time of clinical trial within 30 days prior to screening
- Has been treated, is currently treated, or is expected to require or undergo treatment with any of the following medications:
  - Alpha-glucosidase inhibitor or meglitinide within 30 days of visit 1 (screening)
  - Insulin within 2 weeks prior to visit 1 or insulin for longer than 1 week within 3 months of visit 1
  - Regular use (>14 days) of drugs that directly affect gastrointestinal motility, including but not limited to, anticholinergics, macrolide antibiotics, dopamine antagonists, opiates, opioids, and Reglan (metoclopromide)
  - Regular use (>14 days) of systemic oral corticosteroids by oral, intravenous, or intramuscular route; or potent, inhaled, or intrapulmonary (including AeroBID) steroids known to have a high rate of systemic absorption
  - Regular use (>14 days) of medications with addictive potential such as opiates and opioids
  - Prescription or over-the-counter weight-loss medications within 6 months of visit 1
- Has donated blood within 60 days of visit 1 or is planning to donate blood during the study
- Has had major surgery or a blood transfusion within 2 moths of visit 1
- Has had a surgical gastrointestinal procedure that may impact gastric emptying
- Has known allergies or hypersensitivity to any component of study treatment (including PLG, (b) (4) diluent, acetaminophen)
- Is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the investigative site, or is directly affiliated with the study at the investigative site
- Is employed by Amylin Pharmaceuticals, Inc.; Eli Lilly Company; or Alkermes, Inc. (that is, an employee, temporary contract worker, or designee responsible for the conduct of the study)

Treatments and management: Subjects received exenatide 5 mcg SC BID for a 3 day lead-in. Subjects then received exenatide LAR 2 mg SC weekly (QW) or exenatide 5

mcg SC BID for 4 weeks followed by 10 mcg SC BID for 26 weeks. After 30 weeks of treatment, all subjects received exenatide LAR 2 mg SC QW for at least 22 weeks.

Exenatide BID was administered any time within a 60-minute period before the morning and evening meals, which were at least 6 hours apart. Exenatide LAR was administered at approximately the same time of day each week.

To minimize the risk of hypoglycemia, subjects in both treatment groups who were also treated with SU were required to decrease their dose to the minimum recommended dose on day -3. Following weeks 10 (both treatment groups) and 40 (exenatide [Byetta] group only) SU doses were optimized to reach a fasting blood glucose (FBG) concentration ≤110 mg/dl.

All subjects treated with a SU recorded daily fingerstick glucose measurements during weeks 10-22; exenatide-treated subjects treated with a SU also recorded measurements during weeks 40-52. Subjects were asked to fast at least 8 hours each night during these weeks. These FBG measurements were reviewed weekly by the investigator to determine is subjects treated with SU required optimization of the dose to reach the goal FBG ≤110 mg/dl as follows: If FBG >110 mg/dl on 3 consecutive test days without severe hypoglycemia, the SU dose was doubled, up to the maximum labeled SU dose. Hypoglycemia could result in reduction of SU dose.

In addition to the SU changes described above, concomitant medications were limited as follows:

- Medications listed in the exclusion criteria were excluded.
- Acetominophen and acetaminophen-containing products were not allowed within 24 hours of day -3 and week 14 for subjects participating in the gastric emptying assessment.
- Blood pressure and lipid lowering medications remained stable, unless adjusted by the investigator.
- Existing metformin and TZD therapies were continued at the current dosages, unless adjusted by the investigator or primary care physician.

Study sites including enrollment: The study was conducted at 29 study sites in 303 subjects with T2DM treated with diet and exercise alone or in combination with a stable regimen of metformin, SU, TZD, or combination of metformin and SU, metformin and TZD, or SU and TZD.

Efficacy (exposure/response) assessments:
Efficacy: HbA1c, body weight, and waist and hip circumferences
Pharmacokinetic:

- For subjects randomized to exenatide LAR, plasma exenatide concentrations were measured prior to the injection of exenatide LAR on day 1 and at each applicable visit from week 1 to study termination. For exenatide BID subjects,

levels were measured prior to exenatide LAR injection at week 30 and at each applicable visit to study termination.
- The exenatide LAR group had a 6 hour exenatide PK profile measured on day 1.
- Both exenatide LAR and exenatide BID subjects participating in the gastric emptying cohort had 5 hour exenatide PK profiles measured at week 14.
- The exenatide LAR group had a 6 hour exenatide PK profile measured at week 29.
- Following week 29, exenatide LAR subjects returned to the clinic on any 4 days (visits 16-19) prior to week 30 for plasma exenatide measurements.

Pharmacodynamic: Fasting glucose, lipid, insulin, proinsulin, and glucagon concentrations; postprandial glucose and insulin concentrations; 7-point self-monitored blood glucose (SMBG); circulating acetaminophen (rate of gastric-emptying)
Patient reported outcomes: Diabetes Treatment Satisfaction Questionnaire (DTSQs and DTSQc); Impact of Weight on Quality of Life Questionnaire, Lite Version (IWQOL-Lite)

Safety assessments: Adverse events; concomitant medication reviews, physical examinations, vital signs (blood pressure and heart rate); ECGs; clinical laboratory measurements (hematology, chemistry, and urinalysis assessments); anti-exenatide antibodies

2) 2993LAR-105c: A randomized, open label, multicenter, 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 oral antidiabetic medications

Study phase and dates conducted: Phase 3 study conducted August 14, 2008 – January 15, 2009.

Objectives:
Primary:
- To demonstrate that exenatide LAR from 2 different manufacturing sites exerts a comparable clinical response on glycemic control, as measured by HbA1c, in subjects with T2DM

Secondary:
- To assess the effects of exenatide LAR from 2 different manufacturing sites on fasting plasma glucose concentration (FPG) in subjects with T2DM
- To assess the PK of exenatide LAR from 2 different manufacturing sites in subjects with T2DM
- To assess the effect of exenatide LAR from 2 different manufacturing sites on body weight in subjects with T2DM

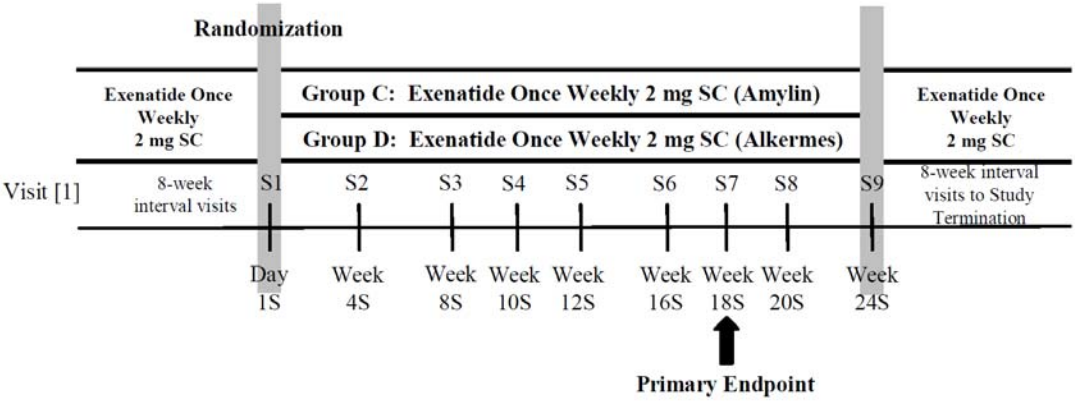
Study design: This phase 3, randomized, open label, multicenter study compared the efficacy (as measured by HbA1c), PD, PK, safety, and tolerability of exenatide LAR 2 mg manufactured at Amylin and Alkermes. The study was conducted in 217 T2DM subjects treated with diet and exercise alone or with a stable regimen of metformin, SU, TZD, or a combination of up to 2 of these oral antidiabetic medications, who completed 30 weeks of assessments and continued into the open-ended assessment period of study 105.

Study 105c included 9 study site visits. All subjects participating in the open-ended assessment period at the time that proposed commercial exenatide LAR became available were randomized on day 1S to (b) (4) Amylin-manufactured or (b) (4) Alkermes-manufactured drug product. The weekly dose of exenatide LAR remained 2 mg SC. Subjects returned to the site for additional efficacy, PD, PK, and safety assessments.

Following week 24, subjects resumed the original visit of study 105's open ended assessment period and all subject commenced treatment with Amylin-manufactured exenatide LAR.

As this was an open label study, the study site staff, investigator, and the sponsor were not blinded to the study medication administered.

Figure 2. Study 105c: Design



Abbreviations: SC, subcutaneous.
Note: See Figure 1 for full study design.
[1] Visit S1 occurred at a scheduled or unscheduled study-site visit during the open-ended assessment period. Visits S2 through S9 occurred at 2- to 4-week (± 2 days) intervals relative to Visit S1. After Visit S8, subjects returned to the site within approximately 48 to 144 hours (2 to 6 days) and prior to the next dose of exenatide once weekly for collection of an additional blood sample. Following Visit S9, subjects resumed the original visit structure, returning to the study site at 8-week intervals for study visits (approximately 8 weeks after Visit S9), and received Amylin-manufactured exenatide once weekly.

NOTE: Reproduced from the sponsor

Table 4. Study 105c: Schedule

Procedure	Assessment Period [1]	
	Visit S1 (Day 1S)	Visits S2 through S9 (Weeks 4S through 24S)
Randomization to Treatment Group	X	
Urine Pregnancy Test (female subjects)	X	X
Vital Signs and Weight	X	X
Injection Site Examination	X	X
Adverse Event and Concomitant Medication Review	X	X
Chemistry, Hematology, Urinalysis	X	X
HbA1c	X	X
Fasting Plasma Glucose	X	X
Antibodies to Exenatide	X	X
Plasma Exenatide	X	X
Dispense Exenatide Once Weekly	X	X [2]
Collect Returned Exenatide Once Weekly	X	X [2]
Timed Blood Sample Collection for Plasma Exenatide		X [3]

[1] Visit S1 (Day 1S) occurred at a scheduled or unscheduled study-site visit during the open-ended assessment after the proposed commercial exenatide once weekly drug product became available (August 2008). Visits S2 through S9 occurred as specified in Figure 2. Subjects who ended study participation prior to Visit S9 completed study termination procedures (see Appendix 1.1 for study termination procedures).

[2] Study medication not dispensed or collected at Visit S4 (Week 10S) and Visit S7 (Week 18S).

[3] Visit S8 (Week 20S) only. Samples collected at time = -15 minutes and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 6 hours relative to exenatide once weekly injection at time = 0. Subjects asked to return within 48 to 144 hours (2 to 6 days) for collection of an additional blood sample to complete Visit S8 (Week 20S).

Cross-Reference: Adapted from Protocol 2993LAR-105 Amendment 08 (Appendix 1.1.3).

NOTE: Reproduced from the sponsor

Inclusion criteria: The inclusion criteria are similar to study 105.

Exclusion criteria: The exclusion criteria are similar to study 105

Treatments and management: Study 105c assessed the clinical comparability of exenatide LAR drug product, manufactured at Amylin Ohio, LLC (Amylin) at the (b) (4) scale (proposed commercial drug product) and Alkermes Inc (Alkermes) at the (b) (4) scale investigational drug product). This comparability assessment occurred during the open ended assessment period (i.e. after week 30) of study 105, thus the treatments and management in study 105c were similar to study 105. However, eligible subjects were re-randomized to receive either the Amylin or Alkermes drug product.

Study sites including enrollment: The study was conducted at 27 sites in 217 T2DM subjects treated with diet and exercise alone or with a stable regimen of metformin, SU, TZD, or a combination of up to 2 of these oral antidiabetic medications, participating in the open-ended assessment period of study 105.

Efficacy (exposure/response) assessments:
Primary: Change in HbA1c from baseline to week 18
Secondary:

- Changes in HbA1c from baseline to subsequent study visits prior to week 18 during comparability assessment period
- Changes in fasting plasma glucose (FPG) from baseline to subsequent study visits prior to and including week 18 during the comparability assessment period
- PK parameters(steady state concentration at baseline [$C_{ss, baseline}$], steady state area under the concentration-time curve at baseline [$AUC_{ss, baseline}$], C_{ss} [calculated over weeks 12 through 20], AUC_{ss}, AUC_{0-168h} at week 20, peak steady state concentration [$C_{max, ss, 0-6h}$] at week 20) were calculated at the individual subject level
- Changes in body weight from baseline to subsequent study visits prior to and including week 18 during the comparability assessment

Safety assessments: Adverse events; vital signs; clinical hematology, chemistry, and urinalysis values; and antibodies to exenatide

COMMENT: As shown in the clinical trials table in section 5.1, all but two studies had an exenatide lead in to exenatide LAR therapy (lead in periods ranged from 3 days to 2 weeks). GWBW evaluated exenatide LAR in 20 Japanese subjects; BCB106 evaluated it in 122 ethnically diverse subjects. Please refer to section 7.4.5 Special Safety Studies/Clinical Trials for more details.

6 Review of Efficacy

Efficacy Summary

The efficacy review focused on pivotal, phase 3 studies 105 and 105c.

Across the development program and including the 4-month safety update, the mean age of subjects in efficacy and safety studies ranged from 52.2-57.3 years in the various treatment groups. Most subjects had normal baseline serum creatinine (43.6-68.6%). Subjects' ethnicity varied between treatment groups, reflecting study enrollment at various locations (e.g. study 105 was conducted in the US and Canada; BCB106 was conducted in the US, Mexico, and India), although the majority of subjects in studies 105 and 105c were Caucasian (~79%.) The mean duration of T2DM ranged from 4.9-6.8 years. A total of 44 (14.9%) subjects were treated with diet and exercise alone, 131 (44.4%) were treated with a single oral agent, and 120 (40.7%) were treated with a combination of oral antidiabetic medications. Please refer to sections 6.1.2 and 6.1.3 for full details.

A total of 217 subjects participating in the open-ended assessment period of study 105 were randomized to a clinical comparability treatment group in study 105c. All subjects received medication and were included in the ITT population. Of those subjects, 9 (4.1%) withdrew during the comparability assessment. With the exception of a subject lost to follow up, the withdrawals occurred among subjects randomized to Amylin drug. A total of 15.2% of study 105c's subjects were treated with diet and exercise alone, 44.2% were treated with a single oral antidiabetic agent, and 40.6% were treated with a combination of oral antidiabetic medications.

The most common concomitant medications, excluding antidiabetic therapies, were those expected in the diabetic population (e.g. HMG-CoA reductase inhibitors, platelet aggregation inhibitors, ACE inhibitors).

The primary efficacy variable for studies 105 and 105c was the change in HbA1c at study endpoint (after 30 or 18 weeks of treatment, respectively) compared to baseline. In study 105, subjects were randomized to 2 mg exenatide LAR weekly (after a 3 day exenatide 5 mcg BID lead-in) or exenatide BID (4 weeks of 5 mcg BID followed by 10 mcg following) for 30 weeks. The mean baseline HbA1c was 8.3% in Study 105. At week 30, the LS mean (SE) change in HbA1c from baseline in the exenatide LAR group was -1.9% (0.1), a statistically significant change when compared to the LS mean -1.5% (0.1) change in HbA1c with exenatide (p=0.0023). In study 105c, 217 subjects participating in the open-ended assessment period of study 105 were randomized to either continue on Alkermes (clinical) or to switch to Amylin (commercial) manufactured exenatide LAR for 18 weeks. Baseline mean HbA1c values were 6.8% and 6.7% for the Alkermes and Amylin subjects, respectively. At week 18, noninferiority between treatments was demonstrated based on the upper limit of the 95% CI of the difference between treatment groups (0.34%) being below the predefined 0.4% margin. The corresponding LS mean difference in the change in HbA1c from baseline of Study 105c between the Amylin and Alkermes-manufactured drug product was 0.17% (0.09). Please refer to the tables in section 6.1.4 Analysis of Primary Endpoint for full details.

The major secondary efficacy parameters were FPG and body weight in both studies, the percentage of subjects achieving HbA1c < 6.5% and < 7% in study 105 and the PK of exenatide LAR from 2 different manufacturing sites in study 105c. A greater percentage of exenatide LAR subjects with baseline HbA1c > 7% achieved HbA1c ≤ 7% when compared to exenatide subjects (73.2% vs. 57.1). Similarly, more exenatide LAR subjects achieved HbA1c ≤ 6.5% (45% vs. 38%).

Fasting plasma glucose was assessed in studies 105 and 105c. In study 105, exenatide LAR resulted in a greater mean reduction from baseline in FPG than exenatide (-45 vs -23 mg/dl). In study 105c, mean baseline FPG concentrations were 127 mg/dl in ITT subjects receiving Alkermes and Amylin manufactured exenatide LAR, respectively. The mean change in FPG concentration from baseline to week 18 between groups was nearly identical (6 and 5 mg/dl, respectively)

The PK of exenatide LAR from two different manufacturing sites (Alkermes [clinical] and Amylin [commercial]) was compared in study 105c. At the comparability assessment baseline, the geometric mean (SE) plasma exenatide concentration for the PK evaluable population was 215 (17.2) pg/ml and 190 (12.6) pg/ml for subjects randomized to receive Alkermes and Amylin drug product, respectively. There was a high degree of variability in the PK assessments in both treatment groups. The coefficients of variation in the geometric means of the plasma exenatide concentrations and PK parameters over time ranged from 60-80% and 55-65%, respectively. The range of Amylin C_{ss} values was within the range of the Alkermes C_{ss} values. Although lower variability was observed with the Amylin drug product, there is 23% mean lower exposure with this drug product. (The 90% confidence interval for the geometric least squares mean of AUC was 0.70, 0.85.) Thus, the sponsor failed to meet the terms for acceptability of the comparability assessment which were specified in the February 2, 2009 letter. However, based on exposure-response data and the variability associated with this drug product, clinical pharmacology concludes that the difference in AUC is likely not to be clinically meaningful; I agree.

Studies 105 and 105c evaluated change in body weight. In study 105, both the exenatide LAR and exenatide groups' mean baseline body weight values were ~102 kg. Exenatide and exenatide LAR had similar effects on body weight, in study 105 (-4.5 and -4.1 kg at 52 weeks), respectively. Alkermes and Amylin drug products had similar effects on body weight in study 105c, although subjects gained a mean of 0.8-1.3 kg. Amlyin subjects gained slightly more weight, although the clinical significance of this likely negligible. These different results in studies 105 and 105c may be partially explained by the fact that subjects enrolled in study 105c were previously enrolled in study 105 and had a mean previous exposure to exenatide LAR of 82-94 weeks. Thus, at a cumulative exposure of 100-112 weeks, it appears that subjects on exenatide LAR do not lose further weight.

The data from study 105 was analyzed by the following subgroups: gender, age < or ≥ 65 years, baseline HbA1c < 9% or ≥ 9%, and concomitant SU use at screening.
In all subgroups, exenatide LAR resulted in a greater change in HbA1c compared to exenatide. The change in HbA1c was generally similar between subgroups when analyzed by treatment, except for baseline HbA1c. Subjects with baseline HbA1c ≥ 9% experienced greater changes in HbA1c, regardless of treatment, when compared to subjects with baseline HbA1c < 9%.

The data from study 105c were analyzed by baseline HbA1c < 6.5% or ≥ 6.5%. Amylin drug product resulted in a greater change in HbA1c compared to the Alkermes drug product, regardless of the baseline HbA1c. As expected, the change in HbA1c from baseline was smaller in study 105c when compared to study 105. This is likely explained by the lower baseline HBA1c (6.5% vs. 9%) and shorter duration of therapy (18 vs. 30 weeks).

Study 105 examined effects at 52 weeks on HbA1c of exenatide LAR administered SC weekly in T2DM subjects. The mean reduction in HbA1c at week 30 in the exenatide LAR group persisted through 52 weeks of therapy. At week 52, the LS mean change in HbA1c from baseline in exenatide LAR group was -2.0%. Subjects in the exenatide group switched to exenatide LAR at week 30; at week 52, the LS mean change in HbA1c from baseline was -2.0% in that group. Despite the lack of a control group in study 105's extension, such preservation of glycemic effect is remarkable.

More exenatide LAR subjects were positive for exenatide antibodies when compared to exenatide subjects (74.3% vs. 49.0%) at week 30 in study 105. The change in HbA1c in exenatide LAR subjects' with low titer positive antibodies was more similar to the change in HbA1c experienced by exenatide LAR antibody negative subjects (-1.8% vs. -2.1) when compared to exenatide (Byetta) subjects (-1.1% vs. -1.7%). In the 9 (6%) exenatide LAR subjects with high titers (≥ 625), the change in HbA1c ranged from -1.4 to +2.3%, suggesting possible decreased effectiveness in these patients. A similar trend was observed when exenatide LAR subjects with high antibody titers were evaluated at week 52 (change in HbA1c range -3.7 to -0.3%); only a minority of those subjects (38%) experienced a reduction in HbA1c ≥ 0.7%.

Table 5. Change in HbA1c from baseline in study 105 by antibody status and treatment group

Study group	Low titer positive antibodies	Negative antibodies
Exenatide LAR	-1.8	-2.1
Exenatide	-1.1	-1.7

6.1 Indication

The sponsor proposes 2 mg exenatide LAR injection subcutaneously weekly as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. The sponsor does not recommend its use in patients with end stage renal disease or severe renal impairment.

6.1.1 Methods

Exenatide LAR has been produced using drug substance from (b) (4) different suppliers, (b) (4) Mallinckrodt, Inc.; and Lonza, SA. It has also been manufactured at (b) (4) different scales ((b) (4)) and at 2 different manufacturing sites (Alkermes, Inc. in Wilmington, Ohio and Amylin Ohio, LLC in West Chester, Ohio. The phase 2 study 2993LAR-104 (study 104) and all prior studies were conducted using the (b) (4) scale. Phase 3 studies used material from all three scales. Pivotal phase 3 study 2993LAR-105 (study 105) started with material from the (b) (4) scale, although (b) (4) scale product was later introduced. Comparability of the Amylin

drug product intended for commercial use and Alkermes drug product intended for clinical development was assessed via glycemic, pharmacokinetic, and safety endpoints in pivotal extension study 105c.

The efficacy review focused on pivotal, phase 3 studies 2993LAR-105 (105) and 2993LAR-105 Comparability (105c), which evaluated multiple doses of the proposed exenatide LAR formulation in T2DM subjects.

6.1.2 Demographics

Across the development program and including the 4-month safety update, the mean age of subjects in efficacy and safety studies ranged from 52.2-57.3 years in the various treatment groups. The proportion of males in the placebo and exenatide LAR treatment groups ranged from 39.1-68.6%. Most subjects had normal baseline serum creatinine (43.6-68.6%). Subjects' ethnicity varied between treatment groups, reflecting study enrollment at various locations (e.g. study 105 was conducted in the US and Canada; BCB106 was conducted in the US, Mexico, and India). The mean BMI was >30. The mean duration of T2D ranged from 4.9-6.8 years.

1) 2993LAR-105: The majority of subjects were Caucasian (78.0%). Roughly half of the subjects were male (53%). The mean BMI was similar between each treatment groups (34.8-35.0 kg/m^2). The mean duration of diabetes ranged between 6.4-7.0 years across treatment groups. The mean HbA1c at baseline was 8.3% in each treatment group.

Table 6. Study 105: Baseline demographics by treatment.

Characteristic	Treatment		All subjects (n=295)
	Ex 10 mcg BID (n=147)	Ex LAR 2 mg QW (n=148)	
Age, mean (SD)	54.9 (9.6)	55.2 (9.7)	55.0 (9.7)
Male (%)	75 (51.0)	82 (55.4)	157 (53.2)
Race			
Caucasian	107 (72.8)	123 (83.1)	230 (78.0)
BMI, mean (SD)	35.0 (5.1)	34.8 (5.0)	34.9 (5.0)
Diabetes duration, mean (SD)	6.4 (4.5)	7.0 (5.5)	6.7 (5.0)
HbA1c, mean (SD)	8.3 (1.0)	8.3 (1.0)	8.3 (1.0)

Source: Study report Table 4

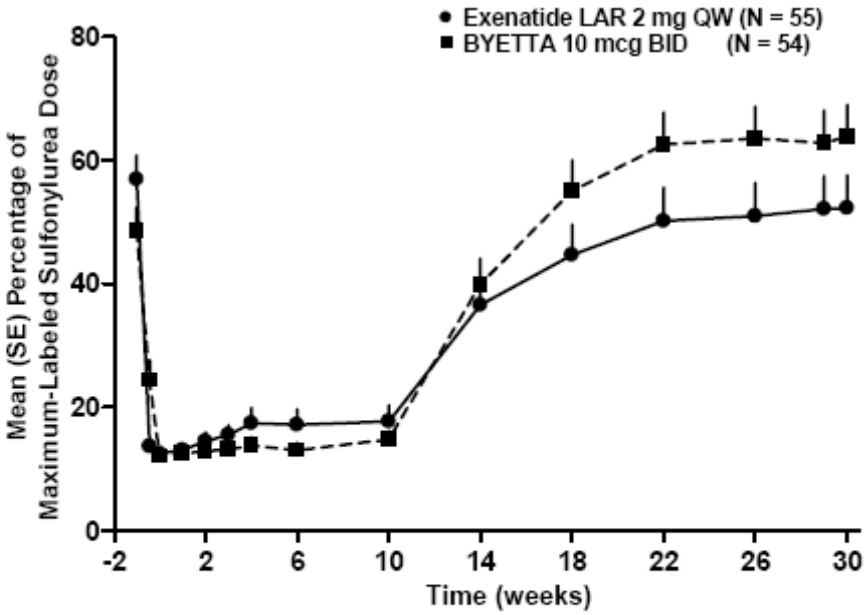
Similar demographic characteristics were observed across treatment groups in the 30 week, 52 week, and PK populations as well as the gastric emptying cohort.

Of the 295 ITT subjects, 44 (14.9%) were treated with diet and exercise alone, 131 (44.4%) were treated with a single oral agent, and 120 (40.7%) were treated with a combination of oral antidiabetic medications. The distribution of background antidiabetic medications was similar between treatment groups and included the range

of treatments (diet and exercise through combination therapy) used in diabetics prior to the initiation of insulin. The use of background antidiabetic medications was similar between treatment groups.

All subjects treated with SU were required to decrease their SU dose to the minimum recommended on day -3. After week 10, the SU dose was optimized for each subject to reach a target FPG goal. After week 10, exenatide subjects required a higher mean percentage of the maximum labeled dose of SU compared to exenatide LAR subjects. (See Figure 3. Study 105: Mean (SE) percentage of maximum labeled SU dose by treatment.) Although there is little efficacy gained by increasing most SU doses to the maximum allowable, the efficacy of exenatide LAR is likely greater than that of exenatide as there was greater HbA1c reduction in the exenatide LAR arm with lower SU doses,.

Figure 3. Study 105: Mean (SE) percentage of maximum labeled SU dose by treatment



Abbreviations: BID, twice daily; LAR, long-acting release; QW, once weekly; SE, standard error.
Notes: Five subjects treated with exenatide LAR and 3 subjects treated with BYETTA increased their SU dose prior to Week 10. These changes were consistent with the general guidance in the protocol for titration of the SU dose and were not considered protocol deviations.
- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

NOTE: Reproduced from the sponsor's study report figure 3

Excluding antidiabetic medications, the most common concomitant medications used by ITT subjects were 3-hyroxy-3-metylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (48.5%), platelet aggregation inhibitors excluding heparin (48.1%), plain angiotensin-converting enzyme (ACE) inhibitors (34.6%), and propionic acid derivatives

(28.5%). Nearly all (277 of 295, 93.9%) of subjects started a new concomitant medication or changes the dose of an existing one after starting the lead-in medication. The sponsor did not analyze the effect of concomitant medications. However, given diabetics' frequent comorbidities, multiple medications are often indicated (e.g. statins, ACE-inhibitors). The change in concomitant medications observed in study 105 is within the expected range.

2) 2993LAR-105c: The majority of subjects were Caucasian (79.3%). Baseline demographic characteristics were similar between treatment groups, with the exception of a higher proportion of male subjects randomized to receive Amylin-manufactured exenatide LAR, a 2 kg difference in body weight and 1 kg/m2 difference in BMI, and a 12 week difference in mean exposure to exenatide LAR between groups (Amylin: 82 weeks; Alkermes: 94 weeks). The distribution of subjects having received exenatide or exenatide LAR was similar between the treatment groups. Characteristics were similar between the evaluable population and PK evaluable population.

Table 7. Study 105c: Baseline demographics by treatment (ITT).

Characteristic	Treatment		All subjects (n=217)
	Alkermes (n=109)	Amylin (n=108)	
Age, mean (SD)	57.7 (8.3)	57.3 (10.1)	57.5 (9.2)
Male (%)	54 (49.5)	63 (58.3)	117 (53.9)
Race			
Caucasian	88 (80.7)	84 (77.8)	172 (79.3)
BMI, mean (SD)	33.2 (5.0)	34.1 (5.1)	33.6 (5.0)
Diabetes duration, mean (SD)	9.2 (5.0)	8.6 (5.6)	8.9 (5.3)
HbA1c, mean (SD)	6.8 (0.9)	6.7 (0.8)	6.8 (0.9)

Source: Study report Table 4

Of the 217 subjects, 15.2% were treated with diet and exercise alone, 44.2% were treated with a single oral antidiabetic agent, and 40.6% were treated with a combination of oral antidiabetic medications. The distribution of antidiabetic medications was similar between treatment groups.

Excluding antidiabetic medications, the most common concomitant medications used by ITT subjects were 3-hyroxy-3-metylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (58.5%), platelet aggregration inhibitors excluding heparin (50.7%), plain angiotensin-converting enzyme (ACE) inhibitors (35.9%), and propionic acid derivatives (25.3%). The majority of subjects (66.8%) of subjects started a new concomitant medication or changed the dose of an existing one after starting the lead-in medication. Excluding antidiabetic medications, most new concomitant medications were influenza vaccine (22.6%) and propionic acid derivatives (6.0%).

6.1.3 Subject Disposition

1) 2993LAR-105: A total of 470 subjects were screened. Of the 303 subjects randomized, 295 received at least 1 dose of lead-in medication and were included in the ITT population. Of the ITT subjects, 2 (0.7%) withdrew during the lead-in period, 35 (11.9%) withdrew during the 30 week assessment period, and 15 (5.1%) withdrew during the first 22 weeks of the open-ended assessment period.

The reasons for withdrawal were similar between treatment groups in the 30 week assessment period, although slightly more exenatide LAR subjects withdrew consent. As expected, the percentage of subjects who withdrew during the first 22 weeks of the open-ended assessment period was less than that of the 30 week assessment period. The reasons for withdrawal were similar between treatment groups in the first 22 weeks of the open-ended assessment period.

Table 8. Study 105: Subject disposition by treatment

Disposition	Treatment		All subjects (n=295)
	Ex 10 mcg BID (n=147)	Ex LAR 2 mg QW (n=148)	
Completed 30 wk assessment	130 (88.4)	128 (86.5)	258 (87.5)
Withdrew during 30 wk	15 (10.2)	20 (13.5)	35 (11.9)
Withdrew consent	1 (0.7)	5 (3.4)	6 (2.0)
Adverse event	7 (4.8)	9 (6.1)	16 (5.4)
Investigator discretion	2 (1.4)	1 (0.7)	3 (1.0)
Protocol violation	1 (0.7)	0 (0.0)	1 (0.3)
Lost to follow up	4 (2.7)	5 (3.4)	9 (3.1)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Loss of glucose control	0 (0.0)	0 (0.0)	0 (0.0)
Completed first 22 wk of open-end assessment	121 (82.3)	122 (82.4)	243 (82.4)
Withdrew during 22 wk	9 (6.1)	6 (4.1)	15 (5.1)
Withdrew consent	5 (3.4)	3 (2.0)	8 (2.7)
Adverse event	0 (0.0)	1 (0.7)	1 (0.3)
Investigator discretion	3 (2.0)	1 (0.7)	4 (1.4)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up	0 (0.0)	1 (0.7)	1 (0.3)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Loss of glucose control	1 (0.7)	0 (0.0)	1 (0.3)

2) 2993LAR-105c: A total of 217 subjects participating in the open-ended assessment period of study 105 were randomized to a clinical comparability treatment group. All subjects received medication and were included in the ITT population. Of those subjects, 9 (4.1%) withdrew during the comparability assessment. With the exception of the subject lost to follow up, the withdrawals occurred among subjects randomized to Amylin drug. The subject who withdrew due to an AE, experienced morphea with

positive centromere antibody. Subject 00905 (Amylin) withdrew consent due to sugars "gradually increasing" (HbA1c 6.6% and FPG 128 mg/dl at study termination). Subject 22411 (Amylin) was withdrawn due to a protocol violation (initiation of insulin; HbA1c 7.2% at study termination). Subject 31206 (Amylin; HbA1c 7.8% at study termination) withdrew consent prior to initiation of insulin therapy.

Table 9. Study 105c: Subject disposition by treatment

Disposition	Treatment		All subjects (n=217)
	Alkermes (n=109)	Amylin (n=108)	
Completed assessment	108 (99.1%)	100 (92.6)	208 (95.6)
Withdrew during assessment	1 (0.9)	8 (7.4)	9 (4.1)
Withdrew consent	0 (0.0)	4 (3.7)	4 (1.8)
Adverse event	0 (0.0)	1 (0.9)	1 (0.5)
Protocol violation	0 (0.0)	1 (0.9)	1 (0.5)
Lost to follow up	1 (0.9)	0 (0.0)	1 (0.5)
Administrative	0 (0.0)	2 (1.9)	2 (0.9)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable for studies 105 and 105c was the change in HbA1c at study endpoint (after 30 or 18 weeks of treatment, respectively) compared to baseline. HbA_{1c} is an appropriate endpoint for the following reasons:

- HbA1c is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months (Nathan DM 1984).
- The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5% (College of American Pathologists 1999; Goldstein 1982).
- HbA1c has excellent reliability, predicts several diabetes-specific complications, and provides the current basis for treatment decisions (American Diabetes Association 2006).
- Lowering HbA1c reduces microvascular complications in patients with type 1 and type 2 diabetes (Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study (UKPDS) Group 1998). There is weaker evidence showing that lowering HbA1c reduces macrovascular complications in patients with type 1 diabetes (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005). (Note, however, that these 2 studies were active-controlled and the agreed upon non-inferiority margin was 0.4%.)

In study 105, subjects were randomized to 2 mg exenatide LAR weekly (after a 3 day exenatide 5 mcg BID lead-in) or exenatide BID (4 weeks of 5 mcg BID followed by 10 mcg following) for 30 weeks. The mean baseline HbA1c was 8.3%. Following 30 weeks of treatment, subjects receiving exenatide were switched to exenatide LAR in the open-ended assessment period.

At week 30, the LS mean (SE) change in HbA1c from baseline in the exenatide LAR group was -1.9% (0.1), a statistically significant change when compared to the -1.5% (0.1) change in HbA1c with exenatide (p=0.0023). The evaluable population (ITT subjects who were in compliance with the protocol and received adequate study medication exposure) yielded similar results to the ITT population (-2.0% exenatide LAR vs. -1.6% exenatide). Decreases in HbA1c were evident at week 6, when HbA1c was first measured during treatment. Significant differences in HbA1c were seen between treatment groups from weeks 10– 30.

NOTE: Statistician Janice Derr, Ph.D. concluded the efficacy of exenatide LAR was supported by a noninferiority comparison to exenatide for change in HbA1c at week 30 compared to baseline, although she too described weakness in the study design. Please refer to her review for full details.

Table 10. Study 105: Change from baseline in HbA1c (ITT)

Study	N	Baseline HbA1c (%) mean (SE)	Change in HbA1c (%) LS mean (SE)	LS mean difference (SE)	95% CI for the LS mean difference	p-value
Exenatide	147	8.3 (0.1)	-1.5 (0.1)			
Ex LAR	148	8.3 (0.1)	-1.9 (0.1)	-0.33 (0.1)	-0.54, -0.12	0.0023

In study 105c, 217 subjects participating in the open-ended assessment period of study 105 were randomized to either continue to receive Alkermes (clinical) or to Amylin (commercial) manufactured exenatide LAR for 18 weeks. Additional PK data was obtained at week 20. Baseline HbA1c values were 6.8% and 6.7% for the Alkermes and Amylin subjects, respectively. At week 18, noninferiority between treatment was demonstrated based on the upper limit of the 95% CI of the difference between treatment groups (0.34%) being below the predefined 0.4% margin. The corresponding LS mean difference in the change in HbA1c from baseline between the Amylin and Alkermes-manufactured drug product was 0.17% (0.1). With the exception of the value at week 16 (0.4%), the upper limit of the 95% CI of the difference in the change in HbA1c from baseline between treatment groups was consistently below the predefined 0.4% margin (0.11 to 0.37%).

Table 11. Study 105c: Change in HbA1c from day 1 to week 18 by treatment

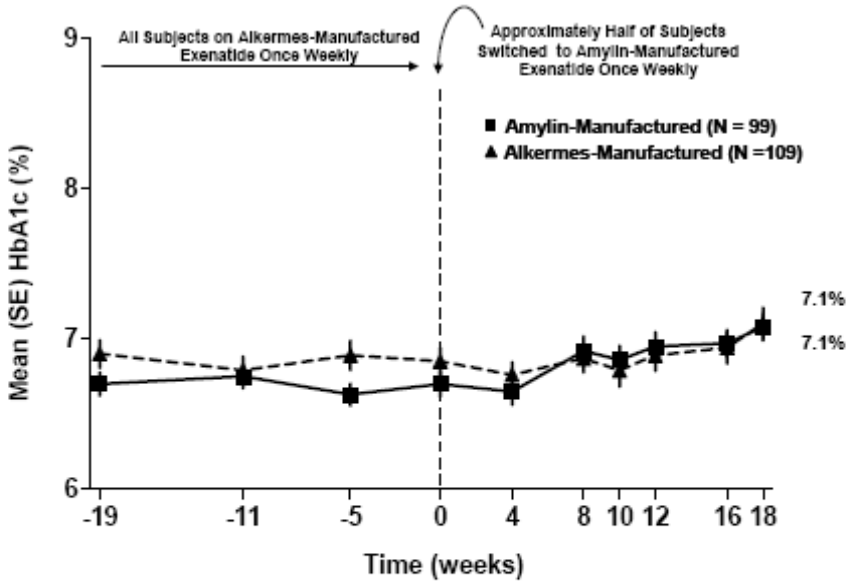
Study	N	Study 105 Day -1 HbA1c (%) mean (SE)	Study 105c Day 1 HbA1c (%) mean (SE)	Change in HbA1c (%) from day 1 to week 18S LS mean (SE)	LS mean difference from day 1 to week 18 (SE)	95% CI for the LS mean difference from day 1 to week 18
105c (Evaluable)						
Alkermes	109	8.4 (1.0)	6.8 (0.1)	0.25 (0.1)		
Amylin	99	8.0 (0.9)	6.7 (0.1)	0.43 (0.1)	0.17 (0.1)	0.01, 0.34
105c (ITT)						
Alkermes	109	8.4 (1.0)	6.8 (0.1)	0.25 (0.1)		
Amylin	108	8.0 (0.9)	6.7 (0.1)	0.40 (0.1)	0.15 (0.1)	-0.1, 0.32

Source: Study report Table 6

In both treatment groups, HbA1c increased over time. The small LS mean difference between treatment groups in the evaluable population was consistent (~0.2%) between weeks 8-18. The ITT population also demonstrated noninferiority of the Amylin drug product compared to the Alkermes drug product (95% CI -0.01%, 0.32%).

The figure below illustrates the mean HbA1c for the evaluable population from the 3 observations prior to the comparability assessment through week 18.

Figure 4. Study 105c: Mean (SE) HbA1c from three observations prior to day 1 through week 18 by treatment



Abbreviations: SE, standard error.

Notes: Mean baseline HbA1c at the 3 observations prior to Day 1S (time = 0) and at Day 1S was 6.8% for the Alkermes-manufactured and 6.7% for the Amylin-manufactured exenatide once weekly drug product.

-For evaluable subjects who did not complete the Week 18S visit, nonmissing data at Week 16S was carried forward to Week 18S.

-The time points at the 3 observations prior to Day 1S (time = 0) are median time points based on observations in the Pharmacokinetic Evaluable Population (N = 196).

NOTE: Reproduced from the sponsor

6.1.5 Analysis of Secondary Endpoints(s)

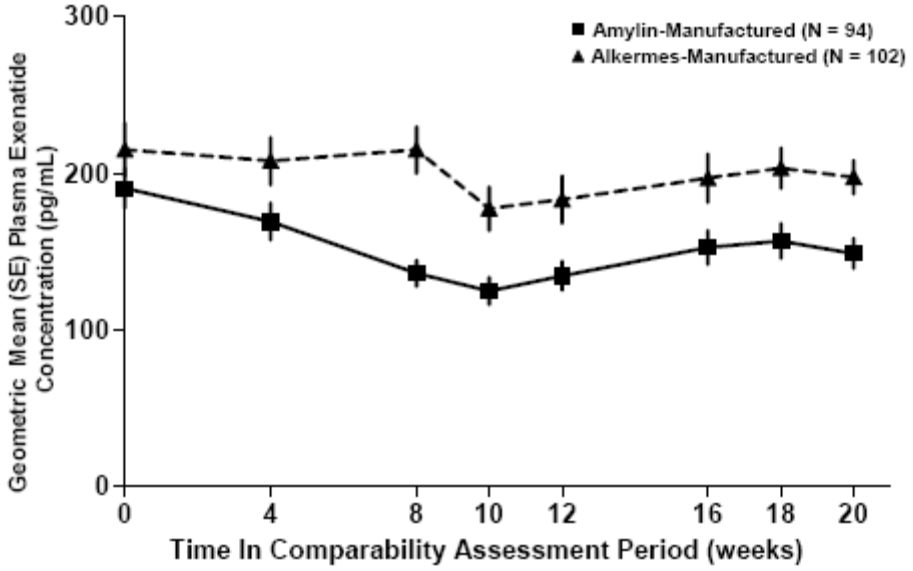
The major secondary efficacy parameters were the percentage of subjects achieving HbA1c < 6.5% and < 7% in study 105 and the PK of exenatide LAR from 2 different manufacturing sites in study 105c as well as FPG and body weight in both studies.

HbA1c < 6.5% and < 7%: The percentage of subjects achieving HbA1c < 6.5% and < 7% at week 30 was assessed in study 105's ITT and evaluable population. In the ITT exenatide LAR group, 104 (73.2%) of 142 subjects with a baseline HbA1c > 7% achieved an HbA1c ≤ 7% at week 30. In the ITT exenatide group, 80 (57.1%) of 140 subjects with a baseline HbA1c > 7% achieved an HbA1c ≤ 7% at week 30. The difference between treatment groups was statistically significant (p=0.0041).

In the ITT exenatide LAR group, 67 (45.3%) of 148 subjects with a baseline HbA1c > 6.5% achieved an HbA1c ≤ 6.5% at week 30. In the ITT exenatide group, 56 (38.1%) of 147 subjects with a baseline HbA1c > 6.5% achieved an HbA1c ≤ 6.5% at week 30.

Pharmacokinetics of exenatide LAR from 2 different manufacturing sites: The PK of exenatide LAR from two different manufacturing sites (Alkermes [clinical] and Amylin [commercial]) was compared in study 105c. At the comparability assessment baseline, the geometric mean (SE) plasma exenatide concentration for the PK evaluable population was 215 (17.2) pg/ml and 190 (12.6) pg/ml for subjects randomized to receive Alkermes and Amylin drug product, respectively. The difference observed between the 2 groups was generally consistent between weeks 10-20. Thus, steady state plasma exenatide concentrations were reached as anticipated based on the 7-10 week duration required for exenatide once weekly to reach steady state. The geometric mean (SE) C_{ss} over weeks 12-20 was 198 (11.4) pg/ml and 147 (8.1) pg/ml in the Alkermes and Amylin groups, respectively.

Figure 5. Study 105c: Geometric mean (SE) plasma exenatide concentration (pg/ml) from day 1 through week 20 by treatment



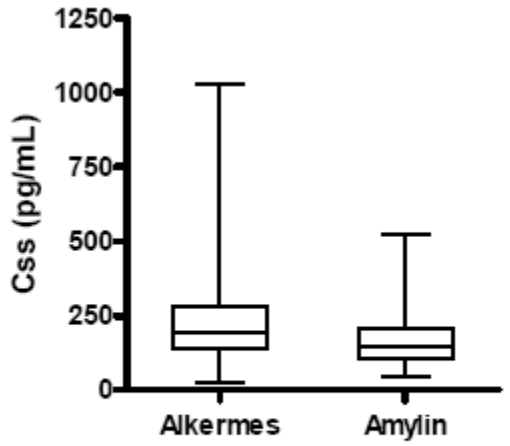
Abbreviation: LLOQ, lower limit of quantitation; SE, standard error.
Note: Any missing concentration or value <LLOQ was treated as missing. Subjects with more than 1/3 of the total number of postdose concentrations <LLOQ were excluded.

NOTE: Reproduced from the sponsor

There was a high degree of variability in the PK assessments in both treatment groups. The coefficients of variation in the geometric means of the plasma exenatide concentrations and PK parameters over time ranged from 60-80% and 55-65%, respectively. The range of Amylin C_{ss} values was within the range of the Alkermes C_{ss} values. Although lower variability was observed with the Amylin drug product, there is 23% lower exposure with this drug product. (The 90% confidence interval for the geometric least squares mean of AUC was 0.70, 0.85.) Thus, the sponsor failed to meet the terms for acceptability of the comparability assessment (i.e. 90% CI for the

ratio of geometric mean AUC within 80-125%) which were specified in the February 2, 2009 letter. However, based on exposure-response data and the variability associated with this drug product, clinical pharmacology accepts the difference in PK. Please also refer to Dr. Jayabharathi Vaidynanathan's clinical pharmacology review.

Figure 6. Study 105c: Css (weeks 12-20, pg/ml) by treatment



Abbreviations: Alkermes, Alkermes-manufactured; Amylin, Amylin-manufactured, C_{ss}, concentration at steady state.

Note: Line represents the median value; box represents the 25th and 75th percentiles; whiskers extend from minimum to maximum values.

NOTE: Reproduced by the sponsor

Table 12. Study 105c: Plasma exenatide PK statistical comparison between treatment groups in study 105c (PK evaluable population)

	Geometric LS mean (SE)		Ratio of Amylin-manufactured to Alkermes-manufactured	
Parameter	Alkermes (n=102)	Amylin (n=94)	Geometric LS Mean	90% CI for Geometric LS mean
AUCss (pg*h/ml)	32673 (1376)	25241 (1107)	0.77	0.70, 0.85
Css (pg/ml)	194 (8)	150 (7)	0.77	0.70, 0.85

Fasting plasma glucose: Fasting plasma glucose and change in body weight were assessed in studies 105 and 105c. In study 105, exenatide LAR resulted in a greater mean reduction from baseline in FPG than exenatide (-45 vs -23 mg/dl). In study 105c, mean baseline FPG concentrations were 127 mg/dl in ITT subjects receiving Alkermes and Amylin manufactured exenatide LAR, respectively. The mean change in FPG concentration from baseline to week 18 between groups was nearly identical (6 and 5 mg/dl, respectively).

Table 13. Change from baseline in FPG (ITT) Studies 105 and 105c

	N	Baseline FPG mean (SD)	Mean Change in FPG (SE in 105; SD in 105c)
Study 105			
Exenatide	147	165 (3)	-23 (3)
LAR	148	173 (4)	-45 (4)
Study 105c*			
Alkermes	109	127 (34)	6 (31)
Amylin	108	127 (29))	5 (25)

* Day -3 (original baseline) mean values were 172 (44.5) mg/dl and 166 (43.2) mg/dl for the Alkermes and Amylin groups, respectively

Body weight: Studies 105 and 105c evaluated change in body weight. In study 105, both the exenatide LAR and exenatide groups' mean baseline body weight values were ~102 kg. Use of concomitant weight loss agents was not allowed during the study and no diet or lifestyle modification regimen was implemented. In both treatment groups, body weight progressively decreased during the 30 week assessment period. At week 30, the LS mean (SE) changes in body weight from baseline were -3.7 (0.47) kg and -3.6 (0.47) kg in the exenatide LAR and exenatide groups, respectively. The difference between treatment groups was not statistically significant. Similar results were observed in the 30 week evaluable population.

In the exenatide LAR and exenatide subjects included in study 105's 52 week evaluable population, mean body weight values were 103 and 102 kg, respectively. At week 30, the LS mean (SE) change in body weight from baseline was -4.0 (0.53) kg and -4.3 (0.54) kg in the exenatide LAR and exenatide groups, respectively. In both treatment groups, reductions in body weight were maintained throughout 52 weeks of therapy. At week 52, the LS mean (SE) change in body weight from baseline was -4.1 (0.6) kg and -4.5 (0.61) kg in the exenatide LAR and exenatide groups, respectively.

In study 105c's ITT population, the mean baseline body weight was 97.0 kg and 98.9 kg in the Alkermes and Amylin groups, respectively. An increase in body weight was observed over time from day 1 to week 18 in both groups. In the ITTpopulation at week 18, the mean change in body weight from baseline in the Alkermes and Amylin treatment groups was 0.8 and 1.3, respectively.

In conclusion, exenatide and exenatide LAR had similar effects on body weight, in study 105 (-4.5 and -4.1 kg at 52 weeks), respectively. Alkermes and Amylin drug products had similar effects on body weight in study 105c, although subjects gained a mean of 0.8-1.3 kg. Amlyin subjects gained slightly more weight, although the clinical significance of this likely negligible. These different results in studies 105 and 105c may be partially explained by the fact that subjects enrolled in study 105c were previously enrolled in study 105 and had a mean previous exposure to exenatide LAR of 82-94 weeks. Thus, at a cumulative exposure of 100-112 weeks, it appears that subjects on exenatide LAR do not lose further weight.

Table 14. NDA 22-200: Change from baseline in weight (kg) at weeks 30 and 18 in studies 105 and 105c, respectively (ITT)

	N	Baseline weight mean (SD)	Mean Change in weight (SE in study 105, SD in study 105c)
Study 105			
Exenatide	147	101.9 (21.0)	-3.6 (0.5)
LAR	148	101.7 (18.8)	-3.7 (0.5)
Study 105c			
Alkermes	109	97.0 (18.5)	0.8 (2.9)
Amylin	108	98.9 (19.1)	1.3 (2.2)

6.1.6 Other Endpoints

Study 105c's endpoints were discussed above.

The Homeostatic Model Assessment-B (HOMA-B, an index of pancreatic beta-cell function) and HOMA-S (an index of target organ sensitivity) were also assessed for exenatide LAR and exenatide in study 105. At week 30, HOMA-B ratios demonstrated improved beta-cell function in both exenatide LAR and exenatide ITT subjects, with a significantly greater improvement in the exenatide LAR group ($p<0.0001$). An approximately 10% increase in insulin sensitivity, as measured by HOMA-S, was observed in both treatment groups.

In the 52 week evaluable population, the geometric LS mean (SE) HOMA-B ratio between week 52 and baseline was 1.8 (0.08) % in the exenatide LAR group and 1.7 (0.08) % in the subjects who had switched from exenatide to exenatide LAR at week 30. The difference between the 2 treatment groups was no longer statistically significant ($p=0.2974$). An approximately 10% increase in HOMA-S was observed in both treatment groups in the evaluable population at week 52.

Of note, the above mathematical models are not well-validated surrogates for insulin sensitivity and beta-cell function, and therefore, do not yet rise to a level of evidence to support inclusion in labeling.

6.1.7 Subpopulations

The data from study 105 was analyzed by the following subgroups: gender, age < or ≥ 65 years, baseline HbA1c < 9% or ≥ 9%, and concomitant SU use at screening.
In all subgroups, exenatide LAR resulted in a greater change in HbA1c compared to exenatide. The change in HbA1c was generally similar between subgroups when analyzed by treatment, except for baseline HbA1c. Subjects with baseline HbA1c ≥ 9% experienced greater changes in HbA1c, regardless of treatment, when compared to subjects with baseline HbA1c < 9%.

Table 15. Study 105: Change in HbA1c at week 30 by gender, age, baseline HbA1c, and concomitant SU use at screening (ITT).

Gender	N	Change in HbA1c (%) mean (SD)
Males	**157**	
Ex BID	75	-1.2 (0.9)
Ex LAR	82	-1.6 (0.9)
Females	**138**	
Ex BID	72	-1.4 (1.1)
Ex LAR	66	-1.7 (1.2)
Age		
< 65 year	**245**	
Ex BID	123	-1.3 (1.1)
Ex LAR	122	-1.6 (1.1)
≥ 65 years	**50**	
Ex BID	24	-1.4 (0.8)
Ex LAR	26	-1.5 (0.8)
Baseline HbA1c		
< 9%	**216**	
Ex BID	107	-1.1 (0.8)
Ex LAR	109	-1.2 (0.8)
≥ 9%	**79**	
Ex BID	40	-1.8 (1.3)
Ex LAR	39	-2.7 (1.0)
Concomitant SU use		
Using	**109**	
Ex BID	54	-1.4 (1.0)
Ex LAR	55	-1.7 (1.1)
Not using	**185**	
Ex BID	93	-1.2 (1.1)
Ex LAR	93	-1.6 (1.0)

Source: SDS 2.1.1.6.3, 2.1.1.7.3, 2.1.1.3.3, 2.1.1.4.3
Note: Please refer to section 5.3 Discussion of Individual Studies/Clinical Trials for a discussion of the use of SU in study 105.

The data from study 105 was analyzed by baseline HbA1c < 6.5% or ≥ 6.5%. Amylin drug product resulted in a greater change in HbA1c compared to the Alkermes drug product, regardless of the baseline HbA1c. As expected, the change in HbA1c from baseline was smaller in study 105c when compared to study 105. This is likely explained by the lower baseline HBA1c (6.5% vs. 9%) and shorter duration of therapy (18 vs. 30 weeks).

Table 16. Study 105c: Change in HbA1c at week 18 in study 105c by baseline HbA1c (ITT).

HbA1c	N	Change in HbA1c (%) mean (SD)
< 6.5%	**90**	
Alkermes	43	0.24 (0.314)
Amylin	47	0.41 (0.362)
≥ 6.5%	**127**	
Alkermes	66	0.26 (0.803)
Amylin	61	0.40 (0.689)

Source: SDS 2.1.1.3.2

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Phase 2 study 104: Multiple-dose PK evaluations in study 2993LAR-104 demonstrated that steady state plasma exenatide concentrations within the targeted therapeutic range (based on a 10 mcg dose of exenatide) were achieved with weekly dosing of 0.8 or 2 mg exenatide LAR. At Week 15, the mean (SE) change in HbA1c compared to baseline was -1.35 (0.30)% and -1.73 (0.32)% for the 0.8 mg and 2 mg exenatide LAR groups, respectively; HbA1c increased by 0.43 (0.27)% for the placebo LAR group. However, the 2 mg dose resulted in steady state plasma exenatide concentrations similar to the mean peak plasma exenatide concentration achieved by exenatide 10 mcg as well as greater weight loss. Therefore, 2 mg exenatide LAR was assessed in phase 3 trials. Please refer to Dr. Jayabharathi Vaidyanathan's clinical pharmacology review for full details.

Phase 3 study 105: Phase 3, 30 week, comparator (Byetta)-controlled study 105 started with Alkermes material from the (b) (4) scale, although the (b) (4) scale product was later introduced. Study 105 also includes an open-ended assessment period in which all subjects are treated with exenatide LAR. At the time of study 105's initiation (April 2006), only (b) (4) Alkermes exenatide LAR material was available for use. In early 2007, (b) (4) Alkermes material became available and was transitioned into the study. Thus, the first 88 (59.5%) subjects that were randomized to the exenatide LAR arm received (b) (4) Alkermes material and the last 60 (40.5%) subjects randomized to the exenatide LAR arm received (b) (4) Alkermes material. Subjects remained on their original assigned scale of material for at least the 30 week, comparator-controlled assessment period of the study. After completion of the 30-week assessment period, subjects originally assigned to exenatide treatment were switched to exenatide LAR treatment. Depending on the timing of their completion of the 30 week assessment period, exenatide subjects initiated exenatide LAR treatment with (b) (4) Alkermes material (84 [64.6%] subjects) or with (b) (4) Alkermes material (46 [35.3%] subjects). Once the (b) (4) Alkermes material was readily available (early 2007), all subjects transitioned to (b) (4) material for ongoing treatment. In August 2008, the ongoing open-ended assessment period was used to compare the (b) (4) Alkermes material to (b) (4) Amylin material. For that assessment, 108 subjects were randomized to (b) (4) Amylin material, and 109 subjects to (b) (4) Alkermes material.

From the initiation of study 105 through week 20 of study 105c, 172 subjects were exposed to (b) (4) Alkermes material and 253 subjects were exposed to (b) (4) Alkermes material. The mean (SD) duration of exposure for the (b) (4) material was estimated by the sponsor to be 41.6 (17.6) weeks, resulting in 137.5 total subject years of exposure. The mean (SD) duration of exposure for the (b) (4) material was estimated to be 63.3 (22.0) weeks, resulting in 307.8 total subject years of exposure.

Although a greater percentage of subjects were 1) originally randomized to (b) (4) Alkermes material (59.5% vs. 40.5%) and 2) switched from exenatide to (b) (4) Alkermes exenatide LAR material (64.6% vs. 35.3%), the total subject years of exposure to the (b) (4) Alkermes material (307.8) was more than double that of the (b) (4) Alkermes material (137.5). Thus, the exposure to (b) (4) Alkermes material in study 105 is adequate and sufficient for comparison to the (b) (4) Amylin material in study 105c.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study 105 examined effects at 52 weeks on HbA1c of exenatide LAR administered SC weekly in T2DM subjects. Mean baseline HbA1c values in exenatide LAR and exenatide subjects in study 105 were 8.3%. At week 30, the LS mean change in the ITT exenatide LAR group was -1.9%, compared to the -1.5% change in the ITT exenatide g roup. The mean reduction in HbA1c at week 30 in the exenatide LAR group persisted through 52 weeks of therapy.

The sponsor did not analyze the 52 week data in the ITT population but used the evaluable population. At week 52, the LS mean change in HbA1c from baseline in exenatide LAR group was -2.0%. Thus, the mean HbA1c in the evaluable exenatide LAR population at weeks 30 and 52 were 6.5% and 6.6%, respectively.

Subjects in the exenatide group switched to exenatide LAR at week 30. These subjects experienced a slight rise in mean HbA1c at week 33 which subsided by week 36 and was followed by additional decreases. At week 52, the LS mean change in HbA1c from baseline was -2.0% in the group that switched from exenatide to exenatide LAR. The mean HbA1c in the evaluable exenatide population at weeks 30 and 52 were 6.8% and 6.6%, respectively.

A similar percentage of subjects with baseline HbA1c > 7% who received exenatide LAR and exenatide through week 30 had a HbA1c level at week 52 ≤ 7% (72.2% and 75.2%, respectively). This represents an improvement in the subjects who previously received exenatide, as only 64.1% of them had HbA1c ≤ 7% at week 30.

Thus, despite the absence of a control group, improvements in HbA1c are likely durable through 52 weeks of exenatide LAR therapy.

6.1.10 Additional Efficacy Issues/Analyses

Effect of anti-exenatide antibodies on efficacy parameters: Exenatide LAR is a slow release formulation of exenatide (Byetta), which is currently on the market. In long-term controlled trials of exenatide, approximately 44% of subjects were positive for antibodies to exenatide after 30 weeks of treatment, with mean titers peaking at around week 6 and subsequently decreasing. Approximately 38% of subjects had low antibody titers (≤ 125) after 30 weeks of exenatide treatment. For subjects with low antibody titers, the efficacy of exenatide as assessed by HbA1c at week 30 was comparable to that for subjects negative for exenatide antibodies. Six percent (6%) of subjects had higher antibody titers at 30 weeks. Approximately half of these subjects (3% of the total) showed an attenuated glycemic response to exenatide; the remainder had a glycemic response comparable to that of subjects without antibodies. After 52 weeks of exenatide treatment, < 5% of subjects maintained a high titer antibody response; of those, approximately half showed improvements in HbA1c compared to baseline.

The formation of antibodies was evaluated in all exenatide LAR clinical studies. The studies using the intended commercial formulation of exenatide LAR (AC2993-F17 [F17]) included studies 102, 103, 104, and 105. Study 105 had the largest subject exposure to exenatide LAR and the longest duration. In addition, study 105 included an exenatide comparator treatment arm for comparison to exenatide LAR.
Thus, the review of exenatide antibody development focused on the results of study 105.

The presence of exenatide antibodies in human sera from subjects treated in clinical study 105 was evaluated using a validated enzyme-linked immunosorbant assay (ELISA) for antibodies to exenatide. The assay detected total antibodies (IgM, IgG, and IgA isotypes) specific to exenatide. Titers were determined by serial 1/5 dilutions after a minimal dilution of 1/25. Antibody titer was expressed as the reciprocal of the highest dilution of sample serum that tested positive in the assay (e.g. a dilution of 1/125 is expressed as an antibody titer of 125). Approximately 5.1% of plasma specimens from exenatide-naïve subjects tested positive (titer ≥ 25) for exenatide antibodies (i.e. false positives or subjects with pre-existing cross reactive antibodies). Subjects were considered positive for treatment-emergent exenatide antibodies if 1) the antibody titer was positive after the first injection of study medication following a negative or missed measurement at baseline or 2) if the titer increased by at least 3 dilutions (at least 125 fold) from a detectable baseline measurement.

During the 30 week assessment period, more exenatide LAR subjects were positive for exenatide antibodies when compared to exenatide subjects (74.3% vs. 49.0%). However, 96% of subjects treated with exenatide LAR exhibited an improvement in HbA1c at week 30. At the last visit on or prior to week 30, 43% of exenatide LAR ITT subjects had low antibody titers with a LS mean change in HbA1c from baseline (-1.8%) that was similar to the 51% of subjects who were negative for exenatide antibodies (-

2.1%). There was considerable interference with the ability to quantify exenatide in samples with high (≥ 625) antibody titers. Nine (6%) of exenatide LAR subjects had high titers at the last visit on or prior to week 30. In these 9 subjects, a wide range of effects on HbA1c was reported (-1.4% to +2.3%), but these effects were attenuated compared to the mean exenatide LAR effect on HbA1c for the entire treatment group.

In the exenatide (Byetta) group, a smaller LS mean change in HbA1c from baseline was seen in subjects with low antibody titer (-1.1%) compared to antibody negative subjects (-1.7%). The effect of exenatide on HbA1c in the 3 subjects with high antibody titers was variable (-1.1% to 0%).

Table 17. Change in HbA1c (%) from baseline in study 105 by antibody status and treatment group

Study group	Low titer positive antibodies	Negative antibodies
Exenatide LAR	-1.8	-2.1
Exenatide	-1.1	-1.7

At week 52, 98% of exenatide LAR subjects' HbA1c values had improved. The majority of subjects who were antibody positive had low titers and an improvement in HbA1c that as similar to that for antibody negative subjects. The 13 subjects with high antibody titers at the last visit on or prior to week 52 experienced a change in HbA1c from -3.7 to +0.3%; 12 of these exenatide LAR subjects demonstrated a loss of detectable plasma exenatide concentration due to high antibody titers. Yet, five of the 13 subjects (38%) had a reduction ≥ 0.7%.

In the subjects who switched from exenatide to exenatide LAR at week 30, similar reductions in HbA1c were observed for the low titer and antibody negative subjects at the last visit on or prior to week 52. Six subjects had higher antibody titers with changes in Hba1c of -1.5 to +0.5%.

In conclusion, more exenatide LAR subjects were positive for exenatide antibodies when compared to exenatide subjects (74.3% vs. 49.0%) at week 30 in study 105. The change in HbA1c in exenatide LAR subjects' with low antibody titer was more similar to the change in HbA1c experienced by exenatide LAR antibody negative subjects (-1.8% vs. -2.1) when compared to exenatide (Byetta) low titer positive and negative antibody subjects (-1.1% vs. -1.7%). In the 9 (6%) exenatide LAR subjects with high titers (≥ 625), the change in HbA1c ranged from -1.4 to +2.3%, suggesting possible decreased effectiveness in these patients. A similar trend was observed when exenatide LAR subjects with high antibody titers were evaluated at week 52 (change in HbA1c range -3.7 to -0.3%); only a minority of those subjects (38%) experienced a reduction in HbA1c ≥ 0.7%.

7 Review of Safety

Safety Summary

Studies 102, 103, 104, and 105 were included in the original integrated summary of safety that was submitted with the NDA, as they used the commercial formulation. Studies 102, 103, and 104 used the Alkermes material from the (b) (4) scale. Phase 3 study 105 started with Alkermes material from the (b) (4) scale, although the (b) (4) scale product was later introduced.

However, the four-month safety update included data from previously completed studies BCB107 and H9O-JE-GWBW and recently completed study BCB106. It included 990 subjects (606 on exenatide LAR), whereas the integrated summary of safety included 409 subjects (366 on exenatide LAR). The four-month safety update pooled studies as follows:

- Clinical pharmacology studies (single-dose)
  - Healthy subjects: 2993LAR-102 and BCB107 (both placebo-controlled)
  - T2DM subjects: 2993LAR-103
- Efficacy and safety studies (repeat dose studies over 15-30 weeks)
  - Placebo-controlled: 2993LAR-104 and H8O-JE-GWBW
  - Comparator-controlled: 2993LAR-105 and BCB106
- Uncontrolled exenatide once weekly exposure: 2993LAR-105 open-label assessment (week 30 – 2 years)

Although I generally agree with the pooled study groups, it must be noted that study GWBW and BCB106 did not include an exenatide BID lead-in and study GWBW was a non-IND study conducted in 30 Japanese subjects.

My safety review focused on the controlled, repeat dose, efficacy and safety studies described in the four-month safety update, especially the larger pivotal study 105. However, I also described findings from the integrated summary of safety, information requests, and the four month safety update supplement when appropriate, particularly in cases in which the four month safety update did not contain the necessary information.

The total exposure of exenatide LAR subjects (233 ≥1 year, 115 ≥1.5 year) is less than the 2,500 exposed subjects (300-500 for ≥1.5 year) recommended in the draft February 2008 diabetes mellitus guidance. However, exenatide LAR makes reference to safety and efficacy data submitted with the exenatide NDA 21-773. As of March 31, 2009, over (b) (4) patients have been exposed to exenatide in the United States. More than 6,000 subjects and healthy volunteers have been exposed to exenatide in clinical trials. Thus, the exposure is adequate.

The sponsor conducted study BCB107, a phase 1, open label, parallel group study in 120 healthy subjects to evaluate the single dose PK profiles of exenatide LAR

formulations to support in vitro/in vivo correlation (IVIVC) analysis. However, on October 29, 2008, the IVIVC bioequivalence-waiver to support a proposed manufacturing site change from the clinical manufacturing site to the intended commercial site was denied because 1) the utilization of rats for BE studies is not acceptable and 2) the IVIVC poorly predicts Cmax. Thus, the sponsor was required to conduct a clinical study (i.e. study 105c) to demonstrate bioequivalence.

Although the sponsor obtained safety evaluations at reasonable time points during the studies, limitations of this testing included the following:

- Serum amylase and lipase was not drawn in key studies 105 or 105c nor in studies 104 or GWBW. However, as the clinical significance of routine amylase and lipase monitoring is not clear, this is acceptable. Furthermore, serum lipase and amylase were monitored in BCB106. The incidence of pancreatitis across completed studies of exenatide LAR and exenatide was summarized in the four-month safety update supplement.
- Calcitonin was not measured in studies submitted to the NDA. However, the NDA contains an analysis of thyroid neoplasms, included nonclinical, exenatide clinical and postmarketing, and exenatide LAR clinical data.

Nonclinical studies have shown that exenatide is predominately eliminated by glomerular filtration with subsequent proteolytic degradation.

The multiple-dose PK of exenatide LAR was evaluated in phase 2 study 104 and long term phase 3 study 105 with a larger and more diverse population. Approximately 7 weeks after the last exenatide LAR injection, mean plasma exenatide concentrations were below the minimally effective threshold (< 50 pg/ml). Mean plasma concentrations approached the lower limit of quantification (10 pg/ml) approximately 10 weeks after discontinuation of therapy.

In the seven completed studies of exenatide LAR as of March 31, 2009, only 1 exenatide LAR subject died. Subject 10802 was a 67 year old American male with a history of T2DM (8 years) and hyperlipidemia who was overweight and died of a fatal myocardial infarction approximately 198 days after initiation of exenatide LAR in study 105. While a study drug effect cannot be fully excluded, the patient's medical history may also explain the adverse event.

I reviewed SAEs in the integrated summary of safety, which included most studies, and relevant study reports, because the sponsor did not include an analysis of SAEs in the four month safety update. In the integrated summary of safety that was submitted with the original NDA, cardiac disorders and infections & infestations were most common SAEs with 5.7% and 1.4% of exenatide LAR subjects experiencing these SAEs, respectively. However, only angina pectoris (n=5, 1.4%) and myocardial infarction (n=2, 0.5%) (i.e. no infections or other cardiac events) occurred in more than one subjects. Gastrointestinal and neoplasm disorders were the second most common SOCs with

SAEs (n=3, 0.8%). However, all gastrointestinal and neoplasms disorders but bladder cancer (n=2) occurred as single events. Please refer to Table 21. Exenatide LAR does not appear to be associated with an increase in SAEs.

Although exenatide LAR does not appear to be associated with an increased rate of withdrawal due to an AE, the most common reasons for withdrawal of exenatide LAR subjects included gastrointestinal disorders and general disorders & administration site conditions.

I reviewed the application for the significant AEs listed with results as follows (see also section 7.3.4):

- Thyroid tumors: No thyroid cancers were identified in the exenatide LAR clinical development program, although the population studied was small. Calcitonin data was not available for review but has been incorporated into more recent trials. The review of exenatide (Byetta) clinical trial and postmarketing data does not suggest an increased risk for thyroid tumors with exenatide. No trend towards an increased risk of other malignancies was identified by my review.
- Acute pancreatitis: Only 1 exenatide LAR subject developed pancreatitis in a clinical trial to date, although the population studied was small. When completed studies of exenatide LAR and exenatide were reviewed, a similar frequency of pancreatitis events was observed (exenatide LAR 0%, exenatide 0.1%, placebo 0.1%, comparator 0.3%). When routine lipase and p-amylase measurement were included in study BCB106, an increase from baseline in mean lipase concentration was observed in the exenatide LAR and sitagliptin groups (+17.1 U/l and +8.5 U/l, respectively); a slight decrease was observed in the pioglitazone group (-3.7 U/l). The proportion of subjects with lipase ≥ 3x ULN at week 26 was similar across groups (1-2%). Mean p-amylase levels were normal and similar for all treatment groups at each time point in study BCB106. No exenatide LAR subject had p-amylase elevations > 3x ULN at any time. When a subset of asymptomatic BCB106 subjects with elevated pancreatic enzymes were imaged, no signs of pancreatitis were seen although gallstones were a common finding. When exenatide postmarketing data was reviewed, the reporting rate and United States incidence rate for pancreatitis were similar, although they cannot be directly compared.
- Gastrointestinal side effects: Exenatide LAR appears to be associated with an increase rate of GI side effects when compared to placebo, sitagliptin, or pioglitazone, although the incidence and severity of nausea and vomiting is lower with exenatide LAR than exenatide.
- Hypoglycemia: Blood glucose decreased was a frequent AE in the placebo controlled efficacy and safety studies of exenatide LAR (i.e. studies 104 and GWBW, as described in the four month safety update). Blood glucose decreased occurred in 3 of these 51 (5.9%) subjects. However, it occurred in no exenatide LAR subjects (n=308) in comparator controlled trials (i.e. studies 105

and BCB106). The incidence of minor hypoglycemia in studies 102-105 was low and less than that seen with exenatide.

- Hypersensitivity: More subjects receiving exenatide LAR develop anti-exenatide antibodies than subjects receiving exenatide (74.3% vs. 49.0% in study 105). The overall incidence of AEs was similar between the exenatide LAR and exenatide. There was no clear effect of antibody status on the overall incidence of AEs. However, more exenatide LAR subjects experienced injection site reactions than exenatide, sitagliptin, and pioglitazone subjects. (Sitagliptin and pioglitazone subjects received weekly placebo injection.) The incidence of injection site reactions was higher in antibody positive than antibody negative exenatide LAR subjects (high positive 36.2%, low positive 11.8%, negative 4.9%). However, injection site reactions uncommonly resulted in study withdrawal (0.3%).
- Renal failure: In the population and under the conditions studies, exenatide LAR does not appear to increase the risk of acute renal failure. Please refer to sections 7.3.4, 7.4.2, and 7.5.4 for more details.

Exenatide and exenatide LAR have not been studied in subjects with acute and chronic hepatic impairment, although hepatic dysfunction is not expected to affect blood concentrations of exenatide; the label will reflect these points

The incidence rates of common adverse events in completed, placebo- and comparator-controlled efficacy and safety studies of exenatide LAR as of March 31, 2009 (studies 104, GWBW, 105, and BCB106) was reviewed. Nausea, diarrhea, vomiting, anorexia, gastroesophageal reflux disease (GERD), and injection site pruritis and erythema occurred more commonly in the exenatide LAR group than comparator. However, nausea and vomiting occurred less often in the exenatide LAR group than in the exenatide group (comparator controlled: 25.3% vs. 34.5% and 11.0% vs. 18.6%, respectively). Gastroenteritis and blood glucose low occurred more often in the exenatide LAR group than placebo group (11.8% vs. 0.0% and 5.9% vs. 0.0%, respectively), but at a similar or lower frequency than comparator groups. Please refer to Table 28.

With regard to laboratory findings, analyses focused on measures of central tendency, outliers or shifts from normal to abnormal, and marked outliers and dropouts for laboratory abnormalities did not reveal clinically significant differences from comparator groups. Please refer to section 7.4.2 for full details.

With regard to vital signs, according to repeat dose, controlled, efficacy and safety studies, exenatide LAR is associated with mean decrease in blood pressure (-3.2/-1.3 mm Hg) and increase in heart rate (1.9 bpm). This is similar to the changes associated with exenatide. These minor changes are likely clinically insignificant.

Although a thorough QT study of exenatide LAR was not performed, study 105 included replicate 12 lead ECGs at baseline and weeks 14 and 30. According to the QT IRT, a dedicated TQT is not needed unless there are CV AEs such as syncope, seizure, ventricular arrhythmias, or sudden death in the clinical development program and postmarketing reports. As this is not the case, the ECG data submitted is acceptable. There is no signal for abnormal ECGs at this time.

With regards to the use of exenatide LAR without an exenatide lead-in, study BCB106 demonstrated that this does not significantly increase the rate of gastrointestinal SAEs; the common AEs of nausea, diarrhea, vomiting, and headache; nor the rate of withdrawal due to gastrointestinal AEs.

The risk of AEs associated with exenatide LAR does not appear to increase with increasing exposure. Please refer to section 7.5.2 for full details.

The sponsor analyzed safety by age, gender, race, and BMI in the summary of clinical safety submitted with the NDA. No clinically relevant differences were seen.

With regards to drug-drug interactions, the sponsor is relying on the exenatide studies, although the effect of exenatide LAR on the rate of gastric emptying was investigated using acetaminophen 1000 mg as a gastric emptying marker with and without a standardized meal in a cohort of subjects in study 105 (N=75). As discussed with clinical pharmacology, although the magnitude of the reduction on the rate of absorption of concomitant oral acetaminophen was less than the reduced acetaminophen absorption reported with exenatide, there was still a 16% decrease under fasting and 5% under fed state in the Cmax of acetaminophen. Thus, the proposed wording for section 7.1 of the label should be revised to more accurately reflect the results of the acetaminophen study.

The sponsor seeks a waiver of exenatide LAR studies in pediatric T2DM subjects aged 0-9 years and a deferral in subjects 10-17 years. Please refer to section 7.6.3 Pediatrics and Assessment of Effects on Growth for the Pediatric Research Committee's (PeRC's) and my full recommendations.

Finally, as exenatide LAR is not a new molecular entity but a reformulation of exenatide which has been on the market since April 2005 without a pre-market signal for increased cardiovascular risk, the overall CV risk-benefit analysis described in section 9.4 supports approval. However, a postmarketing trial of exenatide and/or exenatide LAR is necessary to definitively show that the upper bound of the two-sided 95% CI for the estimated risk ratio is less than 1.3. Trial results should be submitted to both exenatide and exenatide LAR NDAs (21-773 and 22-200, respectively).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies 102, 103, 104, and 105 were included in the original integrated summary of safety that was submitted with the NDA, as they used the commercial formulation. Studies 102, 103, and 104 used the Alkermes material from the (b) (4) scale. Phase 3 study 105 started with Alkermes material from the (b) (4) scale, although the (b) (4) scale product was later introduced.

Safety data from studies BCB107, GWBW, and 105c were not included in the integrated summary of safety in the original NDA submission because these studies were designed with very specific goals and patient populations. Comparability of the (b) (4) Amylin drug product intended for commercial use and (b) (4) Alkermes drug product intended for clinical development was assessed via glycemic, pharmacokinetic, and safety endpoints in extension study 105c. Study BCB107 was a single dose study in healthy subjects to assess the PK of different exenatide once weekly formulations for development of an IVIVC analysis, which later failed. Study GWBW was a non-IND study conducted in 30 Japanese subjects to support registration in Japan.

However, the four-month safety update included data from previously completed studies BCB107 and H9O-JE-GWBW and recently completed study BCB106. It included 990 subjects (606 on exenatide LAR), whereas the integrated summary of safety in the original NDA submission included 409 subjects (366 on exenatide LAR). The four-month safety update pooled studies as follows:

- Clinical pharmacology studies (single-dose)
  - Healthy subjects: 2993LAR-102 and BCB107 (both placebo-controlled)
  - T2DM subjects: 2993LAR-103
- Efficacy and safety studies (repeat dose studies over 15-30 weeks)
  - Placebo-controlled: 2993LAR-104 and H8O-JE-GWBW
  - Comparator-controlled: 2993LAR-105 and BCB106
- Uncontrolled exenatide once weekly exposure: 2993LAR-105 open-label assessment (week 30 – 2 years)

The four-month safety update also included a response to the 74 day letter's request for an updated integrated summary of safety of exenatide and exenatide LAR, which was described in this review where appropriate. However, my safety review focused on the controlled, repeat dose, efficacy and safety studies described in the four-month safety update, especially the larger pivotal study 105.

Study BCB106 is a phase 3, randomized, double blind, comparator controlled, parallel group study in 491 T2DM subjects who received 2 mg exenatide LAR weekly (with no

exenatide BID lead-in), sitagliptin 100 mg daily, or pioglitazone 45 mg daily for 26 weeks. As the study report was submitted in the 4 month safety update but not the original NDA, it was reviewed only with regards to safety, especially exenatide LAR tolerability without an exenatide BID lead-in. As the open-ended assessment period BCB106 is still ongoing, its results are not reviewed here.

The sponsor also included an exenatide LAR antibody summary that is reviewed in section 7.4.6 Immunogenicity.

On November 19, 2009, the sponsor submitted the requested major adverse cardiovascular event (MACE) information, which is described in section 9.4 Exenatide Cardiovascular Safety Submission.

Table 18. NDA 22-200: Overview of safety data for exenatide LAR

Source of data	Details
Clinical pharmacology trials	3 single-dose studies: • Healthy subjects: 2993LAR-102 and BCB107 (both placebo-controlled) • T2DM subjects: 2993LAR-103
Controlled safety/ efficacy trials	**4 studies:** • Placebo-controlled: 2993LAR-104 and H8O-JE-GWBW • Comparator-controlled: 2993LAR-105 and BCB106
Uncontrolled long-term safety data	**1 study:** 2993LAR-105 (week 30 – 2 years)
MACE meta-analysis	**19 studies:** • 12 long-term, randomized, controlled clinical trials of exenatide (2993-112, -113, and -115 as well as H8O-MC-GWAP, -GWAV, -GWBA, -GWBJ, -GWCD, -GWAA, -GWAD, -GWAK, and –GWAO) • The 5 long-term, uncontrolled trials of exenatide that were originally included in the NDA submission (2993-112E, -113E, -115E, -117, and -119) • Exenatide LAR studies 2993LAR-105 and -104

When appropriate, comments pertaining to safety are included from the following ongoing studies of exenatide LAR, as described in the four month safety update:

- 2993LAR-105: Post week 52
- BCB106: Post week 26
- H8O-MC-GWBR: An open label, comparator controlled study to compared the efficacy and safety of exenatide once weekly to that of insulin glargine in subjects with T2DM treated with metformin or metformin in combination with an SU during 26 weeks of treatment.
- H8O-MC-GWCH: A randomized, double blind, comparator controlled trial to compare the efficacy and safety of exenatide once weekly to that of metformin, sitagliptin, and pioglitazone in subjects with T2DM inadequately treated with diet and exercise

- H8O-MC-GWDC: An open label, single arm study to assess the long-term safety and efficacy of exenatide once weekly in subjects with T2DM treated with a TZD during 52 weeks of treatment, followed by an open ended assessment period.
- BCB108: A randomized, open label study to evaluate the glycemic effects, safety, and tolerability of exenatide once weekly in comparison to treatment with Byetta in subjects with T2DM treated with diet and exercise and/or metformin, a sulfonylurea, a TZD, or any dual combination of those medications.

7.1.2 Categorization of Adverse Events

The sponsor's coding and categorization of adverse events was adequate. As described in the four month safety update, the studies submitted used MedDRA versions 10.1, 11.0, and 11.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety review focuses mainly on the controlled, repeat dose, efficacy and safety studies described in the four-month safety update, especially pivotal study 105. Safety data from 8 completed clinical studies were pooled in the four-month safety update, separated by similarity of design into the following 4 groups:

- Clinical pharmacology studies (single-dose)
  - Healthy subjects: 2993LAR-102 and BCB107 (both placebo-controlled)
  - T2DM subjects: 2993LAR-103
- Efficacy and safety studies (repeat dose studies over 15-30 weeks)
  - Placebo-controlled: 2993LAR-104 and H8O-JE-GWBW
  - Comparator-controlled: 2993LAR-105 and BCB106
- Uncontrolled exenatide once weekly exposure: 2993LAR-105 open-label assessment (week 30 – 2 years)

I generally agree with the pooled study groups. However, it must be noted that study GWBW and BCB106 did not include an exenatide BID lead-in and study GWBW was a non-IND study conducted in 30 Japanese subjects.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of the November 15, 2008 cutoff for the original NDA, 860 subjects had been exposed to exenatide LAR (F17 formulation) in 9 ongoing and completed studies. The integrated summary of safety described 366 subjects exposed to exenatide LAR.

As of the March 31, 2009 cutoff date for the four month safety update, 1300 subjects had been exposed to exenatide LAR in completed and ongoing trials. The safety updated described 990 subjects in 7 completed studies, including 606 subjects treated with exenatide LAR.

Table 19. NDA 22-200: Cumulative number of subjects exposed to exenatide LAR as of March 31, 2009.

Study Subgroup	Any Duration	Cumulative Duration (wks)				
		≥12 wk	≥26 wk	≥52 wk	≥78 wk	≥96
Clin Pharm Subtotal	117					
Efficacy & Safety						
Placebo controlled						
LAR104	31	31				
GWBW	20					
Subtotal	51	31				
Comparator controlled						
LAR105	278	268	251	233	115	110
BCB106	160	140	124			
Subtotal	438	408	375	233	115	110
Efficacy & Safety Subtotal	489	439	375	233	115	110
Grand Total	**606**	**439**	**375**	**233**	**115**	**110**

Source: Four month safety update Table 3

The total exposure of exenatide LAR subjects (233 ≥1 year, 115 ≥1.5 year) is less than the 2,500 exposed subjects (300-500 for ≥1.5 year) recommended in the draft February 2008 diabetes mellitus guidance. However, the exenatide LAR NDA makes appropriate reference to the exenatide NDA 21-773, since it is a different formulation with the same active ingredient. As of March 31, 2009, over (b) (4) patients have been exposed to exenatide in the United States. More than 6,000 subjects and healthy volunteers have been exposed to exenatide in clinical trials. Thus, the exposure is adequate.

The demographic and baseline characteristics of subjects included in the repeat dose efficacy and safety studies of exenatide LAR over 15 weeks (i.e. studies 104, 105,

GWBW, and BCB106) are shown below. Approximately half of subjects were male. The mean age ranged from 52.2 - 57.3 years; the majority of subjects were < 65 years. The distribution of races varied by study but, overall, was diverse. The mean BMI ranged from 31.80 – 35.09. The mean HbA1c and duration of diabetes ranged from 8.01-8.49% and 4.9 - 6.6 years, respectively. The majority of subjects were on background antidiabetic medication in addition to diet and exercise. The majority of subjects had normal renal function or mild renal insufficiency.

Table 20. NDA 22-200: Demographic and baseline characteristics treatment in repeat dose, efficacy and safety studies of exenatide LAR over 15 weeks (i.e. studies 104, 105, GWBW, and BCB106) (ITT)

	Placebo Controlled		Comparator Controlled			
	Ex LAR (n=51)	Placebo (n=23)	Ex LAR (n=308)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
Male	35 (68.6)	9 (39.1)	171 (55.5)	74 (51.0)	86 (51.8)	79 (47.9)
Mean age (y)	54.3	57.3	53.7	54.8	52.2	53.0
Age						
≥18-65	40 (78.4)	17 (73.9)	262 (85.1)	122 (84.1)	149 (89.8)	143 (86.7)
≥65	11 (21.6)	6 (26.1)	46 (14.9)	23 (15.9)	17 (10.2)	22 (13.3)
Race						
Caucasian	18 (35.3)	9 (39.1)	176 (57.1)	205 (72.4)	50 (30.1)	65 (39.4)
Black	5 (9.8)	1 (4.3)	28 (9.1)	19 (13.1)	20 (12.0)	13 (7.9)
Asian	21 (41.2)	10 (43.5)	37 (12.0)	1 (0.7)	42 (25.3)	40 (24.2)
Native Am	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)
Hispanic	6 (11.8)	3 (13.0)	66 (21.4)	20 (13.8)	49 (29.5)	44 (26.7)
Other	1 (2.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (1.2)	3 (1.8)
Mean BMI	31.95	31. 89	33.39	35.09	31.80	32.47
Mean HbA1c (%)	8.01	8.07	8.43	8.33	8.49	8.47
Mean T2DM duration (y)	4.9	5.2	6.6	6.4	5.4	5.8
Background diet & exercise only	22 (43.1)	6 (26.1)	21 (6.8)	23 (15.9)	0 (0.0)	0 (0.0)
Renal function						
Normal	35 (68.6)	13 (56.5)	159 (51.6)	82 (56.6)	83 (50.0)	72 (43.6)
Mild	16 (31.4)	9 (39.1)	129 (41.9)	52 (35.9)	69 (41.6)	79 (47.9)
Moderate	0 (0.0)	0 (0.0)	20 (6.5)	11 (7.6)	11 (6.6)	13 (7.9)
Severe	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)

Source: Four month safety update SDS 2

Exenatide should not be used in patients with severe renal impairment or end-stage renal disease (ESRD). It should be used with caution in patients with renal transplantation. Caution should be applied when initiation exenatide or escalating the dose in patients with moderate renal failure. The sponsor proposed to contraindicate exenatide LAR in subject with severe and end stage renal impairment. This is appropriate as studies of exenatide LAR excluded subjects with renal failure as follows:

- Studies 104, 105, 105c: Included male and female subjects with serum creatinine ≤ 1.6 and 1.4 mg/dl, respectively. Excluded subjects with creatinine clearance (CrCl) ≤ 30 mg/dl.
- Study GWBW: Excluded subjects with a history of renal transplantation, currently receiving dialysis, or serum creatinine ≥ 1.5 or 1.4 mg/dl for males or females, respectively
- Study BCB106: Excluded subjects with serum creatinine level > 1.5 or 1.4 mg/dl in men and women, respectively

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide. The proposed exenatide LAR label also states these points. However, studies of exenatide LAR excluded subjects with hepatic impairment as follows:

- Studies 104, 105, 105c, BCB106: Hepatic disease or an ALT or AST > 3x ULN.
- Study GWBW: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or ALT or AST ≥ 2.5x ULN.

7.2.2 Explorations for Dose Response

Multiple-dose PK evaluations in study 2993LAR-104 demonstrated that steady state plasma exenatide concentrations within the targeted therapeutic range (based on a 10 mcg dose of exenatide) were achieved with weekly dosing of 0.8 or 2 mg exenatide LAR. After 15 weeks of treatment, both doses of exenatide LAR were well tolerated and resulted in improved mean HbA1c. However, the 2 mg dose resulted in steady state plasma exenatide concentrations similar to the mean peak plasma exenatide concentration achieved by exenatide 10 mcg as well as greater weight loss. Both the 0.8 and 2 mg doses were well-tolerated; there was no significant difference in death, SAEs, withdrawal rate, or frequent AEs. Therefore, 2 mg exenatide LAR was assessed in phase 3 trials. Please refer to Dr. Jayabharathi Vaidyanathan's clinical pharmacology review for full details.

Dose titration was not conducted in phase 3 studies. However, all phase 2 and 3 studies, except studies GWBW and BCB106, included an exenatide BID lead-in, even if it was only 3 days.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to section 4.3 Preclinical Pharmacology/Toxicology for a discussion of the relevant animal thyroid data with exenatide LAR and related products, exenatide and liraglutide. An epidemiological study to assess the relative risk of thyroid neoplasm with exenatide is required from the sponsor.

As described above, exenatide is associated with pancreatitis, including hemorrhagic and necrotizing pancreatitis. Although the sponsor did not conduct special animal or in vitro studies of pancreatitis with exenatide LAR, an adequately powered epidemiological study to determine the incidence rate, severity, and risk factors for pancreatitis with exenatide and a 3 month pancreatic safety study in a diabetic rodent model treated with exenatide are required from the sponsor.

A thorough QT study was not submitted with NDA 22-200, but to determine whether continuous exposure to therapeutic plasma exenatide concentrations affected overall ECG findings or QT intervals, ECG recordings were performed for subjects treated with exenatide LAR at baseline and weeks 14 and 30 in study 105, after steady state concentrations were achieved. This data was reviewed in section 7.4.4 Electrocardiograms and by the QT IRT.

Study BCB107 was a phase 1, open label, parallel group study in 120 healthy subjects to evaluate the single dose PK profiles of exenatide LAR formulations to support in vitro/in vivo correlation (IVIVC) analysis. Subjects received one exenatide 10 mcg SC injection on day -1 and one dose of their assigned exenatide LAR formulation (10 mg F17 lot S426-2377CA, 10 mg F17 lot S426-2507AA, 8 mg fast-release F28, or 10 mg slow-release F30) on day 1. However, on October 29, 2008, the IVIVC bioequivalence-waiver to support a proposed manufacturing site change from the clinical manufacturing site to the intended commercial site was denied because 1) the utilization of rats for BE studies is not acceptable and 2) the IVIVC poorly predicts Cmax.

7.2.4 Routine Clinical Testing

The sponsor obtained laboratory tests, vital signs, and ECGs at reasonable time points during the studies and under consistent settings, where applicable. I reviewed the timing of these assessments in section 5.3 Discussion of Individual Studies. Limitations of this testing include the following:

- Serum amylase and lipase was not drawn in key studies 105 or 105c nor in studies 104 or GWBW which were included in the safety review. However, as the clinical significance of routine amylase and lipase monitoring is not clear, this is acceptable. Furthermore, serum lipase and amylase were monitored in BCB106 at screening, baseline, week 14 and week 26. The incidence of pancreatitis across completed studies of exenatide LAR and exenatide was summarized in the four-month safety update supplement.
- Calcitonin was not measured in studies submitted to the NDA. However, the NDA contains an analysis of thyroid neoplasms, included nonclinical, exenatide clinical and postmarketing, and exenatide LAR clinical data.

7.2.5 Metabolic, Clearance, and Interaction Workup

Nonclinical studies have shown that exenatide is predominately eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and is independent of the dose.

The multiple-dose PK of exenatide LAR was evaluated in phase 2 study 104 and long term phase 3 study 105 with a larger and more diverse population. Approximately 7 weeks after the last exenatide LAR injection, mean plasma exenatide concentrations were below the minimally effective threshold (< 50 pg/ml). Mean plasma concentrations approached the lower limit of quantification (10 pg/ml) approximately 10 weeks after discontinuation of therapy.

The sponsor is relying on the exenatide drug-drug interaction studies, although the effect of exenatide LAR on the rate of gastric emptying was investigated using acetaminophen 1000 mg as a gastric emptying marker with and without a standardized meal in a cohort of subjects in study 105 (N=75). Acetaminophen is an established marker of gastric empting because it is rapidly and well absorbed. At week 14, small reductions in mean acetaminophen Cmax (16% in fasted state, 5% in fed state) were observed with exenatide LAR coadministration. These changes were less than those observed with exenatide (21% reduction in acetaminophen Cmax). There were slight reductions in the mean acetaminophen AUC (4% in fasted and fed states) with exenatide LAR coadministration. These changes were also less than those observed with exenatide (20% reduction in acetaminophen Cmax). Please refer to section 7.5.5 Drug-Drug Interactions for a discussion of the proposed related labeling.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As discussed in section 2.4 Important Safety Issues with Consideration to Related Drugs, the only GLP-1 mimetic currently approved in the United States is exenatide. Labeled safety concerns with exenatide include:

- Acute pancreatitis
- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions as a result of anti-exenatide antibodies
- Renal failure

Liraglutide, which is currently under NDA review, is associated with thyroid c-cell tumors in rats and mice. See section 2.4 Important Safety Issues with Consideration to Related Drugs.

7.3 Major Safety Results

7.3.1 Deaths

In the completed portions of studies 102, 103, 104, 105, BCB106, BCB107, and GWBW, one sitagliptin 100 mg subject (161030) died of "hypertension" after 119 days of study medication in study BCB106. One exenatide LAR subject (10802) died of a fatal myocardial infarction approximately 198 days after initiation of exenatide LAR in study 105. The exenatide LAR subject was a 67 year old American male with a history of T2DM (8 years) and hyperlipidemia who was overweight. While a study drug effect cannot be fully excluded, the patient's medical history may also explain the adverse event.

7.3.2 Nonfatal Serious Adverse Events

The SAES occurring in studies 102, 103, 104, and 105 were summarized in the integrated summary of safety and are shown below. The majority of events were single events. Cardiac disorders and infections and infestations were most common with 5.7% and 1.4% of exenatide LAR subjects experiencing these SAEs, respectively. However, only angina pectoris (n=5, 1.4%) and myocardial infarction (n=2, 0.5%) (i.e. no infections or other cardiac events) occurred in more than one subjects. Gastrointestinal and neoplasm disorders were the second most common SOCs with SAEs (n=3, 0.8%). However, all gastrointestinal and neoplasms disorders but bladder cancer (n=2) occurred as single events.

Table 21. NDA 22-200: Serious adverse events in studies 102, 103, 104, and 105.

System organ class/Preferred term	Clinical pharmacology			Efficacy and safety					Total
	Study 102	Study 103		Study 104		Study 105			
				Placebo-controlled		Comparator-controlled		Uncontrolled (to 52 wks)	
	LAR (n=10)	LAR (n=47)	Placebo (n=15)	LAR (n=31)	Placebo (n=13)	LAR (n=148)	Exenatide (n=145)	LAR (n=258)	LAR (n=366) N %
All SAEs	0	0	1	2	0	8	5	12	21 (5.7)
Cardiac disorders	0	0	1	1	0	1	1	3	5 (1.4)
Angina pectoris	0	0	0	1	0	0	0	0	1 (0.3)
Arteriosclerosis coronary artery	0	0	0	0	0	0	1	0	0 (0.0)
Atrial fibrillation	0	0	0	0	0	0	0	1	1 (0.3)
Cardiac arrest	0	0	0	0	0	0	1	0	0 (0.0)
Coronary artery disease	0	0	1	0	0	0	0	0	0 (0.0)
Myocardial infarction	0	0	0	0	0	1	0	1	2 (0.5)
Ventricular extrasystoles	0	0	0	0	0	0	0	1	1 (0.3)
Eye disorders	0	0	0	0	0	0	0	1	1 (0.3)
Retinal detachment	0	0	0	0	0	0	0	1	1 (0.3)
GI disorders	0	0	0	0	0	1	0	2	3 (0.8)
Abdominal pain	0	0	0	0	0	0	0	1	1 (0.3)
Diarrhea	0	0	0	0	0	0	0	1	1 (0.3)
Ileus	0	0	0	0	0	0	0	1	1 (0.3)
Tooth impacted	0	0	0	0	0	1	0	0	1 (0.3)
General and admin site disorders	0	0	0	0	0	0	0	1	1 (0.3)
Non-cardiac chest pain	0	0	0	0	0	0	0	1	1 (0.3)
Hepatobiliary disorders	0	0	0	0	0	1	0	1	2 (0.5)
Cholecystitis acute	0	0	0	0	0	1	0	0	1 (0.3)
Cholelithiasis	0	0	0	0	0	0	0	1	1 (0.3)
Infections and infestations	0	0	0	0	0	2	0	4	5 (1.4)
Bacteremia	0	0	0	0	0	1	0	0	1 (0.3)
Diverticulitis	0	0	0	0	0	1	0	1	1 (0.3)
Pneumonia	0	0	0	0	0	0	0	1	1 (0.3)

Urinary tract infection	0	0	0	0	0	0	0	1	1 (0.3)
Urosepsis	0	0	0	0	0	0	0	1	1 (0.3)
Injury, poisoning, and procedural comp	0	0	0	0	0	0	2	2	2 (0.5)
Dislocation of joint prosthesis	0	0	0	0	0	0	1	0	0 (0.0)
Multiple fractures	0	0	0	0	0	0	1	0	0 (0.0)
Procedural pain	0	0	0	0	0	0	0	1	1 (0.3)
Subdural haemorrhage	0	0	0	0	0	0	1	0	0 (0.0)
Traumatic brain injury	0	0	0	0	0	0	0	1	1 (0.3)
Musculoskeletal & connective tissue disorder	0	0	0	0	0	0	2	0	0 (0.0)
Intervertebral disc protrusion	0	0	0	0	0	0	1	0	0 (0.0)
Osteoarthritis	0	0	0	0	0	0	1	0	0 (0.0)
Neoplasms benign, malignant, and unspecified	0	0	0	0	0	2	0	1	3 (0.8)
Bladder cancer	0	0	0	0	0	1	0	1	2 (0.5)
Prostate cancer	0	0	0	0	0	1	0	0	1 (0.5)
Nervous system disorders	0	0	0	0	0	1	1	1	2 (0.5)
Cerebral artery occlusion	0	0	0	0	0	1	0	0	1 (0.3)
Convulsion	0	0	0	0	0	0	1	0	0 (0.0)
Subarachnoid hemorrhage	0	0	0	0	0	0	0	1	1 (0.3)
Renal and urinary disorders	0	0	0	1	0	0	1	0	1 (0.3)
Calculus ureteric	0	0	0	1	0	0	0	0	1 (0.3)
Nephrolithiasis	0	0	0	0	0	0	1	0	0 (0.0)
Renal failure acute	0	0	0	0	0	0	1	0	0 (0.0)
Respiratory, thoracic, and mediastinal disorder	0	0	0	0	0	1	0	0	1 (0.3)
Dyspnea	0	0	0	0	0	1	0	0	1 (0.3)

Source: Integrated summary of safety SDS 5.9

There were no SAEs in study GWBW, one in study BCB107 (erosive esophagitis), and 26 SAEs in 19 subjects in study BCB106. In study BCB106, 4 events occurred in 4 exenatide LAR subjects, 6 events occurred in 5 sitagliptin subjects, and 16 events occurred in 10 pioglitazone subjects. The events which occurred in exenatide subjects in study BCB106 were cryptogenic organizing pneumonia, postoperative wound complication, nephrolithiasis, and viral pericarditis.

Exenatide LAR does not appear to be associated with an increase in SAEs.

7.3.3 Dropouts and/or Discontinuations

The AEs leading to withdrawal in studies 102, 103, 104, and 105 were described in the integrated summary of safety submitted with the NDA and are shown below. Ten (2.7%) of exenatide LAR subjects discontinued due to an AE. The most common SOC for discontinuations were gastrointestinal (n=3), general (n=2), and investigations (n=2). All AEs occurred only once.

Table 22. NDA 22-200: Adverse events leading to withdrawal in studies 102, 103, 104, and 105.

System organ class/Preferred term	Clinical pharmacology			Efficacy and safety					
	Study 102	Study 103		Study 104		Study 105			
				Placebo-controlled		Comparator-controlled		Uncontrolled (to 52 wk)	Total
	LAR (n=10)	LAR (n=47)	Placebo (n=15)	LAR (n=31)	Placebo (n=13)	LAR (n=148)	Exenatide (n=145)	LAR (n=258)	LAR (n=366) N %
All AEs leading to withdrawal	0	0	1	0	0	9	7	1	10 (2.7)
Cardiac disorders	0	0	1	0	0	1	0	0	1 (0.3)
Coronary artery disease	0	0	1	0	0	0	0	0	0 (0.0)
Myocardial infarction	0	0	0	0	0	1	0	0	1 (0.3)
Gastrointestinal disorders	0	0	0	0	0	3	6	0	3 (0.8)
Abdominal pain	0	0	0	0	0	0	1	0	0 (0.0)
Impaired gastric emptying	0	0	0	0	0	1	0	0	1 (0.3)
Nausea	0	0	0	0	0	1	2	0	1 (0.3)
Regurgitation	0	0	0	0	0	0	1	0	0 (0.0)
Vomiting	0	0	0	0	0	1	2	0	1 (0.3)
General disorders & admin site conditions	0	0	0	0	0	2	0	0	2 (0.5)
Injection site nodule	0	0	0	0	0	1	0	0	1 (0.3)
Malaise	0	0	0	0	0	1	0	0	1 (0.3)
Investigations	0	0	0	0	0	2	0	0	2 (0.5)
Blood potassium increased	0	0	0	0	0	1	0	0	1 (0.3)
Weight decreased	0	0	0	0	0	1	0	0	1 (0.3)
Metabolism and nutrition disorders	0	0	0	0	0	0	1	1	1 (0.3)
Anorexia	0	0	0	0	0	0	1	0	0 (0.0)
Diabetes mellitus	0	0	0	0	0	0	0	1	1 (0.3)
Nervous system disorders	0	0	0	0	0	1	0	0	1 (0.3)
Paraesthesia	0	0	0	0	0	1	0	0	1 (0.3)

Source: Integrated summary of safety SDS 5.8

The four month safety update described the events leading to withdrawal in the completed portion of study BCB106. Eleven exenatide LAR subjects, 5 sitagliptin subjects, and 7 pioglitazone subjects discontinued due to AEs. Events that occurred in exenatide LAR subjects included diarrhea (3) and single events of pneumonia, nausea, headache, GERD, musculoskeletal chest pain, injection site mass, depression, and viral hepatitis.

No AEs lead to withdrawal in studies GWBW (placebo-controlled efficacy and safety in Japanese subjects) and BCB107 (single dose clinical pharmacology study in healthy adults).

Thus, exenatide LAR does not appear to be associated with an increased rate of withdrawal due to an adverse event.

7.3.4 Significant Adverse Events

As described in section 2.4, thyroid tumors are an adverse event of special interest with regard to GLP-1 analogues. The exenatide label contains the following safety concerns:

- Acute pancreatitis
- Gastrointestinal side effects
- Hypoglycemia, especially when used in combination with a sulfonylurea
- Hypersensitivity reactions as a result of anti-exenatide antibodies
- Renal failure

Thyroid tumors: Two events of thyroid neoplasms were reported in the exenatide LAR clinical development program, one in study 105 (benign thyroid mass, exenatide LAR subject 2993LAR-105-22415) and one in study BCB106 (papillary thyroid cancer, sitagliptin subject BCB106-175022).

Calcitonin is a marker of both thyroid c-cell hyperplasia and medullary carcinoma. Its intended use is to evaluate at-risk patients, not as general screening tool. Due to the lack of established screening thresholds, routine monitoring could result in unnecessary medical testing and invasive procedures. However, calcitonin measurements have been added to more recent clinical trials of exenatide LAR to characterize any effect on the levels and c-cells over time. The first trial with calcitonin data will be study BCB108, which began in March 2009. Thus, no data on the effect of exenatide LAR on calcitonin levels was available at the time of this review.

There were 5 thyroid neoplasm cases identified in the exenatide development program as of September 30, 2008.

- 2993-107-00915: 42 year old female with a goiter at study 2993-107 entry was diagnosed with a thyroid nodule the day after completing the study, which involved 29 days of exenatide therapy.

- 2993-112-12208: 73 year old male diagnosed with a firm, 2 x 2 cm thyroid nodule after completing study 112 in which he received 211 days treatment with exenatide 5 mcg BID. Eleven days later the nodule resolved.
- 2993-115E-00937: 40 year old female with a goiter at entry into studies 115 and 115E was diagnosed with a mild thyroid nodule at the end of study 115 after 211 days of exenatide 5 mcg BID treatment. She was treated with levothyroxine sodium. It resolved on February 24, 2004.
- H0O-MC-GWAD-4214: 47 year old male diagnosed with a thyroid nodule approximately 1 month after randomization to exenatide 10 mcg BID in study GWAD. The patient refused biopsy, but scintigraphy reportedly suggested the nodule was benign.
- 993-117-24215: 63 year old male diagnosed with a thyroid cyst 446 days after his first exenatide dose. The subject completed the study.

Through March 31, 2009, there have been 26 exenatide postmarketing reports of thyroid neoplasm. Nine were thyroid cancers; 18 were benign thyroid neoplasms. According to the sponsor, the overall spontaneous reporting rate for thyroid cancer with exenatide is 0.9 cases per 100,000 patient years exposure. The background rate in the United States is 9.1 cases per 100,000 patient years.

In summary, no thyroid cancers were identified in the exenatide LAR clinical development program, although the population studied was small. Calcitonin data was not available for review but has been incorporated into more recent trials. The review of exenatide (Byetta) clinical trial and postmarketing data does not suggest an increased risk for thyroid tumors with exenatide. However, due to the nonclinical findings which, at this time, are thought to be class-related, I recommend the label clearly state that exenatide LAR should not be used as a first-line antidiabetic therapy.

Acute pancreatitis: In the exenatide LAR clinical development program, the following 4 cases of acute pancreatitis or elevated amylase/lipase were reported through the 4 month safety update cutoff data (March 31, 2009):

1) 170002: Necrotizing pancreatitis resulted in withdrawal of this pioglitazone subject in study BCB106
2) 125013: Pancreatitis occurred in this pioglitazone subject in study BCB106
3) 3181: Chronic pancreatitis 9 days after starting blinded study medication in study H8O-MC-GWCH
4) 5651: Increased amylase (88 U/l, nl 13-53 U/l) and lipase (152 U/l, nl 0-60 U/l) approximately 6 months after starting blinded study medication in study H80-MC-GWCH. The subject was asymptomatic. No morphological abnormalities were seen on CT scan. The subject remained in the study and continued to receive study medication. Approximately 6 weeks later, lipase levels had dropped to 1.5x ULN. Note, this case does not support a diagnosis of pancreatitis.

In addition, there was 1 event of pancreatitis in study H8O-MC-GWBR in exenatide LAR subject 4050 which occurred on April 7, 2009, after the cutoff date.

When completed studies of exenatide LAR and exenatide were reviewed, a similar frequency of pancreatitis events was observed between treatment groups. There were no events in exenatide LAR subjects, 3 (0.1%) in exenatide subjects, 1 (0.1%) in placebo subjects, and 3 (0.3%) in comparator subjects.

To better understand the potential association between exenatide LAR and pancreatitis, serum lipase and pancreatic amylase (p-amylase) measurements were included in study BCB106 at screening, baseline (day 1), week 14, and week 26. The enzyme elevations that occurred were asymptomatic and transient. At baseline, mean lipase values were normal (40-47 U/l, ULN = 60 U/l). Approximately 11% of subjects had elevated lipase levels, including 2 subjects with values > 3x ULN. At week 26, an increase from baseline in mean lipase concentration was observed in the exenatide LAR and sitagliptin groups (+17.1 U/l and +8.5 U/l, respectively); a slight decrease was observed in the pioglitazone group (-3.7 U/l). The proportion of subjects with lipase ≥ 3x ULN at week 26 was similar across groups (1-2%).

Table 23. BCB106: Summary of lipase concentrations at baseline and week 26

	Exenatide Once Weekly	Sitagliptin	Pioglitazone
Baseline	**N = 156**	**N = 156**	**N = 162**
Mean (SD) (U/L)	42.0 (23.8)	40.3 (21.3)	46.5 (48.0)
>3x ULN (n [%])	1 (0.6)	0 (0.0)	1 (0.6)
>5x ULN (n [%])	0 (0.0)	0 (0.0)	1 (0.6)
>10x ULN (n [%])	0 (0.0)	0 (0.0)	0 (0.0)
Week 26	**N = 122**	**N = 142**	**N = 128**
Mean (SD) (U/L)	60.8 (38.4)	48.7 (30.7)	44.4 (30.9)
Mean (SD) Change from Baseline (U/L)	17.1 (33.1)	8.5 (24.0)	-3.7 (48.2)
>3x ULN (n [%])	2 (1.6)	1 (0.7)	2 (1.6)
>5x ULN (n [%])	0 (0.0)	0 (0.0)	0 (0.0)
>10x ULN (n [%])	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: Reproduced from the Fourth month safety update Table 10

Mean p-amylase levels were normal and similar for all treatment groups at each time point. Two subjects had a p-amylase level > 3x ULN at baseline. None had notable elevations at week 26. No exenatide LAR subject had p-amylase elevations > 3x ULN at any time.

In addition, the sponsor followed an International Expert Panel's (IEP's) recommendation to conduct noninvasive imaging in asymptomatic subjects with abnormal enzyme levels to rule out occult pancreatic inflammation in study BCB106. Results were as follows:

- 112003: 40 year old male with T2DM, hypertriglyceridemia, hyperlipidemia, and occasional nausea/reflux who received pioglitazone x 26 weeks followed by open label exenatide LAR for 26 weeks. Amylase and lipase levels were normal at screening. After 26 weeks treatment with pioglitazone and 14 weeks treatment with exenatide LAR, lipase was 212 IU/l and p-amylase 36 U/l. The subject was asymptomatic but study medication was held until values normalized 1 week later (lipase 23, p-amylase 8). Noncontrast CT scan showed normal pancreas, fatty enlarged liver, and large gallstones.
- 117001: 67 year old male with T2DM received pioglitazone. Prior to his enrollment in the open label exenatide LAR portion of study BCB106, the investigative site contacted the sponsor regarding lipase 251 U/l and p-amylase 159 U/l. The subject was asymptomatic. CT scan with contrast showed fatty liver, gallstones, and unremarkable pancreas. MRCP showed cholelithiasis, no biliary dilatation, and normal pancreas. The subject was discontinued from the study due to cholelithiasis without ever receiving exenatide LAR.
- 134002: 48 year old male with a history of T2DM began exenatide LAR on March 15, 2008. On March 14, 2009, lipase was 263 U/l and p-amylase was 65 U/l. On March 24, lipase was 82 U/l and p-amylase was 47. Noncontrast CT scan showed no pancreatic abnormalities.
- 147006: 50 year old female wit T2DM, HTN, hyperlipidemia, coronary artery disease, obesity, and reflux. Lipase levels fluctuated. She complained of occasional abdominal discomfort after 3 months on study drug. CT scan showed prior cholecystectomy, normal pancreas, and fatty enlarged liver.
- 163003: 76 year old male with T2DM and HTN with elevated lipase at baseline. At week 40, lipase was 125 U/l. Abdominal ultrasound showed normal pancreas.
- 176014: 44 year old male with T2DM, obesity, and GERD who experienced abdominal pain radiating to the back after 6 weeks of pioglitazone. Amylase/lipase levels were normal. CT scan revealed “severe fat atrophy of the pancreas” but no pancreatitis. The subject’s abdominal pain resolved after omeprazole was increased. The subject was later lost to follow up.
- 127003: 47 year old male with T2DM and dyslipidemia who was treated initially with pioglitazone. At week 52 while on exenatide LAR, lipase was 243 U/l and p-amylase was 83 U/l. CT scan with contrast showed normal pancreas. The subject was asymptomatic.
- 152023: 60 year old female with T2DM and elevated amylase and lipase at baseline completed 26 weeks treatment with pioglitazone. Enzymes spiked again on exenatide LAR. CT scan showed multiple gallstones filling gallbladder and normal pancreas.

The postmarketing experience with exenatide and pancreatitis was reviewed in my exenatide monotherapy NDA review as well as discussed at a combined DMEP-OSE regulatory briefing on April 24, 2009. Please refer to these documents for full details. As of March 31, 2009, 639 cases of pancreatitis have been reported since product

launch. Approximately 15 (2.3%) of cases were necrotizing and/or hemorrhagic pancreatitis; this is lower than the 10-15% of expected cases of the severe form. The global reporting rate in exenatide-treated patients was 0.63 per 1000 patient years exposure. While reporting rates and incidence rates cannot be directly compared, the estimated incidence rate for pancreatitis in the United States is 0.7 per 1000 patient years.

In summary, only 1 exenatide LAR subject developed pancreatitis in a clinical trial to date, although the population studied was small. When completed studies of exenatide LAR and exenatide were reviewed, a similar frequency of pancreatitis events was observed (exenatide LAR 0%, exenatide 0.1%, placebo 0.1%, comparator 0.3%). When routine lipase and p-amylase measurement were included in study BCB106, an increase from baseline in mean lipase concentration was observed in the exenatide LAR and sitagliptin groups (+17.1 U/l and +8.5 U/l, respectively); a slight decrease was observed in the pioglitazone group (-3.7 U/l). The proportion of subjects with lipase ≥ 3x ULN at week 26 was similar across groups (1-2%). Mean p-amylase levels were normal and similar for all treatment groups at each time point. No exenatide LAR subject had p-amylase elevations > 3x ULN at any time. When a subset of asymptomatic BCB106 subjects with elevated pancreatic enzymes were imaged, no signs of pancreatitis were seen although gallstones were a common finding. When exenatide postmarketing data were reviewed, the reporting rate and United States incidence rate for pancreatitis were similar, although they cannot be directly compared.

Gastrointestinal side effects: When long term, placebo and comparator controlled studies of exenatide LAR (studies 104, GWBW, 105 through week 30, and BCB106 through week 26) were reviewed, the following frequent gastrointestinal (GI) adverse events were identified. Most GI side effects occurred more commonly in the exenatide LAR and exenatide groups when compared to sitagliptin, pioglitazone, and placebo, including nausea, diarrhea, and vomiting. However, the incidence of nausea and vomiting was lower in the exenatide LAR group when compared to exenatide (25.3% vs 34.5% and 11.0% vs. 18.6%, respectively).

Table 24. NDA 22-200: Frequent AEs (Incidence ≥ 5% in exenatide LAR group) in completed placebo and comparator controlled efficacy and safety studies (studies 104, GWBW, 105, and BCB106) (n=858).

PT	Comparator controlled				Placebo controlled	
	LAR (n=308)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)	LAR (n=51)	Placebo (n=23)
Nausea	78 (25.3)	50 (34.5)	16 (9.6)	8 (4.8)	10 (19.6)	2 (15.4)
Diarrhea	51 (16.6)	19 (13.1)	16 (9.6)	12 (7.3)	5 (9.8)	1 (7.7)
Vomiting	34 (11.0)	27 (18.6)	4 (2.4)	5 (3.0)	1 (2.0)	0 (0.0)
Constipation	25 (8.1)	9 (6.2)	3 (1.8)	2 (1.2)	2 (3.9)	1 (7.7)
Dyspepsia	18 (5.8)	4 (2.8)	6 (3.6)	4 (2.4)	0 (0.0)	0 (0.0)
Anorexia	4 (1.3)	1 (0.7)	1 (0.6)	0 (0.0)	5 (9.8)	0 (0.0)
Gastroenteritis	1 (0.3)	0 (0.0)	3 (1.8)	1 (0.6)	6 (11.8)	0 (0.0)

Source: Four month safety update Table 7

At the time of NDA submission, only 3 exenatide LAR subjects had been withdrawn from studies using the commercial formulation (i.e. studies 102, 103, 104, and 105). There was one event each (0.3%) of impaired gastric emptying, nausea and vomiting. A greater proportion of exenatide subjects were withdrawn due to nausea and vomiting (1.4% each).

In summary, exenatide LAR appears to be associated with an increase rate of GI side effects when compared to placebo, sitagliptin, or pioglitazone, although the incidence and severity of nausea and vomiting is lower with exenatide LAR than exenatide.

Hypoglycemia: Blood glucose decreased was a frequent AE in the placebo-controlled efficacy and safety studies of exenatide LAR (i.e. studies 104 and GWBW, as described in the four month safety update). Blood glucose decreased occurred in 3 of these 51 (5.9%) subjects. However, it occurred in no exenatide LAR subjects (n=308) in comparator controlled trials (i.e. studies 105 and BCB106).

There were no events of major hypoglycemia in the clinical trials that used the commercial formulation and were submitted with the NDA (i.e. studies 102, 103, 104, and 105). The incidence of minor hypoglycemia in these studies is shown below. Overall, the incidence was low and less than that seen with exenatide.

Table 25. NDA 22-200: Incidence of hypoglycemia by study and treatment.

Type of study	Study	Type of control	Treatment (n)	Minor hypoglycemia
Clin pharm	102		Ex LAR (n=10)	0 (0.0)
	103		Ex LAR (n=47)	2 (4.3)
			Placebo (n=15)	0 (0.0)
Efficacy & safety	104	Placebo controlled	Ex LAR (n=31)	0 (0.0)
			Placebo (n=13)	0 (0.0)
	105	Comparator controlled	Ex LAR (n=148)	8 (5.4)
			Exenatide (n=145)	9 (6.2)
		Uncontrolled	Ex LAR (n=258)	9 (3.5)
		Total	Ex LAR (n=366)	18 (4.9)

Source: Integrated summary of safety SDS 5.10

Hypersensitivity reactions as a result of anti-exenatide antibodies: Please refer to section 7.4.6 Immunogenicity.

Renal failure: The incidence of renal failure AEs in long term (≥3 months), controlled studies of exenatide LAR and exenatide was analyzed by the sponsor using the following preferred terms: acute prerenal failure, diabetic and end stage renal disease, diabetic nephropathy, dialysis, hemodialysis, hemolytic uremic syndrome, hepatorenal failure, nephropathy toxic, pancreatorenal syndrome, postoperative renal failure, postrenal failure, renal failure, renal failure acute, renal failure chronic, renal impairment, renal tubular disorders, renal tubular necrosis, tubulointerstitial nephritis. No exenatide LAR subjects experienced those events; only a very small percentage of exenatide, placebo, and comparator subjects did.

Table 26. NDA 22-200: Renal failure analysis of completed exenatide LAR studies and exenatide studies.

	Ex LAR (n=359)	Exenatide (n=2461)	All exenatide (n=2820)	Placebo (n=944)	Comparator (n=989)
Renal failure events (n, %)	0 (0.0)	3 (0.1)	3 (0.1)	2 (0.2)	3 (0.3)
Cr (n)	354	2376	2730	936	943
Change from baseline Cr (mean mg/dl)	0.005	0.0018	0.016	0.001	0.017
>1.5x baseline (n,%)	2 (0.6)	22 (0.9)	24 (0.9)	1 (0.1)	13 (1.4)
BUN (n)	354	1213	1567	538	306
Change from baseline BUN (mean, SD)	-0.2 (1.4)	-0.1 (1.5)	-0.1 (1.5)	0.1 (1.4)	0.1 (1.3)

NOTE: Completed exenatide LAR studies include 104, 105, and BCB106. Completed exenatide studies include 2993-112, -113, -115 and H8O-MCG-GWAP, -GWAC, -GWBA, -GWBJ, -GWCD, -GWAA, -GWAD, -GWAK, and –GWAO.
Source: Four month safety update SDS 5.1, 5.2, and 5.4

When the sponsor analyzed the same trials by change in creatinine and BUN, the change from baseline in creatinine in the exenatide LAR group was small and similar to placebo. The change in the exenatide and all exenatide groups was similar to

comparator. The difference between the exenatide LAR and exenatide groups may be due to the different incidence of nausea and vomiting or sample size (n=359 vs. 2461) with the 2 drugs. The incidence of subjects with creatinine >1.5x baseline was similar among the drugs studied and lowest in the exenatide LAR group (0.6%), excluding placebo. The mean change from baseline BUN was similar between groups.

When shifts from normal to abnormal and vice versa were analyzed in the exenatide LAR and exenatide clinical programs, shifts were generally similar between groups. Approximately 1.5% of placebo and all exenatide subjects experienced a shift from normal to abnormal creatinine, although no exenatide LAR subjects experienced a similar shift.

Table 27. NDA 22-200: Serum creatinine and BUN shift table for ITT subjects receiving randomized dose in exenatide LAR and exenatide clinical programs (n=4678)

	BYETTA [2] and Exenatide Once Weekly Clinical Programs Combined [3]														
	Exenatide Once Weekly (N = 359) Baseline			BYETTA (N = 2461) Baseline			All Exenatide (N = 2820) Baseline			Placebo (N = 994) Baseline			Comparator [4] (N = 989) Baseline		
Analyte (Unit)/ Last Visit	Normal	Abnorm	NA	Normal	Abnorm	NA	Normal	Abnorm	NA	Normal	Abnorm	NA	Normal	Abnorm	NA
Serum Creatinine (umol/L)															
Normal	342	9	0	2277	20	1	2619	29	1	893	11	1	920	6	0
Abnormal	0	3	0	41	38	0	41	41	0	14	18	0	12	5	0
BUN (mmol/L)															
Normal	328	16	0	1082	44	0	1410	60	0	475	21	0	286	7	0
Abnormal	4	6	0	34	53	0	38	59	0	26	16	0	7	6	0

NOTE: Reproduced from the Four month safety update supplement SDS 5.3

In the population and under the conditions studies, exenatide LAR does not appear to increase the risk of acute renal failure.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence rates of adverse events in completed, placebo- and comparator-controlled efficacy and safety studies of exenatide LAR as of March 31, 2009 (studies 104, GWBW, 105, and BCB106) was reviewed. Events which occurred in ≥ 2% in an exenatide LAR dose group are shown below. Nausea, diarrhea, vomiting, anorexia, gastroesophageal reflux disease (GERD), and injection site pruritis and erythema occurred more commonly in the exenatide LAR group than comparator. However,

nausea and vomiting occurred less often in the exenatide LAR group than in the exenatide group (comparator controlled: 25.3% vs. 34.5% and 11.0% vs. 18.6%, respectively). Gastroenteritis and blood glucose low occurred more often in the exenatide LAR group than placebo group (11.8% vs. 0.0% and 5.9% vs. 0.0%, respectively), but at a similar or lower frequency than comparator groups.

Table 28. NDA 22-200: Common AEs (incidence ≥ 2% in the placebo- or comparatory-controlled exenatide LAR group) in completed, placebo- and comparator-controlled efficacy and safety studies (studies 104, GWBW, 105, and BCB106) of exenatide LAR (n=858)

Preferred Term	Placebo controlled		Comparator controlled			
	LAR (n=51)	Placebo (n=23)	LAR (n=308)	Exenatide (n=145)	Sitaglip (n=166)	Pioglit (n=165)
Nausea	10 (19.6)	2 (8.7)	78 (25.3)	50 (34.5)	16 (9.6)	8 (4.8)
Diarrhea	5 (9.8)	1 (4.3)	51 (16.6)	19 (13.1)	16 (9.6)	12 (7.3)
Upper respiratory infection	0 (0.0)	1 (4.3)	18 (5.8)	25 (17.2)	15 (9.0)	17 (10.3)
Vomiting	1 (2.0)	0 (0.0)	34 (11.0)	27 (18.6)	4 (2.4)	5 (3.0)
Injection site pruritis	10 (19.6)	4 (17.4)	35 (11.4)	2 (1.4)	8 (4.8)	2 (1.2)
Headache	1 (2.0)	0 (0.0)	24 (7.8)	7 (4.8)	15 (9.0)	7 (4.2)
Nasopharyngitis	4 (7.8)	2 (8.7)	16 (5.2)	8 (5.5)	4 (2.4)	5 (3.0)
Sinusitis	2 (3.9)	0 (0.0)	12 (3.9)	10 (6.9)	2 (1.2)	11 (6.7)
Injection site erythema	5 (9.8)	0 (0.0)	16 (5.2)	0 (0.0)	4 (2.4)	0 (0.0)
Urinary tract infection	2 (3.9)	1 (4.3)	25 (8.1)	12 (8.3)	9 (5.4)	6 (3.6)
Constipation	2 (3.9)	1 (4.3)	25 (8.1)	9 (6.2)	3 (1.8)	2 (1.2)
Dizziness	2 (3.9)	0 (0.0)	12 (3.9)	9 (6.2)	8 (4.8)	6 (3.6)
Back pain	1 (2.0)	0 (0.0)	14 (4.5)	6 (4.1)	7 (4.2)	5 (3.0)
Injection site hematoma	2 (3.9)	0 (0.0)	10 (3.2)	16 (11.0)	2 (1.2)	4 (2.4)
Fatigue	0 (0.0)	0 (0.0)	18 (5.8)	4 (2.8)	0 (0.0)	5 (3.0)
Injection site pain	1 (2.0)	0 (0.0)	4 (1.3)	3 (2.1)	2 (1.2)	0 (0.0)
Gastroenteritis viral	1 (2.0)	0 (0.0)	15 (4.9)	8 (5.5)	2 (1.2)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	18 (5.8)	4 (2.8)	6 (3.6)	4 (2.4)
Oropharyngeal pain	0 (0.0)	1 (4.3)	5 (1.6)	2 (1.4)	1 (0.6)	1 (0.6)
Cough	0 (0.0)	0 (0.0)	8 (2.6)	2 (1.4)	2 (1.2)	5 (3.0)
Pain in extremity	2 (3.9)	0 (0.0)	8 (2.6)	1 (0.7)	4 (2.4)	2 (1.2)
Arthralgia	0 (0.0)	1 (4.3)	11 (3.6)	5 (4.1)	8 (4.8)	3 (1.8)
Decreased appetite	0 (0.0)	0 (0.0)	9 (2.9)	1 (0.7)	2 (1.2)	0 (0.0)
Gastroesophageal reflux disease	1 (2.0)	0 (0.0)	14 (4.5)	6 (4.1)	2 (1.2)	2 (1.2)
Hypertension	2 (3.9)	0 (0.0)	9 (2.9)	4 (2.8)	5 (3.0)	2 (1.2)
Injection site induration*	16 (31.4)	6 (26.1)	1 (0.3)	0 (0.0)	1 (0.6)	1 (0.6)
Bronchitis	1 (2.0)	1 (4.3)	8 (2.6)	6 (4.1)	3 (1.8)	1 (0.6)
Influenza	2 (3.9)	0 (0.0)	2 (0.6)	3 (2.1)	2 (1.2)	5 (3.0)
Musculoskeletal pain	3 (5.9)	0 (0.0)	3 (1.0)	0 (0.0)	2 (1.2)	3 (1.8)
Flatulence	0 (0.0)	0 (0.0)	9 (2.9)	2 (1.4)	1 (0.6)	1 (0.6)
Eructation	0 (0.0)	0 (0.0)	8 2.6)	0 (0.0)	1 (0.6)	0 (0.0)
Abdominal pain	1 (2.0)	0 (0.0)	8 (2.6)	3 (2.1)	6 (3.6)	2 (1.2)
Depression	2 (3.9)	0 (0.0)	4 (1.3)	4 (2.8)	3 (1.8)	0 (0.0)
Nephrolithiasis	1 (2.0)	0 (0.0)	5 (1.6)	1 (0.7)	0 (0.0)	2 (1.2)
Sinus congestion	1 (2.0)	0 (0.0)	1 (0.3)	2 (1.4)	0 (0.0)	1 (0.6)

Abdominal distension	2 (3.9)	0 (0.0)	6 (1.9)	1 (0.7)	2 (1.2)	1 (0.6)
Dysmenorrhea**	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site hemorrhage	1 (2.0)	0 (0.0)	5 (1.6)	2 (1.4)	2 (1.2)	2 (1.2)
Myalgia	1 (2.0)	0 (0.0)	6 (1.9)	2 (1.4)	2 (1.2)	3 (1.8)
Neck pain	1 (2.0)	0 (0.0)	2 (0.6)	1 (0.7)	1 (0.6)	1 (0.6)
Tooth abscess	2 (3.9)	0 (0.0)	5 (1.6)	1 (0.7)	0 (0.0)	2 (1.2)
Pharyngitis	3 (5.9)	0 (0.0)	4 (1.3)	0 (0.0)	4 (2.4)	3 (1.8)
Toothache	1 (2.0)	0 (0.0)	2 (0.6)	3 (2.1)	2 (1.2)	4 (2.4)
Fall	0 (0.0)	0 (0.0)	3 (1.0)	2 (1.4)	2 (1.2)	2 (1.2)
Gastroenteritis	6 (11.8)	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.8)	1 (0.6)
Otitis media	1 (2.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	5 (9.8)	0 (0.0)	4 (1.3)	1 (0.7)	1 (0.6)	0 (0.0)
Anxiety	2 (3.9)	0 (0.0)	3 (1.0)	3 (2.1)	2 (1.2)	1 (0.6)
Arthritis	1 (2.0)	0 (0.0)	2 (0.6)	2 91.4)	0 (0.0)	0 (0.0)
Pruritis	1 (2.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site rash	3 (5.9)	1 (4.3)	4 (1.3)	1 (0.7)	0 (0.0)	0 (0.0)
Rash	1 (2.0)	2 (8.7)	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)
Dermatitis contact	2 (3.9)	0 (0.0)	1 (0.3)	0 (0.0)	2 (1.2)	1 (0.6)
Joint sprain	1 (2.0)	1 (4.3)	2 (0.6)	3 (2.1)	0 (0.0)	0 (0.0)
Road traffic accident	1 (2.0)	0 (0.0)	1 (0.3)	1 (0.7)	0 (0.0)	0 (0.0)
Ear infection	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.6)	1 (0.6)
Herpes zoster	1 (2.0)	0 (0.0)	2 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)
Angina pectoris	1 (2.0)	1 (4.3)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)
Hypoesthesia	1 (2.0)	0 (0.0)	1 (0.3)	1 (0.7)	2 (1.2)	1 (0.6)
Vision blurred	1 (2.0)	1 (4.3)	1 (0.3)	0 (0.0)	2 (1.2)	1 (0.6)
Wound	1 (2.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (1.2)
Blood amylase increased	2 (3.9)	0 (0.0)	1 (0.3)	0 (0.0)	2 91.2)	0 (0.0)
Blood glucose decreased	3 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gingivitis	1 (2.0)	1 (4.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypogeusia	2 (3.9)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Periarthritis	1 (2.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)
Coronary artery disease	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Faruncle	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.6)	0 (0.0)
Nocturia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Claculus ureteric	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fibromyalgia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal discomfort	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parosmia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respirator tract congestion	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine ketone body present	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urobilin urine present	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
*The majority of subjects in placebo-controlled study GWBW in Japan had injection site induration.						
** Term is only observed in the female population.						
Source: Four month safety update SDS 5.						

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program: Standard safety laboratory data were obtained in all studies at baseline, during the treatment period, and at study end. The frequency of safety laboratory evaluations is shown below. Routine lipase and p-amylase measurement were only included in efficacy study BCB106 and single-dose clinical pharmacology study BCB107. Calcitonin was not measured in clinical studies submitted to the NDA.

Table 29. Safety laboratory evaluations in the exenatide LAR development program

Chemistry [1]	Hematology	Urinalysis	Lipids
Albumin (g/dL)	Basophils (%)	Blood	HDL-C (mg/dL)
Alkaline phosphatase (IU/L)	Eosinophils (%)	Glucose	LDL-C (mg/dL)
ALT (IU/L)	Hematocrit (%)	Ketones	Total cholesterol (mg/dL)
AST (IU/L)	Hemoglobin (g/dL)	pH	Triglycerides (mg/dL)
Bicarbonate (mEq/L)	Lymphocytes (%)	Protein	
BUN (mg/dL)	MCH (pg/cell)	RBC	
Calcium (mg/dL)	MCHC (gHb/dL)		
Chloride (mEq/L)	MCV (fl)		
Creatinine (mg/dL)	Monocytes (%)		
CPK Total (IU/L) [2]	Neutrophils (%)		
GGT (IU/L)	Platelet count ($\times 10^3/\mu L$)		
Phosphate (mg/dL)	RBC ($\times 10^6/\mu L$)		
Potassium (mEq/L)	WBC ($\times 10^3/\mu L$)		
Sodium (mEq/L)			
Total bilirubin (mg/dL)			
Total protein (mg/dL)			
Uric acid (mg/dL)			

NOTE: Reproduced from the sponsor

Table 30. Frequency of safety laboratory evaluations in the exenatide LAR development program

Study	Chemistry, Hematology, and Urinalysis	Lipid Concentrations
2993LAR-102	Screening, Days -14, 1, 2, 3, 4, 7, 14, 21, 28, 35, 42, and 49, Study Termination (Day 56) or Early Termination	Not assessed
2993LAR-103	Screening, Day -14, Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11, Study Termination (Week 12) or Early Termination	Not assessed
2993LAR-104	Screening, Day -3, Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 19, and Study Termination (Week 27) or Early Termination	Screening, Day -3, Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 19, and Study Termination (Week 27) or Early Termination [1]
2993LAR-105 [2]	Screening, Days -3, and 1, Weeks 6, 10, 14, 18, 22, 26, 30, 36, 40, 44, 48, 52, 4-week intervals (through Week 76), 8-week intervals (through Study Termination), and Study Termination (after Week 30) or Early Termination [3]	Days -3, and 1, Weeks 6, 10, 14, 18, 22, 26, 30, 36, 40, 44, 48, 52, 4-week intervals (through Week 76), 8-week intervals (through Study Termination), and Study Termination (after Week 30) or Early Termination [3]
BCB106 [4]	Screening, Day 1, Weeks 14 and 26, and Study Termination (after Week 26) or Early Termination	Screening [5], Day 1, Weeks 4, 6, 10, 14, 18, 22, and 26 and Study Termination (after Week 26) or Early Termination
BCB107	Screening, Day -1 or -2, Day 26, Day 50 and Study Termination (Day 101) or Early Termination	Not assessed
GWBW	Screening, Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, and 18 and Study Termination (Week 20) or Early Termination	Screening, Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, and 18 and Study Termination (Week 20) or Early Termination

[1] Only total cholesterol and triglycerides assessed in Study 2993LAR-104.
[2] Study 2993LAR-105 open-ended assessment period remains ongoing. Data through 2 years included in the analysis.
[3] During comparability assessment period of Study 2993LAR-105, assessments at Day 1S, Weeks 4S, 8S, 10S, 12S, 16S, 18S, 20S, and 24S.
[4] Assessments through Week 26 provided. Open-label treatment period of Study BCB106 remains ongoing, with assessments at 4 to 8 week intervals (lipids) and 12- to 16-week intervals (chemistry, hematology, and urinalysis). Data through 26 weeks included in the analysis.
[5] Only fasting triglycerides assessed at Screening in Study BCB106.

NOTE: Reproduced from the sponsor

The sponsor's criteria for the normal range varied slightly by study, although the thresholds for laboratory values of potential clinical importance (PCI) were similar among studies. Both were acceptable. The normal criteria used in pivotal phase 3 study 105 are shown below.

Table 31. Laboratory test normal (study 105) and markedly abnormal ranges (Subjects ≥ 18 years)

Laboratory test	Normal range in study 105	Lower PCI value	Upper PCI value
Albumin	18-65y 3.5-5.3; 66-90y 3.2-4.6; 91-109y 2.9-4.5	<2.5 g/dL	
Alkaline phosphatase	Male: 45-145	>3x ULN	
	Female: 40-100	>3x ULN	
BUN	0-65y 4-24; 66-90y 8-23; 91-109y 10-31		>45 mg/dL
Basophils	0.0-2.4		
Bicarbonate	22-29	<18 mEq/L	>35 mEq/L
CK-MB	0.0-5.0		
CPK, Total	Male: 18-65y 24-195; 65-109y 20-203		
	Female: 0-65y 24-170; 66-109y 24-160		
Calcium	12-65y 8.4-10.3; 66-90y 8.8-10.2; 91-109y 8.2-9.6	<8 mg/dL	>11 mg/dL
Chloride	0-65y 94-111; 66-90y 95-109; 91-109y 98-111		
Cholesterol		<100 mg/dL	>350 mg/dL
Creatinine	Male: 0.5-1.3		Male: >1.6 mg/dL
	Female: 0.4-1.2		Female: >1.4 mg/dL
Eosinophils	0.0-6.0		
Gamma GT	Male: 18-65y 7-51; 66-90y 11-42; 91-109y 3-47		>3x ULN
	Female: 18-65y 5-49; 66-90y 9-55; 91-109y 4-44		>3x ULN
Hematocrit	Male: 18-65y 40.0-52.0; 66-110y 37.0-50.0	Male: <36%	
	Female: 18-65y 35.0-47.0; 66-110y 33.0-46.0	Female: <30%	
Hemoglobin	Male: 18-65y 13.0-17.5; 66-110 12.6-17.7	Male: <12 g/dL	
	Female: 12-65y 11.6-16.2; 66-110y 11.0-16.1	Female: <10 g/dL	
Lymphocytes	15.5-46.6		
MCH	26-34		
MCV	Male 79-97		
	Female 79-98		
Monocytes	3.1-12.5		
Neutrophils	40.9-77.0		
Phosphorus	66-110y 2.6-4.6	<1 mg/dL	>6 mg/dL
Platelet count	140-450	<75,000 /µL	>500,000 /µL
Potassium	0-65y 3.5-5.5; 66-109y 3.6-5.5	<3.0 mEq/L	>5.5 mEq/L
Red blood cells	Male: 12-65y 4.1-5.9; 66-110y 4.0-5.8		
	Female: 12-65y 3.8-5.5; 66-110 3.8-5.4		

SGOT (AST)	Male: 18-90y 10-45; 91-109y 11-38		>3x ULN
	Female: 18-90y 10-36; 91-109y 10-30		>3x ULN
SGPT (ALT)	Male: 18-90y 6-48; 91-109y 6-38		>3x ULN
	Female: 18-90y 6-37; 91-109y 5-38		>3x ULN
Sodium	0-65y 132-147; 66-90y 135-148; 91-109y 132-146	<130 mEq/L	>150 mEq/L
Total bilirubin	1-90y 0.2-1.2; 91-109y 0.2-0.9		>2 mg/dL
Total protein	18-65y 6.0-8.4; 66-90y 6.0-8.3; 91-109y 6.0-8.0		
Triglycerides			>500 mg/dL
Uric acid	Male: 18-65y 3.6-8.0; 66-90y 3.5-8.0; 91-109y 3.5-8.3		Male: >10 mg/dL
	Female: 18-65y 2.1-6.9; 66-90y 2.2-7.3; 91-109y 2.2-7.7		Female: >8 mg/dL
White blood cells	4.1-12.3 X 10^3	<1,500 /µL	>18,000 / µL
pH	5.0-8.0		

Source: January 18, 2010 Submission Appendices 1 and 2

Selection of studies and analyses for drug-controlled comparisons of laboratory values: On January 18, 2010, the sponsor responded to an information request for a laboratory analysis using the same study pooling strategy as in the four month safety update. My review of laboratory findings is based on this submission and focuses on the repeat dose, safety and efficacy, placebo- and comparator-controlled studies (studies 104, GWBW, 105, and BCB106) (exenatide LAR n=359).

Standard analyses and explorations of laboratory data:

Analyses focused on measures of central tendency: In the repeat dose, safety and efficacy, controlled studies of exenatide LAR included in the four month safety update (i.e. studies 104, GWBW, 105, and BCB106), the mean changes from baseline to endpoint in chemistry, hematology, lipid, and urinary pH were minor, generally similar between treatment groups, and not clinically meaningful. Please refer to Table 32.

Table 32. Change from baseline to endpoint according to laboratory parameter and treatment group in repeat dose, safety and efficacy, controlled studies (studies 104, GWBW, 105, and BCB106)

	Ex LAR (n=359)	Placebo (n=23)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
Chemistry					
ALT (mU/ml)	-4.9 (17.13)	-2.6 (14.72)	-3.6 (12.33)	-2.7 (12.10)	-7.4 (28.97)
AST(mU/ml)	-4.1 (11.07)	-3.0 (12.73)	-3.0 (7.78)	-2.8 (8.92)	-3.9 (11.17)
Alkaline phosphatase (mU/ml)	-1.7 (15.28)	1.3 (14.95)	-2.5 (12.14)	-4.4 (13.46)	-7.2 (17.37)
Bicarbonate	1.2 (3.12)	1.9 (2.56)	-0.7 (3.08)	1.5 (2.56)	1.8 (2.78)

BUN (mg/dl)	-0.5 (3.99)	-0.5 (4.53)	-0.2 (6.81)	0.1 (3.79)	0.4 (3.49)
Calcium (mg/dl)	0.01 (0.473)	0.07 (0.291)	-0.19 (0.454)	0.03 (0.527)	0.00 (0.413)
Creatinine (mg/dl)	0.003 (0.120)	0.021 (0.116)	0.062 (0.844)	0.003 (0.112)	0.010 (0.117)
Potassium	0.04 (0.403)	-0.03 (0.316)	0.02 (0.365)	0.04 (0.422)	-0.01 (0.569)
Sodium	0.4 (2.96)	-0.4 (2.06)	1.0 (2.64)	-0.3 (2.64)	0.2 (2.72)
Total bilirubin (mg/dl)	-0.02 (0.196)	-0.02 (0.114)	-0.09 (0.183)	-0.01 (0.190)	-0.03 (0.157)
Uric acid	0.00 (1.015)	-0.15 (-0.571)	0.05 (0.990)	0.01 (0.913)	-0.09 (1.060)
Hematology					
Eosinophils (%)	0.33 (2.430)	-0.02 (1.368)	-0.04 (1.615)	0.04 (2.742)	0.14 (1.748)
Hematocrit (%)	-0.15 (2.287)	0.60 (2.331)	-0.48 (2.790)	0.37 (2.491)	-0.84 (3.114)
Hemoglobin (g/dl)	-0.08 (0.766)	0.19 (0.697)	-0.22 (0.897)	0.09 (0.854)	-0.32 (1.020)
Lymphocytes (%)	-0.68 (5.614)	1.10 (5.425)	-0.70 (6.396)	-0.94 (6.107)	-1.26 (5.770)
Monocytes	-0.6 (1.813)	-0.40 (1.123)	0.04 (1.841)	-0.16 (1.728)	0.08 (1.625)
Neutrophils (%)	0.37 (6.707)	-0.67 (5.966)	0.61 (7.416)	0.95 (7.232)	0.97 (6.301)
Platelet count ($10^3/mm^3$)	6.9 (37.80)	7.8 (26.66)	1.1 (29.42)	-3.5 (43.77)	-7.0 (45.92)
WBCs ($10^3/mm^3$)	0.12 (1.292)	-0.14 (1.329)	-0.03 (1.283)	0.20 (1.377)	-0.39 (1.336)
Lipids					
HDL (mg/dl)	1.2 (6.18)	2.5 (3.78)	-0.4 (6.35)	1.2 (6.04)	5.5 (8.67)
LDL (mg/dl)	0.4 (23.83)	-1.6 (12.33)	3.8 (25.35)	1.2 (22.91)	-0.5 (29.67)
Tot. cholesterol (mg/dl)	-0.6 (27.95)	12.1 (22.28)	1.8 (31.18)	1.6 (31. 92)	1.8 (34.10)
Triglycerides (mg/dl)	0.92 (0.02)	1.12 (0.08)	0.95 (0.03)	0.97 (0.03)	0.81 (0.03)
Urinalysis					
pH	0.05 (0.539)	0.04 (0.891)	-0.07 (0.450)	-0.02 (0.406)	0.07 (0.542)

Source: January 18, 2010 Submission SDS 1

Analyses focused on outliers or shifts from normal to abnormal: In the repeat dose, safety and efficacy, controlled studies of exenatide LAR included in the four month safety update (i.e. studies 104, GWBW, 105, and BCB106), the percentage of subjects with shifts from normal to abnormal chemistry, hematology, lipid, and urinary pH values was small and generally similar between treatment groups. More exenatide LAR subjects experienced a shift to abnormal biocarbonate levels when compared to placebo, sitagliptin, and pioglitazone but not exenatide (8.4% vs. 4.4%, 7.8%, and 6.1% vs. 16.6%, respectively). More exenatide LAR subjects experienced a shift to abnormal total cholesterol when compared to the same comparators (15.3% vs. 4.4%, 7.8%, 14.0%, and 13.1%). However, since total cholesterol is comprised of HDL, VLDL, and LDL cholesterols, its slight increase may be partly related to the increase in HDL cholesterol that was also observed (7.0% vs. 0%, 6.7%, 3.6%, and 11.7%). Please refer Table 33 for more details. These small changes are likely not clinically meaningful.

Table 33. Number (%) of subjects with shifts from normal to abnormal chemistry, hematology, lipid, and urinary pH values

	Ex LAR (n=359)	Placebo (n=23)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
Chemistry					
ALT (mU/ml)	19 (5.29)	1 (4.35)	4 (2.76)	5 (3.01)	6 (3.64)
AST(mU/ml)	5 (1.39)	0 (0.00)	2 (1.38)	2 (1.20)	2 (1.21)
Alkaline phosphatase (mU/ml)					
Bicarbonate	30 (8.36)	1 (4.35)	24 (16.55)	13 (7.83)	10 (6.06)
BUN (mg/dl)	4 (1.11)	2 (8.70)	1 (0.69)	1 (0.60)	6 (3.64)
Calcium (mg/dl)	17 (4.74)	0 (0.00)	0 (0.00)	3 (1.81)	3 (1.82)
Creatinine (mg/dl)	1 (0.28)	0 (0.00)	2 (1.38)	1 (0.60)	2 (1.21)
Potassium	4 (1.11)	0 (0.00)	3 (2.07)	4 (2.41)	4 (2.42)
Sodium	5 (1.39)	0 (0.00)	1 (0.69)	4 (2.41)	2 (1.21)
Total bilirubin (mg/dl)	5 (1.39)	1 (4.35)	2 (1.38)	2 (1.20)	0 (0.00)
Uric acid	19 (5.29)	1 (4.35)	11 (7.59)	4 (2.41)	6 (3.64)
Hematology					
Eosinophils (%)	16 (4.46)	1 (4.35)	7 (4.83)	5 (3.01)	6 (3.64)
Hematocrit (%)	18 (5.01)	1 (4.35)	11 (7.59)	11 (6.63)	19 (11.52)
Hemoglobin (g/dl)	20 (5.57)	1 (4.35)	8 (5.52)	11 (6.63)	13 (7.88)
Lymphocytes (%)	10 (2.79)	0 (0.00)	0 (0.00)	2 (1.20)	3 (1.82)
Monocytes	12 (3.34)	0 (0.00)	3 (2.07)	6 (3.61)	5 (3.03)
Neutrophils (%)	9 (2.51)	0 (0.00)	3 (2.07)	2 (1.20)	2 (1.21)
Platelet count ($10^3/mm^3$)	12 (3.34)	1 (4.35)	3 (2.07)	3 (1.81)	2 (1.21)
WBCs ($10^3/mm^3$)	6 (1.67)	0 (0.00)	1 (0.69)	3 (1.81)	3 (1.82)
Lipids					
HDL (mg/dl)	25 (6.96)	0 (0.00)	17 (11.72)	11 (6.63)	6 (3.64)
LDL (mg/dl)	18 (5.01)	0 (0.00)	12 (8.28)	12 (7.23)	20 (12.12)
Tot. cholesterol (mg/dl)	55 (15.32)	1 (4.35)	19 (13.10)	13 (7.83)	23 (13.94)
Triglycerides (mg/dl)	25 (6.96)	2 (8.70)	10 (6.90)	11 (6.63)	4 (2.42)
Urinalysis					
pH	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Source: January 18, 2010 Submission SDS 2

The sponsor analyzed the safety laboratory data using the PCI definitions. The percentage of exenatide LAR subjects with laboratory values of PCI was small, generally similar or less than comparators, and not clinically meaningful. Please refer Table 34 for more details.

Table 34. Chemistry, hematology, lipid, and urinalysis values of PCI

	Ex LAR (n=359)	Placebo (n=23)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
Chemistry					
ALT (mU/ml)	4 (1.11)	0 (0.00)	2 (1.38)	0 (0.00)	1 (0.61)
AST(mU/ml)	4 (1.11)	0 (0.00)	6 (4.14)	3 (1.81)	1 (0.61)
Alkaline phosphatase (mU/ml)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Bicarbonate	4 (1.11)	0 (0.00)	6 (4.14)	3 (1.81)	1 (0.61)
BUN (mg/dl)	1 (0.28)	0 (0.00)	1 (0.69)	0 (0.00)	0 (0.00)
Calcium (mg/dl)	6 (1.67)	0 (0.00)	4 (2.76)	3 (1.81)	2 (1.21)
Creatinine (mg/dl)	6 (1.67)	2 (8.70)	5 (3.45)	1 (0.60)	2 (1.21)
Potassium	17 (4.74)	4 (17.39)	7 (4.83)	4 (2.41)	3 (1.82)
Sodium	5 (1.39)	0 (0.00)	2 (1.38)	1 (0.60)	1 (0.61)
Total bilirubin (mg/dl)	1 (0.28)	0 (0.00)	0 (0.00)	1 (0.60)	0 (0.00)
Uric acid	21 (5.85)	1 (4.35)	6 (4.14)	4 (2.41)	1 (0.61)
Hematology					
Hematocrit (%)	8 (2.23)	0 (0.00)	3 (2.07)	4 (2.41)	8 (4.85)
Hemoglobin (g/dl)	10 (2.79)	0 (0.00)	7 (4.83)	5 (3.01)	11 (6.67)
Platelet count ($10^3/mm^3$)	8 (2.23)	0 (0.00)	6 (4.14)	1 (0.60)	1 (0.61)
WBCs ($10^3/mm^3$)	1 (0.28)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Lipids					
Tot. cholesterol (mg/dl)	24 (6.69)	1 (4.35)	7 (4.83)	4 (2.41)	4 (2.42)
Triglycerides (mg/dl)	20 (5.57)	4 (17.39)	8 (5.52)	6 (3.61)	8 (4.85)
Urinalysis					
Protein	6 (1.67)	0 (0.00)	3 (2.07)	3 (1.81)	2 (1.21)

Source: January 18, 2010 Submission SDS 3

Marked outliers and dropouts for laboratory abnormalities (excluding hypo and hyperglycemia): No subjects were withdrawn from clinical pharmacology studies 102, 103, and BCB107 nor safety and efficacy studies 104 and GWBW. Two subjects each were withdrawn from safety and efficacy studies 105 and BCB106. However, only 1 of these subjects (09914) received exenatide LAR.

Table 35. Laboratory abnormalities leading to discontinuation

Study	Subject	Treatment	Preferred term
105	01717	Exenatide	Hepatitis cholestatic
	09914	Exenatide LAR	Blood potassium increased
BCB106	124012	Pioglitazone 45 mg	Blood creatinine phosphokinase MB increased
	145026	Pioglitazone 45 mg	Gamma-glutamyltransferase increased

Source: January 18, 2010 Submission Table 3

Exenatide LAR subject 09914 was a 54 year old female with an 11 year history of T2DM who initiated exenatide LAR on February 8, 2007, after completing a 3 day exenatide BID lead-in. She had an unremarkable past medical history and baseline serum potassium of 4.2 mEq/l (normal 3.5-5.5 mEq/l). On February 8, 2007, she experienced an elevated serum potassium concentration (6.0 mEq/l). Potassium concentrations remained elevated due to an unknown cause (range 5.3-6.3 mEq/l between March 1, 2009 and July 12, 2007). Bicarbonate concentrations ranged 20-24 mEq/l (normal 22-29 mEq/l). Treatment included Lasix, although potassium concentrations did not change significantly. Electrocardiogram was normal at study termination. On 05 July 2007, the subject received the last dose of exenatide LAR. The subject's potassium level returned to normal shortly thereafter (exact concentration and date unspecified). The subject was withdrawn from the study on July 12, 2007, due to the elevated potassium concentration. The elevated potassium was considered resolved on July 16, 2007.

The timing of this event, specifically its onset and offset which coincides with exenatide LAR use, suggests it may be drug related. However, this event occurred in only 1 of 476 (0.2%) subjects exposed to exenatide LAR. The mean change from baseline and shifts from normal to abnormal in potassium were not significantly different from comparators. The abnormality resolved with exenatide LAR discontinuation. Thus, I do not feel this represents a clinically significant safety signal at this time.

The sponsor also analyzed exenatide LAR clinical trials for adverse events assessed as severe by the investigator. Eleven severe AEs were identified in the development program, occurring in 9 subjects. Only 1 of these subjects received exenatide LAR; study 105 subject 00213 had bacteremia and an *Eschesichia coli* urinary tract infection, which were likely not related to study drug.

Special assessments: Renal and hepatotoxicity: The sponsor analyzed the change in renal function using the Cockcroft-Gault (CG) formula which was modified by the use of ideal body weight and the simplified 4-variable Modification of Diet in Renal Disease Study group (MDRD) formula.[1,2]

The mean change in creatinine clearance was greatest in the placebo group, regardless of the formula used (CG -3.22 ml/min, MDRD -4.59 ml/min). The mean change in creatinine clearance in the exenatide LAR group was similar to the other treatment

1 Peck CC, Conner DP, Murphy MG. Bedside clinical pharmaco-kinetics: simple techniques for individualizing drug therapy. Vancouver, Washington: Applied Therapeutics Incorporated; 1989.
2 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70.

groups and less than pioglitazone (exenatide LAR: CG -1.16 ml/min, MDRD -1.03 ml/min). Please refer to Table 36.

Table 36. Mean (SD) change in creatinine clearance by CG and MDRD formulas

	Ex LAR (n=359)	Placebo (n=23)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
CG (ml/min)	-1.16 (12.311)	-3.22 (14.484)	-0.22 (11.904)	-0.66 (11.352)	-1.77 (9.617)
MDRD (ml/min)	-1.03 (15.118)	-4.59 (21.793)	0.56 (15.976)	-0.09 (14.979)	-1.57 (12.503)

Source: January 18, 2010 Submission SDS 4

Shifts between renal function categories in repeat dose, controlled, safety and efficacy studies were similar between treatment groups when analyzed by both the CG and MDRD formulas. However, slightly more placebo subjects shifted to a worse renal function category. Please refer to Table 38 and Table 39.

In summary, exenatide LAR does not appear to be associated with a clinically significant worsening of renal function in the population studied which consisted of mostly subjects with normal renal function or mild renal impairment. Please refer to Table 37.

Table 37. Approximate percentage of subjects in repeat dose, controlled, efficacy and safety trials of exenatide LAR with normal renal function and renal impairment by CG and MDRD formulas

Renal category	CG	MDRD
Normal	39%	51%
Mild renal impairment	44%	42%
Moderate renal impairment	15%	5%
Severe renal impairment	0%	0%

Source: January 18, 2010 Submission SDS 5

Table 38. Shift table for change in renal function by CG formula

	Clinical Pharmacology [1]		Controlled [2]					Uncontrolled [3]
Method/ n(%)	Exenatide Once Weekly (N=117)	Placebo (N=15)	Exenatide Once Weekly (N=359)	Placebo (N=23)	BYETTA (N=145)	Sitagliptin (N = 166)	Pioglitazone (N = 165)	Exenatide Once Weekly (N=258)
Renal Function using Cockcroft-Gault formula [4]								
Normal to Normal	65 (55.56)	4 (26.67)	111 (30.92)	5 (21.74)	41 (28.28)	45 (27.11)	33 (20.00)	63 (24.42)
Normal to Mild	8 (6.84)	1 (6.67)	29 (8.08)	5 (21.74)	10 (6.90)	10 (6.02)	12 (7.27)	27 (10.47)
Normal to Moderate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.39)
Normal to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Mild to Normal	6 (5.13)	1 (6.67)	21 (5.85)	3 (13.04)	9 (6.21)	9 (5.42)	4 (2.42)	11 (4.26)
Mild to Mild	26 (22.22)	6 (40.00)	125 (34.82)	3 (13.04)	52 (35.86)	59 (35.54)	58 (35.15)	90 (34.88)
Mild to Moderate	6 (5.13)	2 (13.33)	12 (3.34)	2 (8.70)	3 (2.07)	7 (4.22)	10 (6.06)	20 (7.75)
Mild to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Moderate to Normal	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.69)	0 (0.00)	1 (0.61)	0 (0.00)
Moderate to Mild	3 (2.56)	0 (0.00)	15 (4.18)	1 (4.35)	6 (4.14)	5 (3.01)	6 (3.64)	5 (1.94)
Moderate to Moderate	2 (1.71)	1 (6.67)	38 (10.58)	3 (13.04)	20 (13.79)	21 (12.65)	24 (14.55)	40 (15.50)
Moderate to Severe	0 (0.00)	0 (0.00)	1 (0.28)	0 (0.00)	1 (0.69)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Normal	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Mild	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Moderate	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.60)	1 (0.61)	0 (0.00)
Missing to Missing	1 (0.85)	0 (0.00)	7 (1.95)	0 (0.00)	2 (1.38)	9 (5.42)	16 (9.70)	1 (0.39)

NOTE: Reproduced from the sponsor's January 18, 2010 Submission SDS 5

Table 39. Shift table for change in renal function by MDRD formula

	Clinical Pharmacology [1]		Controlled [2]					Uncontrolled [3]
Method/ n(%)	Exenatide Once Weekly (N=117)	Placebo (N=15)	Exenatide Once Weekly (N=359)	Placebo (N=23)	BYETTA (N=145)	Sitagliptin (N = 166)	Pioglitazone (N = 165)	Exenatide Once Weekly (N=258)
Renal Function using MDRD formula [5]								
Normal to Normal	75 (64.10)	9 (60.00)	154 (42.90)	14 (60.87)	53 (36.55)	84 (50.60)	56 (33.94)	78 (30.23)
Normal to Mild	12 (10.26)	2 (13.33)	30 (8.36)	3 (13.04)	16 (11.03)	10 (6.02)	17 (10.30)	37 (14.34)
Normal to Moderate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.60)	0 (0.00)	1 (0.39)
Normal to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Mild to Normal	9 (7.69)	2 (13.33)	28 (7.80)	3 (13.04)	14 (9.66)	11 (6.63)	14 (8.48)	17 (6.59)
Mild to Mild	16 (13.68)	1 (6.67)	115 (32.03)	1 (4.35)	46 (31.72)	44 (26.51)	51 (30.91)	88 (34.11)
Mild to Moderate	3 (2.56)	1 (6.67)	8 (2.23)	1 (4.35)	4 (2.76)	2 (1.20)	3 (1.82)	18 (6.98)
Mild to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Moderate to Normal	0 (0.00)	0 (0.00)	1 (0.28)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.61)	1 (0.39)
Moderate to Mild	1 (0.85)	0 (0.00)	9 (2.51)	0 (0.00)	4 (2.76)	2 (1.20)	2 (1.21)	5 (1.94)
Moderate to Moderate	0 (0.00)	0 (0.00)	7 (1.95)	1 (4.35)	5 (3.45)	3 (1.81)	4 (2.42)	12 (4.65)
Moderate to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.69)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Normal	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Mild	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Severe to Moderate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.61)	0 (0.00)
Severe to Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing to Missing	1 (0.85)	0 (0.00)	7 (1.95)	0 (0.00)	2 (1.38)	9 (5.42)	16 (9.70)	1 (0.39)

NOTE: Reproduced from the sponsor's January 18, 2010 Submission SDS 5

When repeat dose, controlled, safety and efficacy studies were reviewed for transaminase elevation and Hy's Law criteria (ALT or AST >3x ULN with total bilirubin ≥2x ULN with alkaline phosphatase <2x ULN), a small number of exenatide LAR subjects had ALT or AST >3x or 5x ULN. The percentage of subjects was small (0.28-1.11%), although it was greater than the other treatment groups. No cases met Hy's Law criteria. Please refer to Table 40.

Table 40. Subjects (n, %) with abnormal transaminases or meeting Hy's Law criteria

	Ex LAR (n=359)	Placebo (n=23)	Exenatide (n=145)	Sitagliptin (n=166)	Pioglitazone (n=165)
ALT					
>3x	4 (1.11)	0 (0.00)	2 (1.38)	0 (0.00)	1 (0.61)
>5x	2 (0.56)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.61)
>10x	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
AST					
>3x	2 (0.56)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>5x	1 (0.28)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>10x	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Hy's Law+*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
*Hy's law criteria: ALT or AST>3x ULN; Alk Phos <2x ULN; and Tot. Bilirubin ≥2x ULN					
Source: January 18, 2010 Submission SDS 6 and 7					

7.4.3 Vital Signs

The mean change from baseline in heart rate and systolic and diastolic blood pressure (SDP and DBP) in controlled studies of exenatide LAR completed as of March 31, 2009 was reviewed (i.e. placebo controlled studies: 104 and GWBW; comparator controlled studies: 105 and BCB106). There was a mean decrease in blood pressure (-3.2/-1.3 mm Hg) and increase in heart rate (1.9 bpm) in the exenatide LAR group. These changes were similar those seen with exenatide (-3.2/-2.0 mm Hg and 1.0 bpm). The placebo group experienced a decrease in mean blood pressure (-2.1/-2.0 mm Hg), and in mean heart rate (-2.0 bpm).

Table 41. NDA 22-200: Mean change in heart rate and blood pressure from baseline in controlled studies of exenatide LAR (ITT, n=858)

Vital Sign (Unit)/ Parameter	Exenatide Once Weekly (N = 359)	Placebo (N = 23)	BYETTA (N = 145)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
Heart Rate (bpm)					
Baseline	73.8	70.1	73.7	72.6	74.1
Change from baseline	1.9	-2.0	1.0	0.7	-0.6
Sitting DBP (mm Hg)					
Baseline	78.7	78.0	79.6	78.9	79.5
Change from baseline	-1.3	-2.0	-2.0	-0.2	-2.6
Sitting SBP (mm Hg)					
Baseline	127.6	128.6	129.6	125.8	126.7
Change from baseline	-3.2	-2.1	-3.2	0.8	-1.4

bpm = beats per minute; DBP = diastolic blood pressure; SBP = systolic blood pressure.

NOTE: Reproduced from the Four month safety update Table 11

When phase 3, comparator controlled trials of exenatide LAR were reviewed separately, a reduction in SBP and DBP (-4.7/-1.7 and -4.2/-2.1 mm Hg) and an increase in heart rate (4.5 and 2.5 bpm) were observed in studies 105 and BCB106 (weeks 30 and 26, respectively). The changes in blood pressure and heart rate were persistent to 52 weeks in study 105 (-6.2/-2.8 mm Hg and 4.1 bpm).

The following relevant AEs occurred in phase 3, comparator controlled studies 105 and BCB106:

- Hypotension: Exenatide LAR subject 40506 in study 105 had a blood pressure of 92/56 mm Hg, which resolved within 15 days. At week 52, HbA1c had improved 3.7%, the subject had lost 18 kg, and blood pressure was 113/64 mm Hg.
- Hypertension: Five exenatide LAR subjects and 4 exenatide subjects experienced hypertension in study 105. The majority of these subjects (3 exenatide LAR and 4 exenatide) experienced worsening of existing hypertension.
- Tachycardia:
    - Exenatide LAR subject 17105 in study 105 experienced intermittent tachycardia after 219 days of therapy, which resolved within 2 days and without study medication interruption. The subject experienced the death of a friend around the time of this event of tachycardia.
    - Exenatide LAR subject 40506 in study 105 had sinus tachycardia at baseline (1 of 3 baseline ECGs showed heart rate 100 bpm). On day 14, heart rate was 107 bpm. The patient continued therapy. At week 52, heart rate was 103 bpm.
    - Exenatide LAR subject 139008 in study BCB106 experienced sinus tachycardia (109 bpm) on day 54. Baseline heart rate was 76 bpm. The sinus tachycardia did not resolve and was treated with atenolol/chlorthialidone. Heart rate remained between 101-105 bpm through week 26.

All of but subject 139008's event can be explained by an improvement in the overall health, subjects' baseline, or trauma. Subject 139008's tachycardia could have been related to study medication, although the severity of tachycardia was mild.

In summary, according to controlled studies 104, GWBW, 105, and BCB106, exenatide LAR is associated with mean decrease in blood pressure (-3.2/-1.3 mm Hg) and increase in heart rate (1.9 bpm). This is similar to the changes associated with exenatide. These minor changes are likely clinically insignificant.

7.4.4 Electrocardiograms (ECGs)

As described in the QT Interdisciplinary Review Team (IRT) consult, there are no apparent QT-prolonging effects of exenatide when administered as extended or immediate release formulations. In study 105, replicate 12 lead ECGs were obtained as baseline and weeks 14 and 30. No subject's post-baseline QTcF measurement was ≥ 450 ms. The mean change from baseline QTcF was < 5 ms.

Although small increases in QTc interval (< ms) could not be ruled out because a dedicated TQT study with positive and placebo controls was not conducted, the average exenatide exposures achieved with the LAR formulation are lower (relative bioavailability is 25%) than approved exenatide BID. According to the QT IRT, a dedicated TQT is not needed unless there are CV AEs such as syncope, seizure, ventricular arrhythmias, or sudden death in the clinical development program and postmarketing reports; this is not the case.

7.4.5 Special Safety Studies/Clinical Trials

In study 105, the use of exenatide LAR was preceded by a 3 day exenatide 5 mcg BID lead in. The only clinical study submitted with the NDA without an exenatide BID lead in was study H8O-JE-GWBW (GWBW), a phase 1, randomized, double blind, placebo controlled, 10 week safety study of exenatide LAR in 30 Japanese subjects. However, the study sample size was small (n=30), and its results may not be directly relevant to the more diverse American population.

The sponsor submitted clinical study report BCB106 in the four month safety update. BCB106 was a randomized, double blind, comparator controlled, 3 arm study in 491 subjects comparing the effects of exenatide LAR, without exenatide BID lead-in, on glycemic control, safety, and tolerability to those achieved by sitagliptin 100 mg and pioglitazone 45 mg over a 26 week treatment period. (Note, the open ended assessment period of BCB106 is still ongoing.) The most frequent AEs in the exenatide LAR group were nausea (23.8%), diarrhea (18.1%), vomiting (11.3%), and headache (9.4%). These rates are similar to those seen when comparator controlled trials of exenatide LAR were pooled in the four month safety update (25.3%, 16.6%, 11.0%, and 7.8%, respectively).

In study BCB106, there were no deaths or gastrointestinal SAEs in exenatide LAR subjects. The SAEs observed in exenatide LAR subjects included cryptogenic organizing pneumonia, postoperative wound complication, nephrolithiasis, and viral pericarditis.

A total of 11 exenatide LAR, 5 sitagliptin, and 7 pioglitazone subjects were withdrawn from study BCB106 due to AEs. Relevant AEs which led to withdrawal in exenatide LAR subjects included diarrhea (3), nausea (1), headache (1), GERD (1), and injection site mass (1). All but the injection site mass were mild or moderate and resolved. (The injection site mass was severe and "resolving".) Three sitagliptin subjects and 2 pioglitazone subject were also discontinued for diarrhea or nausea. One pioglitazone subject was discontinued for pancreatitis.

In summary, study BCB106 demonstrated that the administration of exenatide LAR without an exenatide BID lead-in does not significantly increase the rate of gastrointestinal SAEs or the common AEs of nausea, diarrhea, vomiting, and headache. In addition, the rate of withdrawal due to gastrointestinal AEs was not significantly higher. Although there was one severe case of injection site mass which resulted in withdrawal, pretreatment with exenatide BID would not likely have prevented the AE as use of exenatide LAR is associated with injection site reactions due to its containing PLG.

In the proposed label submitted by the sponsor on November 3, 2009, the sponsor recommends that exenatide LAR 2 mg be once administered weekly. The sponsor does not recommend that patients use exenatide BID prior to exenatide LAR, although advice is provided on switching from exenatide BID to exenatide LAR. This is acceptable based on the safety data from study BCB106.

7.4.6 Immunogenicity

Fifty-two week exenatide study 2993-117 demonstrated no significant treatment-emergent immunogenic cross-reactivity with structurally similar endogenous peptides (i.e. glucagon and GLP-1). Please refer to section 6.1.10 Additional Efficacy Issues/Analyses for a description of the antibodies associated with exenatide, how anti-exenatide antibodies were measured in exenatide LAR trials, the proportion of subjects that were positive, and their effect on efficacy.

In the exenatide LAR program, no deaths were attributed to hypersensitivity reactions. In studies 102, 103, 104, and 105, there were no hypersensitivity SAEs.

During study 105's 30-week assessment period, more exenatide LAR subjects were positive for exenatide antibodies when compared to exenatide subjects (74.3% vs. 49.0%). However, the incidence of AEs was similar between the 2 treatment groups

(87.2% and 81.4%). There was no clear effect of antibody status on the incidence of AEs. AEs were reported in 84.5% of antibody positive (titer ≥ 25) subjects and 94.7% of antibody negative subjects. The incidence of AEs in antibody positive and negative subjects treated with exenatide (Byetta) was 78.9% and 83.8%, respectively. Similar results were observed though week 52 of the study.

Two subjects experience AEs that coded to the preferred term of hypersensitivity during the 30 week assessment period. Neither were likely related to study medication.

- 22411: This exenatide LAR subject experienced mild congestion due to environmental allergies after 71 days of therapy.
- 23104: This exenatide LAR subject experienced mild worsening of allergies following 101 days of therapy.

A comparison of the incidence of potentially immune-related AEs in anti-exenatide antibody positive and negative subjects revealed a greater incidence of injection site pruritis, injection site erythema, and arthralgia in antibody positive, exenatide LAR subjects (21.8% vs. 7.9%, 9.1% vs. 2.6%, and 6.4% vs. 0.0% respectively). However, the overall incidence of arthralgia was similar in the exenatide LAR (4.7%) and exenatide (4.1%) groups. No systemic immune-related respiratory symptoms or anaphylactic reactions were reported.

Table 42. Study 105: Potentially immune-related AEs by antibody status at any time during 30 week assessment period (ITT n=293)

	Treatment							
	BYETTA 10 mcg BID (N = 145)				Exenatide LAR 2 mg QW (N = 148)			
	TEAB Positive (N = 71)		TEAB Negative (N = 74)		TEAB Positive (N = 110)		TEAB Negative (N = 38)	
Preferred Term [1]	Subject [2] n (%)	Events n	Subject [2] n (%)	Events n	Subject [2] n (%)	Events n	Subject [2] n (%)	Events n
All Potentially Immune-Related Treatment-Emergent [3] Adverse Events	8 (11.3)	8	8 (10.8)	9	39 (35.5)	81	5 (13.2)	8
Injection Site Erythema	0 (0.0)	0	0 (0.0)	0	10 (9.1)	10	1 (2.6)	1
Injection Site Induration	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	0 (0.0)	0
Injection Site Nodule	0 (0.0)	0	0 (0.0)	0	2 (1.8)	3	0 (0.0)	0
Injection Site Pruritus	1 (1.4)	1	1 (1.4)	1	24 (21.8)	38	3 (7.9)	3
Injection Site Rash	0 (0.0)	0	1 (1.4)	1	3 (2.7)	3	1 (2.6)	1
Injection Site Swelling	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	0 (0.0)	0
Injection Site Urticaria	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	0 (0.0)	0
Drug Hypersensitivity	0 (0.0)	0	1 (1.4)	1	0 (0.0)	0	0 (0.0)	0
Hypersensitivity	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	1 (2.6)	1
Arthralgia	2 (2.8)	2	4 (5.4)	4	7 (6.4)	10	0 (0.0)	0
Arthritis	2 (2.8)	2	0 (0.0)	0	1 (0.9)	1	1 (2.6)	1
Joint Swelling	1 (1.4)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Periarthritis	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	0 (0.0)	0
Asthma	1 (1.4)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Wheezing	0 (0.0)	0	1 (1.4)	1	1 (0.9)	2	0 (0.0)	0
Dermatitis	0 (0.0)	0	0 (0.0)	0	2 (1.8)	2	0 (0.0)	0
Photosensitivity Reaction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.6)	1
Pruritus	0 (0.0)	0	0 (0.0)	0	2 (1.8)	2	0 (0.0)	0
Rash Erythematous	0 (0.0)	0	0 (0.0)	0	1 (0.9)	1	0 (0.0)	0
Rash Macular	1 (1.4)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Rash Pruritic	0 (0.0)	0	1 (1.4)	1	2 (1.8)	2	0 (0.0)	0
Urticaria	0 (0.0)	0	0 (0.0)	0	1 (0.9)	2	0 (0.0)	0

NOTE: Reproduced from the Study 105 report Table 20

Injection site events (including erythema, pruritis, rash, and swelling) are summarized by treatment and antibody titer below. In controlled studies 105 and BCB106, more exenatide LAR subjects (antibody negative 4.9%, antibody positive 18.3%) experienced injection site reactions than exenatide (antibody negative 1.4%, antibody positive 1.4%), sitagliptin (5.4%), and pioglitazone (1.2%) subjects. (Note, sitagliptin and pioglitazone subjects received placebo injection weekly.) The PLG technology used in the production of exenatide LAR has been associated with local irritation. However, the incidence of injection site reactions was higher in exenatide LAR antibody positive subject than antibody negative subjects.

Table 43. NDA 22-200: Injection site pruritis, erythema, rash, and urticaria by antibody status at any time in controlled studies 105 and BCB106

Treatment	Antibody status	Injection site reaction

Ex LAR (n=3-08)	Negative (n=82)	4 (4.9)
	High positive (n=58)	21 (36.2)
	Low positive (n=161)	19 (11.8)
	Any positive (n=219)	40 (18.3)
Exenatide (n=145)	Negative (n=74)	1 (1.4)
	High positive (n=14)	1 (7.1)
	Low positive (n=57)	0 (0.0)
	Any positive (n=71)	1 (1.4)
Sitagliptin (n=166)		9 (5.4)
Pioglitazone (n=165)		2 (1.2)

Source: Four month safety update SDS 7.2

Out of the 606 exenatide LAR subject included in the four month safety update, only 2 (0.3%) withdrew from studies due to injection site mass or nodule.

In summary, more subjects receiving exenatide LAR develop anti-exenatide antibodies than subjects receiving exenatide (74.3% vs. 49.0% in study 105). The overall incidence of AEs was similar between the exenatide LAR and exenatide. There was no clear effect of antibody status on the overall incidence of AEs.

However, more exenatide LAR subjects experienced injection site reactions than exenatide, sitagliptin, and pioglitazone subjects. (Sitagliptin and pioglitazone subjects received weekly placebo injection.) The incidence of injection site reactions was higher in antibody positive than antibody negative exenatide LAR subjects (high positive 36.2%, low positive 11.8%, negative 4.9%). However, injection site reactions uncommonly resulted in study withdrawal (0.3%).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Key studies 105 and 105c only investigated the safety and effectiveness of 2 mg exenatide LAR once weekly. However, the sponsor analyzed AEs by exenatide concentration (> 384.83 pg/ml, 277.31-384.83 pg/ml, or < 277.31 pg/ml) in 148 exenatide LAR subjects in study 105. Minor dose-related trends in AEs were seen in the blood and lymphatic system (4.1% vs. 4.1% vs. 0.0%), general disorders and administration site conditions (46.9% vs. 42.9% vs. 34.0%), investigations (8.2% vs. 6.1% vs. 4.0%), and musculoskeletal and connective tissue disorders (24.5% vs. 20.4% vs. 14.0%). However, due to the small sample size studied, the interpretability of these trends is limited. Within the system organ classes (SOCs), a dose-related increase in specific preferred terms was not seen. Injection site reactions in the general administration site SOC did not increase dose-proportionately (24 vs. 19 vs. 22) nor did events in the gastrointestinal SOC (59.2% vs. 42.9% vs. 48.0%).

Phase 2 study 104 compared the safety of 0.8 and 2 mg exenatide LAR once weekly. There were no deaths or withdrawals due to AEs in the 31 exenatide LAR subjects studied, although there was 1 SAE in both the 0.8 and 2 mg groups (ureteric calculus and angina pectoris, respectively). A significant dose-related trend in AEs was not observed, although the sample size studied was small.

In addition, the CMC specifications for exenatide LAR's initial release is (b) (4) %. Thus, (b) (4) % of the 2 mg exenatide LAR dose (i.e. (b) (4) mcg) could potentially be administered within the first hour after exenatide LAR injection. This exceeds the maximally recommended dose of exenatide which is 10 mcg BID. However, the worst initial release seen in exenatide LAR clinical trials was 0.7% (i.e. (b) (4) mcg phase 1 burst).

The adverse events of interest with exenatide LAR are acute pancreatitis, gastrointestinal side effects, hypoglycemia, hypersensitivity, renal failure, and thyroid tumors. In addition, exenatide LAR is associated with injection site reactions.

As described in sections 7.3.4 Significant Adverse Events and 7.4.6 Immunogenicity,

- Although the sample size was small, no thyroid cancers were identified in the exenatide LAR clinical development program.
- Only 1 exenatide LAR subject developed pancreatitis. When routine lipase and p-amylase measurement were included in study BCB106, no exenatide LAR subject had p-amylase elevations > 3x ULN at any time and the proportion of subjects with lipase ≥ 3x ULN at week 26 was similar across groups (1-2%).
- When long term, placebo and comparator controlled studies of exenatide LAR were reviewed, the incidence of nausea and vomiting was lower in the exenatide LAR group when compared to exenatide (25.3% vs 34.5% and 11.0% vs. 18.6%, respectively).
- The incidence of hypoglycemia was low and less than that seen with exenatide.
- Exenatide LAR does not appear to increase the risk of acute renal failure.
- More exenatide LAR subjects developed anti-exenatide antibodies than exenatide subjects (74.3% vs. 49.0% in study 105). The overall incidence of AEs was similar between the exenatide LAR and exenatide. There was no clear effect of antibody status on the overall incidence of AEs.
- More exenatide LAR subjects experienced injection site reactions than subjects on sitagliptin or pioglitazone given placebo weekly injections. The incidence of injection site reactions was higher in antibody positive than antibody negative exenatide LAR subjects (high positive 36.2%, low positive 11.8%, negative 4.9%).

Thus, in the small population studied, the use of exenatide LAR does not appear to increase the risk of adverse events of interest. Gastrointestinal side effects and hypoglycemia occur less frequently, although more subjects develop anti-exenatide antibodies and injection site reactions.

I do not believe the development of anti-exenatide antibodies or injection site reactions (because of the PLG polymer used) are increased as a result of a potential greater initial exenatide release with exenatide LAR. Thus, based on the safety data to date, there does not appear to be a clinical reason to reject the sponsor's proposed initial release specifications.

7.5.2 Time Dependency for Adverse Events

Pivotal study 105 included an uncontrolled, open-ended assessment period which, as of the March 31, 2009 four month safety update cutoff, had 205 subjects whom had received more than 2 years of treatment. Only 1 death has been reported in study 105. Subject 10802 died of a fatal MI 198 days (28 weeks) after first dose of exenatide LAR. No additional deaths were reported up to the March 31, 2009 cutoff date.

The nonfatal SAEs which occurred in study 105 up to week 52 are shown in Table 21 (n=258). The rate of SAES (4.7%) in the uncontrolled study up to week 52 was less than that seen in completed, placebo- and comparator-controlled, efficacy and safety studies (6.5% and 5.4%, respectively). Between the November 15, 2008 and March 31, 2009 cutoff dates, 3 additional SAEs were reported (noncardiac chest pain, postoperative wound infection, and dyspnea). Only 1 AE in the metabolism and nutrition disorders SOC lead to withdrawal from the uncontrolled portion of study 105. This event occurred prior to November 15, 2008.

The four month safety update compared the incidence of AEs in placebo- (studies 104 and GWBW) and comparator-controlled studies (studies 105 and BCB106) of exentide LAR as well as the uncontrolled portion of study 105 (up to 2 years). No trend in increasing AEs with time was seen, as shown by the comparison of a selection of the adverse events of interest below.

Table 44. A selection of AEs of interest by placebo- and comparator-controlled trials and uncontrolled (2 year) exenatide LAR groups

Preferred term	Placebo-controlled LAR (n=51)	Comparator-controlled LAR (n=308)	Uncontrolled LAR up to 2 years (n=258)
Nausea	19.6%	25.3%	11.6%
Diarrhea	9.8%	16.6%	12.4%
Vomiting	2.0%	11.0%	8.9%
Injection site pruritis	19.6%	11.4%	4.3%
Injection site erythema	9.8%	5.2%	3.9%
Decreased appetite	0.0%	2.9%	0.8%
Injection site induration	31.4%	0.3%	0.4%
Anorexia	9.8%	1.3%	0.0%

Source: Four month safety update SDS 5.2

In summary, the risk of AEs associated with exenatide LAR does not appear to increase with increasing exposure.

7.5.3 Drug-Demographic Interactions

The sponsor analyzed safety by age, gender, race, and BMI in the summary of clinical safety submitted with the NDA. No clinically relevant differences were seen.

Age: The sponsor analyzed the AE data from the 293 subjects in study 105 by subjects < 65 years and ≥ 65 years. All subjects (100%) ≥ 65 years reported AEs (exenatide LAR n=26, exenatide n=23). A similar proportion of subjects < 65 years reported AEs in the exenatide LAR and exenatide groups (84% and 78%, respectively). Although some AEs such as constipation and diarrhea occurred more often in subjects ≥ 65 years, other events such as nausea and vomiting occurred less frequently, although the number of subjects was small.

In previous studies of exenatide, there were more subjects aged ≥ 65 years. No effect of age was observed on the incidence of AEs.

Gender: The frequency of AEs in males and females was similar (females 91%, males 84%). Female versus male differences were notable for the following events: nausea (38%, 17%), vomiting (17%, 6%), injection site pruritis (24%, 13%), and injection site erythema (12%, 4%).

In previous studies of exenatide, males and females reported a similar incidence of AEs.

Race: As only a small number of Asian (n=28 [9.5%]) and black subjects (n=1 [0.3%]) were included in study 105, the sponsor assessed incidence of AEs for Caucasians (n=230, 78.0%) and Hispanic (n=36, 12.2%) subjects only (AE rate 89% and 81%, respectively). Despite the similar overall rate, there were some differences, including the lower incidence of nausea and vomiting in Hispanic subjects (6% [n=1] and 0%) when compared with Caucasian subjects (30% [n=37] and 11% [n=14]).

Like exenatide LAR, the incidence of AEs with exenatide is similar among racial subgroups. However, the incidence of nausea was lower in Blacks (36%) when compared with Caucasians (44%) and Hispanics (44%).

Body mass index: The incidence of AEs was similar among subjects with baseline BMI < 30 kg/m^2 versus ≥ 30 kg/m^2 (91.7% vs. 86.3%). However, there appeared to be a lower incidence of nausea (24% vs. 38%) and vomiting (10% vs. 17%) in subjects with baseline BMI ≥ 30 kg/m^2. Injection site pruritis was reported more frequently in subjects with BMI ≥ 30 kg/m^2 (21% vs. 4%).

7.5.4 Drug-Disease Interactions

Renal impairment: Exenatide LAR was not evaluated in subjects with severe renal impairment (creatinine clearance [CrC] ≤ 30 ml/min), as these subjects were excluded by the protocol.

A discussion of renal failure as a significant AE is contained in section 7.3.4 and related laboratory findings in section 7.4.2.

In the Summary of Clinical Safety that was submitted with the NDA, the sponsor categorized renal function retrospectively using the Cockcroft and Gault equation. The incidence rate of AEs was approximately the same in subjects treated with exenatide LAR with normal renal function, mildly impaired renal function, and moderate renal function (85% vs. 89% vs. 90%). The sponsor reviewed of AEs by renal function category and indicated that the AE profile of exenatide LAR was not affected by renal function status, although a summary table of this analysis was not provided.

On January 29, 2010, the sponsor submitted a response to an information request which included a summary of the SAES, AES, laboratory abnormalties, and withdrawals of the 21 exenatide LAR and 11 exenatide subjects with moderate renal impairment, described in the four month safety update.

- The same number of exenatide LAR and exenatide subjects experienced SAEs (2,), although the incident rate (10% vs. 18%) and events were different (LAR events: breast cancer with diverticulitis and bladder cancer with cerebral artery occlusion; exenatide events: nephrolithiasis with acute renal failure and appendicitis).
- The incidence of withdrawal was similar in the exenatide LAR and exenatide groups (14% vs. 18%; reasons: withdrawal of consent and AE).
- The incidence of AEs was less in the exenatide LAR group when compared to the exenatide group (80% vs. 100%). The most common AEs occurred in the following SOCs. Only general disorders and administration site conditions were more common in the exenatide LAR group; this was mostly due to inflammation and injection site hemorrhage and pruritis.
    - Gastrointestinal (55% vs. 73%)
    - General disorders and administration site conditions (25% vs. 9%)
    - Infections and infestations (35% vs. 55%)
    - Metabolic and nutrition (15% vs. 27%)
    - Musculoskeletal and connective tissue (10% vs. 9%)

Exenatide is not recommended in severe renal impairment, or end-stage renal disease. Exenatide should be used cautiously in patients with a history of renal transplantation or moderate renal impairment.

In the proposed exenatide LAR label, exenatide LAR is contraindicated in subjects with severe or end stage renal impairment, which is appropriate as these subjects were not included in clinical trials. No dosage adjustment is proposed by the sponsor in patients with mild to moderate renal impairment. However, because there was a 53% increase in exenatide exposure in the subjects with moderate renal impairment (n=10) in study 105 (versus 24% increase in subjects with mild renal impairment), clinical pharmacology and I support labeling which recommends caution when initiating exenatide LAR in patients with moderate renal impairment.

Hepatic impairment: Both the exenatide and proposed exenatide LAR labels state the following: *No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide.*

Studies of exenatide LAR excluded subjects with hepatic impairment as follows:

- Studies 104, 105, 105c, BCB106: Hepatic disease or an ALT or AST > 3x ULN.
- Study GWBW: Obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or ALT or AST ≥ 2.5x ULN

Thus, I agree with the proposed hepatic impairment labeling.

7.5.5 Drug-Drug Interactions

The oral absorption of acetaminophen, a commonly used measure of the rate of gastric emptying, was assessed in a subset of study 105 subjects. The substudy assessed the effects of exenatide LAR and exenatide in the fed state and exenatide LAR in the fasting state. Acetaminophen was measured at baseline (day -3) and week 14, when exenatide LAR concentrations were at steady state. Exenatide LAR in the fed and fasted states produced a smaller reduction on the rate of the absorption of concomitant oral acetaminophen than exenatide. The rate of absorption with exenatide LAR in the fasted stated was marginally slower than in the fed state.

Section 7.1 Orally Administered Drugs of exenatide label reads as follows: *The effect of BYETTA to slow gastric emptying can reduce the extent and rate of absorption of orally administered drugs. BYETTA should be used with caution in patients receiving oral medications that have narrow therapeutic index or require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 hour before BYETTA injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when BYETTA is not administered*. Section 7.2 Warfarin contains a statement regarding postmarketing reports of increased INR sometime associated with bleeding.

However, the sponsor proposed the following wording for section 7.1 of the exenatide LAR label: (b) (4) Section 7.2 Warfarin contains text similar to that in the exenatide label with the addition, *BYDUREON has not be studied with warfarin.*

As discussed with clinical pharmacology, although the magnitude of the reduction on the rate of absorption of concomitant oral acetaminophen was less than exenatide, there was 16% decrease under fasting and 5% under fed state in the Cmax of acetaminophen. Thus, the proposed wording for section 7.1 should be revised to more accurately reflect the results of the acetaminophen study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to section 7.3.4 Significant Adverse Events for a discussion of the risk of thyroid tumors in humans.
No trend towards an increased risk of malignancy was identified by my review of exenatide LAR studies.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to section 8 of the exenatide label for information on its use during pregnancy and in nursing mothers.

In most clinical studies of exenatide LAR, pregnancy or lactation were exclusion criteria and pregnancy during the study was cause for withdrawal. As of March 31, 2009, 2 pregnancies have been reported in 2 exenatide LAR studies. One pregnancy occurred in a healthy volunteer reportedly using double barrier contraceptive method in study BCB107. The subject was discontinued from the study and had a therapeutic/induced abortion at approximately 5 weeks gestation. Another pregnancy was reported in a subject with T2DM in study GWBR which led to withdrawal. At the time of the initial report on September 7, 2008, the pregnancy was without complication. Although additional information was requested, no new information was obtained as of the four month safety update cutoff of March 31,2009.

7.6.3 Pediatrics and Assessment of Effects on Growth

Exenatide LAR has not been studied in pediatric subjects. However, the pediatric program for exenatide BID (NDA 21-773) is currently ongoing. Protocol 2993-124 is a complete clinical PK/PD study in T2DM adolescents; the final report was submitted September 27, 2007. Protocol H8O-MC-GWBQ (GWBQ) is an ongoing long-term safety and efficacy study in T2DM adolescents; the final report will be submitted on or before December 31, 2010.

NOTE: [redacted] (b) (4)

On February 3, 2010, the sponsor revised its pediatric plan. The sponsor now seeks a waiver of exenatide LAR studies in pediatric T2DM subjects aged 0-9 years because the pathogenesis of T2DM is such that it rarely occurs in patients < 10 years of age. I agree with this waiver for the reason provided and the fact that it is consistent with our approach to exenatide NDA 21-773.

The sponsor also now requests a deferral from conducting studies in pediatric T2DM subjects (ages 10-17 years). The sponsor proposes protocol submission [redacted] (b) (4) after approval of NDA 22-200 with study start [redacted] (b) (4) after the protocol is agreed to with the agency and final report submission [redacted] (b) (4) after study start. The sponsor anticipates the pediatric safety and efficacy study with 2mg exenatide LAR will be [redacted] (b) (4)

The pediatric plan for liraglutide, another GLP-1 agonist, was recently deferred in ages 10- 16 (inclusive). I recommend deferring studies in T2DM subjects ages 10-16 years 11 months for the following reasons:

- It is consistent with most other T2DM drug development programs.

- 17 years is closer to the adult range. Without prespecified limits on the number of 17 year old subjects included, less information would be gathered on the effects on puberty, linear growth, and other relevant topics.

I also recommend that the safety and efficacy study in adolescents not be initiated until at least 1 month after the completed study report for the rodent study to determine if exenatide LAR-induced c-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation has been submitted.

The sponsor's proposed pediatric waiver and deferral plans were discussed with the Pediatric Research Committee (PeRC) on February 17, 2010. PeRC concurred with my recommendations to 1) include T2DM subjects ages 10-16 years 11 months in the pediatric safety and efficacy study and 2) defer initiation of that study until after completion of the nonclinical study described. In addition, PeRC recommended the sponsor conduct a PK study in the same population and submit the protocol(s) for these studies with the NDA with a clear timeline (i.e. dates) for completion. I concur with PeRC's two additional recommendations. As discussed with clinical pharmacology, due to the long half-life of exenatide LAR, a single dose PK study would yield little useful information. Clinical pharmacology and I may accept a PK substudy which investigates multiple exenatide LAR doses (e.g. 0.8 and 2 mg) in the proposed safety and efficacy study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no significant SAEs following the 10 mg dose in the phase 1 single dose study of exenatide LAR. There were no overdoses in the completed studies submitted to the NDA. Exenatide LAR will be supplied in single-dose vials, which minimize the potential for overdose.

No animal or human studies have been conducted to assess the dependence potential of exenatide LAR. However, it may be used off-label as a weight loss drug due to its weight loss effect.

In single-dose study 103, mean plasma exenatide concentrations generally returned to preinjection values after approximately 10 weeks. In study 104, subjects received multiple exenatide LAR injections over 15 weeks followed by a 12-week follow up period. Approximately 7 weeks after the last injection of exenatide LAR, mean plasma exenatide concentrations were below the anticipated therapeutic threshold (<50 pg/mL). Mean plasma exenatide concentrations approached the lower limit of quantitation (LLOQ; 10 pg/mL) by 10 weeks after the last injection. No safety issues or evidence of rebound were noted upon withdrawal of exenatide LAR during the 12-week follow-up period although a loss of glycemic control occurred in most subjects as exenatide concentrations returned to baseline.

7.7 Additional Submissions / Safety Issues

The December 22, 2009 DSI review of Dr. Klein's site indicates that some subjects experienced difficulty with administration of study products, both test article and comparator. During the study, the sponsor established a call center to handle product complaints. The complaints documented at the Klein site involved the following subject concerns:

- Priming of the comparator exenatide BID pens, not exenatide LAR
- Clogging of needles: One nurse at the site attributed this to a delay in injection after preparing exenatide LAR for injection; another felt the problem varied from box to box or could be attributed to changes in a subject's technique. The issue seemed to be worse early in the study. Subject 10829 reported needle clogging on 3 occasions.
- Leaking pens: This may have varied from lot to lot. Subject 10827 reported a leaking pen on 2 occasions.

These issues were discussed with DSI and CMC. At this time, I do not believe there is a clinically significant problem with the administration of exenatide LAR for the following reasons:

- DSI's Dr. Susan Leibenhaut described the problems as "not widespread".
- Clinical pharmacology concluded the to-be-marketed product is acceptable.
- The sponsor performed an in-use study to determine the maximum wait time between preparing the suspension and injecting. No problems were reported when the wait time was < 15 minutes. The proposed label recommends administration immediately after suspension.
- Bydureon will be marketed as a single dose kit containing an exenatide vial, syringe with diluent, vial connector, and 2 needles (including 1 spare), which will further lessen administration variability.

8 Postmarket Experience

Exenatide LAR is [redacted] (b) (4).

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to the following sections for my proposed changes and the rationale underlying those changes.

- 4.3 Preclinical Pharmacology/Toxicology
- 4.4.3 Pharmacokinetics
- 7.3.4 Significant Adverse Events
- 7.4.5 Special Safety Studies/Clinical Trials
- 7.5.4 Drug-Disease Interactions
- 7.5.5 Drug-Drug Interactions

9.3 Advisory Committee Meeting

Not applicable.

9.4 Exenatide Cardiovascular Safety Submission

NDAs under review must meet the cardiovascular (CV) safety standards recommended in the December 2008 final diabetes cardiovascular guidance. As exenatide LAR is bridging to exenatide NDA 21-773, it was decided that a meta-analysis of the cardiovascular events in exenatide (Byetta) studies was acceptable for review.

Amylin submitted a meta-analysis of exenatide studies with the goal of assessing the relative cardiovascular risk of exenatide, to comply with the CV guidance. Because it was submitted with NDA 22-200 and because the analysis also contains studies of exenatide LAR, it will be reviewed here. The post-approval requirement for exenatide, or for exenatide and exenatide LAR combined, is 1.3.

The sponsor submitted an exenatide cardiovascular risk meta-analysis with the exenatide LAR NDA. The assessment of risk relied primarily on the existing data from long-term (12-52 week), randomized controlled clinical trials of exenatide (Byetta). A separate analysis of 30 week, exenatide LAR study 105 comparing the CV events in the exenatide LAR and exenatide arms was also submitted. This meta-analysis used the following broad and narrow search criteria:

- Primary major adverse CV events (MACE): A team of Amylin and Eli Lilly physicians independently reviewed the list of preferred terms (PTs) prior to the analysis to focus on terms that would most likely represent CV mortality, myocardial infarction (MI), stroke, acute coronary syndrome (ACS), and revascularization procedures. In addition, all subjects who died were examined to ascertain if the underlying cause was CV-related.
- Secondary MACE: Included all of the primary MACE terms plus terms for arrhythmia, heart failure, and mechanical-related events.

As it was felt that the secondary MACE search criteria were too broad and the primary MACE criteria were discordant with the preferred terms provided to the sponsors of alogliptin, saxagliptin, and liraglutide which performed similar meta-analyses for NDA review, the sponsor was asked to reanalyze the MACE events using the same PTs as the other 3 sponsors. This included both 1) "SMQ major adverse cardiovascular analysis (MACE) analysis" which was the composite endpoint of cardiovascular death and all preferred terms in the standardized MedDRA queries for "myocardial infarction" and "central nervous system haemorrhages and cerebrovascular accidents" and 2) "custom MACE" which was the composite endpoint of cardiovascular death and 34 MedDRA preferred terms.

The "custom MACE" was created as follows. Without considering which events had actually occurred, a panel of 3 FDA clinical reviewers independently reviewed the list of all PTs included in the "SMQ MACE" with the following question in mind, "If I had a patient who actually had a MI or stroke, is this a preferred term that I might actually have chosen for such an event?" The goal was to select only those PTs that seemed highly likely to represent true events of MI or stroke with a mechanism of atherosclerotic plaque development followed by plaque rupture or thrombosis. The lists generated by the 3 clinical reviewers were compared and any PTs for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached regarding inclusion or exclusion for all PTs. The complete list of "custom MACE" PTs is included in the agency's October 17, 2009 information request letter. The sponsor was asked to analyze these PTs in the following:

- The 12 long-term, randomized, controlled clinical trials of exenatide that were originally included in the NDA submission
- The 5 long-term, uncontrolled trials of exenatide that were originally included in the NDA submission (2993-112E, -113E, -115E, -117, and -119)
- Exenatide LAR studies 2993LAR-105 and -104

Table 45. NDA 22-200: Summary of controlled studies of exenatide included in the CV meta-analysis

Study	Concomitant OAD	Duration (Weeks) [1]	Exenatide [2] Subjects (N)	Exenatide [2] Exposure (SY)	Comparator Subjects (N)	Comparator Exposure (SY)
Placebo-Controlled Studies						
2993-112	Met	30 Weeks	223	113.8	113	57.8
2993-113	SU	30 Weeks	254	123.2	123	55.1
2993-115	Met+SU	30 Weeks	486	254.9	247	122.2
H8O-MC-GWAP	TZD or TZD+Met	16 Weeks	121	31.7	112	32.3
H8O-MC-GWAV	SU or Met+SU	12 Weeks	111	23.9	40	9.2
H8O-MC-GWBA	Met or Met+SU	16 Weeks	234	65.5	233	67.3
H8O-MC-GWBJ	None (D+E Only)	24 Weeks	155	65.2	77	33.1
H8O-MC-GWCD	Met and/or TZD	12 Weeks	28	5.8	26	5.7
Active Comparator (Insulin)-Controlled Studies						
H8O-MC-GWAA	Met+SU	26 Weeks	282	122.5	267	124.6
H8O-MC-GWAD	Met+SU	52 Weeks	253	220.1	248	228.6
H8O-MC-GWAK	SU or Meg and/or Met	16 Weeks	33	7.7	16	5.2
H8O-MC-GWAO	Met or SU	16 Weeks [3]	136	37.3	127	38.9
Totals	—	—	**2316**	**1071.6**	**1629**	**779.9**
Placebo-Controlled	—	—	1612	683.9	971	382.7
Active-Controlled	—	—	704	387.6	658	397.2

NOTE: Reproduced from the sponsor's original CV risk meta-analysis Table 2

Table 46. NDA 22-200: Long term uncontrolled clinical trials of exenatide

Study	Description	Subjects (N)
2993-112E	Open-label extension of Study 2993-112	225
2993-113E	Open-label extension of Study 2993-113	223
2993-115E	Open-label extension of Study 2993-115	526
2993-117	Open-label safety and efficacy study (with metformin and/or SU)	155
2993-119	Open-label extension from Studies 2993-107, -108, -116, -112E, -113E, and -115E	454
	Total Number of Unique Subjects	**1271**

NOTE: Reproduced from the original CV risk meta-analysis Table 3

On November 19, 2009, the sponsor submitted the major adverse cardiovascular event (MACE) information, that was requested and is reviewed below. The incidence of CV endpoints was assessed in exenatide LAR studies 104 (placebo comparator) and 105 (exenatide comparator), as requested, and recently completed study BCB106 (sitagliptin and pioglitazone comparators). Please also refer to statistician Dr. Fiona Callaghan's review of the meta-analysis.

The demographic and baseline characteristics of subjects included in studies in the exenatide CV meta-analysis were generally adequate, although they had low baseline CV risk, a relatively short duration of diabetes, and no substantial renal impairment.

Table 47. NDA 22-200: Comparison of SMQ and Custom MACE terms (ITT, n=3945)

System organ class/Preferred term	All Controlled Trials Pooled		Custom MACE	SMQ MACE
	Ex (n=2316)	P-C (n=1629)		
Cardiac disorders				
Acute coronary syndrome	0	1 (<0.1)		X
Acute myocardial infarction	1 (<0.1)	1 (<0.1)	X	X
Atrial fibrillation	1 (<0.1)	0	X	X
Myocardial infarction	4 (0.2)	3 (0.2)	X	X
Silent myocardial infarction	1 (<0.1)	0	X	X
Investigations				
Blood creatinine phosphokin inc	29 (1.3)	13 (0.8)		X
Blood creatinine phosphokin MB inc	2 (0.1)	0		X
Scan myocardial perfusion abnormal	0	1 (<0.1)		X
Nervous system disorders				
Carotid arteriosclerosis	0	1 (<0.1)		X
Cerebral infarction	0	2 (0.1)	X	X
Cerebrovascular accident	1 (<0.1)	1 (<0.1)	X	X
Dysarthria	2 (0.1)	0		X
Lacunar infarction	1 (<0.1)	0	X	X
Transient ischemic attack	1 (<0.1)	1 (<0.1)		X
Custom total	9 (0.4)	7 (0.4)	X	
SMQ total	**43 (1.9)**	**24 (1.5)**	**X**	**X**

Source: November 19, 2009 MACE analysis Table 1

Table 48. NDA 22-200: Risk of cardiovascular endpoints for exenatide relative to pooled comparators

	SMQ MACE Endpoint		Custom MACE Endpoint	
	EX (N = 2316)	P-C (N = 1629)	EX (N = 2316)	P-C (N = 1629)
Primary Analyses				
Incidence (n)	41	24	9	7
Incidence (n/N)	0.018	0.015	0.004	0.004
RR (95%CI)	0.92 (0.56, 1.51)		0.88 (0.33, 2.31)	
Sensitivity Analysis				
Pooled RR (95%CI)	1.20 (0.73, 1.98)		0.90 (0.34, 2.42)	
Shuster's RR (95%CI)	1.00 (0.50, 2.03)		0.92 (0.46, 1.84)	
Hazard Ratio				
Cox HR (95%CI)	0.95 (0.57, 1.58)		0.86 (0.32, 2.35)	
Andersen-Gill HR (95% CI)	0.90 (0.55, 1.48)		0.86 (0.32, 2.35)	
Secondary Analyses				
EAIR (per 1000 years)	38.7 (27.8, 52.6)	31.0 (19.9, 46.2)	8.4 (3.9, 16.0)	9.0 (3.6, 18.5)
RR (95% CI)	1.25 (0.75, 2.07)		0.94 (0.35, 2.51)	
Event Rate (per 1000 years)	40.1 (29.0, 54.1)	32.1 (20.7, 47.3)	8.4 (3.8, 15.9)	9.0 (3.6, 18.5)
RR (95% CI)	1.25 (0.77, 2.05)		0.94 (0.35, 2.51)	

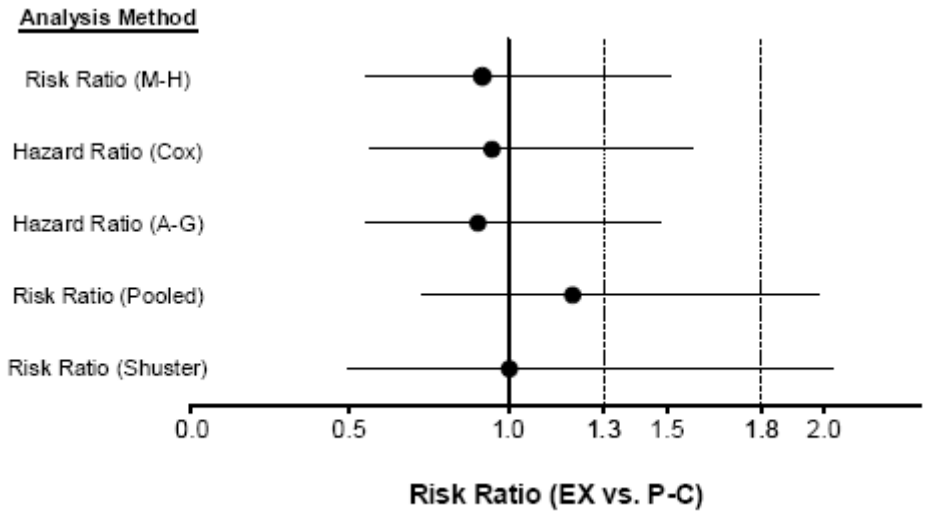
CI = confidence interval; EAIR = exposure-adjusted incidence rate; EX = exenatide; HR = hazard ratio; MACE = major adverse cardiovascular events; P-C = pooled comparator; RR = risk ratio ; SMQ = standardized MedDRA query.

Notes: RR for the incidence was calculated using the Mantel-Hanszel estimate with study as a stratification factor.
- Sensitivity analyses included the pooled RR without stratification by study, and Shuster's method, which weights all trials equally.
- HRs and 95% CIs were obtained from the Cox proportional hazard regression model and the Andersen-Gill model, with adjustment for study.
- EAIR and event rate were calculated based on the Exact method, with corresponding RR calculated using the log-normal approximation.

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis Table 2

The relative risk (RR) point estimate for SMQ MACE based on incidence was 0.92 with a 95% CI of 0.56 to 1.51 (exenatide n=41; pooled comparators n=24). These results were generally consistent with the hazard ratio and secondary analyses. Due to the small number of events observed within each study, the 95% CI for the RR for each study were generally wide. Study 2993-113 had the greatest RR (3.6); most of the subjects with events in this study experienced a nonspecific elevation in blood CPK or CPK-MB (exenatide 12 of 15; placebo 1 of 2).

Figure 7. NDA 22-200: Forest plot of relative risk and 95% CI of SMQ MACE by analysis method



A-G = Andersen-Gill; EX = exenatide; M-H = Mantel-Haenszel; P-C = pooled comparator; RR = risk ratio; SMQ = standardized MedDRA query.

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis Figure 1

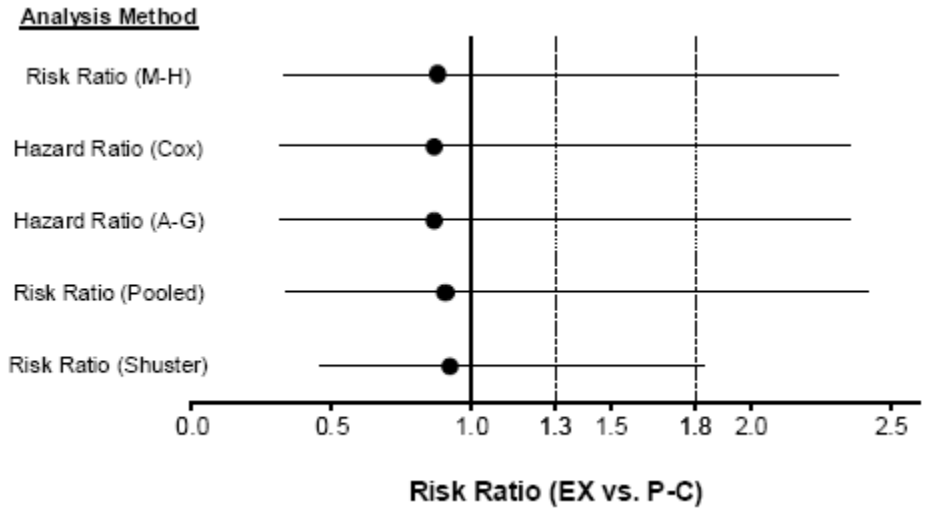
Table 49. NDA 22-200: SMQ MACE analysis by study (ITT)

		Exenatide Event		Insulin Event		Placebo Event		
	Study	Yes	No	Yes	No	Yes	No	Relative Risk (95% CI)
Long-Term Placebo-Controlled	2993-112	6	217			6	107	0.507 (0.167, 1.536)
	2993-113	15	239			2	121	3.632 (0.844, 15.633)
	2993-115	13	473			11	236	0.601 (0.273, 1.321)
	H8OJE-GWAV	3	108			1	39	1.081 (0.116, 10.096)
	H8OMC-GWAP	0	121			0	112	0.926 (0.019, 46.294)
	H8OMC-GWBA	1	233			2	231	0.498 (0.045, 5.453)
	H8OMC-GWBJ	0	155			0	77	0.500 (0.010, 24.964)
	H8OMC-GWCD	0	28			0	26	0.931 (0.019, 45.301)
Long-Term Active Comparator-Controlled	H8OMC-GWAA	0	282	0	267			0.947 (0.019, 47.559)
	H8OMC-GWAD	3	250	2	246			1.470 (0.248, 8.725)
	H8OMC-GWAK	0	33	0	16			0.500 (0.010, 24.128)
	H8OMC-GWAO	0	136	0	127			0.934 (0.019, 46.742)

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis SDS 6.1

The relative risk (RR) point estimate for custom MACE based on incidence was 0.88 with a 95% CI of 0.33 to 2.51. These results were generally consistent with the hazard ratio and secondary analyses. However, the small number of events (exenatide n=9; pooled comparators n=7) likely contributed to the broad confidence intervals. The confidence intervals were broader still when custom MACE was analyzed by study, again due the small number of events.

Figure 8. NDA 22-200. Forest plot of relative risk and 95% CI of custom MACE by analysis method



A-G = Andersen-Gill; EX = exenatide; M-H = Mantel-Haenszel; P-C = pooled comparator; RR = risk ratio.

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis Figure 3

Table 50. NDA 22-200: Custom MACE analysis by study (ITT)

		Exenatide Event		Insulin Event		Placebo Event		
	Study	Yes	No	Yes	No	Yes	No	Relative Risk (95% CI)
Long-Term Placebo-Controlled	2993-112	0	223			0	113	0.509 (0.010, 25.484)
	2993-113	2	252			1	122	0.969 (0.089, 10.578)
	2993-115	3	483			3	244	0.508 (0.103, 2.500)
	H8OJE-GWAV	0	111			0	40	0.366 (0.007, 18.151)
	H8OMC-GWAP	0	121			0	112	0.926 (0.019, 46.294)
	H8OMC-GWBA	1	233			2	231	0.498 (0.045, 5.453)
	H8OMC-GWBJ	0	155			0	77	0.500 (0.010, 24.964)
	H8OMC-GWCD	0	28			0	26	0.931 (0.019, 45.301)
Long-Term Active Comparator-Controlled	H8OMC-GWAA	0	282	0	267			0.947 (0.019, 47.559)
	H8OMC-GWAD	3	250	1	247			2.941 (0.308, 28.081)
	H8OMC-GWAK	0	33	0	16			0.500 (0.010, 24.128)
	H8OMC-GWAO	0	136	0	127			0.934 (0.019, 46.742)

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis SDS 6.2

The sponsor also analyzed MACE events by treatment in exenatide LAR studies 105 and BCB106 (30 and 26 week assessments, respectively). The incidence of events was similar in the exenatide LAR and comparator groups, although the small number of subjects experiencing events limits the conclusions that can be drawn from these analyses.

Table 51. NDA 22-200: Incidence of CV events in exenatide LAR studies 105 and BCB106 (ITT population n=293)

	Study 2993LAR-105		Study BCB106		
	EQW (N = 148)	BYETTA (N = 145)	EQW (N = 160)	Sitagliptin (N = 166)	Pioglitazone (N = 165)
Endpoint	n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events
SMQ MACE	2 (1.4%) 2	2 (1.4%) 4	2 (1.3%) 2	2 (1.2%) 2	4 (2.4%) 4
Custom MACE	1 (0.7%) 1	1 (0.7%) 1	0	1 (0.6%) 1	1 (0.6%) 1

CV = cardiovascular; EQW = exenatide once weekly; MACE = major adverse cardiovascular events; SMQ = standardized MedDRA query.

NOTE: Reproduced from the November 19, 2009 CV risk meta-analysis Table 4

In conclusion, the 95% CI for the estimated risk ratio of the SMQ MACE was 0.56, 1.51. The 95% CI for the custom MACE was broader (0.33, 2.51), although this analysis was based on only 16 events. Similarly, the CIs were generally broad when events were analyzed by exenatide and exenatide LAR studies. **As exenatide LAR is not a new molecular entity but a reformulation of exenatide which has been on the market since April 2005 without a signal for increased cardiovascular risk, the overall CV risk-benefit analysis supports approval. However, a postmarketing trial of exenatide and/or exenatide LAR is necessary to definitively show that the upper bound of the two-sided 95% CI for the estimated risk ratio is less than 1.3.**

A long term CV trial of exenatide LAR (or exenatide bid and exenatide LAR combined) will provide the opportunity to gather limited additional safety data on the exenatide LAR-associated risks of neoplasms and injection site reactions as well as exenatide-associated risks of hypoglycemia, pancreatitis, and hypersensitivity.

On October 30, 2009, the sponsor submitted a draft protocol BCB109, "A randomized, placebo controlled clinical trial to evaluate CV outcomes after treatment with exenatide once weekly in patients with T2DM". Trial results from this or a CV outcomes trial with exenatide should be submitted to both exenatide and exenatide LAR NDAs (21-773 and 22-200, respectively).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	EXENATIDE LAR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S PRATT
02/22/2010

ILAN IRONY
02/22/2010
I concur with Dr. Pratt's review and recommendations for regulatory action.