

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022200Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Promotion (DPP)
Division of Direct-to-Consumer Promotion (DDTCP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 4, 2012

To: Pooja Dharia, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DPP
Kendra Y. Jones, Regulatory Review Officer, DDTCP

CC: Lisa Hubbard, Group Leader, DPP
Shefali Doshi, Group Leader, DDTCP

Subject: NDA #022200 Bydureon (exenatide extended-release for injectable suspension) Labeling Review

OPDP has reviewed the proposed package insert (PI), carton/container labeling, medication guide (Med Guide), and instructions for use (IFU) for Bydureon originally consulted from DMEP to OPDP on August 10, 2011.

Comments regarding the PI, Med Guide, and IFU are provided in the marked versions below.

OPDP has reviewed the following draft carton and container labeling submitted on May 4, 2009. We note that the draft carton, single-dose kit lid label, draft carton-professional sample, and draft single-dose kit lid label – professional sample presents the claim (b) (4) in conjunction with the proposed tradename “BYDUREON.” This claim is considered promotional and we recommend deleting this claim.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI or carton/container labeling please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the Med Guide or IFU please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

For Note to FDA Reviewer:

- Agency content changes that Amylin concurs with have been accepted in the text and are not marked.
- A text box has been inserted prior to sections with Agency comments/changes for which Amylin has questions or alternative suggestions.
- Newly proposed content from Amylin shows as tracked content.

60 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAMUEL M SKARIAH
01/04/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **December 21, 2011**

To: Mary Parks, MD, Director
**Division of Metabolic and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling (Medication Guide and
Instructions for Use)

Drug Name (established name): BYDUREON (exenatide)

Dosage Form and Route: Extended-Release For Injectable Suspension

Application Type/Number: NDA 22-200

Applicant: **Amylin Pharmaceuticals Inc.**

OSE RCM #: 2011-2836

1 INTRODUCTION

On July 27, 2011 Amlyin Pharmaceuticals Inc. resubmitted a New Drug Application (NDA 22200) for BYDUREON (exenatide extended-release for injectable suspension) in response to a March 23, 2010, Complete Response (CR) issued by the FDA. BYDUREON is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BYDUREON (exenatide extended-release for injectable suspension).

DMPP conferred with DMEPA and a separate DMEPA review of the IFU was completed on October 26, 2011.

The REMS was reviewed by DRISK on December 06, 2011 and was provided to DMEP under separate cover.

2 MATERIAL REVIEWED

- Draft BYDUREON (exenatide extended-release for injectable suspension) Medication Guide (MG) and Instructions for Use (IFU) received on July 27, 2011 and received by DMPP on December 14, 2011.
- Draft BYDUREON (exenatide extended-release for injectable suspension) Prescribing Information (PI) received July 27, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on December 14, 2011.
- Approved VICTOZA (liraglutide [rDNA origin] injection) comparator labeling dated May 18, 2011.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible.
- ensured that the MG and IFU is consistent with the prescribing information (PI).
- removed unnecessary or redundant information.
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20 .

- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/21/2011

MELISSA I HULETT
12/21/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 8, 2011

To: Mary Parks, M.D., Director, Division of Metabolism and Endocrinology Products, OND

Thru: Solomon Iyasu, M.D., M.P.H., Director, Division of Epidemiology 1, OSE

From: Diane K. Wysowski, M.P.H., Ph.D., Epidemiology Team Leader, Division of Epidemiology 1, OSE

Subject: Review of protocol for a case-series registry of medullary thyroid cancer (MTC) for exenatide once weekly and discussion regarding other PMR studies

Drug Name(s): Exenatide extended release injection (Bydureon)

Submission Number:

Application Type/Number: NDA 22-200, IND 67,092

Applicant/sponsor: Amylin Pharmaceuticals

OSE RCM #: 2011-2838, TSI 894

CONTENTS

| | |
|--------------------------------------------------------------------------|----|
| EXECUTIVE SUMMARY | 3 |
| 1 BACKGROUND | 4 |
| 2 MATERIALS REVIEWED..... | 5 |
| 3 RESULTS..... | 5 |
| 3.1 Description of MTC registry..... | 5 |
| 3.2 Critique of MTC registry..... | 7 |
| 3.3 Rationale for Other PMR Studies..... | 9 |
| 4 RECOMMENDATIONS re: MTC Registry and Discussion of Other PMR Studies.. | 11 |
| 5 SUMMARY | 13 |
| 6 REFERENCES..... | 14 |

EXECUTIVE SUMMARY

Exenatide extended release (Bydureon) is an injectable glucagon-like peptide-1 (GLP-1) receptor agonist that is being considered for approval as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Two other injectable GLP-1 receptor agonists have been approved by the FDA for treatment of type 2 diabetes mellitus, liraglutide (Victoza) approved in January 2010 and exenatide (Byetta) marketed since May 2005.

Concern exists about a potential safety problem of drugs in the GLP-1 class because of an increase in C-cell tumors of the thyroid gland found in rats during the preclinical phases of liraglutide and exenatide extended release testing. As a result, the FDA has required that the sponsors of drugs in the GLP-1 class conduct postmarketing studies to determine if exposed patients have increased frequencies of medullary thyroid cancer (MTC).

Novo Nordisk, the sponsor of liraglutide, (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] Protocols set up by Novo Nordisk and by Amylin, the sponsor of Bydureon, have been reviewed by DEPI 1 staff. A number of limitations, including participation of state cancer registries (the source of the MTC cases), participation of diagnosed MTC patients (to be interviewed for information on diabetes and antidiabetic drugs), participation of physicians (to provide patient data and verification) have been discussed in DEPI's previous reviews. In addition, previous reviews and an FDA teleconference with Amylin held in May, 2010, emphasized the need for sponsors of GLP-1 drugs to collaborate on establishing and implementing the MTC registry and on sharing data from it.

(b) (4)

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Diane K. Wysowski, Ph.D.

cc: GreenL/PhamQ/DPV1/OSE

EganA/BishaiJ/PrattV/JoffeH/IronyI/DhariaP/MarchickJ/ParksM/DMEP/OND
TossaM/WysowskiD/HamppC/IyasuS/DEPI1/OSE

6 REFERENCES

1. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic and thyroid cancer with glucagon-like peptide-1 based therapies. *Gastroenterol* 2011;141:150-156.
2. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 365;21:2002-2012.
3. Gilsean AW, Harris D, Midkiff KD, Wright J, Andrews EB. Linking with multiple state cancer registries for safety surveillance—Is it feasible? (abstract). *Pharmacoepidemiol Drug Saf* 2011;20: S167.
4. Gilsean AW, Harris D, Midkiff KD, Wright J, Andrews EB. Linking with multiple state cancer registries for safety surveillance—Is it feasible? Poster presented at the 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, August 14-17, 2011.
5. Midkiff KD, Harris D, Gilsean A, Wu Y, Andrews EB. Drug safety studies using cancer registry data: Confluence of elements impacting the interview response rate. Poster presented at the 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, August 14-17, 2011.

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/s/

DIANE K WYSOWSKI
12/08/2011

SOLOMON IYASU
12/08/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 5, 2011

TO: Pooja Dharia, Regulatory Project Manager
Valerie Pratt, Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22200

APPLICANT: Amylin Pharmaceuticals, Inc.

DRUG: Bydureon (exenatide once weekly)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults
with type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: August 12, 2011

DIVISION ACTION GOAL DATE: December 12, 2011

PDUFA DATE: January 28, 2012

I. BACKGROUND:

Amylin Pharmaceuticals resubmitted NDA 22-200 for exenatide once weekly, a human Glucagon-Like Peptide-1 (GLP-1) analog, for the indication as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. For the original application, two clinical investigators were inspected, and there were no significant violations concerning data integrity. On March 12, 2010, the FDA issued a complete response because of manufacturing and product quality issues. For the resubmission, the sponsor conducted an additional clinical trial, Study BCB108, using the to-be-marketed formulation. Clinical inspections were conducted of Study BCB108 in order to assess data integrity and human subject protection. The efficacy results of the study are important in making a regulatory decision with regard to drug approval.

The protocol inspected was Protocol BCB108 entitled “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 Type 2 Diabetes Mellitus.” The study was conducted in the US from March 2009 to October 2009 and enrolled 254 subjects. The primary efficacy endpoint was Hemoglobin A1C (HbA1C) change from baseline to Week 24.

Three clinical investigator sites were inspected in support of this application. The choice of sites was based on site enrollment and numbers of INDs in the DSI database. In addition, because OSI received a complaint from other sources regarding the Dr. Altamirano site at the same time that this inspection assignment was issued, the complaint allegations were also evaluated during the inspection of Dr. Altamirano’s site.

II. RESULTS (by Site):

| Name of Clinical Investigator (CI) | Protocol #/ # Subjects Randomized | Inspection Date | Final Classification |
|---------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------|----------------------------------------------------|
| Dario Altamirano AGA Clinical Trial 900 W. 49 St, Suite 224 Hialeah, FL 33012 | Protocol BCB108/ 22 Subjects | October 17 to November 3, 2011 | Pending (Preliminary classification OAI*) |
| Ernesto Fuentes Elite Research Institute 15705 NW 13 Ave Miami, FL 33169 | Protocol BCB108/ 17 Subjects | November 9 to 28, 2011 | Pending (Preliminary classification VAI) |
| Douglas Denham (Jolene Berg) DGD Research, Inc. 803 Castroville Rd San Antonio, TX 78237 | Protocol BCB108/ 14 Subjects | September 13 to 16, 2011 | NAI |

*Note: In addition to the verification of data for Protocol BCB108, the inspection of Dr. Altamirano site included two ongoing protocols that had been discontinued by sponsors for

GCP violations. The preliminary OAI classification is based on the findings related to inspection of these other protocols, as there were safety issues noted, and Dr. Altamirano's response to the inspectional findings was considered inadequate.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Dr. Dario Altamirano (as pertains specifically to this application related study, Protocol BCB108)**

AGA Clinical Trial, 900 W. 49 St, Suite 224, Hialeah, FL 33012

Note: Observations noted for this site are based on communications with the FDA investigator, review of the Form FDA 483, and Dr. Altamirano's written response to the Form FDA 483 findings. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol BCB108 at this site, 26 subjects were screened and four subjects were considered screen failures. Four (4) subjects withdrew consent, four (4) were considered lost to follow-up, and 17 subjects completed the study. An audit of 17 subjects' records was conducted. During the inspection the following areas were covered: protocol compliance, test article accountability and storage, informed consent process, data accuracy, and site training and monitoring.
- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under reporting of adverse events. Subject 131005 who was initially deemed as a screen failure was authorized by the sponsor to be re-screened as Subject 131027. Only one serious adverse event was reported by this site. Subject 131019 was hospitalized due to an acute cholecystitis. The AE was assessed as not related to the study drug. A Form FDA 483 was issued for protocol violations and Dr. Altamirano responded adequately in a letter dated November 21, 2011. For the observations below he promised corrective action in the form of revised SOPs or further explained the nature of the violation. The following are the items cited that are pertinent to Protocol BCB108:
 1. Failure to maintain adequate records: Per protocol, each subject enrolled/randomized into the study should have been treated with diet and exercise alone or in combination with a stable regime of anti-diabetic drug and/or combination of drug therapies for two months prior to screening. Complete and accurate documentation to verify time on anti-diabetic drug therapy/combination therapies was not available. It was the stated practice of the site to photocopy the labels of the medication bottles to document the

medication taken by a potential subject. In many instances the date of the prescription was not captured on the photocopy.

- i. For some subjects photocopies of oral medication bottles were obtained. However, the referenced photocopies do not show when the medication was dispensed making impossible to verify dosing and length of time subject had been taken the medication. Some examples are: Subjects 131-003, 006, 007, 012, 015, 021, 022, and 023.
- ii. For some subjects photocopies of oral medication bottle labels were not obtained. There are notes indicating subjects did not bring the oral medication bottles at V1 (Screening 0) and at V2 (Randomization) visits. Therefore, verification of length of time subject had been taken the oral anti-diabetic therapy/therapies can not be verified. Some examples are: Subjects 131-001, 002, 013, 009, 011, 008, 025, 026.

Reviewer note: This observation concerning the lack of documentation of the duration of stability of disease on prior diabetic therapy was discussed with the review division in e-mails on November 29 and 30, 2011. This finding may be mitigated by the long-term duration (24 weeks) of the study, and is therefore unlikely to significantly impact data reliability as it pertains to this study.

2. Failure to follow the investigational plan:
 - i. As part of the screening procedures the protocol required that a serum pregnancy test be performed for all females unless has had a hysterectomy. Serum pregnancy test was not performed for the following subjects: 131-015, 022, 009, and 016.
 - ii. The following subjects were randomized prior to reviewing laboratory testing results of blood/urine specimens collected at their corresponding screening visits: 131-119, 021, and 025.

Reviewer note: Given the nature of these violations, this finding is unlikely to impact data reliability.

3. Investigational drug records are not adequate with respect to dates and quantity.
 - i. Subject # 131007 was dispensed with the wrong medication Kit#. Per IVRS, subject was to receive Kit # 11305 but instead was dispensed with Kit # 10305.

Reviewer note: Although this was the wrong kit #, the product was the correct one.

- ii. In several instances subjects' drug compliance was erroneously documented on source documents based on quantities of used/ returned study drug that were later found to be incorrect. Some examples are: Subject #s 131-001, 003, 006, 007, 008, 010, 012, 025.

Reviewer note: In his reply, Dr. Altamirano stated that the research coordinator miscalculated drug compliance of returned drug, and that the mistake was noted in monitoring visits and corrected properly based on physical review of investigational product.

- iii. During Visits 2 and 3 the study medication dosing diary was not given

to multiple subjects randomized to Group A. The subjects were instructed to record the dose and time on the assigned medication boxes. The information was later transferred by the site coordinator into the corresponding diaries. The medication boxes containing the dosing information recorded by the subjects were not kept.

Reviewer note: The lack of source documentation is unlikely to impact data reliability because this was an isolated occurrence that occurred for one week early in the study.

In the written response of November 21, 2011, Dr. Altamirano responded adequately concerning the observations related to this protocol and promised to initiate corrective actions.

- c. **Assessment of data integrity:** The violation concerning lack of documentation of duration of stability on current diabetic medication does not appear likely to impact data reliability. The other violations also are not considered to have impacted significantly on the conduct of the study or on data reliability. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Dr. Ernesto Fuentes**

Elite Research Institute, 15705 NW 13 Ave, Miami, FL 33169

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. At the time of this review, Dr. Fuentes has not responded to the inspectional findings that were discussed with him on November 28, 2011. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol BCB108 at this site, 33 subjects were screened, 17 subjects were enrolled, and 12 subjects completed the study. One subject withdrew due to an adverse event. An audit of all 17 enrolled subjects' records, including informed consent, was conducted. During the inspection the following areas were given coverage: protocol compliance, test article accountability and storage, informed consent process, data accuracy, and site training and monitoring.
- b. **General observations/commentary:** The primary efficacy data were verified and there was no evidence of under-reporting of adverse events. In general, records appeared adequate. Protocol deviations were minimal and all were reported appropriately to Sponsor and/or IRB. The study's CRF's and their transcribed e-versions showed minimal errors. A Form FDA 483 was issued for the following violations:
 1. Inadequate records. The CI did not document the stability or duration of the anti-diabetic regime used by potential subjects prior to enrolling in the study.

2. **Inadequate drug accountability.** The CI failed to identify errors in the accountability of study medication. Drug distribution records at the site indicated that a total of 38 pre-filled Exenatide 10mcg injection pens were sent to the site; however, the records maintained at the site listed the receipt of only 37 injection pens. In addition, there were incongruent dates for the receipt of study drug compared with the distribution records. There was no evidence that dispensing of study drug medication was not performed as per protocol, so this finding is unlikely to impact data reliability.

At the time of this review, Dr. Fuentes has not responded to the inspectional findings that were discussed with him on November 28, 2011.

- c. **Assessment of data integrity:** The first violation concerning lack of documentation of the eligibility criteria was discussed with the review division in e-mails on November 29 and 30, 2011, and given the duration of the study, this finding is unlikely to impact data reliability. Except for this deficiency, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **Dr. Jolene Berg (Douglas Denham)**

DGD Research, Inc. 803 Castroville Rd, San Antonio, TX 78237

- a. **What was inspected:** For Protocol BCB108 at this site, a total of 17 subjects were screened, 14 subjects were enrolled into the study. Six subjects completed the study and eight subjects withdrew. An audit of all 14 enrolled subjects' records was conducted. The review included a comparison of source documentation to (CRFs) and data listings submitted to the NDA. Specific records reviewed included, but were not limited to, adverse event reporting; inclusion/exclusion criteria; test article accountability; informed consent form approvals; monitoring records; adherence to protocol-specified procedures.
- b. **General observations/commentary:** The inspection request from the review division listed the original clinical investigator Dr. Douglas Denham. Dr. Denham resigned from this research site and the current medical director is Dr. Jolene Berg who was listed as a sub-investigator on the 1572 and took responsibility for the medical records. Verification of data line listings for efficacy endpoint data was conducted. There was no evidence of under-reporting of adverse events. No violations were cited, and a Form FDA 483 was not issued.

The FDA investigator noted that Subject 156006 reported three subcutaneous nodules at the injection site, each 1 cm in size. These were not reported to the sponsor as adverse events. This is consistent with the protocol that states in Section 10.1.1, "Small, asymptomatic, SC nodule formation at the injection site is an expected event associated with similar PLG sustained-release delivery systems, and is not necessarily an adverse event."

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this NDA. The primary endpoint data were verified at all sites and there was no evidence of underreporting of adverse events. No violations were found on inspection of Dr. Berger (Denham's) site. Inspection of Drs. Altamirano's and Fuentes's sites found violations concerning documentation of the eligibility criterion for duration of stability of diabetes mellitus. This was discussed with the review division in e-mails and seems unlikely to affect data reliability because of the long duration (24 weeks) of the trial. For all the sites inspected, the data is considered reliable and can be used in support of the application.

Note: Observations noted for the 2 sites (Altamirano and Fuentes) are based on communications with the FDA investigator, the response by the clinical investigator (Altamirano), and review of the Form FDA 483. At the time of this review, Dr. Fuentes has not responded to the inspectional findings that were discussed with him on November 28, 2011. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

Based on results of these inspections it appears that data submitted by the Applicant in support of the requested indication should be considered reliable.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
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Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
12/05/2011

TEJASHRI S PUROHIT-SHETH
12/05/2011

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

| | |
|------------------------------------|-----------------------------------------------------|
| IND or NDA | NDA 22200 & IND 67092 |
| Brand Name | Bydureon |
| Generic Name | Exenatide |
| Sponsor | Amylin pharmaceuticals |
| Indication | Treatment of patients with type 2 diabetes mellitus |
| Dosage Form | Subcutaneous injection |
| Drug Class | Glucagon like Peptide-1 agonist |
| Therapeutic Dosing Regimen | 2 mg once weekly (Bydureon: exenatide LAR) |
| Duration of Therapeutic Use | Chronic |
| Maximum Tolerated Dose | Not identified |
| Submission Number and Date | SDN 043 / July 28, 2011 |
| Review Division | DMEP / HFD 510 |

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of exenatide (up to ~500pg/mL) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between exenatide and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcP}$ (population correction) for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, partially blinded, crossover study, 79 healthy subjects received exenatide, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Exenatide (~200pg/mL, ~300pg/mL and ~500pg/mL) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

| Treatment | Time (hour) | $\Delta\Delta\text{QTcP}$ (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 timepoints.

The geometric mean concentration of the suprathreshold target observed on Day 3 in the TQT study is 627 pg/mL, which is adequate to cover the steady state concentration (254 pg/mL) following the therapeutic dose of Bydureon and the expected high clinical exposure scenario in patients with moderate renal impairment.

1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS TO REVIEW DIVISION

Exenatide increases HR. The mean (largest upper bound of the two-sided 90% CI) of the $\Delta\Delta\text{HR}$ was 12.3 (13.5), 14.4 (15.6) and, 15.6 (16.8) bpm for ~200 pg/mL, ~300 pg/mL and ~500 pg/mL, respectively. It is known that an increase in HR could increase myocardial oxygen demand. The implications of an increase of this magnitude in patients with unstable congestive heart failure or ischemia are unclear.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

Sponsor proposes the following text in the label:

[REDACTED] (b) (4)

2.2 QT-IRT PROPOSED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

The effect of exenatide at therapeutic (253 pg/mL) and suprathreshold (627 pg/mL) concentrations following an intravenous infusion on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) three-period cross over thorough QT study in 79 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one side 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on population correction method (QTcP) was below 10 ms, the threshold for regulatory concern. The geometric mean

concentration of the suprathreshold target was 627 pg/mL and is adequate to represent the high exposure clinical scenario. In this study, the baseline corrected mean increase from placebo (90% CI) in heart rate associated with geometric mean exenatide concentrations of 253, 399 and 627 pg/mL was 12.3 (11.2, 13.5), 14.4 (13.2, 15.6) and 15.6 (14.3, 16.8) bpm, respectively.

3 BACKGROUND

3.1 PRODUCT INFORMATION

The sponsor (Amylin Pharmaceuticals) developed two exenatide formulations. Byetta, which was approved in 2004, is the trade name for the immediate-release formulation with twice daily dosing. Bydureon is the trade name for the extended-release formulation with once weekly dosing. This was reviewed by the QT-IRT and we concluded that this study was adequate to exclude small effects on the QT interval for Byetta. However, no definitive conclusion for the effect of Bydureon on QTc interval could be drawn based on the TQT study (H8O-EW-GWCI) since higher exposures expected with Bydureon were not covered in this study and exenatide appeared to increase QTc interval in a concentration-dependent manner.

3.2 MARKET APPROVAL STATUS

Exenatide immediate release formulation (Byetta) is being marketed. An extended-release formulation of exenatide (BYDUREON™ [exenatide extended-release for injectable suspension] has been approved by the European Commission (17 June 2011).

3.3 PRECLINICAL INFORMATION

From the IB (March 2011)

“Cardiovascular pharmacology studies revealed a transient increase in heart rate and blood pressure in rats that was not evident when exenatide was administered to mice, primates, dogs, or calves and was not evident in most clinical studies or was limited to minor heart rate increases of 10 beats per minute or less. In longer term studies, exenatide decreased blood pressure in both rats and humans. There was no effect on QT segment in chronically treated monkeys, and no effect in vitro on hERG channel current. Exenatide neurological safety pharmacology evaluations in mice revealed slight reductions in grip strength and limb tone at doses ≥ 300 mcg/kg and decreased motor activity at doses ≥ 30 mcg/kg. Exenatide exhibits an acute, yet profound diuretic, natriuretic, and calciuretic effect in rats. These renal effects have not been observed clinically.”

From CSR

“An in vitro assessment of the human ether-a-go-go-related gene (hERG) channel found that exenatide demonstrated no blockade (mean current inhibition of $\leq 0.6\%$ for exenatide versus 0.1% for vehicle and 99.4% for positive control) of the IKr channel at $91 \mu\text{M}$ (>1.8 million-fold human maximum exenatide concentration), suggesting that exenatide would not be expected to produce significant risk of QT interval prolongation or proarrhythmia mediated by IKr blockade. These results are consistent with ECG

assessments in repeat-dose toxicology studies in monkeys and both acute and long-term clinical studies that found no evidence of QT prolongation with exenatide treatment.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From Complete Response Safety Update (2011)

“As of the 30 September 2010 cutoff date, approximately 2622 subjects have been exposed to exenatide once weekly in completed and ongoing trials. In the exenatide once weekly clinical development program, the effect of exenatide on electrocardiograms and QT interval was evaluated in subjects with type 2 diabetes within the pivotal, comparator-controlled Study 2993LAR-105.

“ECG recordings were performed in subjects with type 2 diabetes at baseline and again once steady-state plasma exenatide concentrations had been achieved following at least 14 weeks of exenatide once weekly therapy. The study employed key elements of the ICH E14 thorough QT study guidance, including triplicate ECGs at multiple time points and blinded third-party QT analysis/overreads by a certified cardiologist.

“Table 2 provides a summary of ECG parameters for subjects in the ITT Population treated with exenatide once weekly at baseline, Week 14, and Week 30 or Early Termination. Both QTcF (Fridericia’s correction) and QTcB (Bazett’s correction) 19 heart rate corrections were evaluated. QTcF was selected for more detailed analysis as it more completely corrected for the influence of changes in heart rate on the QT interval. The individual-corrected QT (QTcI) could not be derived as the study did not include a crossover placebo treatment or extended baseline ECG readings at multiple heart rates to permit the determination of individualized corrections. No clinically relevant prolongation of the mean QTcB, QTcF, or model-based QTc interval was observed upon exenatide once weekly treatment.”

Table 2: Change in Electrocardiogram Parameters for Baseline to Week 14 or to Week 30 or Early Termination (Study 2993LAR-105; Intent-to-Treat Population Randomized to Exenatide Once Weekly [N = 148])

| Parameter Statistic | Baseline Value [1] | Change from Baseline to Week 14 | Change from Baseline to Week 30 or Early Termination [2] |
|-----------------------------------------|-----------------------|------------------------------------|-------------------------------------------------------------------|
| Heart Rate (bpm) | | | |
| n | 145 | 135 | 82 |
| Mean (SD) | 71.5 (10.7) | 3.6 (8.7) | 3.5 (8.5) |
| Median | 71.7 | 3.3 | 2.9 |
| Minimum, Maximum | 49.7, 100.0 | -15.7, 27.0 | -11.7, 25.0 |
| 90% CI | (70.1, 73.0) | (2.3, 4.8) | (1.9, 5.0) |
| QT (msec) | | | |
| n | 145 | 135 | 82 |
| Mean (SD) | 382.8 (27.1) | -4.9 (18.7) | -3.7 (20.3) |
| Median | 381.3 | -5.3 | -2.0 |
| Minimum, Maximum | 330.0, 480.7 | -49.3, 60.0 | -62.0, 39.3 |
| 90% CI | (379.0, 386.5) | (-7.5, -2.2) | (-7.4, 0.0) |
| QTcF (msec) | | | |
| n | 145 | 135 | 82 |
| Mean (SD) | 403.3 (16.8) | 1.7 (9.7) | 3.0 (11.4) |
| Median | 404.0 | 1.3 | 2.7 |
| Minimum, Maximum | 370.0, 458.0 | -29.3, 30.2 | -21.0, 39.0 |
| 90% CI | (401.0, 405.6) | (0.3, 3.1) | (0.9, 5.1) |
| QTc (model-corrected) (msec) [3] | | | |
| n | 145 | 135 | 82 |
| Mean (SD) | 405.3 (15.9) | 2.2 (9.5) | 3.5 (10.7) |
| Median | 405.1 | 2.0 | 2.3 |
| Minimum, Maximum | 372.6, 456.1 | -31.4, 29.7 | -19.7, 34.9 |
| 90% CI | (403.1, 407.4) | (0.8, 3.5) | (1.5, 5.4) |

bpm = beats per minute; CI = confidence interval; msec = millisecond; QTc = QT corrected; QTcF = QT corrected (Fridericia); SD = standard deviation.

[1] Baseline = Day -7; if unavailable, a value from an earlier visit (the last measurement prior to the first lead-in injection) was used.

[2] 12-Lead ECG data was collected at Week 30 or Early Termination only for subjects who completed visits prior to 02 July 2007.

[3] Model-corrected QT was derived based on a mixed model including RR as a covariate.

Cross-Reference: Serial 0001, Section 5.3.5.1, Study 2993LAR-105, SDS 3.5.2.

Source: eCTD 2.7, clinical summaries, Table 7, page 48.

“The pattern of adverse events leading to withdrawal in exenatide once weekly subjects was generally consistent with that presented in the original NDA submission, with a similar incidence of subjects with withdrawals for events classified as “gastrointestinal disorders” (2.0% current update versus 0.8% original NDA) “investigations” (0.5% versus 0.5%) or “general disorders and administration site condition” (0.7% versus 0.5%). Nausea was the most common reason for discontinuation due to an adverse event; in the completed, comparator-controlled studies; 5 (0.5%) exenatide once weekly, 4 (1.5%) BYETTA, 1 (0.3%) sitagliptin, 1 (0.3%) pioglitazone, 1 (0.4%) insulin glargine

and no metformin subjects discontinued study participation due to adverse events of nausea.

“Twelve deaths have been reported in the exenatide once weekly development program. None of the events were assessed as related to study medication by the investigator. Overall, 7 exenatide once weekly subjects, 2 liraglutide subjects, 1 BYETTA subject, 1 sitagliptin subject, and 1 metformin subject were reported to have died during the exenatide once weekly development program. Four of these events took place at follow up and 1 event took place 10 weeks after discontinuation of study medication.”

Reviewer’s Comments: We reviewed updated cardiovascular safety information for exenatide once weekly (Bydureon). QT interval was evaluated in subjects with type 2 diabetes in pivotal Study 2993LAR-105 where triplicate ECGs were extracted at multiple time points and blinded third-party QT analysis/overreads was performed by a certified cardiologist. No clinically relevant changes on QTc duration were reported after administration of exenatide once weekly in the ITT population.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of exenatide clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 57725. The sponsor submitted the study report BCB112 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

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 Electrocardiogram Qt Interval In Healthy Subjects

4.2.2 Protocol Number

BCB112

4.2.3 Study Dates

21 February 2011 -- 26 April 2011

4.2.4 Objectives

“The primary objective of this study was:

- To determine, in healthy subjects, that exenatide administered at therapeutic and supratherapeutic concentrations does not differ from placebo in the mean change from predose in 12-lead electrocardiogram corrected QT interval measurements

(such that the upper bound of the 1-sided 95% confidence interval between exenatide and placebo is <10 ms)

“The secondary objectives of this study were:

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

4.2.5 Study Description

4.2.5.1 Design

“A randomized, placebo- and positive-controlled, 3-period, crossover design with a double-blind infusion was implemented for this Phase 1, multicenter, thorough QT study to evaluate potential effects of exenatide on QT interval. This study was conducted at 2 study sites in 94 healthy male or female subjects.”

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The treatment sequences are listed in following table

Table 3: Treatment Sequences

| 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 |

Source: sponsor’s report Table 1

4.2.6.2 Sponsor's Justification for Doses

There primary target concentrations were selected to evaluate a relevant range of exenatide concentrations on QTc. Target concentrations of ~200 pg/mL and ~300 pg/mL were selected to approximate the range of exenatide exposure observed in subjects with normal renal function and with mild to moderate renal impairment, respectively. The suprathreshold concentration of ~500 pg/mL was selected to reflect concentrations significantly higher than those observed in subjects with moderate renal impairment. This upper target was selected to strike a balance between achieving the highest concentrations that could be observed with exenatide once weekly use and acute tolerability issues that could confound the ability to accurately collect and analyze ECG data.

Reviewer's Comments: The target concentrations were acceptable. The observed suprathreshold geometric mean concentration (627 pg/mL) on Day 3 is adequate to cover the expected high clinical exposure scenario with 2 mg QW Bydureon in patients with moderate renal impairment.

4.2.6.3 Instructions with Regard to Meals

Meals were standardized across infusion days (Day -1 to Day 3). Meals were to be consumed within 30 minutes.

Reviewer's Comments: Acceptable. Exenatide is administered through continuous intravenous infusion.

4.2.6.4 ECG and PK Assessments

Intravenous infusion is initiated at $t = 0$ h (approximately 2000 h) on Day -1 and continues through $t=67$ h on Day 3.

Each ECG assessment period was 5 days in duration (Day -2 to Day 3) with subjects discharged at approximately 1800 h on Day 3. ECGs and blood sample collection for exenatide plasma concentration were performed at same relative time on ECG assessment days, approximately 0900 h to 1500 h on Days -1 through 3. Pre-therapy ECG measurements were extracted at 2100 h on Day -2 and 0715, 0800, 0900, 1000, 1100, 1200, 1300, 1400, 1500, 1615, 1700, 1800, and 1900 h on Day -1.

Reviewer's Comments: The ECG/PK sampling schedule is adequate to cover the steady state PK profile of exenatide and assess drug-induced changes in the QT interval at different target concentrations.

4.2.6.5 Baseline

Time-matched baseline measured at Day -1 within the same treatment period was used as baseline.

4.2.7 ECG Collection

Subjects underwent continuous ECG monitoring using an ECG 12-lead digital Holter recorder. The primary ECG assessment period was approximately 0900 h to 1500 h each day, with 1-h interval time points for extraction (using Lead II) of ECGs for analysis.

The ECGs were electronically transmitted to the designated centralized ECG vendor. The cardiologist responsible for overreading the ECGs was blinded to all study

treatments/sequences. The same cardiologist overread all ECGs for a given subject. The central ECG vendor's overread was used for data analysis and report writing purposes.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Of 94 subjects enrolled in the study, 86 (92%) subjects were randomized to a treatment group and received study medication infusion and were included in the randomized and ITT populations. Demographic and baseline characteristics are summarized by treatment sequence in Table 4.

Table 4: Demographic and Baseline Characteristics by Treatment Sequence (Study BCB112; Evaluable Population [N = 74])

| Baseline Characteristics | Treatment Sequence | | | | | | All Subjects (N = 74) |
|-----------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | PEM (N = 11) n (%) | EMP (N = 12) n (%) | MPE (N = 12) n (%) | MEP (N = 13) n (%) | PME (N = 13) n (%) | EPM (N = 13) n (%) | |
| Gender - n (%) | | | | | | | |
| Male | 11 (100.0) | 10 (83.3) | 9 (75.0) | 13 (100.0) | 12 (92.3) | 12 (92.3) | 67 (90.5) |
| Female | 0 (0.0) | 2 (16.7) | 3 (25.0) | 0 (0.0) | 1 (7.7) | 1 (7.7) | 7 (9.5) |
| Age (years) [1] | | | | | | | |
| Mean (SD) | 42.9 (8.8) | 45.8 (12.2) | 43.7 (12.5) | 37.8 (11.1) | 41.6 (14.1) | 40.4 (10.7) | 41.9 (11.6) |
| Minimum, Maximum | 29, 58 | 25, 60 | 28, 64 | 22, 57 | 22, 65 | 24, 60 | 22, 65 |
| Race - n (%) | | | | | | | |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 2 (2.7) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (7.7) | 1 (1.4) |
| Black or African American | 1 (9.1) | 1 (8.3) | 2 (16.7) | 2 (15.4) | 4 (30.8) | 2 (15.4) | 12 (16.2) |
| White | 10 (90.9) | 10 (83.3) | 8 (66.7) | 9 (69.2) | 7 (53.8) | 10 (76.9) | 54 (73.0) |
| Multiple | 0 (0.0) | 1 (8.3) | 1 (8.3) | 1 (7.7) | 2 (15.4) | 0 (0.0) | 5 (6.8) |
| Ethnicity- n (%) | | | | | | | |
| Hispanic or Latino | 2 (18.2) | 2 (16.7) | 2 (16.7) | 1 (7.7) | 1 (7.7) | 1 (7.7) | 9 (12.2) |
| Not Hispanic or Latino | 9 (81.8) | 10 (83.3) | 10 (83.3) | 12 (92.3) | 12 (92.3) | 12 (92.3) | 65 (87.8) |
| Mean (SD) Body Weight (kg) | | | | | | | |
| | 89.3 (7.5) | 79.7 (10.0) | 91.8 (13.1) | 93.9 (12.1) | 90.4 (7.6) | 89.7 (11.0) | 89.2 (11.1) |
| Mean (SD) BMI (kg/m²) | | | | | | | |
| | 28.5 (1.9) | 26.9 (1.2) | 29.3 (2.1) | 28.9 (2.8) | 28.7 (2.6) | 28.2 (2.3) | 28.4 (2.3) |

Abbreviations: BMI, body mass index; E, Exenatide; M, Placebo + Moxifloxacin 400 mg; P, Placebo; SD, standard deviation.

[1] Age at initiation of study medication infusion in Period I.

Cross-Reference: [Appendix 3.3](#) and [SDS 1.4.2](#).

Source: CSR, Table 7.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

“The LS mean changes from baseline in average QTcP (Δ QTcP) at the mean of 3 time points (1300 h, 1400 h, and 1500 h) and the difference between exenatide and placebo ($\Delta\Delta$ QTcP) for QTcP, the heart rate correction method selected as most appropriate for the primary analysis for the Evaluable Population. The upper limit of the 2-sided 90% CI (equivalent to 1-sided 95% CI) for the LS mean difference in the change from baseline in average QTcP between exenatide and placebo ($\Delta\Delta$ QTcP) was <10 ms at all 3 steady-state

target plasma exenatide concentrations (~200 pg/mL, ~300 pg/mL, and ~500 pg/mL) predefined for the primary analysis, and therefore below the threshold of regulatory concern defined in the ICH E14 Guidance, indicating no effect of exenatide on QTcP.

“Analysis of $\Delta\Delta\text{QTcP}_{\text{avg}}$ by individual time point (0900 h through 1500 h) support the primary analysis, as the upper limit of the 2-sided 90% CI for the LS mean difference in the change from baseline between exenatide and placebo in QTcP was <10 ms at all time points in the primary ECG assessment window. Additional QT corrections, including QTcF, QTcI, QTcIL, QTcPL, and QTcM further supported the primary analysis, with similar results observed for the ITT Population.”

Table 5: Statistical Comparison of LS Mean Changes from Baseline in QTcP Between Exenatide (~200 pg/mL, ~300 pg/mL, and ~500 pg/mL) and Placebo During the Primary ECG Assessment Window (Study BCB112; Evaluable Population [N = 74])

| Time (h) | LS Mean (SE) Change in QTcP [1] from Baseline [2] (ΔQTcP) (ms) | | LS Mean Difference in Change From Baseline in QTcP ($\Delta\Delta\text{QTcP}$) (2-sided 90% CI) Exenatide – Placebo (ms) |
|----------------------------------------------------------|--------------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------------------------------------|
| | Exenatide (N = 74) | Placebo (N = 74) | |
| Target Plasma Exenatide Concentration: ~200 pg/mL | | | |
| 0900 h | -2.84 (0.987) | -8.42 (0.904) | 5.58 (3.69, 7.46) |
| 1000 h | -2.99 (0.958) | -7.20 (0.922) | 4.21 (2.34, 6.08) |
| 1100 h | -2.54 (0.878) | -3.06 (0.939) | 0.52 (-1.26, 2.30) |
| 1200 h | -1.97 (0.847) | -1.13 (0.885) | -0.83 (-2.49, 0.83) |
| 1300 h | -1.91 (0.792) | 0.12 (0.728) | -2.03 (-3.38, -0.68) |
| 1400 h | -2.27 (0.887) | -0.54 (0.806) | -1.73 (-3.34, -0.12) |
| 1500 h | -2.57 (0.860) | -2.25 (0.752) | -0.32 (-1.81, 1.18) |
| Target Plasma Exenatide Concentration: ~300 pg/mL | | | |
| 0900 h | -4.19 (0.953) | -8.05 (0.949) | 3.86 (1.96, 5.76) |
| 1000 h | -3.85 (0.899) | -6.64 (0.956) | 2.79 (0.95, 4.63) |
| 1100 h | -3.27 (0.905) | -4.03 (0.944) | 0.76 (-1.07, 2.59) |
| 1200 h | -2.59 (0.865) | -1.66 (0.837) | -0.93 (-2.55, 0.69) |
| 1300 h | -2.45 (0.844) | -0.20 (0.756) | -2.26 (-3.73, -0.78) |
| 1400 h | -2.46 (0.872) | -0.38 (0.775) | -2.08 (-3.62, -0.54) |
| 1500 h | -2.81 (0.859) | -1.09 (0.735) | -1.72 (-3.19, -0.25) |
| Target Plasma Exenatide Concentration: ~500 pg/mL | | | |
| 0900 h | -5.22 (0.933) | -8.35 (0.924) | 3.13 (1.29, 4.97) |
| 1000 h | -4.12 (0.966) | -7.62 (0.887) | 3.50 (1.67, 5.33) |
| 1100 h | -4.14 (0.937) | -6.09 (0.847) | 1.94 (0.20, 3.68) |
| 1200 h | -4.01 (0.874) | -2.16 (0.822) | -1.85 (-3.47, -0.24) |
| 1300 h | -2.40 (0.931) | -2.07 (0.783) | -0.33 (-1.97, 1.31) |
| 1400 h | -3.78 (0.935) | -2.38 (0.835) | -1.39 (-3.11, 0.33) |
| 1500 h | -4.44 (0.936) | -2.78 (0.841) | -1.67 (-3.40, 0.06) |

Source: sponsor’s report Table 12

4.2.8.2.2 Assay Sensitivity

“The results of the statistical comparison of the LS mean changes from baseline in QTcP intervals between moxifloxacin and placebo are presented in following table. The mean ΔQTcP was greater following moxifloxacin administration compared with placebo at all

pre-specified time points (LS mean difference [moxifloxacin – placebo] ranged from 5.5 ms to 10.9 ms) and the lower bound of the 2-sided 90% adjusted CI of the LS mean difference between moxifloxacin and placebo for the change from baseline in QTcP was >5 ms at the 1100 h and 1200 h time points. These results confirm that the procedures employed in the study allowed detection of clinically relevant changes in QTcP, had they existed, thereby affirming assay sensitivity. Further, assay sensitivity was also supported by other correction methods.”

Table 6: Statistical Comparison of LS Mean Changes from Baseline in QTcP between Moxifloxacin (400 mg) and Placebo (Study BCB112; Evaluable Population [N = 74])

| Time (h) | LS Mean (SE) Change in QTcP [1] from | | LS Mean Difference in ΔQTcP (ms) (2-Sided Adjusted 90% CI) Moxifloxacin - Placebo |
|----------|--------------------------------------|---------------------|-----------------------------------------------------------------------------------------|
| | Baseline [2] (ΔQTcP) (ms) | | |
| | Moxifloxacin (N = 74) | Placebo (N = 74) | |
| 1000 h | 1.91 (1.079) | -3.56 (0.953) | 5.47 (2.82, 8.12) |
| 1100 h | 9.75 (0.934) | -0.81 (0.872) | 10.56 (8.46, 12.67) |
| 1200 h | 12.47 (1.011) | 1.56 (0.828) | 10.92 (8.71, 13.13) |

Source: sponsor’s report Table 14

Reviewer’s Comments: The reviewer’s analysis is in section 5.2.

4.2.8.2.3 Categorical Analysis

“No subjects experienced a QTcP >450 ms or a change from baseline in QTcP >30 ms with exenatide or placebo administration. A total of 3 subjects experienced QTcP >450 ms with moxifloxacin administration (none >480 ms) and 3 subjects experienced a change from baseline in QTcP >30 ms with moxifloxacin administration.”

4.2.8.2.4 Additional Analyses

“A summary of the ECG parameters QRS and PR interval by treatment, day, and time point for the Evaluable Population is provided in following table. No clinically relevant, consistent changes in PR or QRS were observed with exenatide administration compared with placebo.”

Table 7: Summary of Mean Baseline QRS and PR Intervals and Changes From Baseline by Treatment, Day, and Time Point (Study BCB112; Evaluable Population [N = 74])

| Time Point (h) | QRS (ms) | | PR (ms) | |
|-------------------------------------------|---------------------|-----------------------|---------------------|-----------------------|
| | Placebo (N = 74) | Exenatide (N = 74) | Placebo (N = 74) | Exenatide (N = 74) |
| Mean (SE) Baseline [1] | 97.2 (0.9) | 97.2 (0.9) | 169.6 (2.3) | 167.5 (2.3) |
| Day 1 | | | | |
| Mean (SE) Change from Baseline to: | | | | |
| 0900 h | -0.7 (0.5) | -1.7 (0.4) | -3.4 (0.9) | -2.4 (1.3) |
| 1000 h | -0.0 (0.5) | -1.4 (0.5) | -2.1 (0.9) | -1.2 (1.2) |
| 1100 h | -0.6 (0.3) | -1.6 (0.4) | -2.1 (0.9) | 0.3 (1.2) |
| 1200 h | -1.3 (0.4) | -1.8 (0.5) | -1.6 (0.9) | -1.4 (1.4) |
| 1300 h | 0.2 (0.4) | -1.1 (0.5) | -1.1 (0.9) | 0.5 (1.2) |
| 1400 h | -0.2 (0.4) | -2.1 (0.5) | -1.3 (0.9) | -0.6 (1.2) |
| 1500 h | -0.8 (0.4) | -2.5 (0.5) | -1.7 (0.9) | -1.0 (1.3) |
| Day 2 | | | | |
| Mean (SE) Change from Baseline to: | | | | |
| 0900 h | -0.5 (0.4) | -1.9 (0.5) | -1.3 (1.0) | -2.0 (1.3) |
| 1000 h | -0.1 (0.4) | -2.0 (0.4) | -0.9 (1.0) | 0.7 (1.4) |
| 1100 h | -0.7 (0.4) | -1.7 (0.5) | 0.1 (0.9) | 0.4 (1.3) |
| 1200 h | -1.1 (0.5) | -2.3 (0.5) | 0.2 (1.0) | 0.2 (1.2) |
| 1300 h | -1.3 (0.5) | -1.5 (0.5) | 0.6 (1.0) | 1.1 (1.2) |
| 1400 h | -1.2 (0.4) | -2.6 (0.5) | 0.4 (0.9) | 0.1 (1.3) |
| 1500 h | -0.8 (0.4) | -1.8 (0.6) | 0.9 (0.9) | -0.5 (1.4) |
| Day 3 | | | | |
| Mean (SE) Change from Baseline to: | | | | |
| 0900 h | -0.1 (0.4) | -2.1 (0.5) | 0.2 (1.1) | 0.0 (1.4) |
| 1000 h | 0.5 (0.5) | -1.9 (0.5) | -0.3 (1.0) | 2.0 (1.3) |
| 1100 h | -0.2 (0.4) | -1.9 (0.5) | -0.2 (1.0) | 2.3 (1.3) |
| 1200 h | 0.2 (0.4) | -1.7 (0.5) | 1.3 (0.8) | 2.5 (1.5) |
| 1300 h | -0.6 (0.4) | -1.3 (0.6) | 1.4 (0.9) | 0.8 (1.3) |
| 1400 h | -0.3 (0.4) | -2.4 (0.5) | -0.7 (1.1) | -0.3 (1.4) |
| 1500 h | -0.6 (0.4) | -2.2 (0.5) | 0.7 (0.9) | 0.5 (1.3) |

Source: Sponsor's report Table 18

4.2.8.3 Safety Analysis

A total of 77 (89.5%) subjects experienced adverse events during the study, with more subjects experiencing adverse events while treated with exenatide (88.8%) compared with placebo (25.0%) and moxifloxacin (22.5%).

One serious adverse event with onset during the moxifloxacin plus placebo infusion treatment period (prior to moxifloxacin administration) led to the subject being withdrawn from study participation. One subject experienced a treatment-emergent serious adverse event (severe blood CPK increase) during the moxifloxacin plus placebo treatment period (Period III). Subject 2030 completed Period I (placebo administration) and Period II (exenatide administration) with no reported adverse events except mild application site irritation (Period II). Upon arriving at the study site for Period III, approximately 6 days after discontinuation of the exenatide infusion in Period II and prior to initiation of placebo infusion in Period III, the subject was observed to have increased

CPK concentration (4125 U/L [normal range 24 to 204 U/L]), assessed as mild in intensity by the investigator, and an AST concentration of 48 U/L [normal range 0 to 40 U/L]).

Two adverse events associated with exenatide administration (mild nausea and moderate vomiting) led to withdrawal from the study.

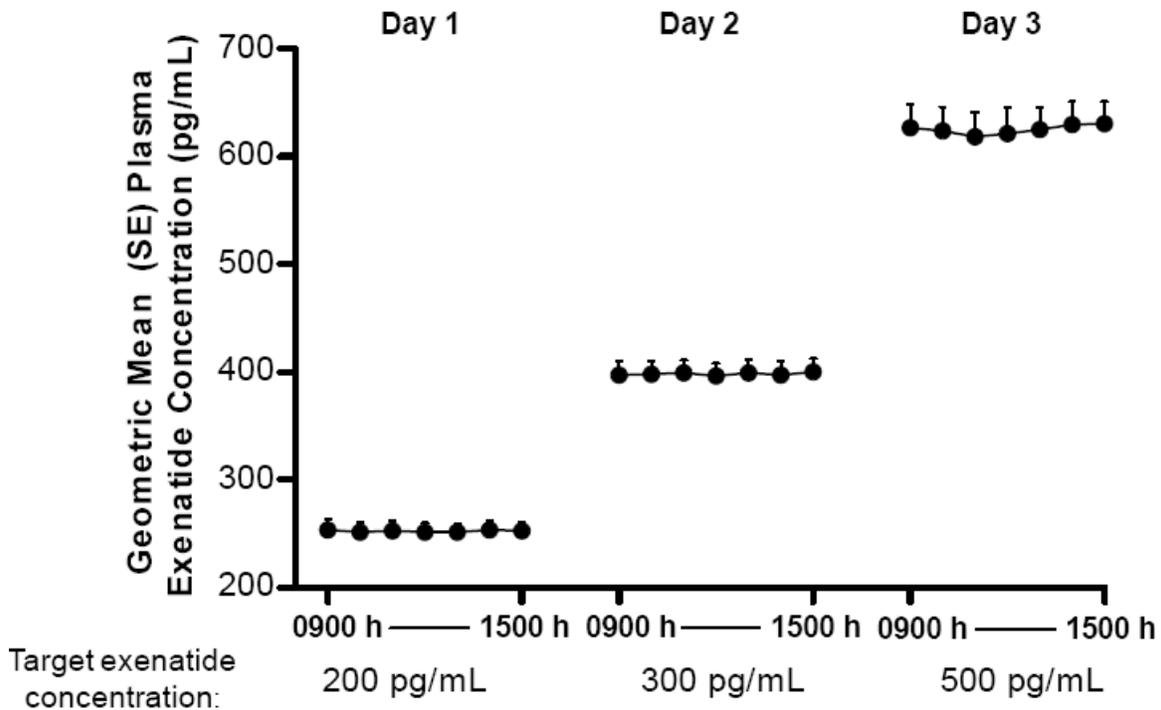
No death was reported during the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentrations of exenatide from 74 subjects are shown in Figure 1. Mean PK parameters are shown in Table 2.

Figure 1: Geometric Mean Concentration-Time Profiles of Exenatide



(Source: Sponsor's Clinical Study Report, Figure 3 on Page 48)

Table 2: Summary of Plasma Pharmacokinetic Parameters for Exenatide

| Study Day | Statistics | Plasma Exenatide Concentration (pg/mL) |
|-----------|-------------------------|----------------------------------------|
| Day 1 | n | 68 |
| | Mean (SD) | 263.11 (89.402) |
| | SE | 10.842 |
| | Geometric Mean (SE) [1] | 252.74 (8.454) |
| | Median | 248.29 |
| | Min, Max | 77.4, 834.4 |
| | 10th, 90th Percentile | 197.1, 327.0 |
| Day 2 | n | 68 |
| | Mean (SD) | 413.21 (136.871) |
| | SE | 16.598 |
| | Geometric Mean (SE) [1] | 399.14 (11.936) |
| | Median | 393.64 |
| | Min, Max | 184.4, 1337.1 |
| | 10th, 90th Percentile | 309.7, 526.9 |
| Day 3 | n | 68 |
| | Mean (SD) | 653.01 (216.719) |
| | SE | 26.281 |
| | Geometric Mean (SE) [1] | 626.65 (21.159) |
| | Median | 619.29 |
| | Min, Max | 299.4, 1904.3 |
| | 10th, 90th Percentile | 484.0, 858.9 |

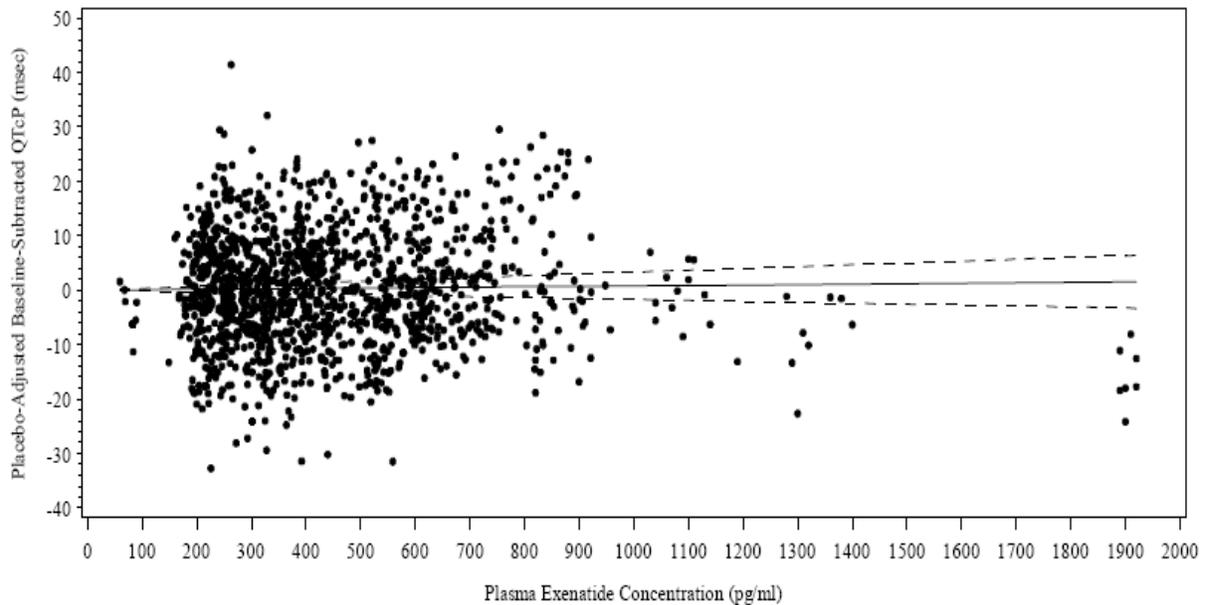
(Source: Sponsor's Clinical Study Report, Supporting Data Summary 2.2.2 on Page 256)

Reviewer's Comments: The sampling schedule appears adequate to characterize the steady state PK profile of exenatide.

4.2.8.4.2 Exposure-Response Analysis

The concentration-QT model results showing the relationships between the placebo adjusted change from baseline in QTcP and exenatide concentrations are shown in Figure 2. The model suggested a flat concentration-QT relationship.

Figure 2: Placebo Adjusted Changes (ms) From Baseline in QTcP versus the Exenatide Concentrations



Abbreviations: LS, least squares; QTcP, population QT correction-log linear.

Notes: -Slope (90% CI) = 0.0008 (-0.0017, 0.0033); p = 0.5962.

(Source: Sponsor's Clinical Study Report, Figure 9 on Page 65)

Reviewer's Comments: The reviewer performed independent analysis (See section 5.3). Consistent with the sponsor's results, the slope of the concentration-QT relationship is relatively flat.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor provided following correction methods: QTcI(Individual QT correction – log linear), QTcIL(Individual QT correction – linear), QTcP(Population QT correction – log linear), QTcPL(Population QT correction – linear), QTcF and QTcB. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

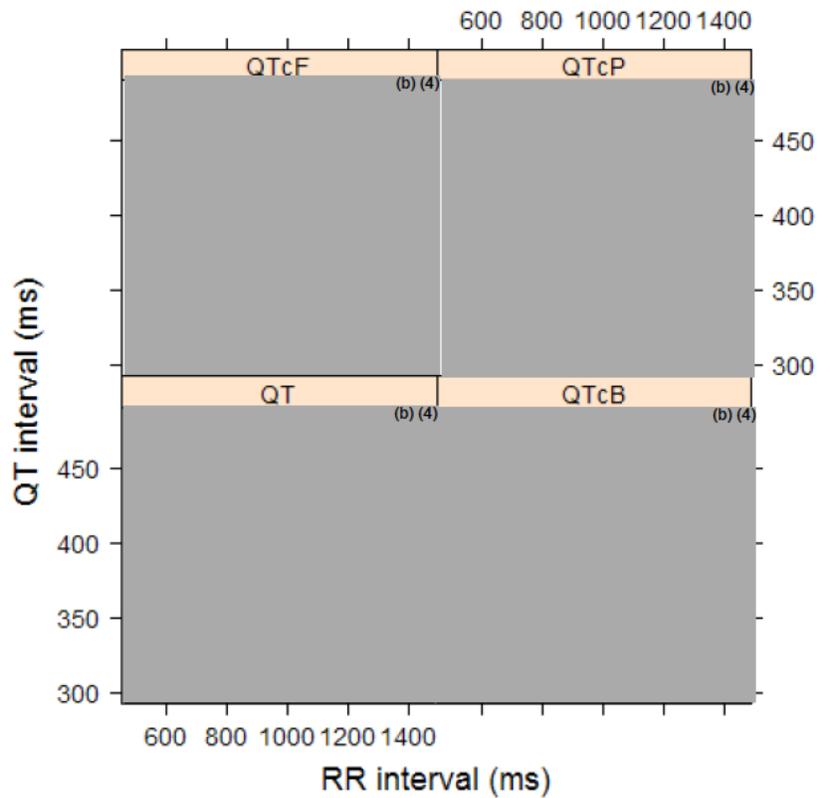
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 9, it appears that QTcP and QTcF are the best correction methods. The sponsor chose QTcP as the primary outcome. This reviewer performed the same analysis using both QTcP and QTcF, and the difference based on the two correction methods is negligible. To be consistent with the sponsor, we also used QTcP for the primary statistical analysis.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

| method | Treatment | | | | | | | |
|--------|-----------|--------|--------------|--------|---------|--------|-----|--------|
| | EXENATIDE | | Moxifloxacin | | PLACEBO | | All | |
| | N | MSSS | N | MSSS | N | MSSS | N | MSSS |
| QTcF | 79 | 0.0016 | 80 | 0.0016 | 83 | 0.0015 | 85 | 0.0011 |
| QTcI | 79 | 0.0028 | 80 | 0.0023 | 83 | 0.0020 | 85 | 0.0013 |
| QTcIL | 79 | 0.0025 | 80 | 0.0022 | 83 | 0.0020 | 85 | 0.0013 |
| QTcP | 79 | 0.0016 | 80 | 0.0016 | 83 | 0.0015 | 85 | 0.0011 |
| QTcPL | 79 | 0.0015 | 80 | 0.0018 | 83 | 0.0017 | 85 | 0.0014 |

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Exenatide

The statistical reviewer used mixed model to analyze the Δ QTcP effect. The model included time, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. Time-matched baseline QTcP at Day -1 in each period was used in the model. The analysis results are listed in the following tables.

Table 10: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP for Treatment Group = Exenatide on Day 1 (~200 pg/mL)

| | Treatment Group | | | |
|----------|-------------------------------------|--------------------------|---------------------|--------------|
| | Exenatide on Day 2 (Δ QTcP) | Placebo (Δ QTcP) | $\Delta\Delta$ QTcP | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | 9.2 | 4.2 | 5.0 | (3.7, 6.3) |
| 10 | 6.6 | 3.0 | 3.5 | (2.2, 4.9) |
| 11 | 5.2 | 3.9 | 1.3 | (-0.1, 2.8) |
| 12 | 0.9 | 2.5 | -1.6 | (-3.0, -0.2) |
| 13 | -0.4 | 2.1 | -2.5 | (-3.8, -1.1) |
| 14 | 0.6 | 2.1 | -1.5 | (-2.8, -0.2) |
| 15 | 0.9 | 2.1 | -1.2 | (-2.5, 0.2) |

Table 11: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP for Treatment Group = Exenatide on Day 2 (~300 pg/mL)

| | Treatment Group | | | |
|----------|-------------------------------------|--------------------------|---------------------|--------------|
| | Exenatide on Day 2 (Δ QTcP) | Placebo (Δ QTcP) | $\Delta\Delta$ QTcP | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | LS Mean (ms) | 90% CI (ms) |
| 9 | 7.8 | 4.2 | 3.6 | (2.3, 5.0) |
| 10 | 5.6 | 3.0 | 2.6 | (1.2, 4.0) |
| 11 | 4.2 | 3.9 | 0.3 | (-1.1, 1.8) |
| 12 | 0.3 | 2.5 | -2.1 | (-3.6, -0.7) |
| 13 | -0.8 | 2.1 | -3.0 | (-4.3, -1.6) |
| 14 | 0.5 | 2.1 | -1.6 | (-3.0, -0.3) |
| 15 | 0.6 | 2.1 | -1.6 | (-2.9, -0.2) |

Table 12: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP for Treatment Group = Exenatide on Day 3 (~500 pg/mL)

| | Treatment Group | | | |
|----------|-------------------------------------|--------------------------|---------------------|--------------|
| | Exenatide on Day 3 (Δ QTcP) | Placebo (Δ QTcP) | $\Delta\Delta$ QTcP | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | 6.9 | 4.2 | 2.7 | (1.4, 4.0) |
| 10 | 5.4 | 3.0 | 2.4 | (0.9, 3.8) |
| 11 | 3.3 | 3.9 | -0.5 | (-2.0, 0.9) |
| 12 | -0.9 | 2.5 | -3.3 | (-4.8, -1.9) |
| 13 | -0.5 | 2.1 | -2.6 | (-4.0, -1.3) |
| 14 | -1.1 | 2.1 | -3.2 | (-4.5, -1.8) |
| 15 | -0.9 | 2.1 | -3.0 | (-4.3, -1.6) |

The largest upper bounds of the 2-sided 90% CI for the mean difference between exenatide (~200, ~300, ~500 pg/mL) and placebo were 6.3 ms, 5.0 ms and 4.0 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 13. The largest adjusted 90% lower confidence interval is 9.0 ms after considering Bonferroni multiple endpoint adjustment of three time points, which indicates that an at least 5 ms QTcP effect due to moxifloxacin can be detected from the study.

Table 13: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP for Moxifloxacin

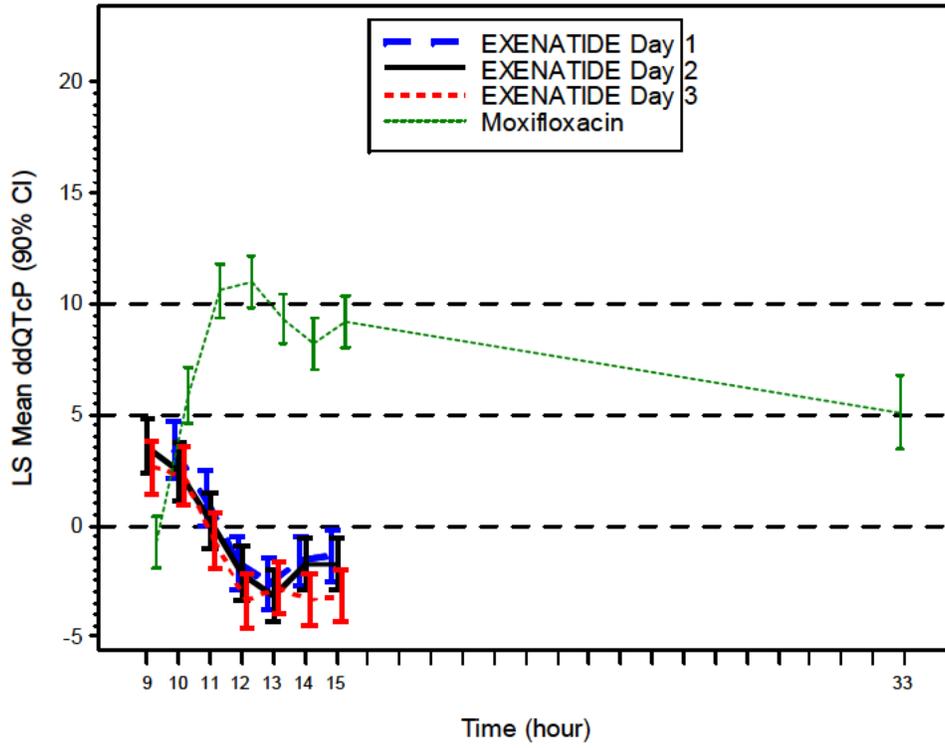
| Time (h) | Treatment Group | | | |
|----------|-------------------------------|--------------------------|---------------------|-------------|
| | Moxifloxacin (Δ QTcP) | Placebo (Δ QTcP) | $\Delta\Delta$ QTcP | |
| | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0 | 1.6 | 2.2 | -0.6 | (-2.9, 1.7) |
| 1 | 7.7 | 1.4 | 6.3 | (3.6, 9.1) |
| 2 | 12.9 | 2.3 | 10.6 | (8.0, 13.1) |
| 3 | 12.7 | 1.4 | 11.4 | (9.0, 13.8) |
| 4 | 10.1 | 1.4 | 8.7 | (6.4, 11.0) |
| 5 | 10.0 | 2.2 | 7.8 | (5.7, 9.9) |
| 6 | 10.9 | 2.6 | 8.3 | (6.2, 10.4) |
| 24 | 8.5 | 3.4 | 5.1 | (2.9, 7.2) |

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcP over Time

The following figure displays the time profile of $\Delta\Delta$ QTcP for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcP Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose QTcP values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcP was above 480 ms.

Table 14: Categorical Analysis for QTcP

| Treatment Group | Total N | | Value \leq 450 ms | | 450 ms<Value \leq 480 ms | |
|-----------------|---------|--------|---------------------|-------------|----------------------------|----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| EXENATIDE Day 1 | 79 | 549 | 79 (100%) | 549 (100%) | 0 (0.0%) | 0 (0.0%) |
| EXENATIDE Day 2 | 77 | 534 | 77 (100%) | 534 (100%) | 0 (0.0%) | 0 (0.0%) |
| EXENATIDE Day 3 | 77 | 536 | 77 (100%) | 536 (100%) | 0 (0.0%) | 0 (0.0%) |
| Moxifloxacin | 79 | 543 | 76 (96.2%) | 540 (99.4%) | 3 (3.8%) | 3 (0.6%) |
| PLACEBO | 83 | 1706 | 83 (100%) | 1706 (100%) | 0 (0.0%) | 0 (0.0%) |

Table 15 lists the categorical analysis results for Δ QTcP. No subject's change from baseline was above 60 ms.

Table 15: Categorical Analysis of Δ QTcP

| Treatment Group | Total N | | Value \leq 30 ms | | 30 ms<Value \leq 60 ms | | Value>60 ms | |
|-----------------|---------|--------|--------------------|-----------------|--------------------------|-------------|-------------|-------------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| EXENATIDE Day 1 | 78 | 534 | 78 (100%) | 534 (100%) | 0 (0.0%) | 0 (0.0%) | 0 (.%) | 0 (0.0%) |
| EXENATIDE Day 2 | 76 | 519 | 75 (98.7%) | 518 (99.8%) | 1 (1.3%) | 1 (0.2%) | 0 (.%) | 0 (0.0%) |
| EXENATIDE Day 3 | 76 | 520 | 76 (100%) | 520 (100%) | 0 (0.0%) | 0 (0.0%) | 0 (.%) | 0 (0.0%) |
| Moxifloxacin | 79 | 538 | 76 (96.2%) | 535 (99.4%) | 3 (3.8%) | 3 (0.6%) | 0 (.%) | 0 (0.0%) |
| PLACEBO | 83 | 1670 | 82 (98.8%) | 1668 (99.9%) | 1 (1.2%) | 2 (0.1%) | 0 (.%) | 0 (0.0%) |

5.2.2 HR Analysis

The same statistical analysis was performed based on heart rate. Time-matched baseline HR at Day -1 in each period was used in the model. The point estimates and the 90% confidence intervals are presented in following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between exenatide (~200, ~300, ~500 pg/mL) and placebo were 13.5 bpm, 15.6 bpm and 16.8 bpm, respectively.

Table 16: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = Exenatide on Day 1 (~200 pg/mL)

| | Treatment Group | | | |
|----------|-----------------------------------|---------------------------|-----------------------------|--------------|
| | EXENATIDE Day 1 (Δ HR) | Placebo (Δ HR) | $\Delta\Delta$ HR | |
| Time (h) | LS Mean (bpm) | LS Mean (bpm) | Diff LS Mean (bpm) | 90% CI (bpm) |
| 9 | 8.7 | 2.0 | 6.7 | (5.5, 7.9) |
| 10 | 11.5 | 1.7 | 9.8 | (8.7, 11.0) |
| 11 | 13.6 | 1.7 | 11.9 | (10.7, 13.1) |
| 12 | 13.1 | 1.5 | 11.6 | (10.4, 12.7) |
| 13 | 13.5 | 1.2 | 12.3 | (11.2, 13.5) |
| 14 | 11.6 | 1.4 | 10.2 | (9.0, 11.3) |
| 15 | 11.7 | 1.8 | 10.0 | (8.8, 11.1) |

Table 17: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = Exenatide on Day 2 (~300 pg/mL)

| | Treatment Group | | | |
|----------|-----------------------------------|---------------------------|-----------------------------|--------------|
| | EXENATIDE Day 2 (Δ HR) | Placebo (Δ HR) | $\Delta\Delta$ HR | |
| Time (h) | LS Mean (bpm) | LS Mean (bpm) | Diff LS Mean (bpm) | 90% CI (bpm) |
| 9 | 11.1 | 2.0 | 9.1 | (7.9, 10.3) |
| 10 | 14.2 | 1.7 | 12.6 | (11.4, 13.8) |
| 11 | 15.4 | 1.7 | 13.7 | (12.5, 14.9) |
| 12 | 15.9 | 1.5 | 14.4 | (13.2, 15.6) |
| 13 | 14.6 | 1.2 | 13.4 | (12.2, 14.5) |
| 14 | 14.0 | 1.4 | 12.6 | (11.4, 13.7) |
| 15 | 13.5 | 1.8 | 11.7 | (10.6, 12.9) |

Table 18: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = Exenatide on Day 3 (~500 pg/mL)

| | Treatment Group | | | |
|----------|-----------------------------------|---------------------------|-----------------------------|--------------|
| | EXENATIDE Day 3 (Δ HR) | Placebo (Δ HR) | $\Delta\Delta$ HR | |
| Time (h) | LS Mean (bpm) | LS Mean (bpm) | Diff LS Mean (bpm) | 90% CI (bpm) |
| 9 | 11.8 | 2.0 | 9.9 | (8.7, 11.1) |
| 10 | 15.0 | 1.7 | 13.4 | (12.2, 14.6) |
| 11 | 17.2 | 1.7 | 15.6 | (14.3, 16.8) |
| 12 | 16.5 | 1.5 | 15.0 | (13.8, 16.2) |
| 13 | 16.7 | 1.2 | 15.5 | (14.3, 16.6) |
| 14 | 15.4 | 1.4 | 14.0 | (12.8, 15.1) |
| 15 | 15.5 | 1.8 | 13.8 | (12.6, 14.9) |

5.2.3 PR Analysis

The same statistical analysis was performed based on PR. Time-matched baseline PR at Day -1 in each period was used in the model. The point estimates and the 90% confidence intervals are presented in following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between exenatide (~200, ~300, ~500 pg/mL) and placebo were 1.3 ms, 2.4 ms and 4.1 ms, respectively.

Table 19: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Exenatide on Day 1 (~200 pg/mL)

| | Treatment Group | | | |
|----------|-----------------------------------|------------------------|-------------------|--------------|
| | Exenatide on Day 1 (Δ PR) | Placebo (Δ PR) | $\Delta\Delta$ PR | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | 1.6 | 4.5 | -3.0 | (-4.7, -1.2) |
| 10 | 2.8 | 3.8 | -1.0 | (-2.6, 0.7) |
| 11 | 3.2 | 3.5 | -0.3 | (-2.0, 1.3) |
| 12 | 1.2 | 4.6 | -3.4 | (-5.1, -1.7) |
| 13 | 3.6 | 5.1 | -1.6 | (-3.2, 0.1) |
| 14 | 2.0 | 3.5 | -1.5 | (-3.4, 0.3) |
| 15 | 5.0 | 7.5 | -2.5 | (-4.2, -0.9) |

Table 20: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Exenatide on Day 2 (~300 pg/mL)

| | Treatment Group | | | |
|----------|-----------------------------------|------------------------|-------------------|--------------|
| | Exenatide on Day 2 (Δ PR) | Placebo (Δ PR) | $\Delta\Delta$ PR | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | 1.9 | 4.5 | -2.6 | (-4.4, -0.8) |
| 10 | 4.5 | 3.8 | 0.7 | (-1.0, 2.4) |
| 11 | 3.1 | 3.5 | -0.4 | (-2.1, 1.3) |
| 12 | 2.7 | 4.6 | -1.8 | (-3.6, -0.1) |
| 13 | 4.2 | 5.1 | -0.9 | (-2.6, 0.8) |
| 14 | 3.0 | 3.5 | -0.5 | (-2.3, 1.3) |
| 15 | 5.9 | 7.5 | -1.6 | (-3.3, 0.1) |

Table 21: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = Exenatide on Day 3 (~500 pg/mL)

| Time (h) | Treatment Group | | | |
|----------|-----------------------------------|------------------------|-------------------|-------------|
| | Exenatide on Day 3 (Δ PR) | Placebo (Δ PR) | $\Delta\Delta$ PR | |
| | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | 3.9 | 4.5 | -0.7 | (-2.4, 1.1) |
| 10 | 6.2 | 3.8 | 2.4 | (0.7, 4.1) |
| 11 | 4.8 | 3.5 | 1.2 | (-0.5, 2.9) |
| 12 | 5.2 | 4.6 | 0.6 | (-1.1, 2.3) |
| 13 | 4.1 | 5.1 | -1.0 | (-2.7, 0.6) |
| 14 | 3.0 | 3.5 | -0.6 | (-2.4, 1.3) |
| 15 | 7.0 | 7.5 | -0.6 | (-2.2, 1.1) |

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS. Time-matched baseline QRS at Day -1 in each period was used in the model. The point estimates and the 90% confidence intervals are presented in following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between exenatide (~200, ~300, ~500 pg/mL) and placebo were -0.2 ms, -0.4 ms and -0.3 ms, respectively.

Table 22: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Exenatide on Day 1 (~200 pg/mL)

| | Treatment Group | | | |
|----------|------------------------------------|-------------------------|--------------------|--------------|
| | Exenatide on Day 1 (Δ QRS) | Placebo (Δ QRS) | $\Delta\Delta$ QRS | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | -3.5 | -2.1 | -1.3 | (-2.1, -0.6) |
| 10 | -2.5 | -0.7 | -1.8 | (-2.5, -1.0) |
| 11 | -2.9 | -1.9 | -1.0 | (-1.7, -0.3) |
| 12 | -3.0 | -1.6 | -1.4 | (-2.2, -0.6) |
| 13 | -3.2 | -2.2 | -1.0 | (-1.8, -0.2) |
| 14 | -3.1 | -1.4 | -1.6 | (-2.4, -0.9) |
| 15 | -3.8 | -1.9 | -1.9 | (-2.6, -1.1) |

Table 23: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Exenatide on Day 2 (~300 pg/mL)

| | Treatment Group | | | |
|----------|------------------------------------|-------------------------|--------------------|--------------|
| | Exenatide on Day 2 (Δ QRS) | Placebo (Δ QRS) | $\Delta\Delta$ QRS | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | -3.7 | -2.1 | -1.6 | (-2.3, -0.8) |
| 10 | -3.1 | -0.7 | -2.4 | (-3.1, -1.6) |
| 11 | -3.0 | -1.9 | -1.2 | (-1.9, -0.4) |
| 12 | -3.2 | -1.6 | -1.5 | (-2.3, -0.7) |
| 13 | -3.5 | -2.2 | -1.3 | (-2.1, -0.5) |
| 14 | -3.3 | -1.4 | -1.9 | (-2.7, -1.1) |
| 15 | -3.2 | -1.9 | -1.3 | (-2.1, -0.5) |

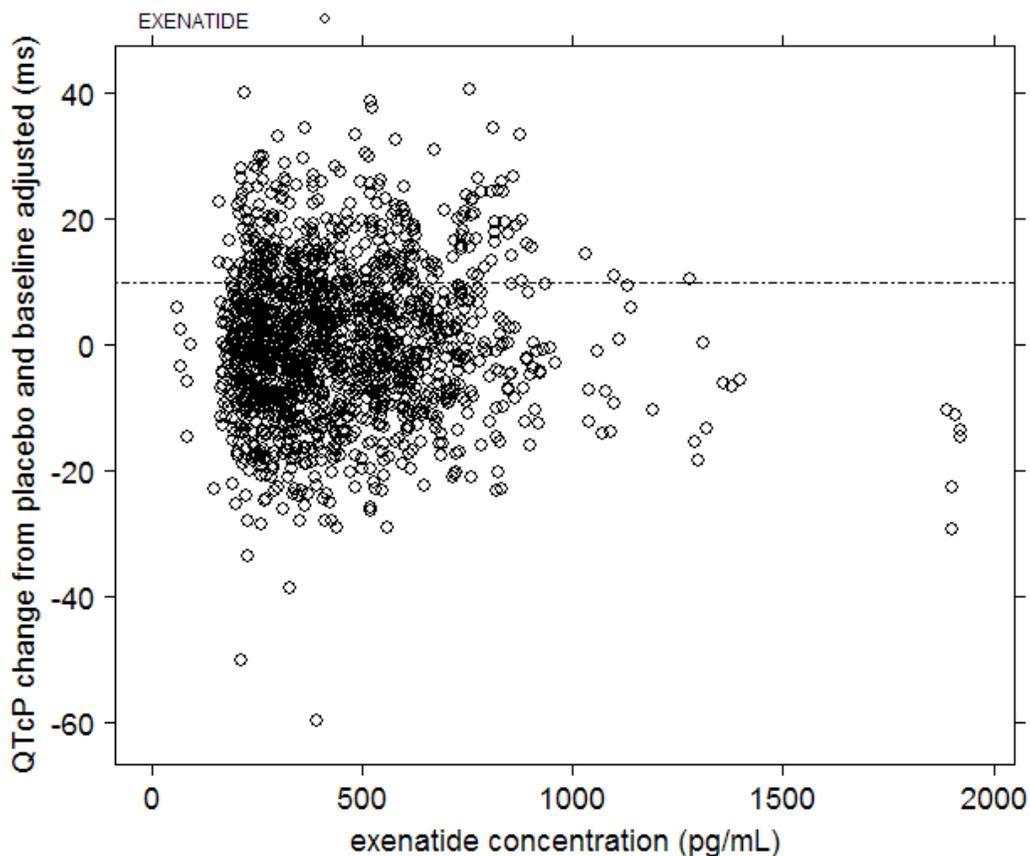
Table 24: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = Exenatide on Day 3 (~500 pg/mL)

| | Treatment Group | | | |
|----------|---------------------------------------|----------------------------|----------------------------|--------------|
| | Exenatide on Day 3 (Δ QRS) | Placebo (Δ QRS) | $\Delta\Delta$ QRS | |
| Time (h) | LS Mean (ms) | LS Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 9 | -3.8 | -2.1 | -1.6 | (-2.4, -0.9) |
| 10 | -2.8 | -0.7 | -2.1 | (-2.8, -1.4) |
| 11 | -3.2 | -1.9 | -1.3 | (-2.1, -0.6) |
| 12 | -2.7 | -1.6 | -1.1 | (-1.9, -0.3) |
| 13 | -3.4 | -2.2 | -1.2 | (-2.0, -0.4) |
| 14 | -3.5 | -1.4 | -2.1 | (-2.9, -1.3) |
| 15 | -3.4 | -1.9 | -1.5 | (-2.3, -0.8) |

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcP and exenatide concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: $\Delta\Delta$ QTcP vs. Exenatide Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.03% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Eight subjects had a post-baseline PR > 200 ms, two of them had PR >200 ms at baseline. In all cases the increase over baseline was <15%.

Eight subjects had a QRS > 110 ms, three of them at baseline. In all cases the increase over baseline was < 10%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

| | | |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic Dose | 2 mg QW | |
| Maximum Tolerated Dose | 10 mg single dose; max tolerated dose not identified (Section 2.7.2.5, Summary of Pharmacokinetic and Exposure-Response Data Supporting the Proposed Therapeutic Dosage Regimen) | |
| Principal Adverse Events | Nausea and Vomiting | |
| Maximum Dose Tested | Single Dose | 10 mg (Section 2.7.2.3.1.1, Single-Dose Pharmacokinetics) |
| | Multiple Dose | 2 mg QW (Section 2.7.2.3.1.2, Multiple-Dose Pharmacokinetics) |
| | Continuous IV Infusion | 3.9 mcg/h (Section 5.3.5.1, BCB112, SDS 2.2.2) |
| Exposures Achieved at Maximum Tested Dose | Single Dose | AUC _(0-last) geometric mean (SE) 203,954 (15,654) pg·h/mL C _{max} (0-last) geometric mean (SE) 641.5 (88.5) pg/mL C _{max} (0-8) geometric mean (SE) 200.3 (18.6) pg/mL (Section 2.7.2.3.1.1, Single-Dose Pharmacokinetics, Table 3) |
| | Multiple Dose | 2993LAR-105, BCB106, and BCB108 - 2 mg QW (N = 299) C _{ss} (pg/mL) at Week 26 or Week 30 Geometric mean 254.1; 10 th -90 th percentile 99.7 – 625.0. (Section 2.7.2.3.5.2.1, Steady-State Concentrations by Renal Function and Scale of Material, Table 10) |
| | Continuous IV Infusion | BCB112 – 3.9 mcg/h (N = 68) C _{ss,ave} Geometric mean (SE) 626.65 (21.159) pg/mL (Section 5.3.5.1, BCB112, SDS 2.2.2) |
| Range of Linear PK | AUC from single doses of 2.5 to 10 mg and AUC _{0-tau,ss} following multiple QW doses of 0.8 to 2 mg appeared to increase dose proportionally (Not statistically tested). (Section 2.7.2.3.1.6, Dose Proportionality of Exenatide Once Weekly) | |
| Accumulation at Steady State | ~8.6 fold following 2 mg QW (Section 2.7.2.3.1.3, Aspects of the Pharmacokinetic Profile Pertinent to the Extended-Release Formulation) | |
| Metabolites | PK parameters for metabolites not applicable. | |
| Absorption | Absolute/Relative Bioavailability | Absolute: Not evaluated for exenatide QW. The absolute bioavailability of BYETTA ranged from LS Mean Ratio (CV) of 113% -121% (71%) at different sites of injection. (NDA 021-773, Serial 0000, 2.7.2.2, 2993-118) Relative (to BYETTA): Mean (90% confidence intervals) bioavailability for steady state weekly 2 mg dosing was 25% (21%, 30%) (Section 2.7.2.3.1.4, Relative Bioavailability of Exenatide Once Weekly Versus the Immediate-Release Formulation (BYETTA)) |
| | T _{max} | Parent: Median (10 th -90 th percentile) at steady-state over a dosing interval, 22.8 h (1.17 – 167.75) (Section 2.7.2.3.1.3.1, Impact of Initial Release After the First Dose and at Steady-State) Metabolites: Not applicable |
| Distribution | V _d /F or V _d | BYETTA (exenatide immediate release) Mean (10 th -90 th percentile) – 28.3 L (15.47 – 62.50 L) (Section 2.7.2.3.1.5, Post-Absorptive Properties of Exenatide Once Weekly: Distribution, Metabolism, and Excretion; NDA 021-773, Serial 0000, 2.7.2.3.1.1) |
| | % bound | 18% bound to erythrocytes (Section 2.6.4.4.2, Protein Binding and Distribution in Blood Cells) Protein binding to serum albumin not determined |

| | | |
|-------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Elimination | Route | <p>Primary: glomerular filtration (Section 2.7.2.3.1.5, Post-Absorptive Properties of Exenatide Once Weekly: Distribution, Metabolism, and Excretion)</p> <p>Percent dose eliminated: estimated to be >80% based on ESRD patients with BYETTA showing a CL/F reduction by 84% compared to normal renal function (Section 2.7.2.3.5.2, Renal Impairment)</p> <p>Proteolytic degradation subsequent to glomerular filtration (Section 2.7.2.3.1.5, Post-Absorptive Properties of Exenatide Once Weekly: Distribution, Metabolism, and Excretion)</p> |
| | Terminal t _{1/2} | <p>The actual half-life of exenatide is geometric mean (10th-90th percentiles) 2.35 hours (1.35 - 4.52h) (NDA 021-773, Serial 0000, Section 2.7.2.3.1.1)</p> <p>BYDUREON achieves its extending exposure through sustained release technologies. The time required for the decline in plasma exenatide exposure following cessation of BYDUREON therapy is approximately 7 weeks after the last injection (Section 2.7.2.3.1.2, Multiple-Dose Pharmacokinetics)</p> <p>Metabolites: Not applicable</p> |
| | CL/F or CL | <p>Mean (10th – 90th percentile) from BYETTA CL/F = 9.1 L/hr (6.15 - 15.86 L/hr) (NDA 021-773, Serial 0000, 2.7.2.3.1.1, Table APP 15)</p> |
| Intrinsic Factors | Age | <p>In adults no relevant change (Section 2.7.2.3.5.4, Demographic Characteristics (Age, Gender, Race); Section 2.7.2.6, Appendix 2, Table 2.4)</p> |
| | Sex | <p>No relevant change (Section 2.7.2.3.5.4, Demographic Characteristics (Age, Gender, Race); Section 2.7.2.6, Appendix 2, Table 2.4)</p> |

| | Race | <p>No relevant change (Section 2.7.2.3.5.4, Demographic Characteristics (Age, Gender, Race); Section 2.7.2.6, Appendix 2, Table 2.4)</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | Hepatic & Renal Impairment | <p>Hepatic: Not evaluated in hepatic impairment; primarily renally cleared. (Section 2.7.2.3.5.6, Hepatic Impairment)</p> <p>Renal</p> <p>2993LAR-105, BCB106, and BCB108 - 2 mg QW C_{ss} (pg/mL) at Week 26 or Week 30 by Baseline Renal Function.</p> <table border="1"> <thead> <tr> <th>Baseline Renal Function</th> <th>Number of Subjects</th> <th>C_{ss} (pg/mL) Geometric Mean</th> <th>10th -90th Percentile</th> </tr> </thead> <tbody> <tr> <td>Normal</td> <td>139</td> <td>210.3</td> <td>88.1 – 463.2</td> </tr> <tr> <td>Mild</td> <td>132</td> <td>289.3</td> <td>141.4 – 674.9</td> </tr> <tr> <td>Moderate</td> <td>26</td> <td>335.6</td> <td>147 – 647</td> </tr> <tr> <td>Severe*</td> <td>2</td> <td>661.0</td> <td>605.5 – 721.5</td> </tr> </tbody> </table> <p>(Section 2.7.2.3.5.2.1, Steady-State Concentrations by Renal Function and Scale of Material, Table 10)</p> <p>BCB112 – Continuous IV Infusion C_{ss,ave} by Baseline Renal Function.</p> <table border="1"> <thead> <tr> <th>Baseline Renal Function**</th> <th>Number of Subjects</th> <th>C_{ss,ave} (pg/mL) Geometric Mean (SE)</th> <th>10th -90th Percentile</th> </tr> </thead> <tbody> <tr> <td colspan="4">1.8 mcg/h</td> </tr> <tr> <td>Normal</td> <td>57</td> <td>244.66(9.27)</td> <td>196.29 – 306.43</td> </tr> <tr> <td>Mild</td> <td>11</td> <td>299.12(10.65)</td> <td>255.00 – 332.29</td> </tr> <tr> <td colspan="4">2.5 mcg/h</td> </tr> <tr> <td>Normal</td> <td>57</td> <td>385.55(12.83)</td> <td>307.86, 463.29</td> </tr> <tr> <td>Mild</td> <td>11</td> <td>477.65(15.50)</td> <td>435.14 – 560.43</td> </tr> <tr> <td colspan="4">3.9 mcg/h</td> </tr> <tr> <td>Normal</td> <td>57</td> <td>603.27(22.71)</td> <td>479.14, – 821.71</td> </tr> <tr> <td>Mild</td> <td>11</td> <td>763.13(29.13)</td> <td>651.29 – 902.57</td> </tr> </tbody> </table> <p>*Not indicated for use in patients with severe renal impairment or end-stage renal disease (please see BYETTA Prescribing Information) **No subjects with moderate or severe renal impairment were enrolled in Study BCB112 (Amylin Pharmaceuticals Inc., data on file)</p> | Baseline Renal Function | Number of Subjects | C _{ss} (pg/mL) Geometric Mean | 10 th -90 th Percentile | Normal | 139 | 210.3 | 88.1 – 463.2 | Mild | 132 | 289.3 | 141.4 – 674.9 | Moderate | 26 | 335.6 | 147 – 647 | Severe* | 2 | 661.0 | 605.5 – 721.5 | Baseline Renal Function** | Number of Subjects | C _{ss,ave} (pg/mL) Geometric Mean (SE) | 10 th -90 th Percentile | 1.8 mcg/h | | | | Normal | 57 | 244.66(9.27) | 196.29 – 306.43 | Mild | 11 | 299.12(10.65) | 255.00 – 332.29 | 2.5 mcg/h | | | | Normal | 57 | 385.55(12.83) | 307.86, 463.29 | Mild | 11 | 477.65(15.50) | 435.14 – 560.43 | 3.9 mcg/h | | | | Normal | 57 | 603.27(22.71) | 479.14, – 821.71 | Mild | 11 | 763.13(29.13) |
| Baseline Renal Function | Number of Subjects | C _{ss} (pg/mL) Geometric Mean | 10 th -90 th Percentile | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Normal | 139 | 210.3 | 88.1 – 463.2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mild | 132 | 289.3 | 141.4 – 674.9 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Moderate | 26 | 335.6 | 147 – 647 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Severe* | 2 | 661.0 | 605.5 – 721.5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Baseline Renal Function** | Number of Subjects | C _{ss,ave} (pg/mL) Geometric Mean (SE) | 10 th -90 th Percentile | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.8 mcg/h | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| 2.5 mcg/h | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Normal | 57 | 385.55(12.83) | 307.86, 463.29 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mild | 11 | 477.65(15.50) | 435.14 – 560.43 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3.9 mcg/h | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| Mild | 11 | 763.13(29.13) | 651.29 – 902.57 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| | | |
|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Extrinsic Factors | Drug interactions | No metabolic interactions; DDI potential is based purely on slowing of gastric emptying which results in non clinically relevant changes in Cmax and no changes in AUC of concomitant oral drugs. (Section 2.7.2.3.6.1, Summary of BYETTA Drug-Drug Interaction Studies) |
| | Food Effects | Not applicable (administered subcutaneously) |
| Expected High Clinical Exposure Scenario | Expected high exposure in moderate renal impairment as the Sponsor proposes to not recommend dosing in patients with ESRD or severe RI (see table above). Given the long-acting nature of the formulation, weekly C _{ss} rather than C _{max,ss} is most therapeutically relevant exposure measure due to large accumulation ratio (8.6 fold). For moderate renal impairment group, geometric mean (SD) C _{ss} (10 th percentile, 90 th percentile) is 335.6 (1.9) pg/mL (147.0, 647.4). Normal renal function group, geometric mean (SD) is 210.3 (2.0) pg/mL (88.1, 463.2). (Section 2.7.2.3.5.2.1, Steady-State Concentrations by Renal Function and Scale of Material, Table 10) | |

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

/s/

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11/28/2011

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: October 26, 2011

Reviewer(s): Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Drug Name(s): Bydureon
(Exenatide Extended-release for injectable suspension)
2 mg/vial

Application Type/Number: NDA 022200

Applicant/sponsor: Amylin Pharmaceuticals, Inc.

OSE RCM #: 2011-2841

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container label, carton labeling, Prescribing Information, Medication Guide, Patient Package Insert labeling, and Patient Instructions for Use for Exenatide Extended-release for Injectable Suspension, 2 mg/vial, for areas of vulnerabilities that could lead to medication errors. This review is in response to the August 11, 2011 request from the Division of Metabolism and Endocrinology products (DMEP) for review of the labels and labeling submitted by Amylin Pharmaceuticals, Inc. on July 28, 2011.

1.1 BACKGROUND OR REGULATORY HISTORY

Bydureon (NDA 022200) is a dual trade of Exenatide Injection that is also currently marketed as Byetta (NDA 021773, approved on April 28, 2005 as an adjunctive therapy, and NDA 021919, approved on October 30, 2009 as monotherapy) by the same Applicant for the same indication for use, but with a different dosage form and frequency of administration.

The proposed proprietary name, Bydureon was found acceptable in OSE review #2009-2193, dated February 2, 2010, and OSE review #2010-1458, dated September 15, 2010. DMEPA also reviewed container labels, carton labeling, Prescribing Information, Medication Guide, Patient Package Insert labeling (PPI), and Patient Instructions for Use in OSE review #2009-2211, dated February 25, 2010, and made recommendations to the Applicant.

This Application received a Complete Response letter from the FDA on March 12, 2010, and again on October 18, 2010. The July 28, 2011 submission is a Complete Response resubmission by the Applicant.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ the principals of human factors, and the lessons learned from postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following (see Appendices A through D for the carton and container labels):

- Container Labels (trade and sample) submitted 7/28/11
- Carton Labeling (trade and sample) submitted 7/28/11
- Prescribing Information submitted 7/28/11
- Medication Guide submitted 7/28/11
- Patient Package Insert labeling submitted 7/28/11
- Patient Instructions for Use submitted 7/28/11

Since Exenatide is currently marketed under the proprietary name, Byetta, the Division of Medication Error Prevention and Analysis would typically conduct a search of the

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Adverse Event Reporting System (AERS) to identify errors that have occurred with Byetta. However, DMEPA recently completed two reviews; OSE review #2011-1007, dated May 25, 2011 (Exenatide Injection Protocol and Labeling Review) and OSE review #2011-427 (Byetta Label and Labeling Review) which conducted AERS searches that ranged from January 1, 2008 to July 5, 2011. The results of these searches will be used in lieu of a new search. See section 3 for a discussion of AERS findings.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following sections describe DMEPA's findings from AERS as well as our findings from the labels and labeling evaluation.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH RESULTS

The April 4, 2011 AERS search conducted for OSE review #2011-1007, retrieved 134 reports. After eliminating cases that were not relevant to Exenatide due to differences in the design and labeling of the devices, the proprietary name 'Byetta', as well as wrong patient and wrong drug, ten cases (n=10) remained. Five cases (n=5) reported the use of the Byetta pen beyond the 30 days expiry period, one case (n=1) involved the wrong administration technique with the Byetta pen, two cases (n=2) involved a product quality issue with the Byetta pen, one case (n=1) involved a dose omission because the medication was not stored in the refrigerator after being used, and one case (n=1) was a product complaint.

The July 5, 2011 AERS search conducted for OSE review #2011-427, retrieved 141 reports. After combining duplicate reports into cases and eliminating cases that did not describe a medication error relevant to this review, ninety-one cases (n=91) remained. However, some of the cases reported multiple errors, which resulted in a total of ninety-eight (n=98) errors. Forty-four cases (n=44) involved dose omissions due to device malfunction (n=2), pen jamming (n=1), and patient hospitalization or patients' forgetting or not wanting to inject Byetta (n=41). Eleven cases (n=11) involved underdoses, mostly due to device malfunction. Twenty-four cases (n=24) involved overdoses, with the majority of the cases resulting from patients re-injecting Byetta because they thought they did not receive the first injection. Eleven cases (n=11) involved the wrong frequency of administration, with 6 cases reporting administering Byetta once daily, 4 cases reporting administering Byetta 3 times daily, and one case reporting administering Byetta 4 times daily (Byetta should be administered twice daily). Six cases (n=6) involved the wrong technique of administration, and two cases (n=2) involved the wrong route of administration. One of the two cases reported the patient may have injected Byetta intramuscularly instead of subcutaneously, and the other case reported the patient may have injected Byetta intravenously instead of subcutaneously.

The majority of medication errors reported above were associated with administration errors of the drug product and the use of the pen device. The errors related to device malfunction, lack of feedback from the pen device, and knowledge deficit about how to use the device. Since Bydureon is not supplied as a pen device, but as a single-dose vial, we do not anticipate the same type of device malfunctions leading to medication errors as seen with Byetta.

Although we do not anticipate similar device issues with the proposed product, we are concerned that similar errors may occur with wrong frequency of administration (n=11), and the wrong route of administration (n=2). Since Bydureon will be administered as a once-weekly subcutaneous injection, it is important for this information to be presented clearly on the container labels, carton labeling, Prescribing Information, Medication Guide, Patient Package Insert, and Patient Instruction for Use to minimize medication errors. This will be especially important for patients switching from the twice daily Byetta injections to the once-weekly Bydureon injections, who may not be used to the new product and the new frequency of administration. Furthermore, the route of administration should also be prominent on the labels and labeling to avoid administering Bydureon via an incorrect route of administration (ex. intravenously, intramuscularly, etc.) as evidenced by the two AERS cases reported in OSE review #2011-427.

3.2 LABELS AND LABELING RISK ASSESSMENT

Although the Applicant implemented most of DMEPA's labels and labeling recommendations from OSE review #2009-2211, dated February 25, 2010, there are areas that can be further improved to minimize the risk of medication errors associated with labels and labeling. We identified the following deficiencies:

- The Applicant relocated the statements 'Rx only' and 'sterile' on the vial labels, next to the route of administration statement, and therefore reducing the prominence of the route of administration statement.
- The Applicant relocated the route of administration statement to appear beneath the established name on the carton labeling, but the statement lacks prominence.
- The 'Once-weekly' reminder does not appear on the container label.
- The route of administration statement does not appear on the side or the back panels of the carton labeling.
- The 'Once-weekly' reminder on the single-dose kit lid labeling lacks prominence.
- In the Prescribing Information, an example of how to change the dosing day of the week is not included.
- In the Patient Package Insert, the paragraph regarding stopping the use of Byetta when starting Bydureon is not relocated to appear at the beginning of section 4.
- In the Patient Package Insert the storage information is inconsistent with the storage information in the Prescribing Information (7 days vs. 4 weeks).
- In the Medication Guide, the paragraph regarding stopping the use of Byetta when starting Bydureon is not relocated from the end of section 5 to section 1.
- In Patient Instructions for Use, under 'Connecting the Parts' subsection 2c, a description of an audible or tactile feedback is not indicated.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant implemented DMEPA's labels and labeling recommendations from OSE review #2009-2211, dated February 25, 2010, however, some areas such as the new

location of ‘Rx only’ and ‘sterile’ statements on the 2 mg vial label, the prominence of the route of administration on the principal display panel of the carton labeling, and the prominence of the product strength on the carton labeling can be further improved.

We provide recommendations in Section 4.1 for the Prescribing Information, Patient Package Insert, and Medication Guide for discussion during future labeling meetings. Additionally, we provide recommendations in Section 4.2 that contain comments to the Applicant that we recommend be implemented prior to approval of the supplement. If you have any questions please contact Margarita Tossa, project manager, at 301-796-4053.

4.1 COMMENTS TO THE DIVISION

Our evaluation of the revised Prescribing Information, Medication Guide, Patient Package Insert, and Patient Instructions for Use, noted that the Applicant implemented the majority of DMEPA’s recommendations in OSE review #2009-2211, dated February 25, 2010. However, the following were not implemented. We request these revisions be implemented prior to approval.

A. Prescribing Information

The Dosage and Administration Section, Section 2.1 “Recommended Dosing” subsection “Changing Weekly Dosing Schedule” may be confusing to the end user(s). Include an example of how to change the dosing day of the week in a similar manner as the example given in the Medication Guide, item 5, subsection “When to use Bydureon” bullet 3 (‘For example, if your current dosing day is Monday and you need to change it to Wednesday, here is what you would do: Take your regular dose on Monday. Then take your next dose on Wednesday of the next week. Wednesday will then be your new dosing day.’) By giving an example, it provides more clarity on how to change the day of the week. Revise accordingly.

B. Patient Package Insert

1. The following statement appears at the end of section 4; subsection “When to use Bydureon”:

This information is only for people who are currently taking BYETTA® (exenatide injection):

- If you are currently taking BYETTA, follow your healthcare provider’s instructions about when to stop taking BYETTA and when to start taking BYDUREON. BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first switch from BYETTA to BYDUREON, your blood sugar levels may be higher than usual. This is normal. Blood sugar levels often improve within about 2 weeks

This information is important for patients who are switching from Byetta to Bydureon by informing them to avoid concomitant use of the two drug products. In its current location, it may not be read or either overlooked. We request that you relocate this information to appear at the beginning of section 4 rather than the end of this section to provide greater prominence to this information.

2. In Section 6, bullet 2, the storage time that the kit can be kept out of the refrigerator is inconsistent with the information provided in section 16.2 (Storage and Handling) of the Prescribing Information (7 days vs. 4 weeks). Ensure the storage time in the Patient Package Insert is consistent with the storage time in the Prescribing Information.

C. Medication Guide

The following statement appears at the end of section 5; subsection “When to use Bydureon”:

This information is only for people who are currently taking BYETTA® (exenatide injection):

- if you are currently taking BYETTA, follow your healthcare provider’s instructions about when to stop taking BYETTA and when to start taking BYDUREON. BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first switch from BYETTA to BYDUREON, your blood sugar levels may be higher than usual. This is normal. Blood sugar levels often improve within about 2 weeks

This information is important for the patient to avoid concomitant use of Byetta and Bydureon. Thus, it is more appropriate under section 1. We request that you relocate this information to section 1 “What is the most important information I should know about Bydureon?”

D. Patient Instructions for Use

Connecting the Parts

In step 2c, if there is audible or tactile feedback when the vial is pressed into the orange connector, indicate what the sound is or what the tactile feedback is (e.g., Press the top of the vial firmly into the orange connector until it clicks or until it snaps on).

4.2 COMMENTS TO THE APPLICANT

A. All Container Labels and Carton Labeling (trade and professional sample)

1. We note the proprietary name is presented in all capital letters (i.e. BYDUREON) which decreases readability. Revise the proprietary name to appear in title case (i.e. Bydureon). Words set in upper and lower case, form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.

B. Container (2 mg vial) Labels (Trade and Professional Sample)

1. Relocate the 'Rx only' and 'Sterile' statements from the principal display panel to the lower right hand side of the label. As currently presented, the placement of the 'Rx only' and 'Sterile' statements next to the route of administration statement distracts from the important information 'Subcutaneous use only'.
2. Increase the prominence of 'Subcutaneous use only' by bolding the statement. As currently presented, this information is embedded in other information on the label. We had identified two medication error cases in which the patients administered Exetanide intramuscularly and intravenously instead of subcutaneously. Therefore, the clear presentation of 'Subcutaneous use only' statement may reduce the risk of medication errors associated with the wrong route of administration.
3. If space permits, include the 'Once-weekly' statement to the area above the proprietary name, similar to the presentation on the carton and lid labeling. Currently, the 'Once-weekly' statement does not appear on the vial labels. We had eleven medication error cases of wrong frequency of administration with another Exenatide formulation. Since your proposed product will also introduce a new frequency of administration in to the market place, this issue becomes even more important for patients who will be switching from the twice daily Byetta to the once-weekly Bydureon. Patients may not recognize that the new product, Bydureon has to be administered once weekly instead of twice daily. Therefore, the prominent presentation of this statement on all labels and labeling may reduce the risk of mediation errors associated with the wrong frequency of administration.

C. Carton Labeling (trade and sample)

1. Increase the prominence of the route of administration statement on the principal display panel by increasing the font size and bolding it. As currently presented, the statement 'Subcutaneous use only' lacks prominence.
2. Revise the color of the strength statement (i.e. 2 mg/vial) to appear in a color that provides more contrast with the white background. As currently presented the color (b) (4) against the white background lacks contrast and is difficult to read. We recommend you use the same font color to represent the product strength that you use for the other labels and labeling (i.e. black or green).

D. Single-dose Kit Lid Label (trade and sample)

1. Increase the prominence of 'Once-weekly' statement on the single-dose kit lid label. However, ensure this statement does not compete with prominence with the proprietary name.

2. Include the statement ‘Discard unused portion’ on the single-dose kit lid label. The statement ‘Discard unused portion’ can be placed immediately following the statement ‘Inject immediately after mixing.’
3. Delete the statement [REDACTED] ^{(b) (4)}
[REDACTED] This information is not required, and it crowds the label.
4. Provide a single space between the ‘0.65’ and ‘mL’ to appear as follows: ‘1 diluent syringe (0.65 mL)’. As currently presented (0.65mL), there is no space between ‘0.65’ and ‘mL’.

E. Diluent Syringe Label

1. Increase the font size of the name ‘Diluent’. As currently presented, ‘Diluent’ lacks prominence because it appears as the same font size as ‘Bydureon’.
2. Revise the name ‘BYDUREON’ to appear in title case (i.e. Bydureon) and decrease the font size of Bydureon to appear smaller than the Name of the product, ‘Diluent’. Additionally, delete ‘suspension of’ from the statement ‘for suspension of Bydureon’. The revised statement should appear as follows:

‘ **Diluent**
for Bydureon’

3. Include the contents of the Diluent on the syringe label. As currently presented, the ingredients of the Diluent do not appear on the label and it is not clear to patients and healthcare professionals what constitutes the Diluent.

REFERENCES

1. *OSE review #2009-2211, Bydureon Label and Labeling Review, February 25, 2010, Duffy, F.*
2. *OSE review #2011-1007, Exenatide Injection Protocol and Labeling Review, May 25, 2011, Maslov, Y.*
3. *OSE review #2011-427, Byetta Label and Labeling Review, July, 2011, Maslov, Y.*

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MANIZHEH SIAHPOUSHAN
10/26/2011

ZACHARY A OLESZCZUK
10/26/2011

CAROL A HOLQUIST
10/26/2011

DSI CONSULT: Request for Clinical Inspections

Date: August 10, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Leibenhaut
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Valerie Pratt/MO/DMEP
Ilan Irony/TL/DMEP

From: Pooja Dharia, Regulatory Project Manager/DMEP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 022200

Applicant/ Applicant contact information (to include phone/email):

Orville Kolterman, MD, Sr. Vice President, Research & Dev.
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121-3030
858-642-7153

Drug Proprietary Name: Bydureon (exenatide extended-release for injectable suspension)
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority – Class 2 resubmission; 6 month review timeline

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Type 2 DM

PDUFA: 1/28/12
Action Goal Date: 12/12/11
Inspection Summary Goal Date: 12/5/11

DSI Consult
version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Please choose 2 or 3 clinical sites for inspection from the list below:

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects (Randomized) | Indication |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------------|--------------------------------------------|
| Dario Altamirano AGA Clinical Trial 900 W. 49 St, Suite 224 Hialeah, FL 33012 USA | BCB108 | 22 | High enroller and high protocol violations |
| Ernesto Fuentes Elite Research Institute 15705 NW 13 Ave Miami, FL 33169 USA | BCB108 | 17 | High enroller and high protocol violations |
| Anna Chang John Muiur Physician Network Clinical Research Center 2700 Grant St, Suite 200 Concord, CA 94520 USA | BCB108 | 10 | High enroller and high protocol violations |
| Douglas Denham DGD Research, Inc. 803 Castroville Rd San Antonio, TX 78237 USA | BCB108 | 14 | High enroller and high protocol violations |

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI’s thoughts on things to consider in your decision making process*

Sites were selected on the bases of high enrollment and protocol violations. OSI review will consult the OSI CI database to determine the actual sites to be inspected from the above list.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Pooja Dharia at 301-796-5332 or Valerie Pratt at 301-796-1050.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5
or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

POOJA DHARIA
08/12/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 9, 2011

TO: File for Complaint #3232

FROM: Dan-My T. Chu, Ph.D.
Regulatory Review Officer
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance

THROUGH: Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance

SUBJECT: Complaint #3232
Amylin Pharmaceuticals
9630 Towne Centre Drive
San Diego, CA 92121

(b) (4)

BACKGROUND:

On February 23, 2011, DSI was forwarded a complaint that was received by the Division of Metabolism and Endocrinology Products (DMEP). In a letter dated (b) (6), the complainant raised concerns about two pending NDAs based on knowledge (b) (6)

Amylin Pharmaceuticals; investigational drug: Bydureon (exenatide LAR) [NDA 22,200]. The complainant alleged that the cardiac toxicity concerns raised by the FDA in the case of Bydureon were related to the microsphere carriers that are incorporated into the investigational drug formulation. Specifically:

- The complainant stated that (b) (4), (b) (6) was made aware of the firm's findings regarding the use of Alkermes polylactide/polyglycolide microspheres. The complainant alleged that at the time, (b) (6), (b) (4) was investigating a (b) (4) that incorporated the active pharmaceutical

ingredient into the Alkermes microspheres. According to the complainant, the development of the investigational product (b) (4)

and the conclusion was that no matter how careful or skilled a physician might be, the route of (b) (4) injection could potentially result in infiltration of the microspheres into the venous system which might result in destruction of cardiac tissue, or cause myocardial infarct or stroke. The complainant noted that the author of the report determined that the causative agent of damage was most likely the microsphere carrier and not the active ingredient. The complainant believed that the (b) (4) reports were still retained by (b) (4), (b) (6).

- With regard to the Bydureon NDA, the complainant alleged that (b) (4), (b) (6)

The complainant alleged that in the case of Bydureon, the same Alkermes microsphere investigated by (b) (6), (b) (4) was now incorporated into the formulation which could have bearing on the cardiac toxicity concerns with respect to the Amylin drug product.



COMPLAINT INVESTIGATION/EVALUATION:

Evaluation of Amylin Pharmaceuticals; investigational drug: Bydureon (exenatide LAR).

- Two clinical investigators were inspected with regard to NDA 22,200. Per the clinical inspection summary (CIS) dated December 29, 2009, data from the inspected sites were recommended as reliable in support of the application.
- In an email dated February 28, 2011, DSI reviewer Susan Leibenhaut was forwarded an assessment of the Bydureon complaint by the Pharm/Tox supervisor, Karen Davis Bruno. Dr. Bruno noted that she wasn't sure if the microsphere formulation used for Bydureon was the same as the Alkermes microsphere formulation referred to by the complainant. Dr. Bruno noted that she did not see a compelling case for the cardiac toxicity for the PLG (polylactide co-glycolide) microspheres in Bydureon as the amount of PLG injected at each dose administration of Bydureon is (b) (4) times lower than that of other approved products containing PLG including Nutropin depot; Zoladex; Risperdal; Lupron;

Sandostatin LAR; and Vivitrol. Dr. Bruno further noted that a literature review showed that there was no indication that PLG or its degradation products cause systemic toxicity, reproductive or developmental effects, genotoxicity or carcinogenicity at clinically relevant doses.

- Review of the documentation in DAARTS shows that the sponsor was issued a complete response letter on March 12, 2010. Prior to the re-submission of a response by the sponsor on April 22, 2010, the FDA was made aware of a QT study (tQT) that took place between April and July 2008 as required by Health Canada. The FDA had not been informed of the study results or concerns raised by Health Canada. The sponsor was requested to submit the study results to FDA. Subsequent to the review of the study, in a letter dated October 18, 2010, DMEP sent the sponsor another complete response letter requesting the sponsor conduct an additional study to examine the safety of the drug and to also provide the results of another recently completed study. The sponsor disputed this complete response letter. In a letter dated May 11, 2011, the FDA informed the sponsor that their request for formal dispute resolution was denied.

The allegations made by the complainant were primarily related to the safety of the investigational drug product. Based on the review division's assessment by Dr. Bruno as discussed above, the allegations do not appear to raise any significant good clinical practice (GCP) concerns.

(b) (4)



nonresponsive



(b) (4)

CONCLUSION:

No further DSI investigation of this complaint is warranted for the following reasons:

- With regard to the allegations made regarding Amylin Pharmaceuticals (investigational drug: Bydureon), the complaint was primarily related to issues regarding the safety of the investigational product. It was noted that a pharm/tox evaluation was conducted and did not find compelling evidence that the microsphere formulation used in the drug product was linked to cardiac toxicity. It is recommended that the review division follows its procedures for examining what additional safety evaluations, if any, will need to be investigated in lieu of the information provided by the complainant. There do not appear to be any GCP-related issues noted by the complainant with regard to Amylin's NDA 22,200.

(b) (4)



{See appended electronic signature page}

Dan-My T. Chu, Ph.D.
Regulatory Review Officer
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

DAN-MY T CHU
06/14/2011

CONSTANCE LEWIN
06/15/2011

**Interdisciplinary Review Team for QT Studies Consultation:
Protocol Synopsis Review**

| | |
|------------------------------------|-----------------------------------------------------|
| IND | IND 67092 & NDA 22200 |
| Generic Name | Exenatide (Bydureon) |
| Sponsor | Amylin Pharmaceuticals |
| Indication | Treatment of Patients with type 2 diabetes mellitus |
| Dosage Form | Subcutaneous injection |
| Drug Class | Glucagon like peptide-1 agonist |
| Therapeutic Dose | 2 mg once weekly (Bydureon: exenatide LAR) |
| Duration of Therapeutic Use | Chronic |
| Maximum Tolerated Dose | Not identified |
| Application Submission Date | October 29, 2010 |
| Review Classification | Priority |
| Date Consult Received | November 8, 2010 |
| Clinical Division | DMEP |

1 SUMMARY

1.1 QT Interdisciplinary Review Team Comments

The following comments should be conveyed to the Sponsor:

1. The suprathereapeutic target of 500 pg/mL is expected to cover the steady state exposures possible with exenatide once weekly formulation in patients with moderate renal impairment. However, according to the proposed design, the PK samples would be collected over a relatively constant target concentration of 300 and 500 pg/mL. Thus, the average increase in concentration is only 1.7 fold which may not be adequate to characterize exposure-response relationship. We recommend sponsor to have additional sampling points early in the infusion cycle (between start of the infusion until 300 pg/mL target is reached) to obtain wide range of exposures and corresponding ECGs.
2. The sponsor proposes to collect multiple (N=11) PK and ECG sample points over 12 h once a target steady state concentration reaches and stabilizes at approximately 300 and 500 pg/mL. Eleven sampling time points over a period of 12 h at relatively constant concentrations may not be needed. Rather, as stated above, we recommend sponsor to collect PK and ECG at lower concentrations for adequate characterization of exposure response relationship.

3. We have concerns about your plan to replace subjects who withdraw from the study. Subject replacement will violate the randomization principle. Efforts should be made to enroll and retain the subjects for the entire study period. If the reasons for withdrawal are related to the treatment, then replacing subjects could bias the results. In addition, having to adjust enrollment due to withdrawals during the trial may pose logistical problems and may affect the integrity of the trial. You might need to consider enrolling more subjects based on the anticipated dropout rate if possible.
4. When using moxifloxacin as the positive control, we want to see that (1) the baseline corrected mean difference of moxifloxacin and placebo on QTc should be greater than 5 ms as evidenced by the largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTc} > 5$ ms and (2) QTc profile of moxifloxacin over time is adequately demonstrated (time-course of $\Delta\Delta\text{QTc}$ follows expected moxifloxacin concentration-time course). To perform this task (1), you will benefit by examining only a few time points where the maximum moxifloxacin effect will occur. For instance, a few time points near T_{max} (between 1 hr to 4 hr after dose). We agree with your plan to adjust multiple endpoints for moxifloxacin.
5. Categorical analyses should summarize the number of subjects as well as the number of observations with QTc intervals > 450 ms, > 480 ms, and > 500 ms and change from baseline in QTc > 30 ms and > 60 ms.
6. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and $\Delta\Delta\text{QTc}$ (time-matched drug-placebo difference in QTc interval, baseline-adjusted). Based upon this relationship, the predicted population average $\Delta\Delta\text{QTc}$ and its corresponding upper 95% 1-sided confidence interval bound may be computed at appropriate concentrations, e.g., the mean maximum plasma concentrations under therapeutic and supratherapeutic doses or other concentrations of interest. In addition to the above analysis, there may be merit in considering alternate dependent variables such as QTc or ΔQTc (baseline-adjusted) to derive the $\Delta\Delta\text{QTc}$ endpoint.

We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

7. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
 - a. Pre-specify the lead for interval measurements
 - b. Baseline and on-treatment ECGs should be based on the same lead
8. We are also interested in the effects of exenatide on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.
9. When you submit your ‘thorough QT study’ report, please include the following items:

- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol
 - d. Electronic or hard copy of the Investigator's Brochure
 - e. Annotated CRF
 - f. A data definition file which describes the contents of the electronic data sets
 - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
 - h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
 - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
 - j. Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
 - k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - l. A completed Highlights of Clinical Pharmacology Table
10. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library.

2 BACKGROUND

Please refer to QT-IRT review dated August 16, 2010 under IND 57725 / NDA 21773 / NDA 22200 / NDA 21929.

The sponsor (Amylin Pharmaceuticals) developed two exenatide formulations. Byetta, which was approved in 2004, is the trade name for the immediate-release formulation

with twice daily dosing. Bydureon is the trade name for the extended-release formulation with once weekly dosing and is currently under NDA review. A thorough QT study (H8O-EW-GWCI) was conducted by using single therapeutic dose (i.e., 10 µg) of Byetta. This was reviewed by the QT-IRT and we concluded that this study was adequate to exclude small effects on the QT interval for Byetta. However, No definitive conclusion for the effect of Bydureon on QTc interval could be drawn based on the TQT study (H8O-EW-GWCI) since higher exposures expected with Bydureon were not covered in this study and exenatide appeared to increase QTc interval in a concentration-dependent manner. The division has issued a complete response letter to the sponsor dated October 18, 2010, advising them to conduct another TQT study with exenatide that would evaluate these higher exposures and the sponsor has submitted a protocol for the same.

2.1 Clinical Pharmacology

Appendix 5.1 summarizes the key features of exenatide's (once weekly formulation) clinical pharmacology.

3 THOROUGH QT STUDY SYNOPSIS

3.1 Title

A randomized, three-period, placebo- and positive-controlled, double-blind, crossover study to assess the electrophysiological effects of exenatide given as a continuous intravenous infusion at concentrations observed in subjects with renal impairment and suprathreshold concentrations on the 12-lead electrocardiogram QT interval in healthy subjects

3.2 Protocol Number

BCB 112

3.3 Study Objectives

3.3.1 Primary

To determine, in healthy subjects, that exenatide given as a continuous intravenous infusion (to achieve exenatide concentrations observed at steady-state in subjects with renal impairment and suprathreshold exenatide concentrations) does not differ from placebo in the mean change from pre-dose in 12-lead electrocardiogram (ECG) corrected QT (QTc) interval measurements (such that the upper bound of the one-sided 95% confidence interval [CI] between exenatide and placebo (exenatide-placebo) is <10 ms).

3.3.2 Secondary

- To evaluate the relationship between plasma exenatide concentrations and QT/QTc intervals at concentrations observed in subjects with renal impairment and suprathreshold concentrations.
- To explore the influence of potential physiological covariates such as plasma glucose, serum insulin, and potassium on the QTc interval.

- To evaluate the safety and tolerability of exenatide given as continuous intravenous infusion over approximately 2 days.

3.4 Study Description

3.4.1 Design

- This study is a Phase 3, randomized, three-period, placebo- and positive-controlled crossover study conducted at a single clinical study site.
- This study will employ a double-blind infusion design in order to avoid the potential for bias in study assessments.
- This study is comprised of an approximately 15-day ECG assessment period that includes 3 treatment periods (see table below).
- At least 60 subjects will be randomly assigned across 6 treatment sequences in a 1:1:1:1:1:1 ratio. Subjects who do not complete the entire data collection period for each of the 3 treatment periods may be replaced.

(b) (4)



Source: Pages 3 & 4 from sponsor's protocol synopsis

3.4.2 Treatment Regimens

3.4.2.1 Treatment Arms

Three treatment arms are being evaluated in the current study:

- Stepped intravenous infusion of exenatide to deliver gradually increasing concentrations to achieve steady state concentrations of 300 pg/mL (Day 1) and 500 pg/mL (Day 2).
- Stepped intravenous infusion of placebo infused at the same rate as of exenatide.
- Moxifloxacin (400-mg tablet, single oral dose) will be provided on the days of positive control assessments.

3.4.2.2 Instructions with Regard to Meals

Exenatide will be administered by intravenous infusion and thus effect of food is not applicable.

3.4.2.3 Sponsor's Justification for Dose

“Steady-state plasma exenatide concentrations from 300 subjects receiving 2 mg exenatide once weekly (QW) treatment across 3 clinical trials (Studies 2993LAR-105, BCB106, and BCB108) were pooled and the resulting geometric mean exenatide

concentration at steady state (C_{ss} overall) was calculated (252 pg/mL). Steady-state exenatide exposure by renal function (normal [creatinine clearance ($CrCl$) >80 mL/min], mild impairment [50 mL/min < $CrCl$ ≤80 mL/min], moderate impairment [30 mL/min < $CrCl$ ≤50 mL/min], or severe impairment [$CrCl$ ≤30 mL/min]) was also examined. Plasma exenatide concentrations increased with decreasing renal function, with a geometric mean average exposure (C_{ss} avg) of 336 pg/mL in subjects with moderate renal impairment, compared to a C_{ss} avg of 206 pg/mL in subjects with normal renal function. Only 2 subjects were identified with severe renal impairment (C_{ss} of 606 pg/mL and 722 pg/mL). Based on these results, 2 primary target concentrations were selected to evaluate a relevant range of exenatide concentrations on QTc prolongation. A therapeutic target concentration of 300 pg/mL was selected to approximate the range of exenatide exposure seen in subjects with mild to moderate renal impairment. At the target median C_{ss} value of 300 pg/ml, 95% of the subjects will achieve a range of exposures between 161-525 pg/mL, and 75% of the subjects will achieve exposures between 242-387 pg/mL.

“The supratherapeutic concentration of 500 pg/mL was selected to reflect concentrations that are significantly higher than that observed in subjects with moderate renal impairment. This upper target was selected to strike a balance between achieving the highest concentrations that could be observed with exenatide QW use and acute tolerability issues that could confound the ability to accurately collect and analyze ECG data. It is estimated that with a target median C_{ss} value of 500 pg/ml, 95% of subjects will achieve a range of exposures between 265-873 pg/mL. In addition, 75% of subjects would achieve exposures between 401-641 pg/mL. The upper end of this range is significantly higher than what is typically observed in patients with moderate renal impairment receiving 2 mg exenatide QW. These plasma concentrations, especially in healthy volunteers, would be expected to cause GI intolerance in some subjects, thus making even higher doses impractical, and subject to potential IRB ethical concerns. In addition, high concentrations of exenatide in healthy volunteers may drive glucose down more than would be expected in patients with diabetes, resulting in a robust counter-regulatory response, further confounding the ability to interpret the QT analysis.”

(Source: Sponsor’s draft-protocol-sum-bcb112, Page 5)

Reviewer’s Comment: Sponsor uses C_{ss_ave} (average concentration at steady state) observed in the phase 3 trials to support their proposed target concentration range. However, mean degree of fluctuation (calculated as $[C_{ss_max} - C_{ss_min}] / C_{ss_ave}$) for exenatide once weekly formulation at steady state over a dosing interval from week 29 to 30 indicates that, relative to the average weekly concentrations, the difference between minimum and maximum concentrations is 78%. It was seen that the C_{ss_max} was 1.4-fold the C_{ss_ave} . Maximum average concentration at steady state observed in patients with moderate renal impairment was 336 pg/mL. Considering a 1.4-fold increase in steady state C_{max} , the maximum mean concentration possible in moderate renal impaired patients would be 482 pg/mL which should be covered by supratherapeutic concentration target of 500 pg/ml proposed by the sponsor.

However, since the PK samples would be collected at a relatively constant target concentration of 300 and 500 pg/mL, the average increase in concentration within a patient is only 1.7-fold which may not be adequate to characterize exposure-response relationship. We recommend sponsor to have additional sampling points early in the

infusion cycle (between start of the infusion until 300 pg/mL target is reached) to obtain wide range of exposures and corresponding ECGs. Furthermore the number of PK and ECG sampling time points proposed at 300 or 500 pg/mL can be reduced (see 3.6.2).

3.4.3 Controls

The study will utilize both negative (placebo) and positive (moxifloxacin) controls.

3.4.4 Blinding

There is no plan to blind administration of moxifloxacin.

3.5 Study Subjects

The study will enroll approximately 70 healthy males or females, 18 to 65 years of age, with a normal 12-lead ECG and BMI between 25 and 35 kg/m².

3.6 Study Assessments

A table of study assessments is presented in Appendix 5.2.

3.6.1 QT Measurement

Continuous 12-lead ECGs will be collected using a 12-lead digital holter recorder. Just prior to collection of the serial ECG measurements, subjects will be asked to lie supine for 10 minutes prior to and 5 minutes after each specified recording period while lying awake but completely still in a quiet room. Serial ECGs will be extracted at times specified in the study plan with four 12-lead H-12 holter ECGs extracted at each time point.

The ECGs will subsequently be electronically transmitted to the centralized ECG vendor as designated by Amylin. The cardiologist responsible for over-reading the ECGs will be blinded to all study treatments/sequences. If more than one cardiologist performs over-reads, the same cardiologist will over-read all ECGs for a given subject.

(Source: Appendix 3, page 17 and 18 from the protocol synopsis)

Reviewer's Comment: Sponsor proposes to collect multiple (N=11) PK and ECG sample points over 12 h once a target steady state concentration reaches and stabilizes at approximately 300 and 500 pg/mL . Eleven sampling time points over a period of 12 h at relatively constant concentrations may not be needed. Rather, we recommend sponsor to collect PK and ECG at lower concentrations (between start of the infusion until 300 pg/mL target is reached) to be able to adequately characterize exposure response relationship.

3.6.3 Safety Assessments

See Appendix 5.2 for safety assessments.

4 DATA ANALYSIS PLAN

4.1 Statistics

4.1.1 Sample Size

Approximately 70 subjects will be enrolled to ensure at least 60 subjects (10 subjects per sequence) complete all 3 periods of the treatment. Subjects who do not complete the entire data collection period for each of the 3 treatment periods may be replaced.

4.1.2 Baseline

The pre-dose baseline QTc values on Day 1 for each treatment will be used for the analysis.

4.1.3 Primary Analysis

4.1.3.1 Primary Endpoint

The choice of the best QTc correction method as the primary endpoint for this study will be selected based on the ability of each method to remove the influence of heart rate on QT.

4.1.3.2 Statistical Analysis

The change from pre-dose to each QT assessment in each treatment period (Δ QTc) will be calculated. A mixed-effects model will be employed with the change in QTc interval from the pre-dose measurement (Δ QTc) as the dependent variable, and with treatment, time, period, sequence, and time-by-treatment interaction as fixed effects. The random effects in the model will include the subject effect, the subject by treatment interaction, and subject-by-time interaction. If the fixed effects for period and/or sequence should prove to be non-significant (that is, if $p > 0.1$), these effects may be removed from the model. An assumption of constant variance at each time point within each treatment will be made in this model. The conclusions from the mixed-effect model based on a constant variance assumption will be compared to the conclusions from a similar mixed-effect model with an unstructured covariance matrix. The mean difference in time matched Δ QTc between the exenatide and placebo ($\Delta\Delta$ QTc) and associated two-sided 90% CI will be computed when plasma exenatide concentration reached approximately 300 pg/mL at $t = 12\text{h}, 13\text{h}, 14\text{h}, 15\text{h}, 16\text{h}, 17\text{h}, 18\text{h}, 19\text{h}, 20\text{h}, 21\text{h}, 22\text{h},$ and 23h , and 500 pg/mL at $t = 36\text{h}, 37\text{h}, 38\text{h}, 39\text{h}, 40\text{h}, 41\text{h}, 42\text{h}, 43\text{h}, 44\text{h}, 45\text{h}, 46\text{h},$ and 47h . If the upper bound of the two-sided 90% CI (equivalent to the upper bound of a one-sided 95% CI) for the largest time-matched mean difference between exenatide and placebo is less than 10 ms, then a “negative thorough QT/QTc study” will be concluded. A “positive thorough QT/QTc study” will be concluded otherwise.

To establish assay sensitivity in the trial, moxifloxacin’s effect on QTc interval will be compared to that of placebo using the same approach employed in the primary analysis. The time-matched mean difference and p-values will be computed at time points coinciding with the 300 pg/mL and 500 pg/mL plasma exenatide concentrations. Assay sensitivity will be established if the time-matched mean difference between moxifloxacin

and placebo is significantly different from 0 at a two-sided 0.05 significance level at one or more time points. To adjust for multiplicity arising in the assay sensitivity analysis, a resampling-based multiple test will be carried out. This test will account for the correlation among the test statistics associated with the moxifloxacin-placebo comparisons at the post-dose time points.

Reviewer's comments: When using moxifloxacin as the positive control, we want to see that (1) the baseline corrected mean difference of moxifloxacin and placebo on QTc should be greater than 5 ms as evidenced by the largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTc > 5$ ms and (2) QTc profile of moxifloxacin over time is adequately demonstrated (time-course of $\Delta\Delta QTc$ follows expected moxifloxacin concentration- time course). To perform task (1), you will benefit by examining only a few time points where the maximum moxifloxacin effect will occur. For instance, a few time points near T_{max} (between 1 hr to 4 hr after dose). We agree with your plan to adjust multiple endpoints for moxifloxacin.

4.1.4 Categorical Analysis

The sponsor has not provided any categorical analysis plan.

4.2 Clinical Pharmacology

4.2.1 Pharmacokinetics

Concentrations of exenatide over 12 h will be assessed after target concentration of 300 and 500 pg/mL is reached. No formal pharmacokinetic data analysis will be performed.

Reviewer's Comment: Acceptable.

4.2.2 Exposure-Response Analysis

“The relationship of QTcI with plasma exenatide concentrations will be assessed using analysis of covariance. To quantify the relationship, a mixed-effects analysis of covariance model will be constructed with $\Delta\Delta QTcI$ as the dependent variable, the time-matched exenatide plasma concentration as a covariate, and subject as a random effect. In addition, simultaneous population pharmacokinetic/pharmacodynamic (PK/PD) modeling approaches may be explored to quantify the influence of exenatide exposure on QTc prolongation. As secondary support for assay sensitivity, the Sponsor may also quantify the PK-QT/QTc relationship of moxifloxacin within the study.”

(Source: Sponsor's draft-protocol-sum-bcb112, Page 9)

Reviewer's Comment: Acceptable. Please refer to our standard comments (comment 6 in section 1.1) for details.

5 APPENDICES

5.1 Highlights of Clinical Pharmacology

| | | |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose | 2 mg QW | |
| Maximum tolerated dose | 10 mg single dose; max tolerated dose not identified [NDA 022-200, 2.7.2.5] | |
| Principal adverse events | Nausea and Vomiting | |
| Maximum dose tested | Single Dose | 10 mg [NDA 022-200, 2.7.2.3.1.1] |
| | Multiple Dose | 2 mg QW safety through 52 weeks [NDA 022-200, 2.7.4.1.2.1, NDA 022-200, 2.7.2.2, Study 2993LAR-105] |
| Exposures Achieved at Maximum Tested Dose | Single Dose | AUC _(0-6h) mean (SE) 203,954 (15,654) pg·h/mL C _{max} (0-6h) mean (SE) 641 (88.5) pg/mL C _{max} (0-8) mean (SE) 200 (18.6) pg/mL [NDA 022-200, 2.7.2.3.1.1, Table 3] |
| | Multiple Dose | C _{ss} max at 29-30 weeks Geometric mean (CV%) 432.7 (86.3) pg/mL AUC _{ss} 50,484 (69.7) pg·h/mL [NDA 022-200, 2.7.2.3.1.2, Table 4] |
| Range of linear PK | AUC from single doses of 2.5 to 10 mg and AUC _{0-tau,ss} following multiple QW doses of 0.8 to 2 mg appeared to increase dose proportionally (Not statistically tested). [NDA 022-200, 2.7.2.3.1.6] | |
| Accumulation at steady state | ~8.6 fold following 2 mg QW [NDA 022-200, 2.7.2.3.1.3] | |
| Metabolites | PK parameters for metabolites not applicable. | |
| Absorption | Absolute/Relative Bioavailability | Absolute: Not evaluated for exenatide QW. The absolute bioavailability of Byetta ranged from LS Mean Ratio (CV) of 113% -121% (71%) at different sites of injection. [NDA 021-773, 2.7.2.2, 2993-118] Relative (to Byetta): Mean (90% confidence intervals) bioavailability for steady state weekly 2 mg dosing was 25% (21%, 30%) [NDA 022-200, 2.7.2.3.1.4] |
| | T _{max} | • Parent: Median (10 th -90 th percentile) at steady-state over a dosing interval, 22.8 h (1.17, 167.75) [NDA 022-200, 2.7.2.3.1.3.1] • Metabolites: Not applicable |
| Distribution | V _d /F or V _d | Byetta (exenatide immediate release) Mean (10 th - 90 th percentile) – 28.3 L (15.47 - 62.50 L) [NDA 022-200, 2.7.2.3.1.5; NDA 021-773, 2.7.2.3.1.1] |
| | % bound | - 18% bound to erythrocytes [NDA 022-200, 2.6.4.4.2] - Protein binding to serum albumin not determined |

| | | |
|-------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Elimination | Route | <ul style="list-style-type: none"> primary: glomerular filtration [NDA 022-200, 2.7.2.3.1.5] percent dose eliminated: estimated to be >80% based on ESRD patients with Byetta showing a CL/F reduction by 84% compared to normal renal function [NDA 022-200, 2.7.2.3.5.2] proteolytic degradation subsequent to glomerular filtration [NDA 022-200, 2.7.2.3.1.5] |
| | Terminal t _{1/2} | <ul style="list-style-type: none"> Not applicable (sustained release) Time required for the decline in plasma exenatide exposure following cessation of exenatide once weekly therapy is approximately 7 weeks after the last injection [NDA 022-200, 2.7.2.3.1.2] Metabolites: Not applicable |
| | CL/F or CL | <p>Mean (10th – 90th percentile) from Byetta CL/F = 9.1 L/hr (6.15 - 15.86 L/hr)</p> <p>[NDA 021-773, 2.7.2.3.1.1, Table APP 15]</p> |
| Intrinsic Factors | Age | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Sex | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Race | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Hepatic & Renal Impairment | <p>Hepatic: Not evaluated in hepatic impairment; primarily renally cleared. [NDA 022-200, 2.7.2.3.5.6]</p> <p>Renal: Median Individual Predicted C_{0,ave} (25th – 75th percentile) (pg/mL) following multiple doses of 2 mg exenatide QW: normal renal function 300.3 (252.7 - 369.6), mild renal impairment 368.7 (282.6 – 436.6), moderate renal impairment 523.4 (398.2 – 714.4) Thus, no relevant change in subjects with mild to moderate renal impairment; however, not recommended for use in patients with severe renal impairment or ESRD. [NDA 022-200, 2.7.2.3.5.2, Table 7]</p> |

| | | |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Extrinsic Factors | Drug interactions | No metabolic interactions; DDI potential is to slow gastric emptying. Acetaminophen absorption as marker of gastric emptying: Acetaminophen C _{max} reduced 16% in the fasted state and 5% in the fed state. AUC reduced 4% in fed and fasted state with exenatide once weekly co-administration. BYETTA: acetaminophen, digoxin, warfarin, lisinopril, lovastatin, ethinyl estradiol and levonorgestrel (CYP3A) studies showed no clinically relevant changes in C _{max} and/or AUC. [NDA 022-200, 2.7.2.3.6.1] |
| | Food Effects | Not applicable (administered subcutaneously) |
| Expected High Clinical Exposure Scenario | Expected high exposure in moderate renal impairment. Predicted weekly C _{ss} is most therapeutically relevant exposure measure due to large accumulation ratio (8.6 fold). For moderate renal impairment group, Maximum value (25 th percentile, median, 75 th percentile) is 1076.8 (398.2; 523.4; 714.4). Normal renal function group, 1074.7 (252.7; 300.3 369.6). [NDA 022-200, 2.7.2.3.5.2, Table 7] | |

(b) (4)



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/s/

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications (DDMAC)**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 24, 2010

To: John Bishai – Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DDMAC
Kendra Jones, Regulatory Review Officer, DDMAC

CC: Lisa Hubbard, Professional Group Leader, DDMAC
Shefali Doshi, Acting Group Leader, DDMAC

Subject: NDA 022200 Bydureon (exenatide extended-release for injectable suspension)

DDMAC labeling comments for Bydureon

DDMAC has reviewed the proposed prescribing information (PI) and MedGuide for Bydureon (exenatide extended-release for injectable suspension) submitted for consult on August 11, 2010 and offers the following comments.

The version of the proposed PI and MedGuide used in this review were accessed from the eRoom on August 19, 2010.

General Comment

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials. If you have any questions on the PI, please contact Samuel Skariah at 301.796.2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

For Note to FDA Reviewer:

- To facilitate review, the Highlights section of this document is presented in a single column format and does not comply with the two column format requirement. This section will be placed in the correct format once final content is negotiated.
- Content changes that we have reviewed and concur with have been accepted in the text and are not marked.
- Agency comments for which Amylin has questions or alternate suggestions, a yellow text box with our proposal has been inserted prior to the respective section. Comment boxes are numbered sequentially for referencing purposes.
- Newly proposed content from Amylin shows as tracked content.

(b) (4)

38 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22200

ORIG-1

AMYLIN
PHARMACEUTICA
LS 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/

SAMUEL M SKARIAH

08/24/2010

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

| | |
|------------------------------------|----------------------------------------------------------------------------------|
| IND or NDA | IND 57725 / NDA 21773 / NDA 22200 / NDA 21929 |
| Brand Name | Byetta; Bydureon |
| Generic Name | Exenatide |
| Sponsor | Amylin pharmaceuticals |
| Indication | Treatment of patients with type 2 diabetes mellitus |
| Dosage Form | Subcutaneous injection |
| Drug Class | Glucagon like Peptide-1 agonist |
| Therapeutic Dosing Regimen | 10 µg bid (Byetta: exenatide bid); 2 mg once weekly (Bydureon: exenatide LAR) |
| Duration of Therapeutic Use | Chronic |
| Maximum Tolerated Dose | Not identified |
| Submission Number and Date | SDN 425 / SDN 001 / SDN 002 / May 13, 2010 |
| Review Division | DMEP / HFD 510 |

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The sponsor developed two exenatide formulations. Byetta, which was approved in 2004, is the trade name for the immediate-release formulation with twice daily dosing. Bydureon is the trade name for the extended-release formulation with once weekly dosing and is currently under NDA review. The thorough QT study was conducted by using single therapeutic dose (i.e., 10 µg) of Byetta and our findings are summarized as follows.

- The thorough QT (TQT) study results can only be applied for Byetta. No significant QT prolongation effect was detected in this TQT study. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean difference between exenatide 10 µg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the placebo-adjusted, baseline-corrected QTcF ($\Delta\Delta\text{QTcF}$) for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established. Therapeutic dose of Byetta is adequate to represent the high clinical exposure scenario. Repeated twice daily dosing yields no substantial systemic accumulation of exenatide (half-life of approximately 2 hours after SC administration). No drug-drug interactions have been observed that would

significantly increase exposure. Exenatide exposure in patients with mild to moderate renal impairment is similar to that of patients with normal renal function. Byetta is contraindicated in patients with severe renal impairment or end-stage renal disease.

- No definitive conclusion for the effect of Bydureon on QTc interval can be drawn based on the TQT study for the following two reasons.
 - The mean maximum concentration (C_{max}) of exenatide observed in the TQT study is 208 pg/mL, which is half the steady state concentration following the therapeutic dose of Bydureon. In addition, following treatment with Bydureon, the clinical exposure of exenatide in patients with moderate renal impairment is expected to be 50-60% higher compared to that in patients with normal renal function.
 - Bydureon may potentially cause QTc prolongation. The current TQT study indicated that exenatide appears to increase QTc interval in a concentration-dependant manner ($P = 0.003$). The projected upper bound of 90% CI for QTc interval following steady state C_{max} of exenatide using Bydureon may exceed 10 ms, given the caveat that the model predictions are mainly based on extrapolation.

In this randomized, placebo-controlled, double-dummy, double-blinded, three-period crossover study, 62 healthy subjects received exenatide 10 µg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Exenatide 10 µg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

| Treatment | Time (hour) | $\Delta\Delta QTcF$ (ms) | 90% CI (ms) |
|----------------------|-------------|--------------------------|--------------|
| Exenatide 10 µg | 2 | 5.7 | (3.7, 7.8) |
| Moxifloxacin 400 mg* | 3 | 14.0 | (12.0, 15.9) |

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 11.4 ms.

1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

- With the updated pharmacokinetic data, another TQT study to characterize QTc and other ECG interval changes following the treatment with Bydureon may be considered as part of the PMR. Given the long half-life and delayed second peak for Bydureon, the TQT study may be conducted using Byetta. A higher than the maximum therapeutic dose of Byetta may be necessary to cover the steady state maximum concentration following the treatment with Bydureon and high clinical exposure scenario. If high dose of Byetta is infeasible in healthy subjects due to safety and tolerability concerns, the TQT study may be conducted in patients.

- 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. This finding may not be clinically significant for Byetta, but effects at higher exposures seen with Bydureon are unclear. PR prolongation may be a significant issue in patients with underlying conduction disorders, elderly, patients with sick-sinus syndrome or concomitant medications that prolong the PR interval (e.g. verapamil). Prolongation of the PR interval is associated with increased risks of AF and pacemaker implantation¹.
- HR was increased from baseline for 1-4 hours post-dosing. The maximum placebo-adjusted HR increase was 10.2 at hour 2 post-dose. It is known that an increase in HR could increase myocardial oxygen demand. The implications of an increase of this magnitude in patients with unstable congestive heart failure or ischemia are unclear.

2 PROPOSED LABEL

The sponsor did not propose any label language. We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

2.1 QT-IRT PROPOSED LABEL FOR BYETTA

The following label recommendation is for Byetta only.

Section 12 (Clinical Pharmacology):

The effect of exenatide 10 µg SC on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) crossover thorough QTc study in 62 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Federica correction (QTcF) was below 10 ms, the threshold for regulatory concern.

2.2 QT-IRT PROPOSED LABEL FOR BYDUREON

The following label recommendation is for Bydureon only since exposures were not covered in this TQT study..

Section 5 (Warnings and Precautions):

Bydureon may potentially cause QTc prolongation. Avoid Bydureon in patient with congenital 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

¹ Long-term Outcomes in Individuals With Prolonged PR Interval or First-Degree Atrioventricular Block JAMA. 2009;301(24):2571-2577

antiarrhythmics and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating Bydureon and monitor these electrolytes periodically during therapy.

3 BACKGROUND

Exenatide was approved in 2004 prior to FDA requirement for TQT of all NMEs. The QT-IRT was consulted for the once weekly extended-release preparation (Bydureon or exenatide LAR) and based on review of clinical trial data/experience and available pharmacokinetic information comparing exenatide LAR to exenatide bid (Byetta), it was determined that this NDA (22200) would not need a TQT study to support approval.

In June 2010 DMEP received a telephone communication from Health Canada regarding TQT study H80-EW-GWCI which was not conducted under a US IND and hence the results were not submitted to the FDA. Health Canada concluded that exenatide prolongs the QT and PR intervals and increases the heart rate. The conclusion on the QTcP effect was based on the fact that the mean effect was over 5 ms [maximum increase of 6.34 (90% CI 4.12, 8.56) ms at 2 hours post-dosing; the mean placebo- and baseline-adjusted change at the individual-specific C_{max} was 7.68 (90% CI 6.03, 9.32) ms]. The Division advised the sponsor to submit the results of the TQT study along with clinical trial and post-marketing data for exenatide and exenatide LAR using the following Standardized MedDRA Queries (SMQs) version 12.1: arrhythmia related investigations, signs, and symptoms; cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias). The QT-IRT has now been consulted to review the report.

3.1 PRODUCT INFORMATION

Exenatide, an incretin mimetic, was approved in April 2005 by the United States Food and Drug Administration (US FDA) and in November 2006 by the European Commission under the trade name BYETTA® (exenatide injection). BYETTA is approved as adjunctive therapy for subjects with type 2 diabetes mellitus who are taking metformin, a sulfonylurea (SU), or a combination of metformin and an SU but have not achieved adequate glycemic control. In the United States, BYETTA is also indicated as a monotherapy or as adjunctive treatment for subjects with type 2 diabetes who are taking a thiazolidinedione (TZD) or a combination of metformin and a TZD but have not achieved adequate glycemic control.

Exenatide once weekly (exenatide LAR) is currently under clinical investigation and FDA review as an extended-release formulation that consists of exenatide-containing polymeric microspheres for suspension in an aqueous diluent.

3.2 PRECLINICAL INFORMATION

Source eCTD module 1.11.2, Sponsor's response to FDA information request dated 5/13/10

“Amylin conducted an extensive nonclinical toxicology assessment for exenatide. The results of the nonclinical safety studies revealed no adverse effects of exenatide on the cardiovascular system, including blood pressure and the potential for QTc prolongation. Exenatide had no effect on hERG-mediated potassium current in vitro (IND 57,725, Serial 0284, Section 4.2.1.3, REST05118), and no adverse effects were observed on arterial blood pressure or ECG parameters, including QT/QTc intervals, in a cardiovascular telemetry study in monkeys (NDA 021-773, Serial 0000, Section 4.2.1.3.2, REST98100R1). Finally, repeat-dose toxicity studies showed no adverse effects on the cardiovascular system in mice (histopathology), rats (histopathology) and monkeys (ECGs including QT/QTc, histopathology) following administration of various formulations of exenatide for up to 2 years in rodents and up to 9 months in monkeys (NDA 021-773, Serial 0000, Sections 2.6.2.3.1 [Effects on the Cardiovascular System] and 2.6.4.2 [Cardiovascular System]; NDA 022-200, Serial 0006, Sections 2.6.6.3 [Repeated Dose Toxicology Studies], and 2.6.6.5 [Carcinogenicity], and IND 107,815, Serial 0000, Section 2.6.6.3.2 [Repeated Dose Toxicology Studies in Monkeys]).”

3.3 PREVIOUS CLINICAL EXPERIENCE

Source eCTD module 1.11.2, Sponsor’s response to FDA information request dated 5/13/10

The clinical trial data was already reviewed in our consult dated December 17, 2009. We concluded that there were no large effects on the QT interval with the exenatide formulations based on the following

- 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 < 5 ms.
- 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.

Results of Requested Analysis of Cardiac Arrhythmia- and Conduction-Related Adverse Events

The sponsor reports that the incidence of arrhythmia and conduction-related adverse events in controlled studies in the BYETTA development program was similar in BYETTA (1.5%) and comparator (placebo/insulin; 1.4%) subjects. In comparator-controlled studies of the exenatide once weekly development program, the incidence of events was similarly low in exenatide once weekly (1.5%), BYETTA (1.1%), sitagliptin (1.2%), pioglitazone (1.2%), and insulin (0.4%) subjects (no events observed in placebo-controlled exenatide once weekly studies). No pattern or clustering of events was observed with BYETTA or exenatide once weekly treatment.

| System Organ Class/ Preferred Term [2] | Placebo-Controlled | | | | Comparator-Controlled | | All Controlled | | Uncontrolled [4] | All [5] |
|---------------------------------------------------------------|------------------------|---------------------|----------------------|----------------------|-----------------------|----------------------|----------------------|-----------------------|--------------------------------|----------------------|
| | BYETTA | | Pooled (N = 1612) | Placebo (N = 971) | BYETTA | | BYETTA | | BYETTA 10 mcg (N = 1271) | Pooled (N = 2919) |
| | 5 mcg [3] (N = 621) | 10 mcg (N = 981) | | | 10 mcg (N = 704) | Insulin (N = 658) | Pooled (N = 2316) | Pbo/Ins (N = 1629) | | |
| All Treatment-Emergent Arrhythmia- and Related Adverse Events | 13 (2.1) | 16 (1.6) | 29 (1.8) | 14 (1.4) | 6 (0.9) | 9 (1.4) | 35 (1.5) | 23 (1.4) | 43 (3.4) | 75 (2.6) |
| CARDIAC DISORDERS | 6 (1.0) | 12 (1.2) | 18 (1.1) | 13 (1.3) | 5 (0.7) | 7 (1.1) | 23 (1.0) | 20 (1.2) | 30 (2.4) | 53 (1.8) |
| ARRHYTHMIA | 0 | 0 | 0 | 1 (0.1) | 1 (0.1) | 1 (0.2) | 1 (0.0) | 2 (0.1) | 0 | 1 (0.0) |
| ATRIAL FIBRILLATION | 1 (0.2) | 0 | 1 (0.1) | 2 (0.2) | 2 (0.3) | 1 (0.2) | 3 (0.1) | 3 (0.2) | 8 (0.6) | 11 (0.4) |
| ATRIAL FLUTTER | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (0.2) | 0 | 2 (0.1) | 1 (0.1) | 1 (0.0) |
| ATRIOVENTRICULAR BLOCK | 0 | 0 | 0 | 2 (0.2) | 0 | 0 | 0 | 2 (0.1) | 0 | 0 |
| FIRST DEGREE | | | | | | | | | | |
| BRADYCARDIA | 1 (0.2) | 0 | 1 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| BUNDLE BRANCH BLOCK | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 1 (0.0) |
| BILATERAL | | | | | | | | | | |
| BUNDLE BRANCH BLOCK LEFT | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 | 1 (0.1) | 0 | 0 |
| BUNDLE BRANCH BLOCK RIGHT | 0 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.0) | 1 (0.1) | 3 (0.2) | 4 (0.1) |
| CARDIAC ARREST | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 1 (0.0) |
| CARDIAC FLUTTER | 0 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.0) | 1 (0.1) | 0 | 1 (0.0) |
| PALPITATIONS | 1 (0.2) | 7 (0.7) | 8 (0.5) | 3 (0.3) | 1 (0.1) | 2 (0.3) | 9 (0.4) | 5 (0.3) | 6 (0.5) | 15 (0.5) |
| SICK SINUS SYNDROME | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 1 (0.0) |
| CARDIAC DISORDERS (Cont'd) | | | | | | | | | | |
| SINUS BRADYCARDIA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.1) |
| SINUS TACHYCARDIA | 0 | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) | 0 | 0 | 1 (0.0) |
| SUPRAVENTRICULAR EXTRASYSTOLES | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 1 (0.0) |
| SUPRAVENTRICULAR TACHYCARDIA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.1) |
| TACHYARRHYTHMIA | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) | 0 | 1 (0.1) | 2 (0.1) |
| TACHYCARDIA | 1 (0.2) | 0 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.2) | 2 (0.1) | 2 (0.1) | 1 (0.1) | 3 (0.1) |
| VENTRICULAR EXTRASYSTOLES | 2 (0.3) | 2 (0.2) | 4 (0.2) | 1 (0.1) | 0 | 1 (0.2) | 4 (0.2) | 2 (0.1) | 1 (0.1) | 5 (0.2) |
| VENTRICULAR TACHYCARDIA | 1 (0.2) | 1 (0.1) | 2 (0.1) | 0 | 0 | 0 | 2 (0.1) | 0 | 0 | 2 (0.1) |
| INVESTIGATIONS | 3 (0.5) | 3 (0.3) | 6 (0.4) | 1 (0.1) | 1 (0.1) | 0 | 7 (0.3) | 1 (0.1) | 4 (0.3) | 11 (0.4) |
| ELECTROCARDIOGRAM ABNORMAL | 0 | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) | 0 | 0 | 1 (0.0) |
| ELECTROCARDIOGRAM QT PROLONGED | 0 | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) | 0 | 0 | 1 (0.0) |
| HEART RATE DECREASED | 1 (0.2) | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) | 0 | 0 | 1 (0.0) |
| HEART RATE INCREASED | 0 | 0 | 0 | 1 (0.1) | 1 (0.1) | 0 | 1 (0.0) | 1 (0.1) | 4 (0.3) | 5 (0.2) |
| HEART RATE IRREGULAR | 2 (0.3) | 1 (0.1) | 3 (0.2) | 0 | 0 | 0 | 3 (0.1) | 0 | 0 | 3 (0.1) |
| NERVOUS SYSTEM DISORDERS | 4 (0.6) | 2 (0.2) | 6 (0.4) | 0 | 0 | 2 (0.3) | 6 (0.3) | 2 (0.1) | 11 (0.9) | 16 (0.5) |
| LOSS OF CONSCIOUSNESS | 1 (0.2) | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.0) | 0 | 0 | 1 (0.0) |
| SYNCOPE | 3 (0.5) | 2 (0.2) | 5 (0.3) | 0 | 0 | 2 (0.3) | 5 (0.2) | 2 (0.1) | 11 (0.9) | 15 (0.5) |

Incidence n (%)

[1] Adverse events that occur for the first time after the first dose at Day 1 (or Week 0) or exist prior to Day 1 (or Week 0) and worsen after the first dose at Day 1 (or Week 0).

[2] MedDRA v. 12.0

[3] Includes 37 subjects who received exenatide 2.5 mcg BID.

[4] Includes treatment-emergent adverse events with onset during the uncontrolled studies.

[5] Unique subjects for the all controlled and uncontrolled studies pooled.

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Population: Intent-to-Treat Subjects Receiving Randomized Dose from Controlled and Uncontrolled Studies in Exenatide Once Weekly Clinical Development Program (N = 1700)

| System Organ Class/ Preferred Term [2] | Efficacy and Safety Studies | | | | | | | | Uncontrolled [3] Exenatide Once Weekly (N = 392) n (%) [5] | All Exenatide Once Weekly [4] (N = 985) n (%) [5] |
|----------------------------------------------------------|----------------------------------------------|----------------------------------|-----------------------------------------------|----------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|----------|------------------------------------------------------------------------|---------------------------------------------------------------|
| | Placebo-Controlled | | Controlled | | | | Comparator-Controlled | | | |
| | Exenatide Weekly (N = 51) n (%) [5] | Placebo (N = 23) n (%) [5] | Exenatide Weekly (N = 670) n (%) [5] | BYETTA (N = 268) n (%) [5] | Sinagliptin (N = 166) n (%) [5] | Pioglitazone (N = 165) n (%) [5] | Insulin (N = 223) n (%) [5] | | | |
| All Treatment-Emergent Arrhythmia Related Adverse Events | 0 (0.0) | 0 (0.0) | 10 (1.5) | 3 (1.1) | 2 (1.2) | 2 (1.2) | 1 (0.4) | 10 (2.6) | 18 (1.8) | |
| Cardiac disorders | 0 (0.0) | 0 (0.0) | 7 (1.0) | 2 (0.7) | 2 (1.2) | 2 (1.2) | 1 (0.4) | 6 (1.5) | 11 (1.1) | |
| Atrial fibrillation | 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) | |
| Atrial flutter | 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) | |
| Atrioventricular block | 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) | |
| Atrioventricular block first degree | 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) | |
| Cardiac arrest | 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) | |
| Cardiac flutter | 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) | |

| Efficacy and Safety Studies | | | | | | | | | |
|-------------------------------------------|---------------------------------|----------------------------------|-----------------------------------------------|----------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|-----------------------------------------------------------|---------------------------------------------------------------|
| System Organ Class/ Preferred Term [2] | Placebo-Controlled | | Controlled | | | | | Uncontrolled [3] Once Weekly (N = 392) n (%) [5] | All Exenatide Once Weekly [4] (N = 985) n (%) [5] |
| | Exenatide Once | | Comparator-Controlled | | | | | | |
| | Weekly (N = 51) n (%) [5] | Placebo (N = 23) n (%) [5] | Exenatide Weekly (N = 670) n (%) [5] | BYETTA (N = 268) n (%) [5] | Sitagliptin (N = 166) n (%) [5] | Pioglitazone (N = 165) n (%) [5] | Insulin (N = 223) n (%) [5] | | |
| Cardiac disorders (Confr'd) | | | | | | | | | |
| Conduction disorder | 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) |
| Palpitations | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 1 (0.6) | 1 (0.6) | 0 (0.0) | 1 (0.3) | 1 (0.1) |
| Sinus tachycardia | 0 (0.0) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) |
| Tachycardia | 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) |
| Ventricular extrasystoles | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 2 (0.2) |
| Ventricular tachycardia | 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) |
| Investigations | | | | | | | | | |
| Electrocardiogram QT prolonged | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.8) | 4 (0.4) |
| Heart rate increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Investigations (Confr'd) | | | | | | | | | |
| Heart rate irregular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) | 3 (0.3) |
| Nervous system disorders | | | | | | | | | |
| Syncope | 0 (0.0) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) | 4 (0.4) |

[1] Adverse events that occur for the first time after the first dose at Day 1 (or Week 0) or exist prior to Day 1 (or Week 0) and worsen after the first dose at Day 1 (or Week 0).

[2] MedDRA (version 12.0) terms.

[3] Includes subjects from GWDC and subjects who completed LAR105 controlled period and enrolled in the uncontrolled period. For LAR105, treatment-emergent adverse events with onset during the uncontrolled period up to 2 years of treatment duration are included in this column.

[4] Unique subjects for the Efficacy and Safety studies pooled.

[5] n=# of subjects. Subjects with >1 episode of a given adverse event are counted once.

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Reviewer's Comments: The health Canada reviewer raised concerns about isolated reports of sudden cardiac death (reported under SMQ for TdP/QT prolongation) and cardiac arrest being observed in the exenatide arms and atrial fibrillation. Since the incidence of these events was very low, we do not believe any conclusions can be drawn from the data.

Spontaneous reports of cardiac arrhythmia and potential conduction-related events in Byetta post-marketing data

The Lilly Safety System (LSS) database was searched for all spontaneous reports regarding BYETTA, from product launch in 2005 through 31 March 2010, using the requested Standardized MedDRA Queries. Cumulatively, the sponsor reports that there have been 1341 cases (8806 events) that met the criteria for the requested queries. The sponsor concludes that review of these events and ongoing surveillance indicates no association between BYETTA and cardiac arrhythmias or conduction-related events.

Reviewer's Comment: We defer to the division/ input from OSE regarding the post-marketing data.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of exenatide clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the meta-analysis results for the same drug prior to conducting this study under NDA22200. The sponsor submitted the study report H8O-EW-GWCI for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

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

4.2.2 Protocol Number

H8O-EW-GWCI

4.2.3 Study Dates

23 April 2008 -- 18 February 2009

4.2.4 Objectives

The primary objective was:

- 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 QTc interval (QT interval corrected for heart rate) measurements (such that the upper bound of the one-sided 95% confidence interval [CI] is <10 ms).

The secondary objectives were:

- 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.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, placebo-controlled, double-dummy, double-blinded, three-period crossover study conducted in healthy male and female subjects.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms including moxifloxacin were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

In Part A, all subjects received SC doses of 10 µg exenatide once daily over 3 days. In Part B, subjects were randomly assigned to one of six treatment sequences, and received the following single dose treatments over three treatment periods: SC exenatide (10 µg)

and oral placebo; oral moxifloxacin (400 mg) plus SC placebo; and SC placebo plus oral placebo. The following table illustrates the treatment sequences used in this study.

| Sequence Group | Part A: 3-day | Part B: ECG Assessments | | |
|----------------|----------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
| | Tolerability Screening | Period I | Period II | Period III |
| 1 | 10 µg exenatide once daily | Placebo exenatide, Placebo moxifloxacin | 10 µg exenatide, Placebo moxifloxacin | Placebo exenatide, 400 mg moxifloxacin |
| 2 | 10 µg exenatide once daily | 10 µg exenatide, Placebo moxifloxacin | Placebo exenatide, 400 mg moxifloxacin | Placebo exenatide, Placebo moxifloxacin |
| 3 | 10 µg exenatide once daily | Placebo exenatide, 400 mg moxifloxacin | Placebo exenatide, Placebo moxifloxacin | 10 µg exenatide, Placebo moxifloxacin |
| 4 | 10 µg exenatide once daily | Placebo exenatide, 400 mg moxifloxacin | 10 µg exenatide, Placebo moxifloxacin | Placebo exenatide, Placebo moxifloxacin |
| 5 | 10 µg exenatide once daily | Placebo exenatide, Placebo moxifloxacin | Placebo exenatide, 400 mg moxifloxacin | 10 µg exenatide, Placebo moxifloxacin |
| 6 | 10 µg exenatide once daily | 10 µg exenatide, Placebo moxifloxacin | Placebo exenatide, Placebo moxifloxacin | Placebo exenatide, 400 mg moxifloxacin |

4.2.6.2 Sponsor’s Justification for Doses

“The tolerability profile of exenatide also prevented the use of suprathreshold (>10 µg) doses. A 10 µg dose was considered the maximally tolerated dose; hence, this dose of exenatide was used to assess QT effects in this study. Furthermore, as exenatide is a peptide that is passively cleared by renal mechanisms, it does not exhibit drug-drug interaction potential that would clinically result in suprathreshold concentrations.”

Reviewer’s Comment: The studied 10-µg Byetta dose is reasonable for testing Byetta. The tolerability profile of exenatide prevented the use of suprathreshold (>10-µg) doses. The 10-µg BID dose was considered the maximally tolerated dose of Byetta. Previous study suggested that repeated BID administration would not result in substantial systemic accumulation of exenatide (half-life of approximately 2 hours after SC administration). No interactions have been observed that would significantly increase exposure. The primary route of elimination was via glomerular filtration. Current Byetta label indicates that in subjects with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide exposure was similar to that of subjects with normal renal function. In subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increases by 3-fold compared to that of subjects with normal renal function. However, Byetta is contraindicated in patients with severe renal impairment or end-stage renal disease. Therefore, the studied dose is reasonable for Byetta.

However, the exenatide C_{max} administered with the 10-µg Byetta dose is 208 pg/mL, which is half the geometric mean of steady-state C_{max,ss} of 433 pg/mL of the 2-mg once weekly (QW) Bydureon therapeutic dose. Moreover, the clinical exposure of exenatide in patients with moderate renal impairment is expected to be 50-60% higher compared to that in patients with normal renal function. Therefore, the exenatide exposure in the current submitted TQT study is not able to cover the expected high clinical exposure

scenario administered with the 2 mg QW Bydureon at steady state (especially in patients with moderate renal impairment).

4.2.6.3 Instructions with Regard to Meals

“Subjects fasted overnight prior to receiving treatment on ECG assessment days and continued fasting following treatment administration until lunch.”

Reviewer’s Comment: Acceptable. Exenatide is administered subcutaneously.

4.2.6.4 ECG and PK Assessments

EEGs and blood samples were collected at -15 minutes (predose), and at 1, 2, 3, 4, 5.5, and 10 hours post-dose for determination of plasma exenatide concentrations.

Reviewer’s Comment: The ECG/PK sampling schedule is adequate to cover the T_{max} (~2 hours) and PK profile of exenatide. However, the ECG/PK sampling schedule is insufficient to cover the potential delayed effect up to 24 hours post-dose.

4.2.6.5 Baseline

Pre-dose QTc within day was used as baseline.

4.2.7 ECG Collection

Source: protocol amendment-March 28, 2008

“Twelve-lead ECGs will be obtained according to the Study Schedule (Protocol Attachment GWCI.1) and will be assessed for two separate purposes: QT measurement and safety assessment.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, for immediate subject management and to determine whether the subject meets entry criteria. If a clinically significant increase in the QTc interval from baseline is present, then the investigator should assess if the subject can continue in the study.

All ECGs will subsequently be transmitted electronically to the centralized ECG vendor designated by Lilly. The centralized ECG vendor’s cardiologist will then complete the ECG overread. The central ECG vendor’s overread will be used for data analysis and report writing purposes.”

4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects

Seventy subjects entered Part A of the study and received at least one dose of exenatide. Sixty-two subjects entered and completed Part B of the study. Eight subjects were withdrawn during Part A, and no subjects were withdrawn during Part B. Seven subjects were withdrawn due to adverse events (mainly nausea and vomiting), and 1 subject withdrew his consent.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The following table presents the results of the statistical comparison of the mean changes from pre-dose in QTc intervals (Δ QTc) between exenatide and placebo. These analyses were performed assuming a constant variance at each time point within each treatment.

For the primary QT correction, 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.

The analysis was repeated using an unstructured covariance matrix (appended in Section 11.2). The results from these analyses were similar to those from the original analyses and confirm the assumption of constant variance in the primary analysis was valid.

| Parameter (msec) | Time (h) | Least Squares Mean Change from Predose | | Least Squares Mean Difference (90% CI) Exenatide - Placebo |
|---------------------------------|-------------|----------------------------------------|-------------------|------------------------------------------------------------------|
| | | 10 μ g Exenatide (N=62) | Placebo (N=62) | |
| QTcF ^a | 1 | 3.58 | -0.36 | 3.93 (1.74, 6.13) |
| | 2 | 5.32 | -0.49 | 5.81 (3.62, 8.00) |
| | 3 | 4.46 | 0.44 | 4.02 (1.82, 6.22) |
| | 4 | 2.65 | 0.95 | 1.70 (-0.49, 3.90) |
| | 5.5 | 0.55 | -0.70 | 1.25 (-0.94, 3.45) |
| | 10 | -3.18 | -4.45 | 1.27 (-0.92, 3.47) |
| QTcI ^b | 1 | 0.73 | -0.32 | 1.06 (-0.98, 3.09) |
| | 2 | 2.41 | -0.03 | 2.44 (0.40, 4.47) |
| | 3 | 1.42 | 0.99 | 0.43 (-1.61, 2.47) |
| | 4 | -0.23 | 1.21 | -1.44 (-3.48, 0.59) |
| | 5.5 | -3.34 | -2.72 | -0.62 (-2.65, 1.41) |
| | 10 | -4.26 | -4.85 | 0.59 (-1.44, 2.63) |
| QTcP ^a | 1 | 3.99 | -0.35 | 4.34 (2.12, 6.56) |
| | 2 | 5.80 | -0.54 | 6.34 (4.12, 8.56) |
| | 3 | 4.93 | 0.39 | 4.53 (2.31, 6.76) |
| | 4 | 3.09 | 0.94 | 2.15 (-0.07, 4.37) |
| | 5.5 | 1.23 | -0.17 | 1.40 (-0.82, 3.62) |
| | 10 | -2.87 | -4.23 | 1.37 (-0.85, 3.59) |
| Model based QTc ^c | 1 | 0.67 | -0.46 | 1.14 (-1.12, 3.39) |
| | 2 | 1.82 | -0.27 | 2.09 (-0.24, 4.43) |
| | 3 | 1.08 | 0.70 | 0.38 (-1.95, 2.71) |
| | 4 | -0.30 | 1.16 | -1.46 (-3.74, 0.82) |
| | 5.5 | -4.70 | -4.84 | 0.14 (-2.00, 2.29) |
| | 10 | -5.10 | -5.97 | 0.87 (-1.27, 3.01) |

Reviewer's Comments: Our independent analysis is summarized in section 5.2.

4.2.8.2.2 Assay Sensitivity

The mean Δ QTcF was greater following moxifloxacin administration compared to placebo at all time points (LS mean difference ranged from 9.3 to 14.1 ms) with the largest lower bound to be 11.43 ms. This confirms that the study was able to detect clinically relevant changes in QTcF if they existed. In addition, the mean change from baseline in QTcP, QTcI, and model based QTc were statistically greater for moxifloxacin compared to placebo at all time points. The detail is in following table:

| Parameter (ms) | Time (h) | Least Squares Mean Change from Predose | | Least Squares Mean Difference (90% CI) Moxifloxacin - Placebo |
|---------------------------------|-------------|----------------------------------------|-------------------|---------------------------------------------------------------------|
| | | 400 mg Moxifloxacin (N=62) | Placebo (N=62) | |
| QTcF ^a | 1 | 11.71 | -0.36 | 12.06 (9.35, 14.77) |
| | 2 | 12.84 | -0.49 | 13.33 (10.62, 16.04) |
| | 3 | 14.58 | 0.44 | 14.14 (11.43, 16.85) |
| | 4 | 13.80 | 0.95 | 12.85 (10.14, 15.56) |
| | 5.5 | 8.64 | -0.70 | 9.34 (6.63, 12.05) |
| | 10 | 5.65 | -4.45 | 10.10 (7.39, 12.81) |
| QTcI ^a | 1 | 10.86 | -0.26 | 11.12 (8.48, 13.75) |
| | 2 | 12.75 | 0.04 | 12.72 (10.08, 15.35) |
| | 3 | 14.66 | 1.06 | 13.61 (10.97, 16.24) |
| | 4 | 14.02 | 1.28 | 12.75 (10.11, 15.38) |
| | 5.5 | 6.16 | -2.66 | 8.81 (6.18, 11.45) |
| | 10 | 4.33 | -4.79 | 9.12 (6.49, 11.76) |
| QTcP ^a | 1 | 11.80 | -0.35 | 12.15 (9.41, 14.89) |
| | 2 | 12.83 | -0.54 | 13.37 (10.63, 16.11) |
| | 3 | 14.59 | 0.39 | 14.20 (11.46, 16.94) |
| | 4 | 13.80 | 0.94 | 12.86 (10.12, 15.60) |
| | 5.5 | 9.19 | -0.17 | 9.35 (6.61, 12.10) |
| | 10 | 5.94 | -4.23 | 10.18 (7.44, 12.92) |
| Model based QTc ^b | 1 | 11.57 | -0.44 | 12.01 (9.29, 14.73) |
| | 2 | 13.24 | -0.38 | 13.62 (10.92, 16.33) |
| | 3 | 14.99 | 0.60 | 14.40 (11.69, 17.11) |
| | 4 | 14.26 | 1.14 | 13.12 (10.41, 15.82) |
| | 5.5 | 5.50 | -3.72 | 9.22 (6.52, 11.92) |
| | 10 | 4.27 | -5.50 | 9.77 (7.06, 12.48) |

Reviewer's Comments: Our independent analysis is summarized in section 5.2.

4.2.8.2.3 Categorical Analysis

No subject had a QTc interval >450 ms following the administration of 10 μ g 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 μ g 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.

4.2.8.3 Safety Analysis

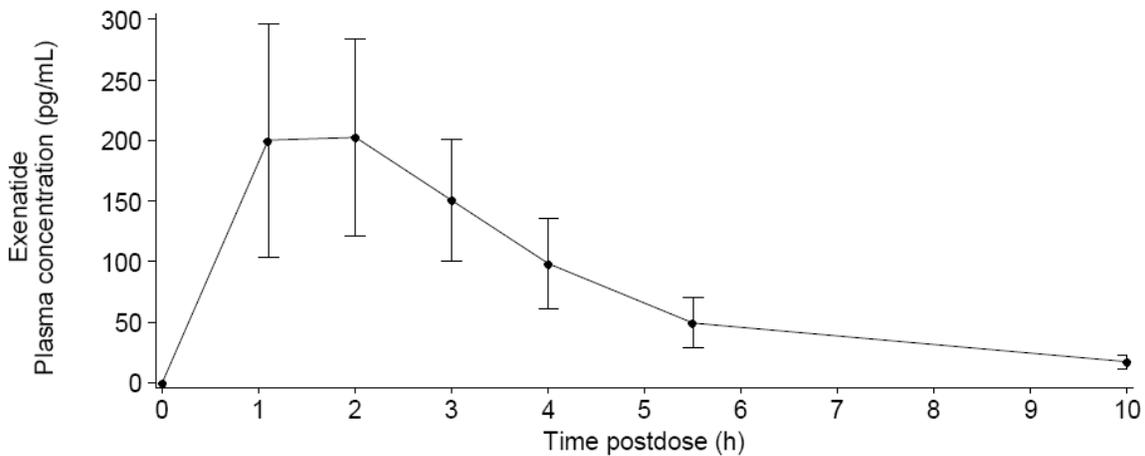
There were no deaths or serious adverse events in the study. No subject discontinued due to AEs in Part B of the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentrations of exenatide from 57 subjects are shown in Figure 1. Mean PK parameters are shown Table 2.

Figure 1: Mean Concentration-Time Profiles of 10 ug Exenatide



(Source: Sponsor's Clinical Study Report, Figure GWCI.7.1. on Page 22)

Table 2: Summary of Plasma Pharmacokinetic Parameters for Exenatide

| Parameter | Geometric Mean (%CV) |
|-------------------------------------|------------------------|
| | 10 µg exenatide (N=62) |
| AUC(0-t _{last}) (pg•h/mL) | 711 (35) |
| AUC(0-∞) (pg•h/mL) | 812 (31) ^b |
| C _{max} (pg/mL) | 208 (40) |
| t _{max} ^a (h) | 2.08 (1.08, 3.08) |
| t _{1/2} (h) | 1.6 (27) ^b |

^a Median (min, max) presented.

^b N = 57.

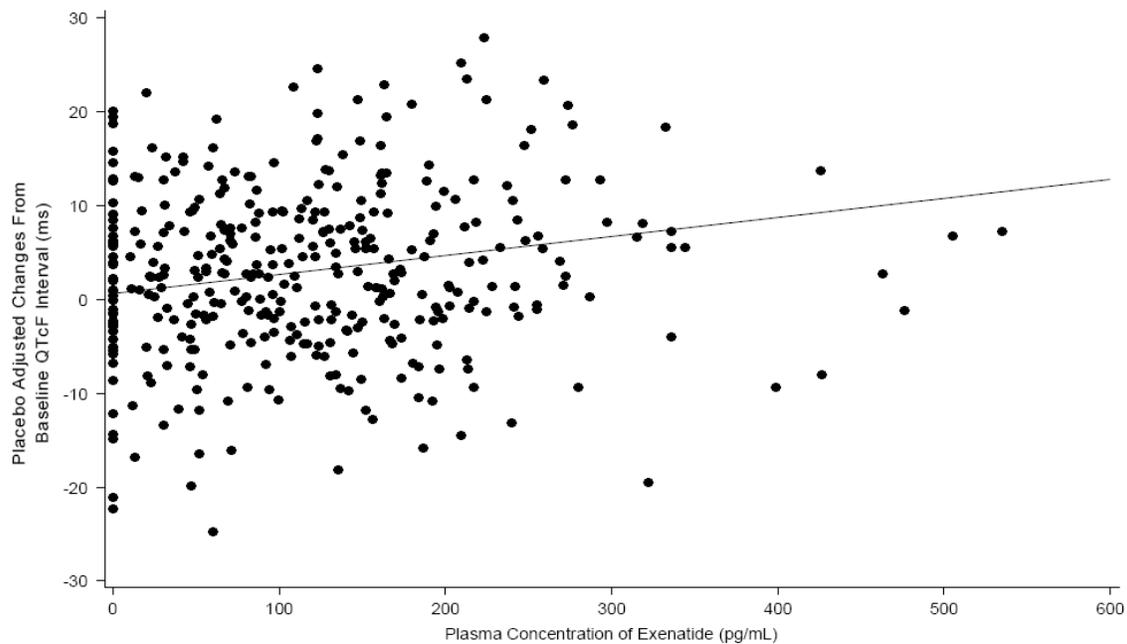
(Source: Sponsor's Clinical Study Report, Table GWCI.7.1. on Page 22)

Reviewer's Comments: The sampling schedule appears adequate to characterize the time course of exenatide.

4.2.8.4.2 Exposure-Response Analysis

The concentration-QT model results showing the relationships between the placebo adjusted change from baseline in QTcF and exenatide concentrations are shown in Figure 2. The model suggested a significantly positive but relatively flat slope.

Figure 2: Placebo Adjusted Changes (ms) from Baseline in QTcF versus the Exenatide Concentrations



Slope (95% CI) from linear mixed effects model = 0.02 (0.01, 0.03) [p-value <0.001]

— Regression line from linear mixed effects model

Predicted $\Delta\Delta$ QTcF (90% PI) = 4.82 (3.12, 6.52) at observed geometric mean C_{\max} : 208 pg/mL

Predicted $\Delta\Delta$ QTcF (90% PI) = 11.50 (8.86, 14.14) at observed maximum C_{\max} : 536 pg/mL

(Source: Sponsor's Clinical Study Report, Figure GWCI.7.4. on Page 30)

Reviewer's Analysis: The reviewer performed independent analysis (See section 5.3). Consistent with the sponsor's results, the slope of the concentration-response relationship is significantly greater than 0, but relatively flat.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The QT-RR interval relationship is presented in Figure 3 together with the Fridericia (QTcF), population-specified correction (QTcP) and individual correction (QTcI).

Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 3, it appears that over all, QTcF had slightly smaller absolute slopes than QTcI.

Table 3: Comparison of QTcF and QTcI Using the Mixed Model

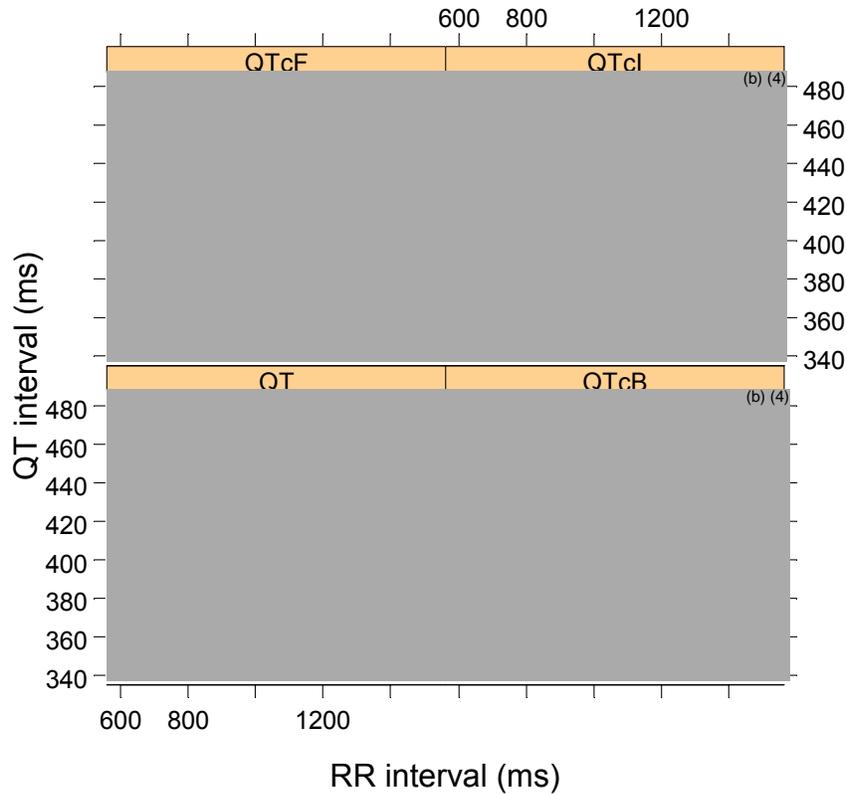
| Treatment Groups | Slope of QTcF | Slope of QTcI | diff_p_value |
|---------------------|---------------|---------------|--------------|
| All | -0.00427 | 0.01226 | 0.00000 |
| 10 µg Exenatide | -0.01540 | -0.00824 | 0.15621 |
| 400 mg Moxifloxacin | 0.00230 | 0.03264 | 0.00000 |
| Placebo | 0.00597 | 0.01442 | 0.05149 |

We also used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following table, it appears that QTcP, QTcF and QTcI are similar. The FDA reviewers used QTcF as the primary correction method which is also consistent with the sponsor.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

| | Treatment | | | | | | | |
|--------|-----------------|--------|---------------------|--------|---------|--------|-----|--------|
| | 10 µg Exenatide | | 400 mg Moxifloxacin | | Placebo | | ALL | |
| Method | N | MSSS | N | MSSS | N | MSSS | N | MSSS |
| QTcF | 62 | 0.0021 | 62 | 0.0021 | 62 | 0.0013 | 62 | 0.0014 |
| QTcI | 62 | 0.0015 | 62 | 0.0026 | 62 | 0.0013 | 62 | 0.0014 |
| QTcP | 62 | 0.0022 | 62 | 0.0020 | 62 | 0.0014 | 62 | 0.0014 |

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Exenatide

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes time point, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Exenatide 10 μ g

| | Exenatide 10 μg ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|------------------|-----------------------------------------------------------------------|--------------------------------------------|--------------------------------------|--------------------|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 1.00 | 3.7 | -0.2 | 3.8 | (1.7, 6.0) |
| 2.00 | 5.4 | -0.3 | 5.7 | (3.7, 7.8) |
| 3.00 | 4.6 | 0.6 | 3.9 | (2.0, 5.9) |
| 4.00 | 2.6 | 1.0 | 1.6 | (-0.4, 3.7) |
| 5.50 | 0.8 | -0.2 | 1.0 | (-0.9, 2.9) |
| 10.00 | -3.6 | -4.6 | 1.0 | (-0.6, 2.6) |

The largest upper bound of the 2-sided 90% CI for the mean difference between exenatide 10 μ g and placebo was 7.8 ms occurred at 2 hours after dose.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest unadjusted 90% lower confidence interval is 12.0 ms. By considering Bonferroni multiple endpoint adjustment of three time points, the largest lower confidence interval is 11.4 ms, which indicates that an at least 5 ms $\Delta\Delta$ QTcF effect due to moxifloxacin can be detected from the study.

Table 6: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin

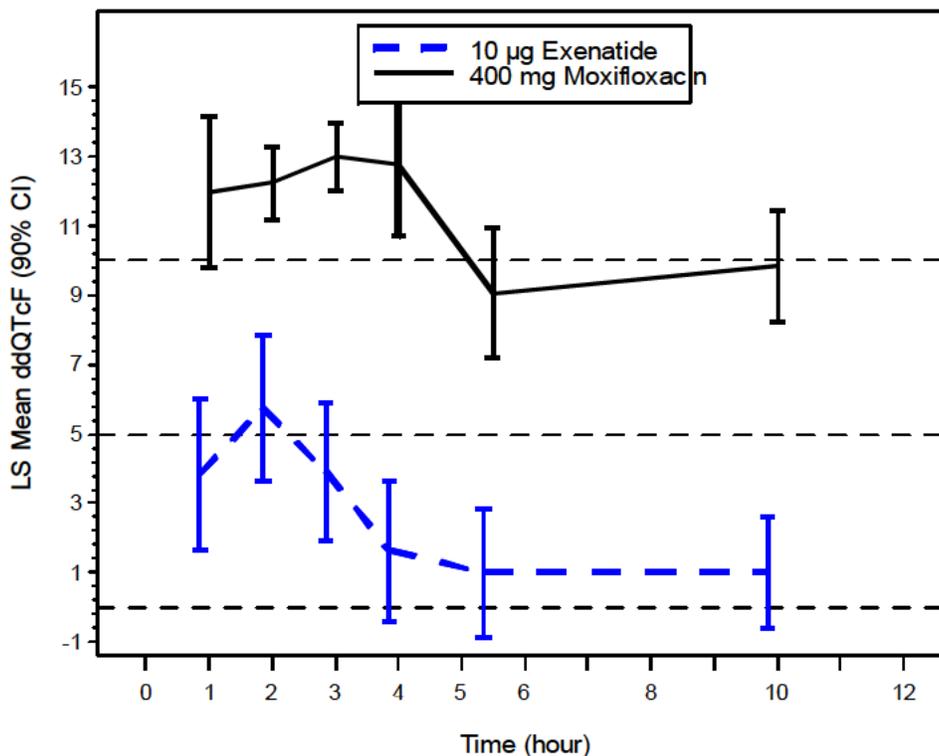
| | Moxifloxacin 400 mg ΔQTcF | Placebo ΔQTcF | $\Delta\Delta$QTcF | |
|------------------|------------------------------------------------------------|--------------------------------------------|--------------------------------------|---------------------|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms)* |
| 1.00 | 11.8 | -0.2 | 12.0 | (9.1, 14.8) |
| 2.00 | 13.0 | -0.3 | 13.3 | (10.6, 16.0) |
| 3.00 | 14.6 | 0.6 | 14.0 | (11.4, 16.5) |
| 4.00 | 13.8 | 1.0 | 12.8 | (10.1, 15.4) |
| 5.50 | 8.9 | -0.2 | 9.1 | (6.6, 11.5) |
| 10.00 | 5.3 | -4.6 | 9.8 | (7.7, 11.9) |

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 7 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 7: Categorical Analysis for QTcF

| Treatment Group | Total N | | Value ≤ 450 ms | | 450 ms < Value ≤ 480 ms | |
|---------------------|---------|--------|---------------------|-------------|------------------------------|----------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| 10 µg Exenatide | 62 | 371 | 62 (100%) | 371 (100%) | 0 (0.0%) | 0 (0.0%) |
| 400 mg Moxifloxacin | 62 | 372 | 58 (93.5%) | 365 (98.1%) | 4 (6.5%) | 7 (1.9%) |
| Placebo | 62 | 372 | 61 (98.4%) | 371 (99.7%) | 1 (1.6%) | 1 (0.3%) |

Table 8 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 8: Categorical Analysis of Δ QTcF

| Treatment Group | Total N | | Value \leq 30 ms | | 30 ms < Value \leq 60 ms | |
|----------------------|---------|--------|--------------------|----------------|----------------------------|-------------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| 10 μ g Exenatide | 62 | 371 | 62 (100%) | 371 (100%) | 0 (0.0%) | 0 (0.0%) |
| 400 mg Moxifloxacin | 62 | 372 | 58 (93.5%) | 368 (98.9%) | 4 (6.5%) | 4 (1.1%) |
| Placebo | 62 | 372 | 62 (100%) | 372 (100%) | 0 (0.0%) | 0 (0.0%) |

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper limits of 90% CI for the PR mean differences between exenatide 10 μ g and placebo was 9.5 ms.

The outlier analysis results for PR are presented in Table 10.

Table 9: Analysis Results of Δ PR and $\Delta\Delta$ PR for Exenatide 10 μ g

| Time/(hr) | Exenatide 10 μ g Δ PR | Placebo Δ PR | $\Delta\Delta$ PR | |
|-----------|----------------------------------|---------------------|-------------------|-------------|
| | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 1.00 | 6.4 | -0.8 | 7.1 | (4.8, 9.5) |
| 2.00 | 5.8 | -0.9 | 6.6 | (3.9, 9.4) |
| 3.00 | 5.9 | -0.8 | 6.7 | (4.4, 9.0) |
| 4.00 | 4.0 | -0.9 | 4.9 | (2.5, 7.3) |
| 5.50 | -2.3 | -4.7 | 2.4 | (0.5, 4.3) |
| 10.00 | -2.3 | -6.0 | 3.7 | (1.4, 6.1) |

Table 10: Categorical Analysis for PR

| Treatment Group | Total | | Value ≤ 200 ms | | Value > 200 ms | |
|---------------------|---------|--------|----------------|----------------|----------------|---------------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| 10 µg Exenatide | 62 | 371 | 50 (80.6%) | 322 (86.8%) | 12 (19.4%) | 49 (13.2%) |
| 400 mg Moxifloxacin | 62 | 372 | 54 (87.1%) | 344 (92.5%) | 8 (12.9%) | 28 (7.5%) |
| Placebo | 62 | 372 | 54 (87.1%) | 342 (91.9%) | 8 (12.9%) | 30 (8.1%) |

Table 11: Categorical Analysis for Observations PR > 200 ms under Treatment

| ID | Baseline | 1 h | 2 h | 3 h | 4 h | 5.5 h | 10 h |
|----|----------|-----|-----|-----|-----|-------|------|
| 1 | 196 | 204 | | 210 | 200 | 207 | |
| 3 | 208 | 216 | 216 | 216 | 216 | 208 | |
| 10 | 218 | 232 | 236 | 224 | 224 | 216 | 204 |
| 24 | 204 | 204 | | 210 | 212 | 216 | 220 |
| 25 | 196 | 210 | 202 | 210 | 216 | | |
| 27 | 172 | | 200 | 200 | | | |
| 30 | 212 | 224 | 228 | 224 | 226 | 224 | 206 |
| 31 | 198 | | | | | 202 | 200 |
| 36 | 200 | 224 | 222 | 226 | 242 | 208 | 228 |
| 37 | 184 | | | | | 204 | 202 |
| 45 | 200 | 214 | 214 | 212 | 216 | 206 | |
| 54 | 212 | 208 | 212 | 202 | | | 206 |
| 66 | 194 | 208 | 206 | | | | |

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the QRS mean differences between exenatide 10 µg and placebo was 1.7 ms. There are 19.4% subjects who experienced QRS interval greater than 110 ms in 10-µg exenatide group.

The outlier analysis results for QRS are presented in Table 13 and Table 14.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Exenatide 10 μ g

| | Exenatide 10 μ g Δ QRS | Placebo Δ QRS | $\Delta\Delta$ QRS | |
|-----------|-----------------------------------------|-------------------------|----------------------------|-------------|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 1.00 | -0.5 | -0.2 | -0.3 | (-1.2, 0.7) |
| 2.00 | -0.3 | -0.3 | -0.0 | (-0.9, 0.8) |
| 3.00 | -0.5 | -0.5 | -0.0 | (-1.1, 1.0) |
| 4.00 | -0.9 | -0.4 | -0.5 | (-1.4, 0.4) |
| 5.50 | 0.7 | 1.2 | -0.5 | (-1.5, 0.5) |
| 10.00 | 0.1 | -0.5 | 0.6 | (-0.5, 1.7) |

Table 13: Categorical Analysis for QRS

| Treatment Group | T | | Value \leq 100 ms | | 100 ms<Value \leq 110 ms | | Value>110 ms | |
|------------------------|------------|-----------|------------------------|----------------|----------------------------------|----------------|-----------------|---------------|
| | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. | # Subj. | # Obs. |
| 10 μ g Exenatide | 62 | 371 | 21 (33.9%) | 185 (49.9%) | 29 (46.8%) | 141 (38.0%) | 12 (19.4%) | 45 (12.1%) |
| 400 mg Moxifloxacin | 62 | 372 | 21 (33.9%) | 184 (49.5%) | 30 (48.4%) | 152 (40.9%) | 11 (17.7%) | 36 (9.7%) |
| Placebo | 62 | 372 | 24 (38.7%) | 190 (51.1%) | 24 (38.7%) | 139 (37.4%) | 14 (22.6%) | 43 (11.6%) |

Table 14: Categorical Analysis for Observations QRS >110 ms under Treatment

| ID | Baseline | 1 hr | 2 hr | 3 hr | 4 hr | 5.5 hr | 10 hr |
|----|----------|------|------|------|------|--------|-------|
| 6 | 112 | 116 | 116 | 114 | 116 | 114 | 110 |
| 8 | 122 | 118 | 118 | 122 | 124 | 122 | 122 |
| 10 | 116 | 116 | 116 | 116 | 118 | 118 | 118 |
| 17 | 110 | 114 | 110 | 112 | 112 | 114 | |
| 18 | 110 | 116 | 110 | 114 | 114 | 114 | 118 |
| 21 | 108 | | | 110 | | 114 | 112 |
| 22 | 120 | 122 | 124 | 122 | 122 | 124 | 122 |
| 27 | 110 | 112 | 112 | 110 | 112 | 112 | 112 |
| 29 | 108 | | | | | | 110 |
| 31 | 108 | | | | | | 110 |
| 51 | 110 | | 110 | 110 | | 110 | |
| 57 | 104 | | | | | 112 | |
| 59 | 106 | 110 | | | | 110 | 116 |
| 66 | 110 | 110 | | 112 | | 112 | 110 |
| 70 | 104 | 110 | | | 112 | | 116 |

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean exenatide concentration-time profile is illustrated in Figure 1. Exenatide appears to be associated with an average increase of heart rate for about 10 bpm (Figure 6) as compared to placebo group.

The relationship between $\Delta\Delta\text{QTcF}$ and exenatide concentrations is visualized in Figure 5. The linear regression analysis 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 Byetta, the predicted $\Delta\Delta\text{QTcF}$ (90% PI) is 4.92 (2.64, 7.20), which is below the clinical threshold per ICH E-14, 10 ms. However, the predicted values (90% PI) of $\Delta\Delta\text{QTcF}$ are 9.58 (5.63, 13.53) and 14.07 (8.16, 19.99) at the geometric mean of steady-state $C_{\text{max_ss}}$ of 433 pg/mL with the 2 mg QW Bydureon and the clinical exposure $C_{\text{max_ss}}$ of 650 pg/mL in patients with moderate renal impairment (assuming 50% increase in $C_{\text{max_ss}}$) respectively.

These results seem to suggest a potential effect of exenatide on QT prolongation. However, prediction (especially at 650 pg/mL) from the linear regression model should be taken with caution due to extrapolation.

Figure 5: $\Delta\Delta$ QTcF vs. Exenatide Concentration

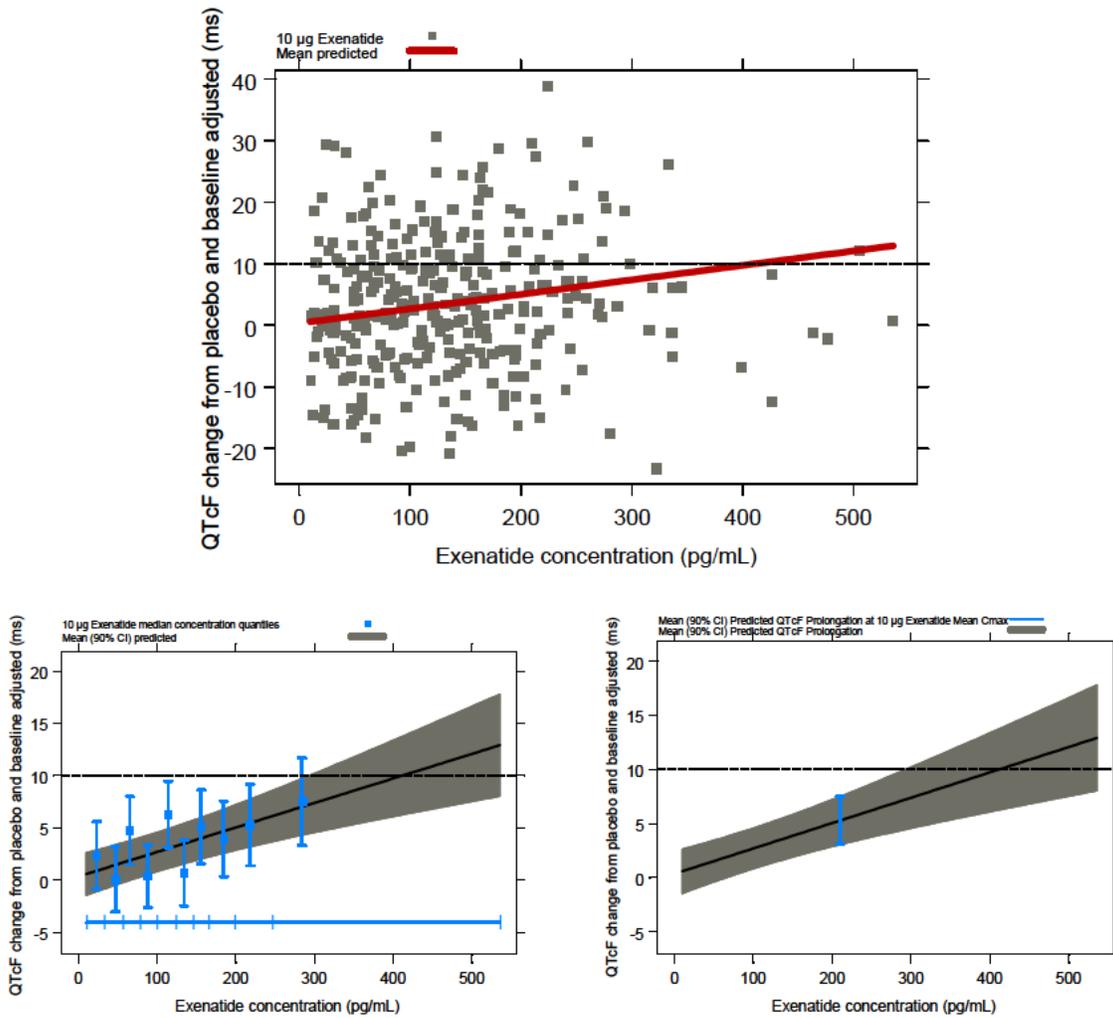
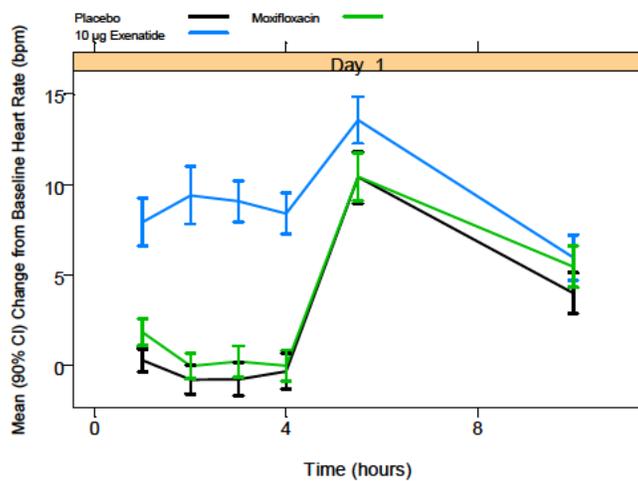


Figure 6: Heart Rate Change following the Administration of Exenatide



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. The global emdian beat was used for analysis with 12 lead overlay. Less than 0.05% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR, QRS Interval and HR effects

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.

HR was increased from baseline for 1-4 hours post-dosing. The maximum placebo-adjusted HR increase was 10.2 at hour 2 post-dose.

5.4.4 MGPS data mining analysis

We conducted an MGPS data mining analysis of AERS for AEs related to QT prolongation, conduction disorders and arrhythmias (including tachyarrhythmias). To capture events noted in the Health Canada report, EBGM value was set at “0”. It is to be noted that the signal score (EBGM value) was less than 2 for all PTs indicating incidence similar to background rate. However this data alone is not indicative of the absence of association and hence we defer to the division/OSE opinion in this regard.

Configuration: CBAERS BestRep (S) (v2) Run : Generic (S) Run ID: 3407

Dimension: 2 Selection Criteria: Generic name(Exenatide) + PT(...)

39 rows Sorted by Generic name, EBGm desc

| Generic name | PT | HLT | N | EBGM | EB05 | EB95 |
|--------------|-------------------------------------|--------------------------------------------|-----|-------|-------|-------|
| Exenatide | Heart alternation | Rate and rhythm disorders NEC | 1 | 1.25 | 0.292 | 3.91 |
| Exenatide | Cardiac flutter | Rate and rhythm disorders NEC | 21 | 1.04 | 0.719 | 1.46 |
| Exenatide | Atrioventricular dissociation | Cardiac conduction disorders | 1 | 0.726 | 0.170 | 2.25 |
| Exenatide | Wolff-Parkinson-White syndrome | Cardiac conduction disorders | 1 | 0.601 | 0.140 | 1.86 |
| Exenatide | Extrasystoles | Rate and rhythm disorders NEC | 18 | 0.566 | 0.380 | 0.816 |
| Exenatide | Cardiac fibrillation | Ventricular arrhythmias and cardiac arrest | 3 | 0.528 | 0.206 | 1.16 |
| Exenatide | Sudden cardiac death | Death and sudden death | 6 | 0.410 | 0.207 | 0.747 |
| Exenatide | Cardiac death | Death and sudden death | 1 | 0.382 | 0.089 | 1.19 |
| Exenatide | Atrial fibrillation | Supraventricular arrhythmias | 100 | 0.366 | 0.310 | 0.430 |
| Exenatide | Atrial flutter | Supraventricular arrhythmias | 11 | 0.364 | 0.219 | 0.576 |
| Exenatide | Tachyarrhythmia | Rate and rhythm disorders NEC | 4 | 0.362 | 0.158 | 0.734 |
| Exenatide | Sinus arrhythmia | Supraventricular arrhythmias | 2 | 0.333 | 0.109 | 0.833 |
| Exenatide | Arrhythmia | Rate and rhythm disorders NEC | 51 | 0.289 | 0.228 | 0.361 |
| Exenatide | Supraventricular extrasystoles | Supraventricular arrhythmias | 5 | 0.273 | 0.130 | 0.522 |
| Exenatide | Ventricular extrasystoles | Ventricular arrhythmias and cardiac arrest | 15 | 0.263 | 0.171 | 0.392 |
| Exenatide | Bundle branch block right | Cardiac conduction disorders | 6 | 0.255 | 0.129 | 0.465 |
| Exenatide | Electromechanical dissociation | Ventricular arrhythmias and cardiac arrest | 3 | 0.235 | 0.092 | 0.518 |
| Exenatide | Bundle branch block | Cardiac conduction disorders | 1 | 0.232 | 0.054 | 0.721 |
| Exenatide | Bundle branch block left | Cardiac conduction disorders | 5 | 0.222 | 0.105 | 0.424 |
| Exenatide | Atrioventricular block complete | Cardiac conduction disorders | 6 | 0.215 | 0.108 | 0.391 |
| Exenatide | Conduction disorder | Cardiac conduction disorders | 1 | 0.210 | 0.049 | 0.651 |
| Exenatide | Sinus arrest | Supraventricular arrhythmias | 1 | 0.203 | 0.047 | 0.631 |
| Exenatide | Supraventricular tachycardia | Supraventricular arrhythmias | 6 | 0.164 | 0.083 | 0.299 |
| Exenatide | Atrioventricular block | Cardiac conduction disorders | 4 | 0.163 | 0.071 | 0.331 |
| Exenatide | Ventricular arrhythmia | Ventricular arrhythmias and cardiac arrest | 1 | 0.146 | 0.034 | 0.452 |
| Exenatide | Tachycardia | Rate and rhythm disorders NEC | 34 | 0.140 | 0.105 | 0.183 |
| Exenatide | Ventricular tachycardia | Ventricular arrhythmias and cardiac arrest | 9 | 0.129 | 0.074 | 0.214 |
| Exenatide | Atrioventricular block first degree | Cardiac conduction disorders | 2 | 0.128 | 0.041 | 0.319 |
| | Atrioventricular block second | | | | | |

| Generic name | PT | HLT | N | EBGM | EB05 | EB95 |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|----|-------|-------|-------|
| Exenatide | degree | Cardiac conduction disorders | 1 | 0.125 | 0.029 | 0.389 |
| Exenatide | Sick sinus syndrome | Supraventricular arrhythmias | 1 | 0.115 | 0.027 | 0.357 |
| Exenatide | Sudden death | Death and sudden death | 5 | 0.101 | 0.048 | 0.193 |
| Exenatide | Cardiac arrest | Ventricular arrhythmias and cardiac arrest | 21 | 0.085 | 0.059 | 0.120 |
| Exenatide | Sinus tachycardia | Supraventricular arrhythmias | 4 | 0.084 | 0.037 | 0.171 |
| Exenatide | Ventricular fibrillation | Ventricular arrhythmias and cardiac arrest | 4 | 0.084 | 0.037 | 0.171 |
| Exenatide | Convulsion | Seizures and seizure disorders NEC | 37 | 0.083 | 0.063 | 0.108 |
| Exenatide | Cardio-respiratory arrest | Ventricular arrhythmias and cardiac arrest | 8 | 0.068 | 0.038 | 0.116 |
| Exenatide | Sinus bradycardia | Supraventricular arrhythmias | 2 | 0.064 | 0.021 | 0.160 |
| Exenatide | Bradycardia | Rate and rhythm disorders NEC | 9 | 0.059 | 0.033 | 0.097 |
| Exenatide | Electrocardiogram QT prolonged | ECG investigations | 1 | 0.022 | 0.005 | 0.070 |
| ID: | 3407 | | | | | |
| Type: | MGPS | | | | | |
| Name: | Generic (S) | | | | | |
| Description: | Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information | | | | | |
| Project: | CBAERS Standard Runs | | | | | |
| Configuration: | CBAERS BestRep (S) (v2) | | | | | |
| Configuration description: | CBAERS data; best representative cases; suspect drugs only; with duplicate removal | | | | | |
| As of date: | 07/22/2010 00:00:00 | | | | | |
| Item variables: | Generic name, PT | | | | | |
| Stratification variables: | Standard strata | | | | | |
| Highest dimension: | 2 | | | | | |
| Minimum count: | 1 | | | | | |
| Calculate PRR: | Yes | | | | | |
| Calculate ROR: | Yes | | | | | |
| Base counts on cases: | Yes | | | | | |
| Use "all drugs" comparator: | No | | | | | |
| Apply Yates correction: | Yes | | | | | |
| Stratify PRR and ROR: | No | | | | | |
| Fill in hierarchy values: | Yes | | | | | |
| Exclude single itemtypes: | Yes | | | | | |
| Fit separate distributions: | Yes | | | | | |
| Save intermediate files: | No | | | | | |
| Created by: | Empirica Signal Administrator | | | | | |

| | |
|-------------------------|------------------------------------------------------------------------------------------------------------------|
| Created on: | 07/30/2010 21:19:46 EDT |
| User: | Suchitra Balakrishnan |
| Source database: | Source Data: CBAERS data from Extract provided by CBER as of 07/22/2010 00:00:00 loaded on 2010-07-29 04:21:23.0 |

Dimension: 2 Selection Criteria: Generic name(Exenatide) + PT(Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Chronotropic incompetence, Conduction disorder, Electromechanical dissociation, Extrasystoles, Foetal arrhythmia, Foetal heart rate deceleration, Foetal heart rate disorder, Heart alternation, Heart block congenital, Long QT syndrome, Long QT syndrome congenital, Lown-Ganong-Levine syndrome, Neonatal tachycardia, Nodal arrhythmia, Nodal rhythm, Pacemaker complication, Pacemaker generated arrhythmia, Parasystole, Paroxysmal arrhythmia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Reperfusion arrhythmia, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital, Convulsion, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged)

```
SELECT * FROM OutputData_3407 WHERE (DIM=2 AND ((P1='D' AND ITEM1 IN ('Exenatide') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Adams-Stokes syndrome','Agonal rhythm','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial tachycardia','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Bifascicular block','Bradyarrhythmia','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardiac flutter','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Chronotropic incompetence','Conduction disorder','Electromechanical dissociation','Extrasystoles','Foetal arrhythmia','Foetal heart rate deceleration','Foetal heart rate disorder','Heart alternation','Heart block congenital','Long QT syndrome','Long QT syndrome congenital','Lown-Ganong-Levine syndrome','Neonatal tachycardia','Nodal arrhythmia','Nodal rhythm','Pacemaker complication','Pacemaker generated arrhythmia','Parasystole','Paroxysmal arrhythmia','Postural orthostatic tachycardia syndrome','Rebound tachycardia','Reperfusion arrhythmia','Rhythm idioventricular','Sick sinus syndrome','Sinoatrial block','Sinus arrest','Sinus arrhythmia','Sinus bradycardia','Sinus tachycardia','Sudden cardiac death','Sudden death','Supraventricular extrasystoles','Supraventricular tachyarrhythmia','Supraventricular tachycardia','Tachyarrhythmia','Tachycardia','Tachycardia foetal','Tachycardia paroxysmal','Torsade de pointes','Trifascicular block','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia','Wandering pacemaker','Withdrawal arrhythmia','Wolff-Parkinson-White syndrome','Wolff-Parkinson-White syndrome congenital','Convulsion','Electrocardiogram QT interval','Electrocardiogram QT interval abnormal','Electrocardiogram QT prolonged')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY (EXENATIDE ONCE WEEKLY)

| | | |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose | 2 mg QW | |
| Maximum tolerated dose | 10 mg single dose; max tolerated dose not identified [NDA 022-200, 2.7.2.5] | |
| Principal adverse events | Nausea and Vomiting | |
| Maximum dose tested | Single Dose | 10 mg [NDA 022-200, 2.7.2.3.1.1] |
| | Multiple Dose | 2 mg QW safety through 52 weeks [NDA 022-200, 2.7.4.1.2.1, NDA 022-200, 2.7.2.2, Study 2993LAR-105] |
| Exposures Achieved at Maximum Tested Dose | Single Dose | AUC _(0-48h) mean (SE) 203,954 (15,654) pg·h/mL C _{max (0-48h)} mean (SE) 641 (88.5) pg/mL C _{max (0-8)} mean (SE) 200 (18.6) pg/mL [NDA 022-200, 2.7.2.3.1.1, Table 3] |
| | Multiple Dose | C _{ss max} at 29-30 weeks Geometric mean (CV%) 432.7 (86.3) pg/mL AUC _{ss} 50,484 (69.7) pg·h/mL [NDA 022-200, 2.7.2.3.1.2, Table 4] |
| Range of linear PK | AUC from single doses of 2.5 to 10 mg and AUC _{0-tau,ss} following multiple QW doses of 0.8 to 2 mg appeared to increase dose proportionally (Not statistically tested). [NDA 022-200, 2.7.2.3.1.6] | |
| Accumulation at steady state | ~8.6 fold following 2 mg QW [NDA 022-200, 2.7.2.3.1.3] | |
| Metabolites | PK parameters for metabolites not applicable. | |
| Absorption | Absolute/Relative Bioavailability | Absolute: Not evaluated for exenatide QW. The absolute bioavailability of Byetta ranged from LS Mean Ratio (CV) of 113% -121% (71%) at different sites of injection. [NDA 021-773, 2.7.2.2, 2993-118] Relative (to Byetta): Mean (90% confidence intervals) bioavailability for steady state weekly 2 mg dosing was 25% (21%, 30%) [NDA 022-200, 2.7.2.3.1.4] |
| | T _{max} | • Parent: Median (10 th -90 th percentile) at steady-state over a dosing interval, 22.8 h (1.17, 167.75) [NDA 022-200, 2.7.2.3.1.3.1] • Metabolites: Not applicable |
| Distribution | V _d /F or V _d | Byetta (exenatide immediate release) Mean (10 th - 90 th percentile) – 28.3 L (15.47 - 62.50 L) [NDA 022-200, 2.7.2.3.1.5; NDA 021-773, 2.7.2.3.1.1] |
| | % bound | - 18% bound to erythrocytes [NDA 022-200, 2.6.4.4.2] - Protein binding to serum albumin not determined |

| | | |
|-------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Elimination | Route | <ul style="list-style-type: none"> primary: glomerular filtration [NDA 022-200, 2.7.2.3.1.5] percent dose eliminated: estimated to be >80% based on ESRD patients with Byetta showing a CL/F reduction by 84% compared to normal renal function [NDA 022-200, 2.7.2.3.5.2] proteolytic degradation subsequent to glomerular filtration [NDA 022-200, 2.7.2.3.1.5] |
| | Terminal t _{1/2} | <ul style="list-style-type: none"> Not applicable (sustained release) Time required for the decline in plasma exenatide exposure following cessation of exenatide once weekly therapy is approximately 7 weeks after the last injection [NDA 022-200, 2.7.2.3.1.2] Metabolites: Not applicable |
| | CL/F or CL | Mean (10 th – 90 th percentile) from Byetta CL/F = 9.1 L/hr (6.15 - 15.86 L/hr) [NDA 021-773, 2.7.2.3.1.1, Table APP 15] |
| Intrinsic Factors | Age | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Sex | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Race | No relevant change [NDA 022-200, 2.7.2.3.5.4; NDA 022-200, 2.7.2.6, Appendix 2, Table 2.4] |
| | Hepatic & Renal Impairment | Hepatic: Not evaluated in hepatic impairment; primarily renally cleared. [NDA 022-200, 2.7.2.3.5.6] Renal: Median Individual Predicted C _{ss, ave} (25 th – 75 th percentile) (pg/mL) following multiple doses of 2 mg exenatide QW: normal renal function 300.3 (252.7 - 369.6), mild renal impairment 368.7 (282.6 – 436.6), moderate renal impairment 523.4 (398.2 – 714.4) Thus, no relevant change in subjects with mild to moderate renal impairment; however, not recommended for use in patients with severe renal impairment or ESRD. [NDA 022-200, 2.7.2.3.5.2, Table 7] |

| | | |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Extrinsic Factors | Drug interactions | No metabolic interactions; DDI potential is to slow gastric emptying. Acetaminophen absorption as marker of gastric emptying: Acetaminophen C _{max} reduced 16% in the fasted state and 5% in the fed state. AUC reduced 4% in fed and fasted state with exenatide once weekly co-administration. BYETTA: acetaminophen, digoxin, warfarin, lisinopril, lovastatin, ethinyl estradiol and levonorgestrel (CYP3A) studies showed no clinically relevant changes in C _{max} and/or AUC. [NDA 022-200, 2.7.2.3.6.1] |
| | Food Effects | Not applicable (administered subcutaneously) |
| Expected High Clinical Exposure Scenario | Expected high exposure in moderate renal impairment. Predicted weekly C _{ss} is most therapeutically relevant exposure measure due to large accumulation ratio (8.6 fold). For moderate renal impairment group, Maximum value (25 th percentile, median, 75 th percentile) is 1076.8 (398.2; 523.4; 714.4). Normal renal function group, 1074.7 (252.7; 300.3 369.6). [NDA 022-200, 2.7.2.3.5.2, Table 7] | |

6.2 TABLE OF STUDY ASSESSMENTS

Study Schedule Protocol H80-EW-GWCI[®]

| Period Day | Admit to CRU | Discharge from CRU | Study Drug | 12-lead ECG (hours) | Phys Exam | Med History | Clin Lab Tests | Urine Drug Scr & Ethanol Test | Vital Signs | Height & Weight | Samples for Electrolytes | PK Samples | PD Samples |
|--------------------------------------------------------------|--------------|--------------------|------------|------------------------------------------|-----------|-------------|----------------|-------------------------------|-------------|-----------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Screening (within 28 days) | | | | | | | | | | | | | |
| --- | | | | Single (safety) | X | X | X | X | X | X | | | |
| Part A (Tolerability Screening) | | | | | | | | | | | | | |
| 1 | X | | X | | | | | X | X (0 h) | | | | |
| 2 | | | X | | | | | | | | | | |
| 3 | | X | X | | | | | | X (d/c) | | | | |
| Washout Period: Approximately 5 days until next study period | | | | | | | | | | | | | |
| Part B: Period I (ECG Assessments) | | | | | | | | | | | | | |
| -1 | X | | | | | | | | | | | | |
| 1 | | | X | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | | | | X | X | | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h |
| 2 | | X | | Single (Safety) | X | | X | | X | | | | |

continued

Study Schedule Protocol H80-EW-GWCI[®] (concluded)

Confidential

| Period Day | Admit to CRU | Discharge from CRU | Study Drug | 12-lead ECG (hours) | Phys Exam | Med History | Clin Lab Tests | Urine Drug Scr & Ethanol Test | Vital Signs | Height & Weight | Samples for Electrolytes | PK Samples | PD Samples |
|---------------------------------------------------------------------|--------------|--------------------|------------|------------------------------------------|-----------|-------------|----------------|-------------------------------|-------------|-----------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Washout Period: Approximately 5 days until next study period | | | | | | | | | | | | | |
| Part B: Period II (ECG Assessments) | | | | | | | | | | | | | |
| -1 | X | | | | | | | | | | | | |
| 1 | | | X | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | | | | X | X | | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h |
| 2 | | X | | Single (Safety) | X | | X | | X | | | | |
| Washout Period: Approximately 5 days until next study period | | | | | | | | | | | | | |
| Part B: Period III (ECG Assessments) | | | | | | | | | | | | | |
| -1 | X | | | | | | | | | | | | |
| 1 | | | X | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | | | | X | X | | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h | -15 min, 1 h, 2 h, 3 h, 4 h, 5.5 h, 10 h |
| 2 | | X | | Single (Safety) | X | | X | | X | | | | |
| Poststudy Follow-up Visit | | | | | | | | | | | | | |
| --- | | | | | X | | | | X | | | | |

Confidential

Abbreviations: Clin Lab = clinical laboratory; CRU = clinical research unit; d/c = discharge; ECG = electrocardiogram; h = hour(s); Med History = medical history; min = minute(s); PD = pharmacodynamic; Phys Exam = physical exam; PK = pharmacokinetic; Scr = screen; Temp = temperature.

* The priority of study assessments will be ECGs, vital sign measurements, blood sampling, and then any other scheduled assessments. The timing and number of safety measurements may be modified based on clinical evaluations.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------------------------|-----------------------------------------|
| NDA-21773 | ORIG-1 | AMYLIN PHARMACEUTICALS INC | BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML |
| NDA-22200 | ORIG-1 | AMYLIN PHARMACEUTICALS INC | Bydureon (exenatide LAR) |
| IND-57725 | ORIG-1 | AMYLIN | BYETTA (EXENATIDE INJECTION) |

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/s/

HAO ZHU
08/11/2010

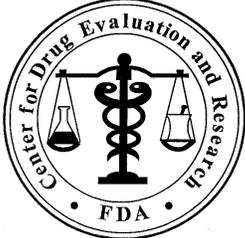
JIANG LIU
08/11/2010

JOANNE ZHANG
08/12/2010

Dr. Qianyu Dang was the primary statistician for this study review.

DEVI KOZELI on behalf of SUCHITRA M BALAKRISHNAN
08/16/2010

NORMAN L STOCKBRIDGE
08/16/2010

| | |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology</p> |
| Date: | August 19, 2010 |
| To: | <p>Mary Parks, MD, Director Division of Metabolism and Endocrinology Products (DMEP)</p> |
| Through: | <p>Mary Willy, PhD, Deputy Director Division of Risk Management (DRISK)</p> <p>LaShawn Griffiths, MSHS-PH, BSN, RN, Acting Team Leader Division of Risk management (DRISK)</p> |
| From: | <p>Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer Division of Risk Management (DRISK)</p> |
| Subject: | DRISK Review of Patient Labeling (Medication Guide) and Patient Instructions for Use (PIFU) |
| Drug Name(s): | BYDUREON (exenatide) extended-release For Injectable Suspension |
| Application Type/Number: | NDA 22-200 |
| Applicant/sponsor: | Amylin Pharmaceuticals Inc. |
| OSE RCM #: | 2009-1053 |

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Patient Instructions for Use (PIFU) for Bydureon (exenatide) extended-release for Injectable Suspension. Please let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed Communication Plan REMS is being reviewed by DRISK and will be provided to DMEP under separate cover.

2 BACKGROUND

On March 12, 2010, a Complete Response (CR) was issued to Amylin for Bydureon (exenatide) extended-release for injectable suspension citing Microbiology and REMS issues. On April 22, 2010, the FDA received Amylin's resubmission with an action goal date set for October 22, 2010.

3 MATERIAL REVIEWED

- Draft BYDUREON (exenatide) extended-release for injectable suspension Prescribing Information (PI) submitted April 22, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on July 27, 2010.
- Draft BYDUREON (exenatide) extended-release for injectable suspension Medication Guide (MG) submitted on April 22, 2010, revised by the review division throughout the review cycle, and received by DRISK on July 27, 2010.
- Draft BYDUREON (exenatide) extended-release for injectable suspension Patient Instructions for Use (PIFU) submitted on April 22, 2010, and received by DRISK on July 27, 2010.

4 RESULTS OF REVIEW

In our review of the MG and the Patient Instructions for Use we have:

- ensured to the extent possible that the MG for Bydureon is consistent with the MG for Victoza and Byetta
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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

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/s/

LASHAWN M GRIFFITHS
08/19/2010
DRISK MG IFU final review

MARY E WILLY
08/19/2010
I concur



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 26, 2010
Mary Parks, MD, Director

To: **Division of Metabolism and Endocrinology Products (DMEP)**

Through: Mary Willy, PhD, Deputy Director
Division of Risk management (DRISK)

LaShawn Griffiths, MSHS-PH, BSN, RN, Acting Team Leader
Division of Risk management (DRISK)

From: Shawna Hutchins, BSN, RN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Kendra Worthy, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Subject: Memo to File re: Review of Medication Guide (MG) and Patient Instructions for Use (PIFU)

Drug Name(s): BYDUREON (exenatide) For Injectable Suspension

Application Type/Number: NDA 22-200

Applicant/sponsor: Amylin Pharmaceuticals Inc.

OSE RCM #: 2009-1053

The Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 22-200 submitted by Amylin Pharmaceuticals Inc. for BYDUREON (exenatide) For Injectable Suspension.

Due to outstanding clinical, REMS, and labeling deficiencies, DMEP plans to issue a Complete Response (CR) letter. DRISK defers review of the proposed REMS until the sponsor resubmits a complete response.

Please send us a new consult request at that time. This memo serves to close-out the consult request for BYDUREON, NDA 22-200.

Please let us know if you have any questions.

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

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/s/

SHAWNA L HUTCHINS
04/26/2010

LASHAWN M GRIFFITHS
04/26/2010



IND 057725
IND 067092

ADVICE/INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.
Orville Kolterman, M.D.
Sr. Vice President, Research & Development
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for **exenatide** and **exenatide long acting release (LAR)**.

We also refer to your amendment dated **April 9, 2010**, submitted to IND 057725, containing an annual report that describes three clinical studies **H8O-MC-GWAN** entitled, *An Open-Label Study Examining the Long-Term Safety of Exenatide Given Twice Daily to Subjects With Type 2 Diabetes Mellitus*, **H8O-US-GWAY** entitled, *An Evaluation of the Metabolic Effects of Exenatide, Rosiglitazone, and Exenatide Plus Rosiglitazone in Subjects With Type 2 Diabetes Mellitus Treated with Metformin*, and **H8O-US-GWBM** entitled, *Effect on Weight Loss of Exenatide Versus Placebo in Subjects With Type 2 Diabetes Participating in a Lifestyle Modification Program*, completed between the reporting period of October 1, 2008 – September 30, 2009.

We have the following comments and requests for additional information. Please note that these requests are not clinical hold issues. However, written response to them is requested:

- 1. We currently track all post-approval studies for new molecular entities. Clinical trial GWCI, “A placebo and positive controlled study of the electrophysiological effects of a single 10 mcg dose of exenatide on the 12 lead electrocardiogram (ECG) QT interval in healthy subjects”, is of interest to us as Byetta (exenatide) was approved without a Thorough QT study. According to clinicaltrials.gov, study GWCI has been completed. Per the e-mail communications between Staci Ellis (Amylin) and Dr. Amy Egan (FDA) on April 15th, 2010, please submit the final GWCI study report and related datasets. You may submit the other documents listed in the e-mail communication at your earliest convenience for our review.**
- 2. Please submit all clinical trial and post-marketing data for exenatide and exenatide LAR using the following Standardized MedDRA Queries (SMQs) version 12.1: arrhythmia related investigations, signs, and symptoms; cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias).**

We also refer to your amendments dated **October 30, 2009 and April 6, 2010**, submitted to IND 067092, containing a draft protocol for Protocol BCB109 titled, “A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus.”

We have the following comments and requests for additional information.

- 3. Provide a detailed description of the proposed interim analysis of the primary composite cardiovascular outcome. We have the following concerns:**
 - a. The Type I error for this endpoint should be controlled, using standard group sequential or alpha spending function statistical approaches that adjust Type I error for multiple analyses over time. For group sequential approaches, the exact amount of information (events) that will be included in each analysis should be specified. The version of the protocol in this submission (Draft V08 26OCT2009), only describes a review of data every six months or more frequently by the Data Safety and Monitoring Board (DSMB), with stopping guidelines to be detailed in the DSMB charter (see part 9.11). The DSMB charter is not included in this submission. The protocol notes that the overall alpha of 0.05 will be preserved by limiting the number of interim superiority analyses, but does not describe the approach to be used to control Type I error.**
 - b. We would like to know whether or not the DSMB board will consider stopping the study early with a decision of non-inferiority. If so, the interim analysis plan should allow for this possibility in pre-specifying the control of Type I error for the primary composite endpoint. We note that the study is sized and powered for a superiority analysis of exenatide once weekly vs. placebo (see part 9.2). This will be a larger study (based on 1592 composite cardiovascular events) than is needed for a non-inferiority analysis with a margin of 1.3 (approximately 611 events).**
- 4. Please provide a more detailed description of the statistical decision process to be used in evaluating the primary composite cardiovascular outcome and the secondary endpoints (see parts 9.6 and 9.7). Describe how the superiority evaluation and the non-inferiority evaluation are incorporated into this decision process.**
- 5. Page 23 of the draft protocol states full details will be provided in a separate Statistical Analysis Plan (SAP). We encourage you to submit this document for review and await our comments prior to commencing study BCB109. In the future, we encourage you to submit the SAP with the protocol. Please submit the CEC charter, endpoint definitions, and definitions for events of special interest prior to commencing CV study BCB109.**

The July 2009 Endpoints and Standardized Data Collection for CV Outcomes Trials: Draft Recommendations and March 2010 Standardized Definitions for CV Outcomes Trials: Draft Recommendations are attached. Please note that revised definitions will be posted on the CDISC website for 30 days of public comment. Additional recommendations may be forthcoming.

- 6. We strongly recommend the CV trial assess adverse events of interest including the long-term effects of exenatide and exenatide LAR on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as the long-term effects on neoplasms (thyroid and pancreatic), serious hypoglycemia, pancreatitis, immunogenic potential, hypersensitivity, injection site reactions, neoplasms, and renal safety.**
- 7. BCB109 should include robust ECG and pharmacokinetic monitoring in a subset of subjects.**

In addition, we have the following responses to your questions. Your questions are repeated below and our responses follow in **bold** print.

1. Does the agency agree with the overall design of the proposed CV outcomes trial, including study duration, number of patients, and definition of the primary endpoint (with possible adjustment as appropriate to include selected additional terms beyond CV related death, nonfatal MI, or nonfatal stroke), and that the data from this study will be sufficient to characterize the CV benefit/risk profile of exenatide?

FDA Response: No, we do not agree with the overall design of CV study BCB109.

You plan to randomize (1:1) subjects to exenatide once weekly (EQW) 2 mg or placebo. We recommend the randomization be stratified by factors predictive of outcome (e.g. use of statins or other relevant background medications and history).

2. Does the agency agree with the proposed approach to monitoring and reporting AEs, including but not expediting events that reflect study CV outcome endpoints, as described in the draft protocol?

FDA Response: Yes, your plan to record expected events (defined in Appendix 1 Clinical Events List) in the eCRF but not have them reported to the sponsor or regulatory agencies as expedited safety reports is acceptable as 1) these events will be reviewed (at least every six months) by the DSMB and 2) events of pancreatitis, thyroid carcinoma, and pancreatic cancer will be reported to the respective IND(s).

3. Does the agency agree with the proposed approach, as highlighted in this letter and in the protocol, for monitoring for cases of pancreatitis, thyroid neoplasms, and pancreatic

cancer, including the approach to specific laboratory measurements (amylase/lipase and calcitonin)?

FDA Response: Draft protocol BCB109 only includes serum calcitonin measurement at screening. As visits are planned every six months, please also monitor calcitonin annually and at endpoint, as recommended on August 27, 2009. Although we recognize that, if exenatide LAR is approved, annual serum calcitonin measurements will not likely be recommended, the data gathered will help us better understand the medullary thyroid carcinoma safety issue. Please refer subjects with elevated calcitonin measurements for follow up to determine the appropriateness of further evaluation and/or thyroid surgery.

Please ensure that investigators are aware of the risk of pancreatitis and measure pancreatic enzymes when clinically indicated. As recommended in prior communications:

Please exclude subjects with a history of chronic or idiopathic acute pancreatitis from exenatide LAR studies, including BCB109. Please interrupt treatment with study medication if pancreatitis is suspected. Measure serum amylase and lipase in subjects with persistent (e.g. ≥ 3 days) nausea and/or vomiting with or without abdominal pain. Initiate appropriate treatment and carefully monitor the patient until recovery, if pancreatitis is confirmed. Study medication should not be restarted in patients diagnosed with pancreatitis.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
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**Standardized Definitions for
Cardiovascular Outcomes Trials:
Draft Recommendations**

DRAFT

March 24, 2010

Table of Contents

Introduction..... 3
CHAPTER 1. Definition of Cardiovascular Death..... 4
CHAPTER 2. Definition of Non-Cardiovascular Death 7
CHAPTER 3. Definition of Undetermined Cause of Death..... 8
CHAPTER 4. Definition of Myocardial Infarction 9
CHAPTER 5. Definition of Hospitalization for Unstable Angina..... 16
CHAPTER 6. Definition of Transient Ischemic Attack and Stroke 18
CHAPTER 7. Definition of Heart Failure Requiring Hospitalization..... 20
CHAPTER 8. Interventional Cardiology Definitions..... 22
CHAPTER 9. Definition of Peripheral Arterial Revascularization Procedure..... 25
CHAPTER 10. Definition of Stent Thrombosis..... 26
CHAPTER 11. Bleeding Definitions 28
References..... 34

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Introduction

The purpose of this document is to provide a framework of definitions for cardiovascular endpoint events in clinical trials. These definitions are based on clinical and research expertise, published guidelines and definitions, and our current understanding of the specific laboratory tests, diagnostic tests, and imaging techniques used in clinical practice to diagnose these events.

It is recognized that definitions of cardiovascular endpoints may change over time, as new biomarkers or other diagnostic tests become available that may refine prior definitions or as standards evolve and thresholds of importance become modified. Nevertheless, endpoint definitions are necessary in clinical trials so that events are clearly characterized by objective criteria and reported uniformly. Where the person performing the adjudication of an event is blind to the treatment allocation, any errors will be random, rather than systematic. As a consequence, any noise introduced by slight misclassifications of events will not bias the result towards one arm or another, but may mask a true difference in effectiveness or safety or increase the chance of concluding non-inferiority.

Advances in database technologies and statistical methodologies have created opportunities to aggregate large trial datasets. If uniformly defined, events in drug development programs or among different clinical trials may be analyzed more easily and trends and other safety signals may be identified. More consistent definitions could improve the ability to estimate event rates in a contemplated clinical trial.

All definitions have limitations and will not seem satisfactory for every case. The goal of this document is to propose definitions that will be suitable for study endpoints in cardiovascular trials and as events of interest in assessing cardiovascular safety.

Keeping in mind the value and limitations of any type of standardization, the following definitions are proposed to simplify the conduct of cardiovascular trials. Flexibility in these definitions may be necessary to address the particulars of a drug product, clinical trial, or study population. Nevertheless, these definitions are intended to form a basis on which to design clinical trials.

This document includes eleven chapters. Each chapter provides the definition for a particular cardiovascular event.

CHAPTER 1. Definition of Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:
 - a. Death witnessed and instantaneous without new or worsening symptoms
 - b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
 - c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
 - d. Death after unsuccessful resuscitation from cardiac arrest
 - e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
 - f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as an "Unwitnessed Death." Typical scenarios include
 - Subject well the previous day but found dead in bed the next day
 - Subject found dead at home on the couch with the television on
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "Undetermined Cause of Death" (see Chapter 3).

2. **Death due to Acute Myocardial Infarction** refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a “break” (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood should be considered death due to acute myocardial infarction.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

3. **Death due to Heart Failure* or Cardiogenic Shock** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure (see Chapter 7) without evidence of another cause of death.

Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- c. Confinement to bed predominantly due to heart failure symptoms

- d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- e. Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m²

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin), phentermine (ionamin), and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death due to Stroke:** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.
5. **Death due to Other Cardiovascular Causes:** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if “non-cardiovascular” in nature, should be classified as cardiovascular deaths.

CHAPTER 2. Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. Suggested categories* include:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Accidental/Trauma
- Hemorrhage, not intracranial
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular, specify: _____

*Categorization may vary between trials, diseases, and interventions, but should be planned so that trials are able to define the effects of drugs on causes of death that are relevant to the disease under study. Death due to a gastrointestinal bleed should **not** be considered a cardiovascular death.

CHAPTER 3. Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g. presumed cardiovascular death).

Nevertheless, categorization may vary between trials, diseases, and interventions.

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CHAPTER 4. Definition of Myocardial Infarction

1. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction.

For each MI type, one must consider the totality of clinical, electrocardiographic, and cardiac biomarker information to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis.

a. Spontaneous MI

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]**
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK may be used in the absence of CK-MB.

****ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**

- ST elevation
New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

*****Definition of a pathological Q-wave**

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)^a

^aThe same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

b. Percutaneous Coronary Intervention-Related Myocardial Infarction

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL* within 48 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL* (Troponin or CK-MB $> 3 \times 99^{\text{th}}$ percentile URL*) are consistent with PCI-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to PCI, a $\geq 50\%$ increase of the value in the second cardiac biomarker sample within 48 hours of the PCI (and Troponin or CK-MB $> 3 \times 99^{\text{th}}$ percentile URL*) **and** documentation that cardiac biomarker values were decreasing (two samples **3-6 hours apart**) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

Symptoms of cardiac ischemia are not required.

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- either new pathological Q waves in at least 2 contiguous leads that persist through 30 days or new persistent non-rate related LBBB *or*
- angiographically documented new graft or native coronary artery occlusion or other complication in the operating room resulting in loss of myocardium *or*
- imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to CABG, a $\geq 50\%$ increase of the value in the second cardiac biomarker sample within 72 hours of CABG (and Troponin or CK-MB > 5 x 99th percentile URL) **and** documentation that cardiac biomarker values were decreasing (two samples **3-6 hours apart**) prior to the suspected recurrent MI plus any of the three bullets above is consistent with a periprocedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

d. Pathological findings of an acute myocardial infarction

2. Criteria for Silent Myocardial Infarction or Prior Myocardial Infarction (with or without Symptoms)

No evidence of acute myocardial infarction AND any one of the following criteria:

- Appearance of new persistent pathological Q waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)^a
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

^aThe same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

3. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction should be diagnosed if there is a $\geq 20\%$ increase of the value between a measurement (cardiac biomarker) made at the time of the initial presentation and a further sample taken 3-6 hours later. This value should also exceed the 99th percentile URL.*). This scenario applies to patients enrolled in a clinical trial with an acute myocardial infarction who experience a recurrent myocardial infarction post-enrollment or in patients enrolled in a clinical trial without an acute myocardial infarction but who subsequently experience a myocardial infarction during the course of the trial and a recurrent myocardial infarction.

If cardiac biomarkers are elevated prior to the suspected new MI, there must be decreasing cardiac biomarker values on two samples at least 3 hours apart prior to the suspected new MI in combination with other criteria for reinfarction (ECG, imaging).

If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

4. Clinical Classification of Different Types of Myocardial Infarction

- a. For certain types of trials, it may be helpful to distinguish between particular categories of myocardial infarction (MI) using the following guidelines:
 - **Type 1**
Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
 - **Type 2**
Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
 - **Type 3**
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
 - **Type 4a**
Myocardial infarction associated with PCI

- **Type 4b**
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
 - **Type 5**
Myocardial infarction associated with CABG
- b. For each myocardial infarction (MI) identified by the CEC, the type of MI may also be described as:
- ST-Elevation MI (STEMI)
 - Also categorize as:
 - Q-wave
 - Non-Q-wave
 - Unknown (no ECG or ECG not interpretable)
 - Non-ST-Elevation MI (NSTEMI)
 - Also categorize as:
 - Q-wave
 - Non-Q-wave
 - Unknown (no ECG or ECG not interpretable)
 - Unknown (no ECG or ECG not interpretable)
- c. For trials in which it would be helpful to distinguish between particular categories of myocardial infarction, consider
- Reporting MI type by treatment group as follows:

Table 1. Sample Clinical Trial Tabulation of Randomized Patients by Types of Myocardial Infarction

| Types of MI | Treatment A | Treatment B |
|---------------------|---------------------------|---------------------------|
| | Number of patients (N =) | Number of patients (N =) |
| MI Type 1 | n, % | n, % |
| MI Type 2 | n, % | n, % |
| MI Type 3 | n, % | n, % |
| MI Type 4 | n, % | n, % |
| MI Type 5 | n, % | n, % |
| Total number | n, % | n, % |

N = total number of patients; n = number of patients with a particular MI.

- Reporting data as multiples of the 99th percentile URL of the applied biomarker as follows:

Table 2. Classification of the Different Types of Myocardial Infarction According to Multiples of the 99th Percentile URL of the Applied Cardiac Biomarker

| Multiples X 99 % | MI Type 1 (spontaneous) | MI Type 2 (secondary) | MI Type 3* (sudden death) | MI Type 4 ** (PCI) | MI Type 5** (CABG) | Total Number |
|-------------------------|------------------------------------|----------------------------------|--------------------------------------|-------------------------------|-------------------------------|-------------------------|
| 1-2 X | | | | | | |
| 2-3 X | | | | | | |
| 3-5 X | | | | | | |
| 5-10 X | | | | | | |
| >10 X | | | | | | |
| Total number | | | | | | |

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.

**For the sake of completeness, the total distribution of biomarker values should be reported.

The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

General Considerations

- For a diagnosis of acute myocardial infarction, elevation of cardiac biomarkers should be present. However, myocardial infarction may be adjudicated for an event that has characteristics (i.e., ischemic symptoms) of a myocardial infarction but which does not meet the strict definition because biomarker or electrocardiographic results are not available (e.g. not measured) or are non-contributory (e.g. may have normalized).
- Whenever possible, all investigators within a clinical trial should employ the same cardiac troponin assay in order to reduce the inter-assay variability. If reasonable, using a core laboratory with the same assay for all measurements would be optimal.
- Entry criteria for the diagnosis of myocardial infarction in clinical trials may be different than endpoint criteria. For example, use of prior myocardial infarction as an entry criterion may require documentation in the record of “prior MI” and clinical details; however, cardiac enzymes, 12-lead ECG evidence, and cardiac catheterization/percutaneous coronary intervention results may not be required.
- For procedure-related myocardial infarction, all available biomarker information will be taken into account. Furthermore, in cases where the cardiac biomarker is elevated prior to PCI or CABG, the $\geq 20\%$ increase of the value in the secondary cardiac biomarker sample within 48 hours of PCI and within 72 hours of CABG, per the Universal MI definition, is somewhat arbitrary. Some studies may want to use a different percentage, such as $\geq 50\%$ increase. Data should be collected in such a way that analyses using $\geq 20\%$ or $\geq 50\%$ could both be performed.
- There is considerable discussion that in the setting of PCI or CABG, a three-fold increase in CK-MB may not be equivalent to a three-fold increase in troponin and that a five-fold increase in CK-MB may not be equivalent to a five-fold increase in troponin, respectively. Furthermore, it is unclear if this biomarker elevation by itself requires additional confirmation with new ECG changes, procedural complications, or new imaging evidence similar to that required for spontaneous myocardial infarctions or myocardial infarctions occurring in the setting of CABG.
- The prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, and outcomes should be evaluated separately for these two subsets of patients.
- Not infrequently, patients with renal disease or congestive heart failure may have elevated cardiac biomarkers. In these circumstances, the Clinical Endpoints Committee must use the totality of the evidence to determine whether the cardiac biomarker elevation or underlying condition represents the primary process or endpoint event.

CHAPTER 5. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

- a. New or worsening ST or T wave changes on resting ECG
 - ST elevation
New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
 - ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs
- c. Angiographic evidence of $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs
- d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β -blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.
2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned rehospitalization for performance of an elective revascularization in the absence of symptoms at rest prompting admission should not be considered a hospitalization for unstable angina. For example, a patient with stable exertional angina whose admission for coronary angiography and PCI is prompted by a positive outpatient stress test should not be considered a hospitalization for unstable angina.
4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

CHAPTER 6. Definition of Transient Ischemic Attack and Stroke

Introduction

These definitions of Transient Ischemic Attack and Stroke apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with contemporary understanding of the pathophysiology of stroke. This approach enables trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke

Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

2. Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases. For example, the modified Rankin Scale may be used to address this requirement:

| Scale | Disability |
|--------------|-----------------------------------------------------------------------------------------------------------------------------|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

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CHAPTER 7. Definition of Heart Failure Requiring Hospitalization

Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

- a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24* hour stay (or a date change if the time of admission/discharge is not available).

*For this endpoint in any given clinical trial, there should be some flexibility in the required duration of stay, depending on the population and the adverse event profile of the drug to be studied. For example, a clinical trial studying patients with NYHA Class III/IV heart failure may not wish to capture hospitalizations less than 24 hours in duration, because this population may have frequent hospital visits requiring short-term therapy. On the contrary, clinical trials in patients with NYHA Class I/II heart failure may wish to capture shorter hospitalizations that may be predictive of subsequent decompensation.

AND

- b. Clinical symptoms of heart failure, including at least one of the following:

New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

- c. Physical signs of heart failure, including at least two of the following:

1. edema (greater than 2+ lower extremity)
2. pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
3. jugular venous distension
4. tachypnea (respiratory rate > 20 breaths/minute)
5. rapid weight gain
6. S3 gallop
7. increasing abdominal distension or ascites
8. hepatjugular reflux
9. radiological evidence of worsening heart failure
10. A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg or a cardiac output < 2.2 L/min/m²

NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).

AND

- d. Need for additional/increased therapy
 1. Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following:
 - Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
 - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
 - Uptitration of intravenous therapy, if already on therapy
 - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

- e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

NOTE: It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary disease process accounting for the above signs and symptoms.

CHAPTER 8. Interventional Cardiology Definitions

- 1. Coronary Revascularization Procedure:** A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow. Catheter-based tools (e.g., balloon catheters, cutting balloons, atherectomy devices, lasers, bare metal stents, and drug-eluting stents) improve myocardial blood flow by increasing the luminal area at a site of an obstructive coronary lesion. Aortocoronary bypass grafts (arterial, venous, or synthetic) improve myocardial blood flow by providing a conduit for blood flow distal to an obstructive coronary lesion. Insertion of a guidewire through a coronary guide catheter into a coronary vessel or aortocoronary bypass graft for the purpose of percutaneous coronary intervention (PCI) is considered intention for PCI. However, in the assessment of the severity of intermediate lesions with the use of intravascular ultrasound, Doppler flow velocity, or fractional flow reserve, insertion of a guidewire will NOT be considered PCI.
- 2. Procedural Success:** Achievement of <30 % residual diameter stenosis of the target lesion assessed by visual inspection or quantitative coronary angiography (QCA) and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

***Comment:** For some devices or clinical settings (e.g., plain old balloon angioplasty (POBA) for patients undergoing non-cardiac surgery), achievement of < 50% diameter stenosis by visual inspection is an acceptable definition for procedural success.*

3. Elective and Non-elective Procedures:

Elective: An elective procedure is one performed on a patient with stable cardiac function in the days or weeks prior to the procedure. Elective cases are usually scheduled at least 1 day prior to the procedure.

Non-Elective: A non-elective procedure is one performed on a patient who has been stabilized following initial treatment of acute coronary ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours.

OR

A procedure that is performed without delay on a patient with evidence of ongoing refractory ischemia with or without hemodynamic instability.

4. **Target Lesion:** A target lesion is any lesion treated or attempted to be treated during the trial procedure with the study device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the study device (stent, in most cases).
5. **Target Vessel:** A target vessel is any native coronary vessel (e.g., left main coronary artery (LMCA), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), or right coronary artery (RCA)) or aortocoronary bypass graft to the LAD, LCX, or RCA containing the target lesion. The target vessel includes the target lesion as well as segments of the vessel that are upstream and downstream to the target lesion, including side branches (native vessel).
6. **Non-Target Lesion:** A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.
7. **Non-target Vessel:** A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.
8. **Target Vessel, Non-Target Lesion:** Any lesion or revascularization of a lesion in the target vessel other than the target lesion.
9. **Target Lesion Revascularization (TLR):** Target lesion revascularization is any repeat percutaneous intervention of the target lesion (including 5 mm proximal and distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical Events Committee (CEC) for review.
10. **Target Vessel Revascularization (TVR):** Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.
11. **Clinically-Driven Target Lesion Revascularization:** Revascularization is clinically-driven if the subject has a target lesion diameter stenosis $\geq 50\%$ by QCA and clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:
 - a. A history of angina pectoris, presumably related to the target vessel
 - b. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel
 - c. Abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve or fractional flow reserve (FFR))
 - d. A diameter stenosis $\geq 70\%$ by QCA even in the absence of the above signs or symptoms.

Comment: *In the absence of QCA data or if a <50% stenosis is present, TLR may be considered clinically-driven by the CEC if severe ischemic signs and symptoms attributed to the target lesion are present.*

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CHAPTER 9. Definition of Peripheral Arterial Revascularization Procedure

1. **Peripheral Arterial Revascularization Procedure:** A peripheral arterial revascularization procedure is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, aneurysm/dissection repair, angioplasty, and stent placement.

The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

The target vessel(s) should be specified (e.g., carotid, vertebral, aorta, renal, iliac, femoral) and recorded as well as the type of revascularization procedure (e.g., surgical, angioplasty, stent placement, thromboembolectomy, aneurysm repair).

2. **Procedural Success:** In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a final residual diameter stenosis $< 30\%$ by angiography at the end of the procedure without any in-hospital major adverse events (death, acute onset of limb ischemia, need for urgent/emergent vascular surgery). The balloon inflation and/or stent placement may be preceded by device activation (e.g., angiojet, directional or rotational atherectomy, lasers).

3. **Elective and Non-Elective Procedures:**

Elective: An elective procedure is one that is scheduled and is performed on a patient with stable peripheral arterial disease.

Non-Elective: A non-elective procedure is one that is performed immediately upon diagnosis because of urgency of the medical condition (e.g., acute limb ischemia, acute stroke, acute aortic dissection, acute aneurysm rupture).

4. **Target Vessel:** A target vessel is any vessel (e.g., carotid, peripheral artery, mesenteric/renal artery) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as segments of the vessel that are upstream and downstream to the target lesion, including side branches (native vessel).
5. **Non-target Vessel:** A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

CHAPTER 10. Definition of Stent Thrombosis

Stent Thrombosis: Timing

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the cardiac catheterization laboratory.

Timing

- Acute stent thrombosis¹: 0-24 hours post stent implantation
- Subacute stent thrombosis¹: > 24 hours – 30 days post stent implantation
- Late stent thrombosis²: > 30 days – 1 year post stent implantation
- Very late stent thrombosis²: > 1 year post stent implantation

¹Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0-30 days) will be used herein.

²Includes “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Stent Thrombosis: Categories

We propose three categories of evidence to define stent thrombosis, as follows:

1. Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation:

a. Angiographic confirmation of stent thrombosis^a

- Thrombolysis in Myocardial Infarction (TIMI) flow is:
 - TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus^{b,c} **OR**
 - TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus^{b,c}

AND at least one of the following criteria has been fulfilled within a 48 our time window:

- New acute onset of ischemic symptoms at rest (typical chest pain with duration > 20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (See definition of non-procedural-related MI (i.e. spontaneous MI) in Chapter 4.

^aThe incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

^bNon-occlusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream

^cOcclusive thrombus: TIMI 0 or TIMI 1 flow intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch)

b. Pathologic Confirmation of Stent Thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

2. Probable Stent Thrombosis

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- a. Any unexplained death within the first 30 days§
- b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

§In patients undergoing PCI for STEMI, one may consider excluding unexplained death within 30 days of the procedure as evidence of probable stent thrombosis.

3. Possible Stent Thrombosis

Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

CHAPTER 11. Bleeding Definitions

1. GUSTO

a. **Severe or Life Threatening**

Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention

b. **Moderate**

Bleeding that requires blood transfusion but does not result in hemodynamic compromise

c. **Mild**

Bleeding that does not meet the criteria for severe or moderate

2. TIMI

a. **Types of TIMI Bleeding**

1. **Major**

- Any intracranial bleeding

OR

- Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL.

2. **Minor**

Any clinically overt signs of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL

3. **Medical Attention:**

Any overt sign of hemorrhage that requires medical evaluation, medical treatment (including discontinuation of medications), or surgical treatment, and that does not meet criteria for a major or minor bleeding event, as defined above.

4. **Minimal**

Any overt bleeding event that does not meet the criteria above

NOTE: To account for transfusions, Hgb measurements will be adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase by 1 gm/dL in Hgb. Thus, to calculate the true change in hemoglobin, if there has been an intervening transfusion between two blood measurements, the following

calculations should be performed: $\Delta \text{Hgb} = [\text{Baseline Hgb} - \text{Post transfusion Hgb}] + [\# \text{ transfused units}]$.

b. Relationship of Bleeding to Death

1. Fatal Bleeding

Death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

2. Bleeding Contributed to Death

Death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to the subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

c. Bleeding in the Setting of Coronary Artery Bypass Graft Surgery (CABG)

Minor and minimal bleeding are not adjudicated in the setting of CABG.

As a drop in hemoglobin and transfusions are commonplace in routine CABG cases, one of the following criteria must be met to qualify for major bleeding in any of the preceding definitions:

1. Fatal bleeding (i.e., bleeding that directly results in death)
2. Perioperative intracranial bleeding
3. Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding
4. Transfusion of ≥ 5 units of packed red blood cells (PRBCs) or whole blood within a 48 hour period. Cell saver transfusion will not be counted in calculations of blood products
5. Chest tube output > 2 L within a 24 hour period

3. CURE

a. Major Bleeding episodes are those which are:

1. Substantially disabling
2. Intraocular bleeds leading to loss of vision
3. Require at least 2 units of blood transfusion

b. Major bleeds are to be classified as life-threatening if they meet one or more of the following criteria:

1. Fatal, symptomatic intracranial bleed
2. Reduction in hemoglobin of at least 5 g/dL
3. Transfusion of at least 4 units of blood or packed cells, associated with substantial hypotension requiring the use of intravenous inotropic agents
4. Necessitated surgical intervention

c. Minor Bleeding

1. Other hemorrhages that led to interruption of the study medication

4. ACUTY

a. Major Bleeding is defined as

1. Intracranial bleeding
2. Intraocular bleeding
3. Access site hemorrhage requiring intervention
4. ≥ 5 cm diameter hematoma
5. Reduction in hemoglobin concentration of ≥ 4 g/dL without an overt source of bleeding
6. Reduction in hemoglobin concentration of ≥ 3 g/dL with an overt source of bleeding
7. Reoperation for bleeding
8. Use of any blood product transfusion

b. Minor bleeding

Clinically overt bleeding that did not meet criteria for major bleeding.

5. PLATO

- a. Major Bleed—Fatal/life-threatening bleeding is defined as any one of the following:**
1. Fatal
 2. Intracranial
 3. Intrapericardial bleed with cardiac tamponade
 4. Hypovolemic shock or severe hypotension due to bleeding requiring pressors or surgery
 5. Clinically overt or apparent bleeding associated with a decrease in Hgb of more than 50 g/L
 6. Transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding
- b. Major Bleed—Other is defined as any one of the following:**
1. Significantly disabling (e.g., intraocular with permanent vision loss)
 2. Clinically overt or apparent bleeding associated with a decrease in hemoglobin of 30 g/L (tetramer: 1.9 mmol/L, monomer: 0.465 mmol/L) to 50 g/L (3.1 mmol/L; 0.775 mmol/L)
 3. Transfusion of 2-3 units (whole blood or PRBCs) for bleeding
- c. Minor Bleed**
Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing)
- d. Minimal Bleed**
All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

6. RELY

- a. Major bleeding is defined by ≥ 1 of the following criteria:**
1. Bleeding associated with reduction in hemoglobin level of at least 2.0 g/L
 2. Leading to transfusion of at least 2 units of blood or packed cells; or
 3. Symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding

Furthermore, major bleed is classified as life-threatening if they met ≥ 1 of the following criteria:

1. Fatal, symptomatic intracranial bleed;
2. Reduction in hemoglobin level of at least 5.0 g/L;
3. Transfusion of at least 4 U of blood or packed cells;
4. Associated with hypotension requiring the use of intravenous inotropic agents; or
5. Necessitated surgical intervention

b. Minor bleeds

Clinical bleeds that do not fulfill the criteria for major bleeds

7. ISTH

a. Major Bleed

- Fatal bleed

and/or

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome

and/or

- Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or leading to transfusion of two or more units of whole blood or red cells

b. Minor Bleed

All non major bleeds will be considered minor bleeds. Minor bleeds will be further divided to those that are clinically relevant and those that are not

c. Clinically Relevant Minor Bleed

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission for bleeding
- **OR** a physician guided medical or surgical treatment for bleeding
- **OR** a change in antithrombotic therapy (including interruption or discontinuation of study drug)

8. ESTEEM

a. Major Bleeding must satisfy one or more of the following criteria:

- Fatal
- Clinically overt bleeding associated with a reduction in hemoglobin of at least 2 g/dL or leading to a transfusion of at least 2 units of blood or packed red blood cells
- Bleeding in areas of special concern such as: intraocular, intracranial, intraspinal, retroperitoneal, pericardial or atraumatic intra-articular bleeding

b. Minor bleeds must satisfy either

- Minor bleeds causing permanent stop of medication

or

- Other minor bleeds such as epistaxis, gingival bleeds, and microscopic hematuria

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**Endpoints and Standardized Data
Collection for Cardiovascular
Outcomes Trials:
Draft Recommendations**

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research (CDER)

**July 22, 2009
Clinical/Medical**

Table of Contents

APPENDIX 1. Primary Endpoint: General Recommendations for DMEP Cardiovascular Outcomes Trials 3

APPENDIX 2. Enrichment of the Study Population 4

APPENDIX 3. Endpoints of Interest that Require Adjudication..... 5

APPENDIX 4. Other Endpoints of Interest that Do Not Require Formal Adjudication..... 6

APPENDIX 5. Source Documents 7

APPENDIX 6. Information to be Submitted for the Cardiovascular Outcomes Trial 8

APPENDIX 7. Data Sets to be Submitted with the Clinical Study Report 9

APPENDIX 8. Listings to be Submitted with the Clinical Study Report 10

APPENDIX 9. Standardised MedDRA Queries (SMQs) for DMEP Cardiovascular Outcomes Trials 11

APPENDIX 10. System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Cardiovascular Outcomes Trials 12

APPENDIX 11. Standardised MedDRA Queries (SMQs), System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Obesity Trials..... 13

APPENDIX 12. Recommended Methods of Addressing Elevated CPKs at Routine Follow-Up Appointments in DMEP Clinical Trials..... 15

APPENDIX 1. Primary Endpoint: General Recommendations for DMEP Cardiovascular Outcomes Trials

Major Adverse Cardiovascular Events (MACE)

1. Cardiovascular Death (CV Death)
2. Nonfatal Myocardial Infarction (NFMI)
3. Nonfatal Stroke

APPENDIX 2. Enrichment of the Study Population

Enrollment of study subjects with higher risk characteristics, including:

- Duration of diabetes mellitus for at least 7 but preferably 10 years
- Insulin requiring diabetes mellitus
- Age \geq 65 years of age
- History of acute coronary syndrome $>$ 2 months from index event
- History of prior myocardial infarction
- History of prior coronary artery bypass graft (CABG) surgery
- History of prior percutaneous coronary intervention (PCI)
- History of hypertension
- History of hyperlipidemia
- History of coronary artery disease
- Family history of premature coronary artery disease
- History of tobacco use
 - any use (# of years)
 - current use
 - prior use
 - never used
- Peripheral vascular disease
- History of carotid/vertebral artery disease
- History of transient ischemic attack (TIA) or stroke
- History of congestive heart failure
- Renal insufficiency
 - glomerular filtration rate $<$ 60 mL/min/1.73 m² per MDRD or $<$ 60 mL/min per Cockcroft-Gault equation
 - Urine Albumin to Urine Creatinine Ratio
 - microalbuminuria (30-300 mg Albumin/g Creatinine)
 - macroalbuminuria ($>$ 300 mg Albumin/g Creatinine)
- History of arrhythmia

APPENDIX 3. Endpoints of Interest that Require Adjudication

- Death
 - All Cause Mortality
 - Cardiovascular Death
 - Non-Cardiovascular Death

- Acute Coronary Syndrome
 - Myocardial Infarction
 - Hospitalization for Unstable Angina

- Cerebrovascular Events
 - Cerebrovascular Event (Stroke)
 - Ischemic (Non-hemorrhagic)
 - Hemorrhagic
 - Unknown
 - Transient Ischemic Attack

- Coronary Revascularization Procedures
 - Coronary Artery Bypass Graft Surgery
 - Percutaneous Coronary Intervention

- Hospitalization for Heart Failure

- Stent Thrombosis (clinical adjudication)
 - Data needed
 - Name of device (Bare metal stent versus Drug eluting stent) as well as stent diameter and length
 - Coronary reference vessel diameter (RVD) and lesion length
 - Date of implantation
 - Date of stent thrombosis
 - Indication for index PCI [ACS (indicate STEMI, non-STEMI, or UAP), non-ACS]
 - Did patient have multivessel disease?
 - Did patient undergo multivessel (three-vessel disease) or left main treatment?
 - Left ventricular function
 - Overlapping stents
 - Bifurcation lesion stenting
 - Bypass graft (arterial or venous conduit) stenting
 - Presence or absence of renal disease based on glomerular filtration rate as determined by the Cockcroft-Gault Equation
 - Was patient on dual antiplatelet therapy (yes/no), and if not, date of aspirin or P2Y12 inhibitor discontinuation?

APPENDIX 4. Other Endpoints of Interest that Do Not Require Formal Adjudication

- Hospitalization for other CV causes
 - Pulmonary Embolus
 - Aortic Dissection
 - Ruptured Aortic Aneurysm
- Carotid Artery Revascularization (surgical versus percutaneous)
- Other Peripheral Vascular Revascularization (lower extremity, renal, mesenteric, iliac, subclavian, and aortic etc.) (surgical versus percutaneous)
- Lower Extremity Amputation
- Hospitalization for Cardiac Arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement)

APPENDIX 5. Source Documents

Check boxes should be created so that investigator reported adverse events will trigger Clinical Endpoints Committee (CEC) review. Check boxes should also be created for CEC adjudication. Records should be obtained for all hospitalizations, and autopsies should be obtained for all deaths and submitted to the CEC for review. Source documents are needed for events to include but not be limited to:

1. Death
 - a. Autopsy (if performed)
 - b. Code summary (if available)
 - c. Death/Hospital summary (if death occurred in-hospital)
2. Myocardial Infarction/Hospitalization for Unstable Angina/Stent Thrombosis
 - a. Admission History and Physical
 - b. ECG tracings (prior to event, during event, and following event resolution)
 - c. Cardiac biomarkers (all troponin/CK-MB results for hospitalization and prior 30 days) Record units, normal ranges, and myocardial necrosis and myocardial infarction reference limits)
 - d. Other laboratory reports, if requested
 - e. Procedure reports (Cardiac Catheterization, PCI, CABG)
 - f. Other imaging reports (MRI, CTA, Echocardiogram, Nuclear Medicine)
 - g. Discharge Summary
3. Stroke or TIA
 - a. Neurology Consult
 - b. Imaging reports (MRI, CT, or other imaging reports including transthoracic and/or transesophageal echocardiograms)
 - c. Discharge Summary
4. Coronary Revascularization Procedures
 - a. Procedure reports (Cardiac catheterization, PCI, CABG)
 - b. Discharge Summary
5. Hospitalization for Heart Failure
 - a. Admission History and Physical
 - b. ECG tracings
 - c. Cardiac markers (troponin/CK-MB results)
 - d. Other laboratory reports (e.g., BNP)
 - e. Chest X-Ray report
 - f. Discharge Summary
6. Acute Pancreatitis
 - a. Imaging reports
 - b. Discharge Summary

APPENDIX 6. Information to be Submitted for the Cardiovascular Outcomes Trial

The sponsor should submit the following information for Division review prior to initiating their Cardiovascular Outcomes Trial:

- Proposed protocol
- Definitions for all protocol endpoints and events of special interest
- Case Report Form
- Clinical Endpoints Committee (CEC) Charter, including algorithms to be used for endpoint events
- Statistical Analysis Plan (SAP)

APPENDIX 7. Data Sets to be Submitted with the Clinical Study Report

The Division requires that **verbatim terms** are included in the adverse events data sets submitted to the Agency.

NOTE: All raw data sets as well as derived data sets are to be submitted with the Clinical Study Report.

APPENDIX 8. Listings to be Submitted with the Clinical Study Report

All of the prospectively collected cardiovascular (CV) events described in Appendix 3 should be reviewed by the Clinical Events Committee (CEC), as discrepancies between investigator-reported and adjudicated events may arise. With the clinical study report, the sponsor should submit data sets for both the investigator-reported and CEC adjudicated cardiovascular events. Additionally, the sponsor should submit the following 5 listings:

- All investigator-reported CV events
- All CEC-adjudicated CV events
- All investigator-reported CV events that were also adjudicated by the CEC to be events
- All investigator-reported CV events that were not thought to be events by the CEC (“downgrades”)
- All CEC-adjudicated CV events that were not considered to be events by the investigator (“upgrades”)

APPENDIX 9. Standardised MedDRA Queries (SMQs) for DMEP Cardiovascular Outcomes Trials

In addition to CEC adjudication of triggered events, we recommend searching the following standardised MedDRA queries (SMQs) for other possible cardiovascular events that may also require adjudication:

1. Myocardial Infarction
2. Ischaemic Heart Disease
3. Cardiac Arrhythmias
4. Cardiac Failure
5. Embolic and Thrombotic Events
6. Shock
7. Torsade de pointes/QT prolongation
8. Cerebrovascular Disorders
9. Central Nervous System Haemorrhages and Cerebrovascular Accidents
10. Vasculitis

APPENDIX 10. System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Cardiovascular Outcomes Trials

The Division also recommends searching the following system organ classes (SOCs), high level terms (HLT), lower level terms (LLTs), and preferred terms (PTs) for cardiovascular events that may also require adjudication:

1. SOC: Cardiac Disorders
2. SOC: General Disorders and Administration Site Conditions
3. SOC: Injury, Poisoning, and Procedural Complications
4. SOC: Investigations
5. SOC: Musculoskeletal and Connective Tissue Disorders
6. SOC: Nervous System Disorders
7. SOC: Respiratory, Thoracic, and Mediastinal Disorders
8. SOC: Surgical and Medical Procedures
9. SOC: Vascular Disorders
10. LLT: Cerebral Revascularization Synangiosis (search value: revascularization)
11. LLT: Coronary Revascularization (search value: revascularization)
12. LLT: Peripheral Revascularization (search value: revascularization)
13. LLT: Renal Revascularization (search value: revascularization)
14. LLT: Transmyocardial Revascularization (search value: revascularization)
15. LLT: Acute myocardial ischemia (search value: myocardial ischemia)
16. LLT: ECG signs of myocardial ischemia (search value: myocardial ischemia)
17. LLT: Myocardial ischemia (search value: myocardial ischemia)
18. LLT: Myocardial ischemia recurrent (search value: myocardial ischemia)
19. LLT: Silent myocardial ischemia (search value: myocardial ischemia)
20. PT: Acute Myocardial Infarction (search value: myocardial infarction)
21. PT: Myocardial Infarction (search value: myocardial infarction)
22. PT: Post Procedural Myocardial Infarction (search value: myocardial infarction)
23. PT: Silent Myocardial Infarction (search value: myocardial infarction)

APPENDIX 11. Standardised MedDRA Queries (SMQs), System Organ Classes, Lower Level Terms, and Preferred Terms for DMEP Obesity Trials

In addition to CEC adjudication of triggered events, we recommend searching the following standardised MedDRA queries (SMQs) for other possible cardiovascular events that may also require adjudication:

Standardised MedDRA Queries (SMQs)

1. Myocardial Infarction
2. Ischaemic Heart Disease
3. Cardiac Arrhythmias
4. Cardiac Failure
5. Cardiomyopathy
6. Embolic and Thrombotic Events
7. Hypertension
8. Pulmonary Hypertension
9. Rhabdomyolysis/Myopathy
10. Shock
11. Torsade de pointes/QT prolongation
12. Cerebrovascular Disorders
13. Central Nervous System Haemorrhages and Cerebrovascular Accidents
14. Vasculitis

Furthermore, the Division also recommends searching the following system organ classes (SOCs), high level terms (HLT), lower level terms (LLTs), and preferred terms (PTs) for cardiovascular events that may also require adjudication:

1. SOC: Cardiac Disorders
2. SOC: General Disorders and Administration Site Conditions
3. SOC: Injury, Poisoning, and Procedural Complications
4. SOC: Investigations
5. SOC: Musculoskeletal and Connective Tissue Disorders
6. SOC: Nervous System Disorders
7. SOC: Respiratory, Thoracic, and Mediastinal Disorders
8. SOC: Surgical and Medical Procedures
9. SOC: Vascular Disorders
10. HLT: Cardiac valve disorders NEC
11. HLT: Pulmonary hypertensions
12. LLT: Cardiac valvulopathy
13. LLT: Cerebral Revascularization Synangiosis (search value: revascularization)
14. LLT: Coronary Revascularization (search value: revascularization)
15. LLT: Peripheral Revascularization (search value: revascularization)
16. LLT: Renal Revascularization (search value: revascularization)
17. LLT: Transmyocardial Revascularization (search value: revascularization)
18. LLT: Acute myocardial ischemia (search value: myocardial ischemia)

19. LLT: ECG signs of myocardial ischemia (search value: myocardial ischemia)
20. LLT: Myocardial ischemia (search value: myocardial ischemia)
21. LLT: Myocardial ischemia recurrent (search value: myocardial ischemia)
22. LLT: Silent myocardial ischemia (search value: myocardial ischemia)
23. PT: Acute Myocardial Infarction (search value: myocardial infarction)
24. PT: Myocardial Infarction (search value: myocardial infarction)
25. PT: Post Procedural Myocardial Infarction (search value: myocardial infarction)
26. PT: Silent Myocardial Infarction (search value: myocardial infarction)
27. PT: Cardiac valve disease
28. PT: Pulmonary hypertension

APPENDIX 12. Recommended Methods of Addressing Elevated CPKs at Routine Follow-Up Appointments in DMEP Clinical Trials

For creatine phosphokinase elevation of $> 2X$ ULN, the investigator should clearly document (by use of a check-box) whether or not symptoms consistent with a cardiac etiology coincided with this elevation. If coincident cardiac symptoms were reported, additional testing with 12-lead electrocardiograms and troponins should be considered.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-----------------------------------|---------------------------------------------|
| IND-67092 | GI-1 | AMYLIN PHARMACEUTICA LS INC | EXENATIDE LA (SYNTHETIC EXENDIN-4)INJECT |
| IND-67092 | ORIG-1 | AMYLIN PHARMACEUTICA LS INC | EXENATIDE LA (SYNTHETIC EXENDIN-4)INJECT |
| IND-57725 | ANRPT-11 | AMYLIN | BYETTA (EXENATIDE INJECTION) |

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/s/

MARY H PARKS
04/20/2010

Executive CAC

Date of Meeting: January 19, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Team Leader
Tim Hummer, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Tim Hummer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #22-200

Drug Name: Bydureon (exenatide QW)

Sponsor: Amylin Pharmaceuticals

Background:

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that is currently marketed as Byetta for the treatment of type 2 diabetes mellitus. Exenatide mimics several glucoregulatory actions of the endogenous incretin, GLP-1, including glucose-dependent enhancement of insulin synthesis and secretion, inhibition of glucagon secretion, and slowing of gastric emptying. Exenatide QW (Bydureon) is a sustained release formulation of exenatide that was developed by formulating exenatide with PLG microspheres (50:50 mix of poly(D,L-lactide-co-glycolide)), thereby allowing once weekly injections in the clinic rather than the twice daily injections required for Byetta. Amylin previously conducted a rat and mouse carcinogenicity study with immediate release exenatide to support the marketing approval of Byetta. The results of these studies indicated a slight increase in benign thyroid c-cell adenomas at 250 µg/kg/d in female rats only. The current study under review evaluated the carcinogenic potential of exenatide when formulated with PLG microspheres in rats with dosing every 2 weeks. The proposed clinical dosing is once weekly. Amylin has submitted the data from all three carcinogenicity studies to characterize the carcinogenic potential of exenatide QW and to support the marketing application for Bydureon.

GLP-1 receptor agonists as a class have shown a risk for the development of thyroid c-cell tumors in both rats and mice. Based on the available information regarding the carcinogenic potential of GLP-1 receptor agonists, the data indicate that long-acting GLP-1 agonists or formulations that allow a steady state exposure to be reached (in contrast to immediate release exenatide) have a higher risk for inducing thyroid c-cell tumors with a lower clinical exposure margin. This effect, at least in part, is thought to be due to the continuous exposure of c-cells to exenatide versus a pulsatile exposure observed with short-lived GLP-1 receptor agonists.

Rat Carcinogenicity Study:

The sponsor conducted a 2-year bioassay in Sprague-Dawley rats with the sustained release formulation of exenatide (exenatide QW). Rats (70/sex/group) were administered exenatide QW (0.3, 1, or 3 mg/kg), diluent vehicle, or diluent plus microspheres (without exenatide) once every 2 weeks by subcutaneous injection. The study was found to be adequately designed and conducted. Based on the review of the study report, neoplastic findings believed to be related to exenatide QW included thyroid c-cell tumors (adenomas plus carcinomas) at all doses in males and females (the value for low-dose males lacked statistical significance but was greater than the upper historical control range [the specific vehicle used for the historical control range was not provided]) and skin fibromas in high-dose males. Systemic exposures at the low-, mid-, and high-dose levels were approximately 2-, 9-, and 26-fold higher than the maximum anticipated clinical exposure, respectively. At the injection site for high-dose males, the amount of drug injected was approximately 10% less than the amount of exenatide administered clinically (~1.8 mg versus 2 mg), based on an average male rat weight of 0.6 kg. A summary of tumor incidence observed in males and females is shown in the tables below.

Summary of Tumor Incidence in Males

| Dose (mg/kg) | Diluent Control | Microsphere Control | 0.3 | 1.0 | 3.0 | Historical Control |
|------------------------------------|-------------------------------------|--------------------------------------|---------------------------|--------------------------------------|--------------------------------------|---------------------------|
| Thyroid, c-cell hyperplasia | 15/70 (21%) | 10/70 (14%) | 23/70 (33%) | 19/70 (27%) | 23/70 (33%) | NP |
| c-cell adenoma | 9/70 (14%) p<0.001† | 9/70 (14%) p<0.001† | 20/70 (29%) p=0.038 | 32/70 (46%) p<0.001* | 33/70 (47%) p<0.001* | 8.8% (1.9-15.4%) |
| c-cell carcinoma | 0/70 (0%) p=0.164 | 1/70 (1.4%) p=0.237 | 2/70 (2.9%) p=0.268 | 5/70 (7.1%) p=0.036* | 3/70 (4.3%) p=0.133 | 0.6% (0-1.7%) |
| c-cell adenoma + carcinoma | 9/70 (13%) p<0.001† | 10/70 (14%) p<0.001† | 22/70 (31%) p=0.019 | 34/70 (49%) p<0.001* | 35/70 (50%) p<0.001* | NP |
| Skin, subcutis, Fibroma | 0/70 (0%) p=0.004† | 3/70 (4.3%) p=0.034 | 4/70 (5.7%) p=0.069 | 2/70 (2.9%) p=0.273 | 8/70 (11%) p=0.004* | 2.2% (0-5%) |

Historical control data from 11 studies; NP = not provided.

*Statistically significant by pair-wise analysis compared with diluent control.

†Statistically significant for dose response.

Summary of Tumor Incidence in Females

| Dose (mg/kg) | Diluent Control | Microsphere Control | 0.3 | 1.0 | 3.0 | Historical Control |
|-----------------------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|---------------------|
| Thyroid, c-cell hyperplasia | 13/70 (19%) | 12/70 (17%) | 31/70 (44%) | 29/70 (41%) | 40/70 (57%) | NP |
| c-cell adenoma | 5/70 (7.1%) p=0.024 | 9/70 (13%) p=0.072 | 22/70 (31%) p<0.001* | 19/70 (27%) p=0.003* | 21/70 (30%) p<0.001* | 8.1% (2.0-11.4%) |
| c-cell carcinoma | 0/70 (0%) p=0.014 | 1/70 (1.4%) p=0.042 | 1/70 (1.4%) p=0.533 | 1/70 (1.4%) p=0.517 | 4/70 (5.7%) p=0.064 | 0.6% (0-4.0%) |
| c-cell adenoma + carcinoma | 5/70 (7%) p=0.003† | 10/70 (14%) p=0.016 | 23/70 (33%) p<0.001* | 20/70 (29%) p=0.002* | 25/70 (36%) p<0.001* | NP |

Historical control data from 11 studies; NP = not provided.

*Statistically significant by pair-wise analysis compared with diluent control.

†Statistically significant for dose response.

Executive CAC Conclusions:

- The Committee agreed that the study was valid.
- The Committee found that the study was positive for drug-related thyroid c-cell tumors (adenomas plus carcinomas) in males and females at all doses tested and for fibromas of the skin in high dose males.
- The Committee noted that a mouse carcinogenicity study with exenatide QW was not warranted.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DMEP

KDavisBruno, DMEP

THummer, DMEP

JBishai, DMEP

/ASeifried, OND IO

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-----------------------------------|---------------|
| NDA-22200 | ORIG-1 | AMYLIN PHARMACEUTICA LS INC | EXENATIDE LAR |

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/s/

ADELE S SEIFRIED
02/01/2010

DAVID JACOBSON KRAM
02/01/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: February 25, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Through: Kellie Taylor, PharmD, MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MEd, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Bydureon
(Exenatide for Extended-release Injectable Suspension)
2 mg per vial

Application Type/Number: NDA 022200

Applicant: Amylin

OSE RCM #: 2009-2211

CONTENTS

| | | |
|-----|-----------------------------------------|---|
| 1 | INTRODUCTION..... | 3 |
| 1.1 | Regulatory History..... | 3 |
| 2 | METHODS AND MATERIALS | 3 |
| 2.1 | Adverse Event Reporting System | 3 |
| 3 | RECOMMENDATIONS | 3 |
| 3.1 | Comments to the Division and DRISK..... | 4 |
| 3.2 | Comments to the Applicant..... | 6 |
| | APPENDICES | 8 |

1 INTRODUCTION

This review is written in response to a request from the Division of Metabolism and Endocrinology Products for evaluation of the labels and labeling of Bydureon to identify areas that could contribute to medication errors. The Applicant submitted proposed container labels, carton and insert labeling, patient package insert labeling (PPI) and instructions for use for our review and comment.

1.1 REGULATORY HISTORY

Bydureon is a dual trade name request. Exenatide injection is currently marketed as Byetta (NDA 021773) by the same Applicant for the same indication for use, but with a different dosage form and frequency of administration. The proposed proprietary name was found acceptable under separate review (OSE review 2009-2193).

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling, patient package insert labeling, and instructions for use submitted November 3, 2009 (see Appendices A through D). Additionally, the Applicant submitted revised container labels containing a bar code via email on February 22, 2010 (see Appendix E).

2.1 ADVERSE EVENT REPORTING SYSTEM

Since exenatide is currently marketed, the Division of Medication Error Prevention and Analysis reviewed OSE review #2007-1413 (Byetta User Manual Labeling Revisions) which contains postmarketing data extrapolated from the FDA Adverse Events Reporting System (AERS) pertaining to exenatide.

In OSE review #2007-1413 (Byetta User Manual Labeling Revisions), we reviewed postmarketing data from the FDA Adverse Events Reporting System (AERS) pertaining to exenatide. The majority of medication errors with exenatide were associated administration errors of the drug product and the use of the multi-dose pen device. The errors related to the lack of feedback from the pen device, device malfunction, and knowledge deficit about how to use the device. Since Bydureon is not supplied as a multi-dose pen device, we do not anticipate the same type of medication errors as seen with Byetta.

There were no reports of name confusion with Byetta or with the established name, exenatide.

3 RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. Additionally, the Division asked if the active ingredient vial and diluent need a bar code. We confirmed with Compliance, the Federal Food, Drug, and Cosmetic Act (Chapter II, Section 201(g)(1)(D)), and with the CFR regulations (21 CFR 201.25), that both the active ingredient container label and diluent container label require distinct bar codes. The review Division communicated this information to the Applicant and they submitted revised labels with bar codes for the active ingredient vial and diluent.

We provide recommendations on the insert labeling, patient package insert labeling and the instructions for use in *Section 3.1 Comments to the Division and DRISK* for discussion during the review team's label and labeling meetings. *Section 3.2 Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Margarita Tossa, OSE Project Manager, at 301-796-4053.

3.1 COMMENTS TO THE DIVISION AND DRISK

We request the Division consider all physician insert comments and DRISK to review and consider our recommendations for the patient package insert, the Medication Guide and the Instructions for Use as discussed in sections C, D, and E below.

A. General Comment for All Labels and Labeling

Per email communication with the chemist, DMEPA was informed that the established name should be “exenatide for extended-release injectable suspension”. We concur with CMC. Therefore, we request you revise the established name per CMC’s advice throughout the labels and labeling for consistency.

B. Package Insert

1. Indications and Usage Section

In section 1.2 “Important Limitations of Use”, the second sentence of the second paragraph, “Bydureon and Byetta both contain the same active ingredient, exenatide, and therefore should not be used together”, should appear as a separate paragraph on its own as it is an important statement that communicates avoiding concomitant use of Bydureon and Byetta. Therefore, we request you revise this section by making this statement the third paragraph of this section.

2. Dosage and Administration Section

Section 2.1 “Recommended Dosing” subsection “Changing Weekly Dosing Schedule” may be confusing to the reader. Include an example of how to change the dosing day of the week in a similar manner as the example given in the Medication Guide, item 5, subsection “When to use Bydureon” bullet 3. By giving an example, it provides more clarity on how to change the day of the week. It is important to indicate that it is okay to take 2 doses in the same week when changing the dosing day. Revise accordingly.

3. How Supplied/Storage and Handling Section

The description of the needles provided in the kit is vague. Include the needle gauge and length in the description of the needles supplied with the kit.

C. Patient Package Insert

1. The following statement appears at the end of section 4, subsection “When to use Bydureon”:

This information is only for people who are currently taking BYETTA® (exenatide injection):

- If you are currently taking BYETTA, follow your healthcare provider’s instructions about when to stop taking BYETTA and when to start taking BYDUREON. BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first switch from BYETTA to BYDUREON, your blood sugar levels may be higher than usual. This is normal. Blood sugar levels often improve within about 2 weeks

Relocate this information to appear at the beginning of section 4 rather than the end of this section to provide greater prominence to this information. This information is important for

- patients who are switching from Byetta to Bydureon by informing them to avoid concomitant use of the two drug products. In its current location, it may not be read or either overlooked.
2. In section 6, bullet 2, the storage time that the kit can be kept out of the refrigerator is inconsistent with the information in the section 16.2 (Storage and Handling) of the package insert (7 days vs. 4 weeks). Ensure the storage time in the package insert is consistent with the storage time in the package insert.

D. Medication Guide

The following statement appears at the end of section 5, subsection “When to use Bydureon”:

This information is only for people who are currently taking BYETTA® (exenatide injection):

- If you are currently taking BYETTA, follow your healthcare provider's instructions about when to stop taking BYETTA and when to start taking BYDUREON. BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first switch from BYETTA to BYDUREON, your blood sugar levels may be higher than usual. This is normal. Blood sugar levels often improve within about 2 weeks

Relocate this information to section 1 “What is the most important information I should know about Bydureon?” This information is important for the patient to avoid concomitant use of Byetta and Bydureon. Thus, it is more appropriate under section 1.

E. Instructions for Use

1. Connecting the Parts

In step 2c, if there is audible or tactile feedback when the vial is pressed into the orange connector, indicate what the sound is or what the tactile feedback is (e.g., Press the top of the vial firmly into the orange connector until it clicks or until it snaps on).

2. Mixing the Medicine and Filling the Syringe

- a. In the “Important” boxed statement: DMEPA defers to DRISK for the proper wording for this section as patients may not know what “reconstitution” or “suspension” means.
- b. In step 3a, provide a description of what the patient is doing by pressing the plunger. For example:

With your thumb, push down the plunger until it stops.

This pushes the diluent into the vial.

The plunger may feel like it is springing back a little.

- c. In step 3e, clarify this step by adding wording to indicate that the vial will be upside down in this step. For example:

Now, hold the vial upside down so the syringe is pointing up and the plunger is pointing down towards the ground. With your thumb, push in the plunger until it stops, and keep holding it in place.

- d. In step 3i, revise the statement so that it is clear that the patient will remove the orange connector from the syringe:

With one the other hand, twist the orange connector to remove it from the syringe.

Be careful not to push in the plunger.

3. Injecting the Medicine

- a. In step 4a, revise the statement so it is clear that the needle is still covered:

Pick up the covered needle. Twist the needle onto the syringe until snug. Do not remove the needle cover yet.

- b. Include as statement or step between step 4d and 4e to instruct the patient to clean the injection site with an alcohol swab prior to injecting the medication.

4. Common Questions and Answers

At the end of questions 2, indicate the steps which relate to the questions, in a similar manner that was done at the end of questions 4 and 5. For example: (This question relates to steps 3a through 3d shown on pages 18 through 20).

3.2 COMMENTS TO THE APPLICANT

A. Vial Label: Professional Sample and Trade (2 mg vial)

1. Revise the established name to read as “exenatide extended-release for injectable suspension” on all container labels and carton labeling.
2. Relocate the product strength to appear beneath the established name.
3. On the professional sample, the dark-green box highlighting the professional sample statement is more prominent than the proprietary name and product strength. Decrease the prominence of the dark-green boxed professional sample statement by lightening the green color and de-bolding the professional sample statement or some other means.
4. Revise the statement “Single dose” to read as: “Single dose. Discard unused portion”.
5. Since the vial label is small, relocate the “Rx Only” statement towards the side of the label and decrease its prominence. In its current presentation, the “Rx Only” statement as it appears more prominent than the product strength.
6. To accommodate for the small size of the vial label, relocate the word “Sterile” towards the side of the label in order to minimize crowding on the principle display panel.

B. Lid Label: Professional Sample and Trade

1. Increase the prominence of “Once-weekly” on the lid label.
2. Increase the prominence of the product strength and relocate it to appear beneath the established name.
3. On the professional sample, the dark-green box highlighting the professional sample statement is more prominent than the proprietary name and product strength. Decrease the prominence of the dark-green boxed professional sample statement by lightening the green color and de-bolding the professional sample statement or some other means.
4. Relocate the route of administration statement “Subcutaneous use only” to appear closer to the established name to provide more prominence to this statement and in order to avoid this information from getting lost amongst all the other information on the label.
5. Consider boxing the statement “Do not substitute the supplies provided” to highlight this information as it is easily lost with all of the other information on the label.
6. Under the description of the kit contents, the bullets concerning the vial, needles, and diluent is vague. For example, the kit is described as containing “1 vial”, but it does not indicate

what the vial contains. Additionally, the description of the kit indicates that there are “2 needles” in the kit. The size of the needles is not indicated. Furthermore, the description of the diluent is vague. Provide more information on the vial, needles, and diluent. For example, single-dose kit contains:

- 1 vial of exenatide or “Bydureon”
- 2 needles (23 G, 5/16” [include needle gauge and length])
- 1 x xxmL diluent syringe

C. Diluent Label

1. Increase the prominence of the word “Diluent”, and decrease the prominence the proprietary name so that users are not confused that the syringe contains any active ingredient (e.g. **Diluent** for suspension of Bydureon). We recommend not using the green text for the Bydureon name. The word “Diluent” should appear more prominent than the word “Sterile” and the “Rx Only” phrase.
2. By presenting the proprietary name on the diluent label in the same manner as it is presented on the carton labeling and container labels, patients may be confused that the diluent syringe already contains active ingredient. Therefore, revise the proprietary name “Bydureon” so it appears in the same font and as the phrase “Diluent for suspension of....”
3. Delete the established name as the diluent does not contain the active ingredient (exenatide for injectable suspension).

D. Carton Labeling: Professional Sample and Trade

1. Revise the established name to read as “exenatide extended-release for injectable suspension” per Chemistry recommendations on all container labels and carton labeling.
2. Increase the prominence of the product strength.
3. Relocate the route of administration statement “Subcutaneous administration only” to appear beneath the established name.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-----------------------------------|---------------|
| NDA-22200 | ORIG-1 | AMYLIN PHARMACEUTICA LS INC | EXENATIDE LAR |

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/s/

FELICIA DUFFY
02/25/2010

KELLIE A TAYLOR
02/25/2010

CAROL A HOLQUIST
02/25/2010

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 022200/BYDUREON (exenatide extended-release for injectable suspension)

PMR/PMC Description: Deferred randomized, double-blind, controlled pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the safety, efficacy, and pharmacokinetics of BYDUREON for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10-17 years (inclusive)

PMR/PMC Schedule Milestones: Final Protocol Submission: 04/30/2012
Study/Trial Completion: 01/31/2017
Final Report Submission: 07/30/2017
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

BYDUREON is ready for approval for use in adults; however, pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The safety and effectiveness of BYDUREON in adults with T2DM has been established; however, pediatric patients with T2DM have not been studied. The goal of the study is to establish the pharmacokinetics, safety and efficacy of BYDUREON in the pediatric sub-population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred randomized, double-blind, controlled pediatric study to evaluate the safety, efficacy, and pharmacokinetics of BYDUREON 2 mg weekly for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10-17 years (inclusive). The study will include a 14-week placebo-controlled period and 52-week open-label extension. The primary endpoint will be the change in HbA1c at week 14.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Subpopulation: Pediatric patients ages 10-17 years (inclusive) with type 2 diabetes mellitus
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 022200/BYDUREON (exenatide extended-release for injectable suspension)

PMR/PMC Description: A 2-year study in mice to determine the reversibility of C-cell hyperplasia, the potential of hyperplasia to progress to neoplasia, and GLP-1 receptor expression on C-cells after 6 months of treatment with exenatide extended-release for injectable suspension.

PMR/PMC Schedule Milestones: Final Protocol Submission: 09/30/2012
Study/Trial Completion: 05/31/2015
Final Report Submission: 03/30/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Bydureon (exenatide extended-release for injectable suspension), a long-acting GLP-1 receptor agonist, is a nongenotoxic carcinogen causing thyroid C-cell tumors in both genders of rats exposed to the drug over a lifetime (2 years). Although the carcinogenicity of exenatide extended-release for injectable suspension has not been tested in mice, it is known that C-cell hyperplasia, a preneoplastic lesion, is observed in mice within 3 months of treatment. Additionally, other long-acting GLP-1 agonists have been shown to induce C-cell tumors in mice, suggesting that a 2-year exposure to exenatide extended-release for injectable suspension would also induce C-cell tumors in mice. It is uncertain whether a short-term exposure to exenatide extended-release for injectable suspension that induces hyperplasia will increase the lifetime risk of C-cell tumors even after treatment is discontinued. Although the human risk of exenatide extended-release for injectable suspension is unknown, there has been no evidence of drug-induced C-cell tumors in clinical studies of Bydureon.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In carcinogenicity studies in rats exposed to exenatide extended-release for injectable suspension for most of their lifetime, thyroid C-cell tumors were observed in both genders of rats after 2 years of treatment. Although carcinogenicity studies have not been conducted with exenatide extended-release for injectable suspension in mice, Knudsen et al. (2010, Endocrinology 151(4):1473-86) demonstrated that continuous, steady-state exposure to exenatide results in C-cell proliferation, a preneoplastic lesion, in mice within 12 weeks of treatment. This finding in conjunction with the observation that other long-acting GLP-1 receptor agonists induce C-cell tumors in mice strongly suggests that exenatide extended-release for injectable suspension will induce C-cell tumors in mice if treated for a lifetime. It is unknown whether C-cell hyperplasia is completely reversible once treatment with exenatide extended-release for injectable suspension is discontinued. Therefore, the goal of this study is to determine whether a short-term exposure to exenatide extended-release for injectable suspension that induces hyperplasia will increase the lifetime risk of C-cell tumors even after treatment is discontinued. A second goal is to determine whether there is a correlation between the level of GLP-1 receptor expression and the degree of C-cell hyperplasia.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In this 104-week study, mice will be treated with exenatide extended-release for injectable suspension at three doses yielding multiples of human exposure for 26 weeks, at which time a subgroup of animals from each treatment group will have thyroids evaluated for C-cell hyperplasia and neoplasia. The remaining subgroups will have their thyroids evaluated for C-cell hyperplasia and neoplasia after a 1.5 year treatment-free period. Additionally, thyroids collected at the 6 month time point should be evaluated for GLP-1 receptor expression using a quantitative technique to determine whether there is a correlation between the level of GLP-1 receptor expression and the degree of C cell proliferation.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The level of GLP-1 receptor expression on thyroid C-cells will be compared between humans, rats, and mice. GLP-1 receptor expression levels should be measured on C-cells from human thyroid biopsy samples with the following histopathology findings: 1) normal tissue; 2) non-neoplastic C-cell hyperplasia; 3) neoplastic C-cell hyperplasia (microcarcinoma); and 4) C-cell carcinoma. Rat thyroids should be collected from untreated animals and can be isolated freshly or used from archived tissue samples. GLP-1 expression data for mice can be derived from the expression data that will be collected in either nonclinical PMR 1860-2 or nonclinical PMR 1860-4. The same quantitative technique (e.g., real-time PCR, immunohistochemistry, radioligand binding) should be used for the measurement of GLP-1 receptor expression for all three species.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 022200/BYDUREON (exenatide extended-release for injectable suspension)

PMR/PMC Description: This study will evaluate the dependence of the GLP-1 receptor for exenatide-induced C-cell hyperplasia and investigate the expression of growth regulatory genes in wild-type and GLP-1 receptor knock-out mice.

PMR/PMC Schedule Milestones: Final Protocol Submission: 09/30/2012
Study/Trial Completion: 06/30/2013
Final Report Submission: 12/31/2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Exenatide extended-release for injectable suspension (Bydureon), a long acting GLP-1 receptor agonist, is a nongenotoxic carcinogen causing thyroid C-cell tumors in both genders of rats exposed to the drug over a lifetime (2 years). Although the human risk of Bydureon-induced C-cell tumors is unknown, Bydureon did not cause C-cell tumors in clinical studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In carcinogenicity studies in rats exposed to exenatide extended-release for injectable suspension for most of their lifetime, thyroid C-cell tumors were observed in both genders of rats after 2 years of treatment. Although carcinogenicity studies have not been conducted with exenatide extended-release for injectable suspension in mice, Knudsen et al. (2010, Endocrinology 151(4):1473-86) demonstrated that continuous, steady-state exposure to exenatide results in C-cell proliferation, a preneoplastic lesion, in mice within 12 weeks of treatment. This finding in conjunction with the observation that other long-acting GLP-1 receptor agonists induce C-cell tumors in mice strongly suggests that exenatide extended-release for injectable suspension will induce C-cell tumors in mice if treated for a lifetime. Although a GLP-1 receptor-mediated mechanism is suspected, it still has not been demonstrated that thyroid C-cell hyperplasia and tumorigenesis is mediated through the GLP-1 receptor. Knowledge that C-cell hyperplasia is dependent on the GLP-1 receptor is essential for the validity of the hypothesis that low GLP-1 receptor expression makes humans less susceptible to this drug-induced effect. The goal of this study is to determine whether the GLP-1 receptor is required for exenatide-induced C-cell hyperplasia.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

GLP-1 receptor knock-out mice and their corresponding wild-type strain will be treated with exenatide extended-release for injectable suspension for 13 weeks using doses that have been demonstrated to induce C-cell hyperplasia in wild-type mice. If data are not currently available, a pilot study should be conducted to evaluate the dose and dosing duration that is required to induce C-cell hyperplasia in wild-type mice. To better ascertain the growth promoting pathways that are involved in the hyperplastic process, gene expression analysis should be conducted on C-cells from each animal. The gene expression analysis should include a number of genes involved in growth promoting, growth inhibitory, and apoptotic pathways as well as the GLP-1 receptor.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 022200/BYDUREON (exenatide extended-release for injectable suspension)

PMR/PMC Description: Medullary thyroid carcinoma (MTC) case series registry

| | | |
|------------------------------|----------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>07/31/2012</u> |
| | Study/Trial Completion: | <u>09/15/2027</u> |
| | Final Report Submission: | <u>09/15/2028</u> |
| | Other: | _____ |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Glucagon-like peptide-1 (GLP-1) agonists have been associated with thyroid C-cell tumors, based on nonclinical studies. In a 2-year carcinogenicity study of Bydureon, rats developed thyroid C-cell tumors at clinically relevant exposures. Cases of MTC were not seen in clinical trials, but the duration of blinded controlled study was not adequate to assess the risk fully in the premarketing setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the registry is to detect the majority of cases of MTC which occur in North America over the 15 year period after marketing approval of Bydureon, to evaluate all cases for risk factors for MTC and for exposure to diabetes medications, and to determine whether there is a relationship between Bydureon exposure and risk for MTC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A case series registry which seeks to identify all possible cases of MTC which occur in North America during the fifteen year period after approval of Bydureon. Ascertainment of cases should be as extensive as possible, including such sources as cancer registries; cancer center hospitals; medical centers with endocrinology fellowship programs; and professional organizations such as the American Thyroid Association, North American members of the International Thyroid Oncology Group, The Endocrine Society and the American Association of Clinical Endocrinologists. All cases will be evaluated for risk factors for MTC and for exposure to exenatide or other diabetes medications. Analyses will be conducted to determine whether Bydureon appears to be a risk factor for MTC. Reporting is to occur annually.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 022200/BYDUREON (exenatide extended-release for injectable suspension)

PMR/PMC Description: A randomized, double-blind, placebo-controlled trial evaluating the effect of BYDUREON on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). 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 long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and/or necrotizing forms), pancreatic cancer, injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

PMR/PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: 07/31/2018
Final Report Submission: 12/31/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There have been signals of a serious risk of cardiovascular (CV) events with some medications developed for the treatment of T2DM, and available data have not definitely excluded the potential for this serious risk with BYDUREON.

A meta-analysis of the long-term, randomized, controlled, clinical trials of exenatide did not demonstrate an overall increased risk of major adverse cardiovascular events (MACE). However, the population studied had low baseline cardiovascular risk, the program was not prospectively designed to assess cardiovascular risk, and few MACE occurred.

We have determined that only a clinical trial will be sufficient to definitively exclude any evidence of cardiovascular harm associated with the use of BYDUREON.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To support approvability and continue marketing, sponsors of unapproved drugs and biologics developed for the treatment of T2DM should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry, "Diabetes Mellitus - Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes". This trial is intended to demonstrate that BYDUREON does not increase the risk for MACE (myocardial infarction, stroke, and cardiovascular death).

The sponsor has already provided sufficient evidence that BYDUREON does not unacceptably increase cardiovascular risk to support approval. This trial will more definitively exclude evidence of unacceptable cardiovascular harm associated with the use of BYDUREON. Consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with BYDUREON to that observed in the control group is less than 1.3.

The trial must also assess adverse events of interest including the long-term effects of BYDUREON on potential biomarkers of medullary thyroid carcinoma (MTC) (e.g. serum calcitonin) as well as the long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and/or necrotizing forms), pancreatic cancer, injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double blind, placebo-controlled, event-driven cardiovascular outcomes trial to be conducted in approximately 12,000 subjects with T2DM and increased CV risk. The primary endpoint will be the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

The trial must also assess adverse events of interest including the long-term effects of BYDUREON on potential biomarkers of medullary thyroid carcinoma (MTC) (e.g. serum calcitonin) as well as the long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and/or necrotizing forms), pancreatic cancer, injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

AMY G EGAN
01/25/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 28, 2009

TO: John Bishai, Regulatory Project Manager
Valerie Pratt, M.D., Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-200

APPLICANT: Amylin Pharmaceuticals, Inc.

DRUG: Bydureon (exenatide once weekly)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: August 13, 2009

DIVISION ACTION GOAL DATE: March 5, 2010
PDUFA DATE: March 5, 2010

I. BACKGROUND:

Amylin Pharmaceuticals has submitted NDA 22-200 for exenatide once weekly, a human Glucagon-Like Peptide-1 (GLP-1) analog, for the indication as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The efficacy results of the studies are important in making a regulatory decision with regard to drug approval. The choice of sites was based on site enrollment and numbers of INDs in the DSI database. (b) (6)

The protocols inspected included:

- A. Protocol 2993LAR-105 entitled “A Phase 3, Randomized, Open-label, Multicenter, Comparator-controlled Study to Examine the Effects of Exenatide Long-Acting Release (LAR) on Glucose Control (HBA1C) and Safety in Subjects with Type 2 Diabetes Mellitus Managed with Diet Modification and Exercise and/or Oral Antidiabetic Medications” and
- B. Protocol 2993LAR-105c entitled “A Phase 3, Randomized, Open-label, Multicenter, Comparator-controlled Study to Examine the Effects of Exenatide Long-Acting Release (LAR) on Glucose Control (HBA1C) and Safety in Subjects with Type 2 Diabetes Mellitus Managed with Diet Modification and Exercise and/or Oral Antidiabetic Medications (Comparability Study).”

II. RESULTS (by Site):

| Name of Clinical Investigator (CI) and Location | Protocol #/ # of Subjects | Inspection Dates | Final Classification |
|-----------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------|---------------------------------------------|
| CI #1 Dean Kereiakes, M.D. The Lindner Clinical Trial Center 2123 Auburn Ave, Suite 424 Cincinnati, OH 45219 | 2993LAR-105/ 22 subjects | October 19 to 28, 2009 | Pending (Preliminary classification NAI) |
| | 2993LAR-105c/ 18 subjects | | |
| CI #2 Eric Klein, M.D. 110 Delphi Road, NW Suite 101 Olympia, WA 98502 | 2993LAR-105/ 39 subjects | October 8 to 19, 2009 | VAI |
| | 2993LAR-105c/ 34 subjects | | |

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Dean Kereiakes, M.D.
The Lindner Clinical Trial Center, 2123 Auburn Ave, Suite 424
Cincinnati, OH 45219

Note: Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** At this site, 33 subjects were screened, 22 subjects were enrolled, and seventeen subjects completed the studies. An audit of records for 10 subjects was conducted. A complete audit of 10 subjects' records, including primary efficacy endpoint, was conducted.
 - b. **General observations/commentary:** There was no under reporting of adverse events or protocol deviations and the primary endpoint data were verifiable. The records associated with this inspection were organized, legible and easy to follow.
 - c. **Assessment of data integrity:** At this site, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
2. Eric Klein, M.D.
110 Delphi Road, NW, Suite 101
Olympia, WA 98502
 - a. **What was inspected:** At this site, 41 subjects were screened and 39 subjects were randomized into Protocol 2993LAR-105. A total of 36 subjects completed through Week 52 and 35 subjects completed Protocol 2993LAR-105c through Week S9. An audit of 22 subjects' records was conducted.
 - b. **General observations/commentary:** The primary endpoint data were verifiable. A Form FDA 483 was issued because the clinical investigator did not follow the protocol in the following instances:
 1. There was no documentation of stable weight for Subjects 10823, 10825, and 10833 prior to enrollment.
 2. 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.

An additional observation by the FDA investigator was 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 and distributed example questions to be used for reporting complaints. The complaints documented at the Klein site involved subject concerns about priming of the pens used for the comparator exenatide BID, clogging of needles, and leaking pens. These observations were conveyed to Drs. Pratt and Stephens in DMEP in an e-mail on December 3, 2009, and preliminary discussions appear to indicate that these issues are unlikely to impact data reliability.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As discussed above, audits of the above sites were able to validate the primary endpoint and determine that there was no under reporting of adverse events except for a subject at Dr. Klein's site who had instances of vomiting, bloating and headache that were not reported. Observations concerning potential product issues noted at the Klein site were conveyed to the DMEP reviewers on December 3, 2009, and appear unlikely to significantly impact data integrity. The data from these sites in support of the application are considered reliable.

The final classification for the inspection of Dr. Kereiakes is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIR for this inspection.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|-----------------------------------|---------------|
| NDA-22200 | ORIG-1 | AMYLIN PHARMACEUTICA LS INC | EXENATIDE LAR |

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/s/

SUSAN LEIBENHAUT
12/29/2009

TEJASHRI S PUROHIT-SHETH
12/29/2009



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 17, 2009

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: John Bishai
Regulatory Project Manager
Division of Metabolism and Endocrine Products

Subject: QT-IRT Consult to NDA 22-200

This memo responds to your consult to us dated May 5, 2009 regarding QTc interval evaluation for exenatide, sponsored by Amylin Pharmaceuticals. The QT-IRT received and reviewed the following materials:

- Your consult
- Meta-analysis report: Effect of exenatide on QT interval of subjects with type 2 diabetes participating in studies 2993-112, 2993-113 and 2993-115 (May 27, 2004)
- Clinical Overview for NDA 22-200
- Technical report REST080229: Retrospective assessment of the bioavailability of subcutaneously administered exenatide once-weekly relative to subcutaneous exenatide injectable solution in single and multiple dose clinical studies

QT-IRT Comments for DMEP

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.

BACKGROUND

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist (39 amino acids, 4.2 kDa). BYETTA® (exenatide) was approved on April 28, 2005 as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. BYETTA 5 µg or 10 µg is administered twice daily by subcutaneous injection within 60 minutes prior to meals.

On May 4, 2009, the sponsor submitted a new drug application for an extended-release formulation of exenatide, BYDUREON™ (NDA 22-200). BYDUREON formulation entraps exenatide in biodegradable poly microspheres that allow for extended release. The proposed dosing regimen is once-weekly. Since BYDUREON and BYETTA share the same active ingredient, the BYDUREON application references the safety and efficacy information in the BYETTA NDA (NDA 21-773).

We have been asked by DMEP to review the ECG data to determine if exenatide prolongs the QTc interval.

Overview of Clinical Pharmacology

Following initiation of weekly administration of 2 mg BYDUREON, mean drug concentrations exceeded minimal efficacious concentrations (~ 50 pg/mL) by 2 weeks with gradual increase in the average plasma exenatide concentration over 6 to 7 weeks. After 6 to 7 weeks, mean exenatide concentrations of approximately 300 pg/mL were maintained indicating that steady-state was achieved.

Sponsor's Table 3 from the Clinical Overview provides a summary of exenatide once weekly 2 mg pharmacokinetic parameters.

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

| Parameter | Units | n | Geometric | | |
|--------------------------------------------------------------|---------|-----|---------------|---------|------------------------------------------------|
| | | | Mean (SE) [1] | CV% [2] | 10 th , 90 th Percentile |
| Day 1_(0-6h) | | | | | |
| C _{max} | pg/mL | 127 | 44.5 (2.4) | 76.1 | 23.4, 84.3 |
| T _{max} | h | 127 | 4.0 | | 1.5, 6.0 |
| Week 29 to Week 30 Dosing Interval_(0-168h) | | | | | |
| C _{ss ave} | pg/mL | 114 | 300.2 (23.4) | 69.8 | 145.1, 702.2 |
| C _{ss max} | pg/mL | 114 | 432.7 (35.7) | 86.3 | 213.9, 1186.1 |
| T _{ss max} | h | 114 | 22.8 | | 1.2, 167.8 |
| AUC _{ss} | pg·h/mL | 114 | 50,484 (3932) | 69.7 | 24,274, 117,796 |

AUC_{ss} = steady-state area under the concentration-time curve; C_{max} = maximum concentration;

C_{ss ave} = steady-state average concentration; C_{ss max} = steady-state maximum concentration;

SD = standard deviation; SE = standard error; T_{max} = time to maximum concentration;

T_{ss max} = time to steady-state maximum concentration.

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

[2] CV% = $100 \times \text{SD} / \text{Mean}$.

Cross-Reference: Study 2993LAR-105, [SDS 2.12.2.4](#).

Source: Clinical Overview, page 20

Clinical pharmacokinetic exposure from multiple dose Studies 2993LAR-104 and 2993LAR-105 at the dose of 2 mg (AUC₀₋₁₆₈) were compared to the AUC_{0-inf} data obtained for subcutaneously (SC) administered exenatide immediate release treatment (BYETTA) in Study 2993-118 (dose 10 µg/day BID) to estimate the relative bioavailability of exenatide once weekly. The overall bioavailability is approximately 25% at the intended dose regimen of 2.0 mg once-weekly (data shown in Sponsor's Table 2). This was computed by comparing AUC_{0-168h} at week 30 for exenatide once-weekly to product of AUC_{0-8h}*14 for immediate-release exentide (10 µg /day 7 days of BID dosing).

Table 2: Pharmacokinetics and Relative Bioavailability of Multiple Dose Subcutaneous Administered Exenatide Once Weekly in Clinical Study 2993LAR-105 as Compared to Subcutaneously (SC) Administered Exenatide Injectable Solution in Clinical Study 2993-118 (Dose 10 µg/day BID) ^a

| AUC _{0-last} Exenatide once weekly (pg·h/mL) (Geometric Mean) 10 th -90 th percentile | Geometric Mean percent Bioavailability to 10 mg dose (90% confidence interval) |
|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Study 2993LAR-105 | |
| All | |
| 50483.54 24274 - 117796 | 24% 20-29% |
| Antibody negative | |
| 52639.74 32,515 – 100,948 | 25% 21-30% |

^aAUC_{0-last} exenatide injectable solution estimated by multiplying 0-8 hr AUC (1036 pg·h/mL) by 14 (7 days of BID dosing) to yield 14504 pg·h/mL.

Source: Technical Report REST080229, page 9

Reviewer's Comments: Because the average exposures achieved with the extended-release formulation are lower than the approved formulation, a dedicated TQT study might not be needed if there are no cardiovascular safety signals in the clinical development program and post-marketing reports.

Electrocardiograms Results in Study 2993LAR-105

In Study 2993LAR-105, 12-lead ECGs were performed in subjects treated with exenatide once weekly at baseline and after steady-state plasma exenatide concentrations had been achieved (Week 14 and Week 30 or Early Termination). Standard 12-lead ECGs were performed in triplicate after approximately 5 minutes of quiet rest with the subject in a supine position. The ECGs were transmitted to the centralized ECG vendor for overread.

The mean (SD) QTcF interval at baseline was 403.3 (16.8) ms, with a change from baseline to Week 14 of 1.7 (9.7) ms and a change from baseline to Week 30 or Early Termination of 3.0 (11.4) ms. In BYETTA-treated subjects, the mean (SD) QTcF interval at baseline was 403.8 (17.4) ms, with a mean change from baseline to Week 30 or Early Termination of -0.67 (11.3) ms (Supporting Data Summary 3.5.2). No individual subject post-baseline QT measurements during the study consistently met the criteria of clinically meaningful QT prolongation (QT interval \geq 500 ms and QTcF or QTcB interval \geq 450 ms).

| Parameter/ Visit/ Statistics | Treatment [1] | | All Subjects (N = 295) |
|-----------------------------------------------------------------|-----------------------------------|------------------------------------|---------------------------|
| | Exenatide 10 mcg BID (N = 147) | Exenatide LAR 2 mg QW (N = 148) | |
| QTcF (msec) | | | |
| Baseline [2] | | | |
| n | 145 | 145 | 290 |
| Mean (SD) | 403.83 (17.425) | 403.30 (16.830) | 403.56 (17.102) |
| Median | 402.00 | 404.00 | 403.17 |
| Min, Max | 367.0, 460.7 | 370.0, 458.0 | 367.0, 460.7 |
| 90% C.I. | (401.4, 406.2) | (401.0, 405.6) | (401.9, 405.2) |
| Change from Baseline to Week 14 | | | |
| n | | 135 | 135 |
| Mean (SD) | | 1.70 (9.694) | 1.70 (9.694) |
| Median | | 1.33 | 1.33 |
| Min, Max | | -29.3, 30.2 | -29.3, 30.2 |
| 90% C.I. | | (0.3, 3.1) | (0.3, 3.1) |
| Change from Baseline to Week 30 or Early Termination [3] | | | |
| n | 85 | 82 | 167 |
| Mean (SD) | -0.67 (11.328) | 2.98 (11.357) | 1.12 (11.455) |
| Median | 0.33 | 2.67 | 2.00 |
| Min, Max | -41.3, 18.3 | -21.0, 39.0 | -41.3, 39.0 |
| 90% C.I. | (-2.7, 1.4) | (0.9, 5.1) | (-0.3, 2.6) |

Note: Model-Corrected QT was derived based on a mixed model including RR and visit number.

[1] Exenatide 10 mcg BID: Exenatide 5 mcg SC BID for the first 4 weeks and 10 mcg SC BID for the next 26 weeks followed by exenatide LAR 2 mg QW.

Exenatide LAR 2 mg QW: Exenatide LAR 2 mg SC weekly.

[2] Baseline = Day -7.

[3] 12-Lead ECG data was collected at Week 30 or Early Termination only for subjects who completed visits prior to 02 July 2007.

Cross Reference: Appendix 3.15.3.

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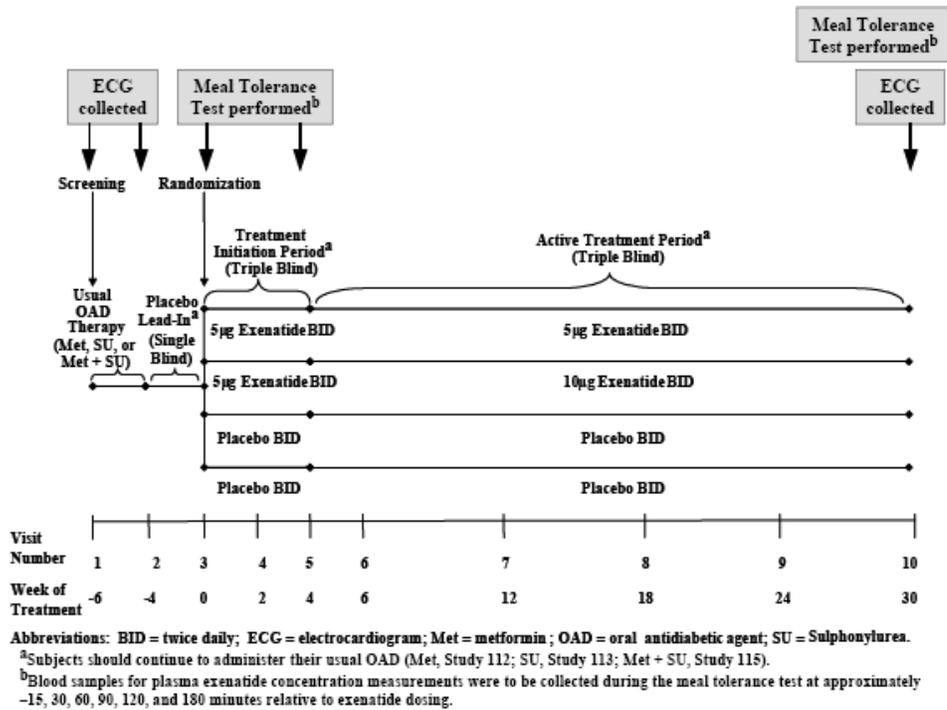
Version: 01JUL2008: 1:06

Source: CSR 2993LAR-105 (Through Week 52), page 3611

Meta-Analysis for QTc Prolongation

To support NDA 21-773 (BYETTA, exenatide immediate release), the sponsor conducted a retrospective meta-analysis to explore the relationship between QT interval and exenatide more extensively using QT data from electrocardiogram (ECG) measurements collected during those three Phase 3 clinical trials of exenatide. Data from a total of 105 subjects treated with exenatide or placebo for 30 weeks were evaluable for this meta-analysis. ECGs and plasma exenatide concentrations were collected during the 4-hour period after exenatide dosing, a time interval when systemic exenatide concentrations are in the therapeutic range.

Studies 112, 113, and 115 were Phase 3, randomized, placebo-controlled, parallel-design clinical trials testing the safety and efficacy of exenatide in subjects with type 2 diabetes. Subjects were to add placebo or exenatide (5 µg or 10 µg twice daily [BID]) to their metformin (Study 112), sulphonylurea (Study 113), or metformin plus sulphonylurea treatment (Study 115) for 30 weeks. All subjects assigned to exenatide treatment were to administer 5 µg BID during the first 4 weeks of treatment and, according to treatment assignment, either 5 µg or 10 µg BID for the remaining 26 weeks. A schematic of the study design for the phase 3 studies is shown below.



Source: Meta-analysis report, page 8

A total of 105 subjects from the meal tolerance subgroups of Studies 112, 113, and 115 had ECG values within 4 hours after administration of placebo or exenatide at Week 30. Of those subjects, 59 had evaluable plasma exenatide concentrations for comparison with QT intervals.

No apparent QTc-prolonging effects were observed in the meta-analysis:

1. Only 1 subject had a QTcF >470 ms at Week 30 of treatment (sponsor's Table 5.3). However, this subject had a baseline QTcF of 505 ms, resulting in a change from baseline of -17 ms (sponsor's Table 5.4). No subjects had change from baseline >60 ms.
2. Differences between the placebo group and the 5-µg and 10-µg groups are not statistically significant or clinically meaningful, as assessed by the 95% confidence intervals for the difference in change from baseline (shown in Sponsor's Table 5.6).
3. The scatterplots of plasma exenatide concentration and change in QTcF intervals from baseline do not show any obvious pattern, and no slope estimates from the regressions were statistically different from 0 (sponsor's figure 5.3).

Table 5.3. Summary of Subjects Who Had Normal, Borderline, or Prolonged QT and QTcF at the Study Termination Visit of Studies 112, 113, and 115a, b

| Gender | n | Treatment | Reference Range (msec) | Subject Frequencies n (%) | |
|--------|----|-----------|---------------------------|------------------------------|-------------|
| | | | | QT | QTcF |
| Male | 16 | Placebo | ≤430 | 14 (87.50%) | 13 (81.25%) |
| | | | >430 - ≤450 | 2 (12.50%) | 3 (18.75%) |
| | | | >450 | 0 (0.00%) | 0 (0.00%) |
| | 18 | 5 µg | ≤430 | 18 (100.0%) | 17 (94.44%) |
| | | | >430 - ≤450 | 0 (0.00%) | 1 (5.56%) |
| | | | >450 | 0 (0.00%) | 0 (0.00%) |
| | 25 | 10 µg | ≤430 | 22 (88.00%) | 21 (84.00%) |
| | | | >430 - ≤450 | 2 (8.00%) | 4 (16.00%) |
| | | | >450 | 1 (4.00%) | 0 (0.00%) |
| Female | 13 | Placebo | ≤450 | 13 (100.0%) | 12 (92.31%) |
| | | | >450 - ≤470 | 0 (0.00%) | 0 (0.00%) |
| | | | >470 | 0 (0.00%) | 1 (7.69%) |
| | 17 | 5 µg | ≤450 | 17 (100.0%) | 17 (100.0%) |
| | | | >450 - ≤470 | 0 (0.00%) | 0 (0.00%) |
| | | | >470 | 0 (0.00%) | 0 (0.00%) |
| | 16 | 10 µg | ≤450 | 14 (87.50%) | 14 (87.50%) |
| | | | >450 - ≤470 | 1 (6.25%) | 1 (6.25%) |
| | | | >470 | 1 (6.25%) | 1 (6.25%) |

Abbreviations: n = number of subjects; QTcF = QT interval corrected using Fridericia's formula.

^a The study termination visit corresponds to Week 30 of treatment.

^b The QT and QTcF reference ranges were defined for males as normal (≤430 msec), borderline (>430 - ≤450 msec) and prolonged (>450 msec), and for females as normal (≤450 msec), borderline (>450 - ≤470 msec) and prolonged (>470 msec).

Source: Meta-analysis report, page 14

Table 5.4. Summary of Subjects with Prolonged QT/QTcF Intervals at the Study Termination Visit (Studies 112, 113, 115)

| Study | Subject ID | Gender | Treatment Group | QT Interval | | QTcF Interval | |
|-------|------------|--------|-----------------|---------------------------------------|-----------------------------------------------|---------------------------------------|-----------------------------------------------|
| | | | | Baseline ^a Value (msec) | Study Term Visit ^b Value (msec) | Baseline ^a Value (msec) | Study Term Visit ^b Value (msec) |
| 113 | 611 | Female | 10 µg | 467 | 473 | 505 | 488 |
| 115 | 15301 | Male | 10 µg | 399 | 451 | 424 | 441 |
| 115 | 1209 | Female | Placebo | 413 | 431 | 447 | 474 |

Abbreviations: ID = identification number; ; QTcF = QT interval corrected using Fridericia's formula.

^a Baseline QT data were collected at Visit 2 (4 weeks prior to treatment assignment). If Visit 2 data were unavailable at the time of the meta-analysis, Visit 1 (screening) data were used.

^b The study termination visit corresponds to Week 30 of treatment.

Source: Meta-analysis report, page 15

Table 5.6. Comparison of QT and QTcF Change from Baseline Between Dose Groups (Placebo, 5 µg, and 10 µg Twice Daily Exenatide) – Studies 112, 113, 115

| Parameter (units) | Treatment | LS Mean | LS Mean Difference (Active Trt-Placebo) | 95% C.I. on Difference (Lower, Upper) |
|-------------------|-----------|---------|-----------------------------------------|---------------------------------------|
| Delta QT (msec) | Placebo | -5.5 | | |
| | 5 µg | -15.9 | -10.4 | (-29.3, 8.5) |
| | 10 µg | -5.5 | 0.1 | (-17.7, 17.8) |
| Delta QTcF (msec) | Placebo | -0.8 | | |
| | 5 µg | -12.5 | -11.7 | (-32.0, 8.6) |
| | 10 µg | -1.5 | -0.7 | (-19.7, 18.3) |

Abbreviations: CI = confidence interval; LS = least squares; QTcF = QT interval corrected using Fridericia's formula; Trt = treatment.

Source: Meta-analysis report, page 16

Exenatide (AC2993, LY2148568)
Meta-Analysis Report (ECG)

Confidential

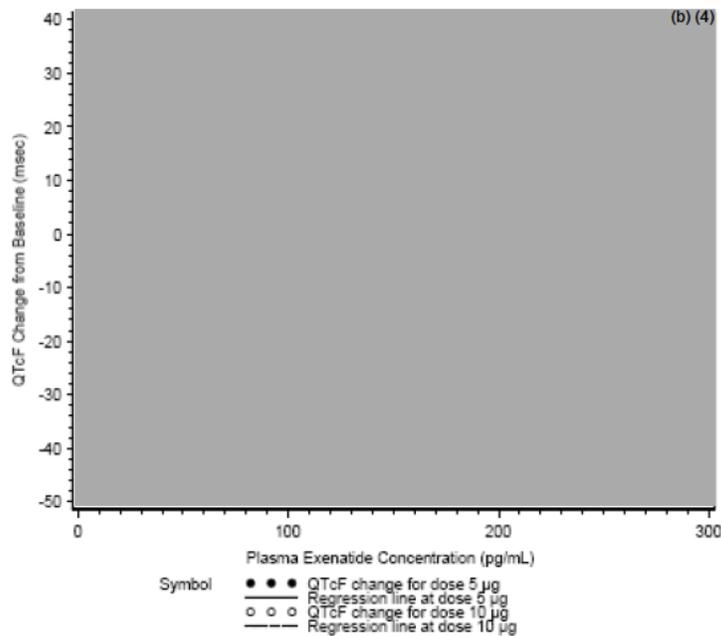


Figure 5.3. Relationship between plasma exenatide concentrations and change in QTcF for 5-µg and 10-µg dose groups (excluding an outlier, Subject 115-612).

The slope estimates for 5-µg and 10-µg dose groups are -0.04 (p-value=0.53) and 0.06 (p-value=0.17), respectively.

Source: Meta-analysis report, page 20

If you have any questions regarding this review, please feel free to contact us via email at cdcrdpqt@fda.hhs.gov

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/s/

CHRISTINE E GARNETT
12/17/2009

NORMAN L STOCKBRIDGE
12/17/2009



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 14, 2009

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products

Subject: Cardiovascular risk analysis for Bydureon, NDA 22,200

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: John Bishai, Project Manager
Division of Metabolism and Endocrinology Products

This memo responds to your consult to us dated August 28, 2009, requesting our review of a proposed cardiovascular (CV) risk meta-analysis (MA) for Bydureon. Bydureon is a once weekly formulation of exenatide (Byetta), a synthetic peptide with incretin-mimetic actions (with activity at the glucagon-like peptide-1 (GLP-1) receptor) approved by you in 2005 as twice-daily adjunctive therapy to improve glycemic control in type 2 diabetics. The sponsor based the CV MA on Byetta studies because there are no large, long-term studies of Bydureon. While the sponsor's CV MA appears to have some significant flaws and limitations, neither it nor our MA of the data suggests any significant CV risks for exenatide. However, the paucity of events for these MAs makes further study advisable. We summarize below our understanding of the sponsor's MA interspersed with our comments and followed by our analyses and recommendations.

The sponsor based the CV MA on the 12 long-term, randomized controlled trials of Byetta shown in Table 1.

Table 1: Summary of Trials Included in the CV MA

| Study | Concomitant OAD | Duration (Weeks) [1] | Exenatide [2] | | Comparator | |
|-------------------------------------------------------|----------------------|----------------------|---------------|---------------|--------------|---------------|
| | | | Subjects (N) | Exposure (SY) | Subjects (N) | 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 |

D+E = diet and exercise therapy; Meg = meglitinide; Met = metformin; OAD = oral antidiabetic medications; SU = sulfonylurea; SY = subject-years; TZD = thiazolidinedione.

Note: Subject number is based on the Intent-to-Treat Population.

[1] Duration of treatment with randomized study medication.

[2] Includes treatment with exenatide 2.5 mcg or 5 mcg BID for duration of study, or 4 weeks of exenatide 5 mcg BID followed by exenatide 10 mcg BID for remainder of study.

[3] Study H8O-MC-GWAO had a crossover design, with 16 weeks per period (exenatide or insulin glargine).

The sponsor excluded clinical-pharmacology trials and other short-term trials (duration ≤ 1 month). For the primary analysis the sponsor also excluded longer-term uncontrolled trials but did provide additional analyses of the latter.

COMMENT: The sponsor does appear to have used for the MA all trials that provide significant exposure and a controlled comparison. However, the total exposure for this CV MA is limited, about 1000 person-exposure years on drug. The sponsor also notes that “subjects were generally excluded from the study if they had a clinically significant history of cardiac disease or presence of active cardiac disease within 1 year prior to the study, including myocardial infarction, clinically significant arrhythmia, unstable angina, moderate to severe congestive heart failure, coronary artery bypass surgery, or angioplasty; if they had poorly controlled blood pressure at screening; or if they had a clinically significant electrocardiogram abnormality at screening.” Hence the numbers of events are small.

The sponsor did not assemble a blinded adjudication committee but used MedDRA terms and “A team of Amylin and Eli Lilly physicians from Clinical Development and Global Safety

independently reviewed the list of preferred terms prior to the analyses to focus on those that would most likely represent true events of interest, regardless of whether they actually occurred in the clinical trial database. In addition, all data for subjects who died were examined to ascertain if the underlying cause was cardiovascular-related based on the preferred terms and a review of the case details.” Using the terms the sponsor defined a primary endpoint, referred to as “Primary MACE”, consisting of cardiovascular mortality, myocardial infarction (MI), stroke, acute coronary syndrome, and revascularization procedures, and a “Secondary CV Endpoint” consisting of the Primary MACE events plus arrhythmia, heart failure, and mechanical-related events. The sponsor alleges the Secondary CV Endpoint “is defined to include all relevant cardiovascular adverse events.”

COMMENT: The lack of an independent, blinded adjudication is a deficit that makes scrutiny of the event adjudication critical. We did that and did find some problems that we present below. We also disagree with the sponsor’s primary endpoint of Primary MACE: the FDA guidance recommends including CV mortality, MI, and stroke and possibly including hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, and other events. Because, as the sponsor notes, “the studies were not specifically designed to assess cardiovascular events”, we favor restricting the primary analysis to the more serious events of CV mortality, MI, and stroke that are more likely to be reliably described and reported. For secondary endpoints we favor including events that are indicative of new problems, e.g., the FDA guidance mentions “urgent” revascularization rather than any revascularization because the former should be urgent because of some new manifestation or event. The sponsor’s Secondary CV Endpoint is seriously flawed by including many minor arrhythmias such as sinus tachycardia and ambiguous events such as palpitations. We present our findings on the event adjudications below after a brief summary of the sponsor’s CV MA results.

We show the sponsor’s primary analyses for both endpoints of the CV MA in Table 2.

Table 2: Sponsor’s Primary Analyses for CV MA

| | Primary MACE Endpoint | | Secondary CV Endpoint | |
|-------------------------------------------------|-----------------------|-------------------|-----------------------|-------------------|
| | EX (N = 2316) | P-C (N = 1629) | EX (N = 2316) | P-C (N = 1629) |
| Primary Analyses | | | | |
| Incidence (n) | 20 | 18 | 46 | 42 |
| Incidence (n/N) | 0.009 | 0.011 | 0.020 | 0.026 |
| RR (95%CI) | 0.70 (0.38, 1.31) | | 0.69 (0.46, 1.03) | |
| RR = relative risk by Mantel-Haenszel procedure | | | | |

By the sponsor’s analyses the point estimates of the RR of the CV endpoints is favorable for exenatide compared to the control groups. The upper confidence interval (CI) of the RR for the Primary MACE Endpoint just exceeds the cutoff, specified in the FDA guidance, below which a postmarketing safety trial may not be necessary. Note that the number of events is small.

From the SAS data sets we were able to confirm the sponsor’s CV MA results for the Primary MACE Endpoint in Table 2 based on the sponsor’s encoding of AEs. However, we found both errors of commission and errors of omission in the sponsor’s encodings of Primary MACE:

- For errors of commission (events coded as a Primary MACE Endpoint whose descriptions do not match the included events), we identified nine patients with such events in each of the drug and control groups. The miscodings were predominantly angina or a stress test not qualified in the AE listings as unstable angina or for which an intervention was done, but also included TIA. It is possible that some of these may have had an intervention not listed as an AE but described elsewhere in the sponsor’s records. While these are evenly distributed and hence don’t appear biased, they do inflate the event rates in both groups such that the confidence interval on the relative risk is smaller including them compared to excluding them.
- For errors of omission (events not coded as a Primary MACE Endpoint whose descriptions could match the included events), we identified one patient in a drug group and eight patients (10 events) in the control groups with AEs described as coronary artery disease. For the drug patient and five of the control patients the investigator reported the event as serious and severe. The SAS datasets and the case report forms we checked do not include more information regarding the nature of the coronary artery disease event.

The problems described above with the event adjudications reinforced our belief that we should base the primary analysis on CV death, MI, and stroke—there is no discrepancy between the sponsor’s and our adjudication of these most serious events. Hence we performed a MA, using the sponsor’s primary Mantel-Haenszel fixed effect analysis as well as a Dersimonian-Laird random effects analysis, of the guidance-recommended endpoint. We also performed a secondary analysis including all additional, non-intervention related CV events: coronary artery disease, unstable angina, and angina; heart failure; and transient ischemic attack. We excluded the arrhythmia events. We show the results of our MA in Table 3.

Table 3: DCRP CV MA

| | 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)

COMMENT: For our MAs the point estimates of the relative risk of CV disease with exenatide compared to control are close to one. Additionally, because there are few serious events, the confidence intervals are wide and exceed the guidance criteria for which the guidance recommends further study.

Because the sponsor provided data sets with all AEs and because exenatide is from a drug class with some preclinical signals of carcinogenicity, we also examined cancer events. We show our cancer MA results in Table 4.

Table 4: DCRP Cancer MA

| | malignancies excl. skin | | +skin cancer | |
|--------------------------|-------------------------|------|-----------------|------|
| | EX | P-C | EX | P-C |
| Patients at risk (N) | 2316 | 1629 | 2316 | 1629 |
| Patients with events (n) | 11 | 2 | 14 | 4 |
| Percentage (n/N x 100) | 0.5% | 0.1% | 0.6% | 0.2% |
| Mantel-Haenszel RR | 2.0 (0.7 - 6.4) | | 1.7 (0.7 - 4.6) | |
| I-squared | 0 | | 0 | |
| Dersimonian-Laird RR | 1.8 (0.5 - 7.1) | | 1.7 (0.6 - 5.0) | |

* RR = relative risk (95% confidence interval)

In Table 4 “malignancies excl. skin” includes all malignancies except skin cancers. We believe that excluding non-melanoma skin cancers is appropriate because they are rarely life-threatening or serious and hence ascertainment of them is erratic. (There were no melanomas in the exenatide studies.) For completeness we have included a MA of all malignancies including skin cancers in the second column.

COMMENT: The point estimate for the RR of all malignancies (excluding skin cancer) for exenatide compared to control is about two. There were no thyroid malignancies reported and the one pancreatic cancer occurred in a control group patient. The numbers of malignancies are small so the confidence intervals are very wide. We believe that any future CV outcome studies should also collect data on malignancies.

Recommendations

1. While it is reassuring that the point estimates of the relative risk of exenatide compared to control for CV events are about one or less than one, the confidence intervals on our estimates are wide and exceed the criterion above which the FDA guidance recommends further study. The sponsor’s report states that “the sponsor is planning a cardiovascular outcomes trial designed to demonstrate superiority of exenatide once weekly...” We recommend that you designate such a trial as a post-marketing requirement. We have the following recommendations about the trial:
 - a. The trial should use the Standardized Data Collection for Cardiovascular Trials data elements and endpoint recommendations.
 - b. The trial case report forms should also capture the investigators’ verbatim description of the cardiovascular AEs such that a clinician can understand the nature of the event. An ambiguous description such as “coronary artery disease” is unacceptable. A description of ten words or less should usually suffice.
 - c. The sponsor should submit SAS data sets with both the initial verbatim terms recorded by the investigators and the final versions that the sponsor’s representatives (CROs) have influenced through a data clarification process. For the cardiovascular trials we see CROs frequently influence the wording of the

verbatim terms through a data clarification process. The rewordings are usually but not invariably improvements.

- d. The sponsor should have the events adjudicated by a blinded-to-treatment, independent adjudication committee. The sponsor should submit all records kept on the adjudication procedures. In particular, if the adjudications involve an initial review by more than one adjudicator, the sponsor should submit data sets documenting the agreement or disagreement of the initial adjudicators and the logic justifying the final adjudication.
 - e. The sponsor should submit complete CRFs for all adjudicated or suspected cardiovascular events. The submitted CRFs should include Medwatch forms and all other forms or hospital records, procedure reports, etc., obtained by the sponsor for the adjudications.
2. The sponsor should collect data on malignancies in the CV outcomes trials. We have the following recommendations about malignancy data collection:
- a. The CRFs should capture any baseline history of malignancies.
 - b. The data collected on any treatment-emergent, neoplasm-related event should be sufficient to characterize whether the neoplasm is benign or malignant and whether it is new or recurrent. The investigators should submit procedure records and histopathologic reports whenever possible.
 - c. The trial need not collect detailed information on non-melanoma skin cancers, e.g., procedure records and histopathologic reports are not necessary.

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/s/

THOMAS A MARCINIAK
09/14/2009

NORMAN L STOCKBRIDGE
09/15/2009

DSI CONSULT: Request for Clinical Inspections

Date: 8/13/09

To: Tejashri Purohit-Sheth M.D., Branch Chief, GCP11, HFD-45
Susan Leibenhaut, M.D., Medical Officer, GCP2, HFD-45

Through: Valerie Pratt, M.D., Division of Metabolism and Endocrinology Products /HFD-510
Ilan Irony, M.D., Team Leader /Division of Metabolism and Endocrinology Products /HFD-510

From: John Bishai Ph.D., Regulatory Health Project Manager/Division of Metabolism and Endocrinology Products/HFD-510

Subject: Request for Clinical Site Inspection(s)

I. General Information

Application#: NDA-22,200
Sponsor/Sponsor contact information (to include phone/email): Amylin Pharmaceuticals, Inc.
Drug: Bydureon (exenatide once weekly)
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: No
Pediatric exclusivity: No

PDUFA: March 5, 2010
Action Goal Date: March 5, 2010
Inspection Summary Goal Date: **December 5, 2009**

II. Background Information

Amylin Pharmaceuticals has submitted a NDA for Bydureon (exenatide for injectable suspension). The proposed indication for Bydureon is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Bydureon contains the same active ingredient, exenatide, as the commercial product Byetta (exenatide) injection (NDA 21-773). Byetta is administered twice daily (BID) at doses of 5 mcg or 10 mcg by SC injection. Exenatide is an incretin mimetic agent that stimulates glucose-dependent insulin secretion and has several other antihyperglycemic actions. In contrast to the exenatide solution used in Byetta formulation, Bydureon formulation entraps exenatide in biodegradable polymer microspheres that allow for

extended release. Bydureon is also referred as 'exenatide once weekly' or exenatide LAR (long acting release) in this submission.

The exenatide once weekly drug product kit consists of microsphere powder in a (b) (4) vial, diluent in a (b) (4) syringe, injection needles, and a vial connector. The exenatide once weekly dose is prepared by mixing one vial of microspheres with one syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single dose kit are to be administered subcutaneously once per week.

The proposed dosing recommendation is as follows:

- Exenatide LAR (2 mg per dose) should be administered once weekly. The dose can be administered at any time of the day, with or without meals.
- A reduction in the dose of concomitant sulfonylurea may be considered to mitigate the risk of hypoglycemia.

Clinical concerns with this product include possible elevated serum calcitonin and medullary thyroid cancer as well as hemorrhagic or necrotizing pancreatitis (HNP). Complete ascertainment of these adverse events is very important. At whatever site(s) the DSI team choose(s), please look for any evidence that there were cases of elevated calcitonin, thyroid cancer, or HNP that were not included in the NDA submission. This would be in addition to the usual items for which the DSI team routinely inspects.

III. Protocol/Site Identification

The Division of Metabolism and Endocrinology Products suggests inspection of two of the following sites. These are suggestions; the Division of Scientific Investigations may use discretion in the choice of site(s).

| Site # (Name, Address, Phone number, email, fax#) | Protocol # | Number of Subjects | Indication |
|----------------------------------------------------------|-------------------|---------------------------|------------------------------------------------------------------------------------|
| 405, Dean Kereiakes, Cincinnati, OH | 105 & 105c | 22 enrolled/18 completed | (b) (4) Last inspection Oct 1996 (VAI due to inadequate and inaccurate records) |
| 108, Eric J. Klein, Olympia, WA | 105 & 105c | 39 enrolled/34 completed | High enrollment (b) (4) |

IV. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

(b) (4)

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify)

Five or More Inspection Sites:

Not applicable.

Should you require any additional information, please contact John Bishai (RPM) at 301-796-1311 or Valerie Pratt (Medical Officer) at 301-796-1050.

Concurrence:

Valerie Pratt, M.D., Medical Reviewer
Ilan Irony, M.D., Medical Team Leader
Mary Parks, M.D., Director, Division Director

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|-----------------|------------------------|
| ----- NDA 22200 | ----- ORIG 1 | ----- AMYLIN | ----- EXENATIDE LAR |

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/s/

JOHN M BISHAI
08/13/2009