

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125431Orig1s000**

**OTHER REVIEW(S)**

## 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.

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NDA/BLA #                      BLA 125431  
Product Name:                 Tanzeum (albiglutide)

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PMR/PMC Description:      A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of TANZEUM (albiglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Oct 2014</u>
	Study/Trial Completion:	<u>Apr 2020</u>
	Final Report Submission:	<u>Oct 2020</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

Albiglutide is ready for approval for use in adults. However, pediatric studies had been deferred until adequate safety data is available.

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.”

This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to assess the pharmacokinetics, efficacy and safety of albiglutide in pediatric patients age 10 to < 18 years with T2DM.

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 single study of albiglutide in pediatric patients with T2DM will be a randomized, double-blind, multicenter, placebo-controlled study to evaluate dose selection (Part A: PK/PD, safety and tolerability) and efficacy (Part B: glycemic parameters, safety and tolerability added on to metformin) of albiglutide given by SC injection in pediatric subjects aged >10 and <18 years.

Part A: PK/PD, safety and tolerability study in pediatric patients with type 2 diabetes mellitus. (b) (4)

(b) (4)

(b) (4)

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)
- 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

Continuation of Question 4

- 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 subjects ages 10 to <18 years with T2DM

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

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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?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(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.

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NDA/BLA #                      BLA 125431  
Product Name:                Tanzeum (albiglutide)

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PMR/PMC Description:            A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of TANZEUM (albiglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of TANZEUM (albiglutide).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Oct 2014</u>
	Study/Trial Completion:	<u>Dec 2029</u>
	Final Report Submission:	<u>Dec 2030</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

Based on nonclinical studies Glucagon-like peptide-1 (GLP-1) agonists have been associated with thyroid C-cell tumors.

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 medullary thyroid carcinoma (MTC) which occur in North America over the 15 year period after marketing approval of albiglutide, and to evaluate all cases for risk factors for MTC and for exposure to diabetes medications, and to determine whether there is a relationship between albiglutide 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 albiglutide. 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 albiglutide or other diabetes medications. Analyses will be conducted to determine whether albiglutide 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)
- 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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

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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

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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?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(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.

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NDA/BLA #                      BLA 125431  
Product Name:                 Tanzeum (albiglutide)

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PMR/PMC Description:     A randomized, double blind, placebo-controlled trial evaluating the effect of TANZEUM (albiglutide) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with albiglutide to that observed in the placebo group is less than 1.3. This trial must also assess the following adverse events: development of thyroid cancer, hematologic malignancies, pancreatic cancer, pancreatitis, overall injection site reactions, immunological reactions including serious hypersensitive reactions, serious hypoglycemia events, hepatic events, hepatic enzyme elevations (including gamma-glutamyl transpeptidase [GGT]), serious gastrointestinal events, appendicitis, atrial fibrillation/flutter, pneumonia, worsening renal function, and diabetic retinopathy.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Sep 2014</u>
	Study/Trial Completion:	<u>May 2019</u>
	Final Report Submission:	<u>Nov 2019</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

An estimate of cardiovascular risk derived from a meta-analysis of cardiovascular data across the albiglutide Phase 2 and 3 programs has provided sufficient evidence that albiglutide does not unacceptably increase cardiovascular risk to support marketing.

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 continued 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*". The applicant conducted a meta-analysis intended to demonstrate that albiglutide therapy does not result in an unacceptable increase in the risk for MACE (i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). The applicant has already provided sufficient evidence that albiglutide does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded an unacceptable level of cardiovascular risk. In the pre-specified meta-analysis of 9 phase 2/3 trials, the hazard ratio (HR) for the primary endpoint (CV death, myocardial infarction, stroke and hospitalization for unstable angina) was 0.93 (95% CI of 0.55-1.58).

Therefore, consistent with the above guidance, the primary objective of the required post-marketing 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 albiglutide to that observed with placebo is less than 1.3.

The following Adverse Events of Special Interest were pre-specified in the albiglutide clinical program and should also be monitored in this trial: development of thyroid tumors, pancreatic cancer, overall injection site reactions, serious hypoglycemia events, serious gastrointestinal events, hepatic events, pancreatitis, pneumonia, atrial fibrillation/flutter and serious hypersensitivity reactions. Immunogenicity data and the development of anti-drug antibodies should also be collected with any relationship to reduced efficacy, injection site reactions and hypersensitivity reactions.

Signals for the following adverse events should also be monitored in the CVOT: appendicitis, diabetic retinopathy, imbalances in hepatic enzymes (including gamma-glutamyl transpeptidase (GGT) levels) that were noted in the clinical program. In addition, the development of renal impairment in subjects with gastrointestinal adverse events has been observed with other GLP-1 agonists and should also be further assessed in this trial.

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 trial evaluating the effect of albiglutide on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM at high risk for cardiovascular disease. The primary endpoint will be the time to first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.

The long-term effects of albiglutide on the development of thyroid tumors, pancreatic cancer, overall injection site reactions, serious hypoglycemia events, serious gastrointestinal events, hepatic events, pancreatitis, pneumonia, atrial fibrillation/flutter and serious hypersensitivity reactions, Immunogenicity data, appendicitis, diabetic retinopathy, imbalances in hepatic enzyme gamma-glutamyl transpeptidase (GGT) levels and the development of renal impairment in subjects with gastrointestinal adverse events should also be assessed.

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)
- 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

Continuation of Question 4

- 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?
- 
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(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.

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)
- 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

Continuation of Question 4

- 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)  
Study assessing gallbladder motility.
- 

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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(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.

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NDA/BLA # 125431 TANZEUM (albiglutide)  
Product Name: \_\_\_\_\_

PMR/PMC Description: To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.

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PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: Aug 2015  
Other: \_\_\_\_\_

6. 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

The sponsor utilizes cIEF, and RP-HPLC to monitor a number of product related variants and product related impurities in the (b) (4) drug product. The current control strategy for release and stability of drug substance and drug product is adequate to monitor product quality and consistency of manufacturing. (b) (4). The development of the UPLC analytical method for release and stability of (b) (4) drug product will provide improved monitoring of product related variants and impurities compared the current RP-HPLC analytical method.

7. 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 sponsor currently utilizes cIEF, and RP-HPLC to monitor a number of product related variants and product related impurities. With manufacturing process improvements the levels of variants and impurities decreased, (b) (4) The UPLC analytical method will provide superior resolution of variant and impurity peaks compared to RP-HPLC for release and stability of (b) (4) drug product.

8. 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?

9. 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.

To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.

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)
- 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

Continuation of Question 4

- 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  
Specification development, validation, and implementation
- 

10. 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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**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/BLA # 125431 TANZEUM (albiglutide)

Product Name:

PMR/PMC Description:

To develop, validate, and implement a neonatal Fc receptor binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability

---

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_

Study/Trial Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

May 2015

Other: \_\_\_\_\_

11. 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

(b) (4)

(b) (4)

The current control strategy for release and stability of drug substance and drug product are adequate to monitor product quality and consistency of manufacturing. The FcRn binding assay assesses the functionality of the albumin moiety, (b) (4). The development of the FcRn binding assay method for release and stability of drug substance and drug product will provide improved monitoring of functionality of the albumin moiety, which is critical for maintaining the products pharmacokinetic profile, and will complement current physio-chemical release and stability specifications to better control product quality.

12. 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.”

Development of an FcRN binding assay allows more direct control of human serum albumin moiety function than the current physio-chemical release and stability specifications. (b) (4)

However these methods do not directly measure functionality. The human serum albumin moiety is large (b) (4). Therefore the binding assay will be important for ensuring the functionality of this moiety.

13. 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?

14. 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.

To develop, validate, and implement an FcRN binding assay to indirectly monitor functionality of human albumin portion of drug substance and drug product for release and stability

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)
- 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

Continuation of Question 4

- 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  
Specification method development, validation, and implementation
- 

15. 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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**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/BLA # 125431 TANZEUM (albiglutide)

Product Name: \_\_\_\_\_

PMR/PMC Description: To conduct a bulk drug substance stability study using samples stored for the desired shelf life in the (b) (4) Stability testing should be performed on drug substance aliquots removed following (b) (4)

---

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_

Study/Trial Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

Jan 2015

Other: \_\_\_\_\_

16. 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

Currently the drug substance shelf life is (b) (4) which was awarded based on real time stability data for process 2 and process 3 drug substance results, using small volume samples in stability sample container closure. Recently, (b) (4) were observed in the (b) (4). Therefore, there is a gap in our understanding of (b) (4) as the effect of the (b) (4) presence of (b) (4). An (b) (4) that uses samples obtained from (b) (4) for the desired time and storage temperature is essential to establish an appropriate drug substance expiry. The risk to patients is considered low because the (b) (4)

17. 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.”

This stability study is essential to evaluate the long term impact on drug substance critical quality attributes of the (b) (4)

This stability is required to establish an appropriate expiry for bulk drug substance.

18. 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?

19. 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.

To perform a bulk drug substance stability study using samples stored for the desired shelf life in the (b) (4) Stability testing should be performed on drug substance aliquots removed from the (b) (4)

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)
- 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

Continuation of Question 4

- 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
- 

20. 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**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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(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/BLA # 125431 TANZEUM (albiglutide)

Product Name:

PMR/PMC Description:

To implement CAPAs to establish a (b) (4) for bulk drug substance

---

PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_

Study/Trial Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

Other: Implementation date: \_\_\_\_\_

Jun 2015

21. 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

The current drug substance container closure system for albiglutide is a (b) (4), the sponsor needs to implement a corrective action/preventative action (CAPA) to establish a (b) (4) for bulk drug substance to ensure highest quality of drug substance. This can be done as a PMC because the risk to patients is low because the (b) (4)

22. 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.”

Implementation of a (b) (4) for bulk drug substance is important to ensure the highest quality of drug substance.

23. 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?

24. 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.

To implement CAPAs to establish a (b) (4) for bulk drug substance.

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)
- 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

Continuation of Question 4

- 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  
Corrective action/preventative action
- 

25. 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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(signature line for BLAs)



The sponsor should conduct studies to understand the mechanism of low endotoxin recovery. In addition, the sponsor should determine whether alternative endotoxin test methods can accurately detect endotoxin in the product and develop and validate a reliable endotoxin test method for the albiglutide drug product in-process and release samples.

28. 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?

29. 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.

Conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product. In addition, develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in the relevant containers.

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)
- 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

Continuation of Question 4

- 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
- 

30. 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?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEHREEN HAI  
04/14/2014

JEAN-MARC P GUETTIER  
04/14/2014  
Signing on behalf of Dr. Jennifer R. Pippins.

## **SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies**

<b>Product Title<sup>1</sup></b>	<b>TANZEUM (albiglutide) for injection, for subcutaneous use</b>
Applicant	GlaxoSmithKline, LLC
Application/Supplement Number	BLA 125431
Type of Application	Original Submission
Indication(s)	AS AN ADJUNCT TO DIET AND EXERCISE TO IMPROVE GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS
Office/Division	ODE II/DMEP
Division Project Manager	Raymond Chiang
Date FDA Received Application	March 13, 2013
Goal Date	April 15, 2014
Date PI Received by SEALD	April 11, 2014
SEALD Review Date	April 11, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

# Selected Requirements of Prescribing Information

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:** *Top margin > 1/2 inch; bottom margin < 1/2 inch; margin between two columns < 1/2 inch. Margins should be 1/2 inch on all sides and between columns.*

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

## Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** Must include 4-digit year (i.e., 2014), not "201X."

## Selected Requirements of Prescribing Information

### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.  
Comment:
- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
Comment:
- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
Comment:
- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.  
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.  
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.  
Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

## Selected Requirements of Prescribing Information

### Comment:

#### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

### Comment:

#### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

### Comment:

#### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

### Comment:

#### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Must insert revision date (i.e., April 2014), not "Month 201X."*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:* For subsection headings 2.2, 2.3, 5.3, and 14.3 the word "With" should be "with." Use lower case "w" for the word "with." The same applies to these subsection headings in the FPI. Also, for subsection heading 2.2 in the TOC, the second line of this subsection heading is not indented. Must indent.
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

**Comment:** For 6<sup>th</sup> bulleted item in Section 17, reference the section not (b) (4). It should read [see How Supplied/Storage and Handling (16.2)], (b) (4).

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

**Comment:**

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** All FDA-approved patient labeling [i.e., Medication Guide (MG), Instructions for Use(IFU)] must appear at the end of the PI upon approval. The MG and IFU are missing.

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

- [text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEANNE M DELASKO  
04/11/2014

ERIC R BRODSKY  
04/11/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)**

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

## Memorandum

**Date:** April 8, 2014

**To:** Raymond Chiang, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Kendra Y. Jones, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** BLA 125431  
OPDP labeling comments for TANZEUM (albiglutide) for injection,  
for subcutaneous use

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OPDP has reviewed the proposed draft prescribing information (PI), Medication Guide, Instructions for Use and carton container labeling for TANZEUM (albiglutide) for injection, for subcutaneous use submitted for consult on March 1, 2013. OPDP's comments regarding the proposed draft PI are provided directly on the marked version attached.

Our comments on the PI are based on the version entitled, "albiglutide label submitted on 3.14.14" located in Sharepoint (last modified April 7, 2014).

### **Carton/Container Labeling**

OPDP's comments on the carton/container labeling are based on the version sent via email by Ray Chiang (RPM) on April 4, 2014. OPDP recommends deleting the following underlined information and/or presentations because they are promotional in tone:

- (b) (4) take your next dose of medicine within 3 days after your usual day. Then return to your usual day for your next dose.
- "Please visit TANZEUM.com to (b) (4) get other helpful information."
- Call 1-855-TANZEUM if you have any questions about this product (b) (4)

- “Use your smart phone to scan this code or visit TANZEUM.com to see (b) (4) on how to use the Tanzeum Pen.”

OPDP notes its recommendation to remove the (b) (4) statement that appears above the proprietary name of the carton/container labeling. However, OPDP also notes that the currently approved carton for Bydureon (a competitor product) also includes the (b) (4) phrase above the proprietary name.

### **Medication Guide and Instructions for Use**

Please note, OPDP’s comments regarding the draft medication guide and instructions for use (IFU) were provided under separate cover on April 4, 2014, in conjunction with the Division of Medical Policy Programs (DMPP). Therefore, OPDP’s comments regarding these materials are not included in this review.

Thank you for the opportunity to comment on the proposed draft PI and carton container labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or [Kendra.jones@fda.hhs.gov](mailto:Kendra.jones@fda.hhs.gov).

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KENDRA Y JONES  
04/08/2014

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: April 4, 2014

TO: Kaveeta Vasisht, M.D., Pharm, D., Medical Officer  
Ali Mohamadi, M.D., Medical Team Leader  
Raymond Chiang, MPT, M.S., M.S., Regulatory Health Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125431

APPLICANT: GlaxoSmithKline LLC

DRUG: Tanzeum (albiglutide/ GSK716155)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: A GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

CONSULTATION REQUEST DATE: March 18, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: November 8, 2013

DIVISION ACTION GOAL DATE: Initially January 14, 2014

PDUFA DATE: Initially January 14, 2014\*

*\*In response to an FDA information request, the sponsor submitted information to the application that was considered a major amendment, and the review timeline for the BLA was extended. The new PDUFA goal date is April 15, 2014.*

## I. BACKGROUND

GlaxoSmithKline LLC (GSK) is seeking approval of albiglutide (GSK716155), a glucagon-like peptide-1 receptor (GLP-1R) agonist, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The application is based on the results of eight well-controlled Phase 3 studies in adult patients with T2DM. At the time of submission, five of these Phase 3 studies were ongoing to 3 years; all subjects are past the primary endpoint time point. To ensure the integrity of the studies, the GSK albiglutide development team implemented a “masked” procedure which remaps subject IDs and site IDs so the real subject IDs and site IDs are not revealed to anyone other than the application submission unblinded team. The study reports and the submission documents are based on masked subject/investigator IDs down to the individual subject level. Actual subject or investigator IDs were not used in the analyses or reporting.

Albiglutide is available in a fixed-dose, single use, fully disposable pen injector system for manual subcutaneous injection at alternating sites usually on a weekly or biweekly basis. The container closure system for albiglutide for injection is composed of a dual chamber cartridge (DCC) assembled within the pen injector. The pen injector presentation enables the patient to perform reconstitution without the requirement of an additional vial of diluent and transfer device and syringe. The drug product is designed to deliver 30 mg or 50 mg of albiglutide in a 0.5 mL aqueous solution delivered volume.

The studies requested for inspection were:

- a. **GLP108486** A Randomized, Open-Label, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Albiglutide Administered in Combination With Insulin Glargine as Compared with the Combination of Insulin Glargine and Prandial Lispro Insulin in Subjects With Type 2 Diabetes Mellitus

This study was conducted in 159 study centers in 14 countries from November 2, 2009 to November 14, 2011. A total of 40 study sites in the United States did not randomly assign any subjects, and were closed due to inactivity. A total of 920 subjects were screened and 586 randomized.

The primary objective of the study was to evaluate the efficacy of albiglutide in combination with insulin glargine as compared with the combination of lispro and insulin glargine on the glycosylated hemoglobin (HbA1c) change from Baseline at Week 26. The primary efficacy assessment was HbA1c at Week 26.

- b. **GLP112753** A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin Plus Sitagliptin, Metformin Plus Glimepiride, and Metformin Plus Placebo in Subjects With Type 2 Diabetes Mellitus

This study was conducted at 289 sites in 10 countries from March 3, 2009 to January 13, 2012. There were 1525 subjects screened and 1049 randomized into one of four treatment groups.

The primary efficacy objective of the study was to evaluate the efficacy of albiglutide administered in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo on HbA1c change from Baseline at Week 104. The primary efficacy endpoint was change from Baseline HbA1c at Week 104.

- c. **GLP112754** A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus

This study was conducted at 222 centers in 4 countries from February 17, 2009 to November 30, 2011. A total of 1060 subjects were screened and 779 subjects were randomly assigned: 516 to albiglutide and 263 to insulin glargine. At a subset of sites, it was planned that approximately 55 subjects per treatment group undergo 24-hour glucose monitoring. However, only a few subjects entered the substudy.

The primary objective of the study was to evaluate the efficacy of albiglutide as compared with insulin glargine on glycosylated hemoglobin (HbA1c) change from Baseline at Week 52. The primary efficacy assessment/endpoint was HbA1c at Week 52.

- d. **GLP112755** A Randomized, Double-Blind, Placebo- Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Pioglitazone With or Without Metformin in Subjects with Type 2 Diabetes Mellitus

The study was conducted at 158 centers in 4 countries from January 26, 2009 to November 30, 2011. There were 450 subjects screened and 310 subjects randomized to one of two treatment groups.

The primary objective of the study was to evaluate the efficacy of albiglutide administered in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin) on glycosylated hemoglobin (HbA1c) change from Baseline at Week 52. The primary efficacy assessment/endpoint was HbA1c at Week 52.

- e. **GLP112756** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Two Dose Levels of Albiglutide Compared With Placebo in Subjects With Type 2 Diabetes Mellitus

This study was conducted at 143 sites in 2 countries from April 1, 2009 to November 17, 2011. A total of 479 subjects were screened and 309 subjects were randomized: 102 in the albiglutide 30-mg group, 102 in the albiglutide 50-mg group, and 105 in the placebo group.

The primary objective of the study was to evaluate the efficacy of albiglutide as compared with placebo on HbA1c change from Baseline at Week 52. The primary efficacy endpoint was HbA1c at Week 52.

- f. **GLP112757** A Randomized, Double-Blind, Placebo- and Active Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Administered in Combination With Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Placebo and With Metformin Plus Glimepiride and Pioglitazone in Subjects With Type 2 Diabetes Mellitus

This study was conducted at 234 sites in 9 countries from April 13, 2009 until January 31, 2012. There was one amendment to the protocol. A total of 992 subjects were screened and 685 subjects were randomized. Subjects completed a minimum of 2 years of treatment and the application contains this data. The study continued as a blinded study for up to 3 years.

The primary objective of the study was to evaluate the efficacy of albiglutide administered in combination with metformin and glimepiride compared with metformin plus glimepiride and placebo and with metformin plus glimepiride and pioglitazone on glycosylated hemoglobin (HbA1c) change from Baseline at Week 52. The primary efficacy endpoint is the change from Baseline in HbA1c at Week 52.

- g. **GLP114130** A Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Sitagliptin in Subjects With Type 2 Diabetes Mellitus With Renal Impairment

This study was conducted at 134 study centers in 15 countries from May 7, 2010 to May 30, 2012. A total of 771 subjects were screened and 507 subjects were randomized.

The primary objective of the study was to evaluate the efficacy of albiglutide as compared with sitagliptin on the glycosylated hemoglobin (HbA1c) change from Baseline at Week 26. The primary efficacy assessment was HbA1c at Week 26.

- h. **GLP114856** A Multidose Study in Subjects With Type 2 Diabetes Mellitus to Assess the Pharmacokinetics and Pharmacodynamics of Albiglutide

This Phase 1/2a study was conducted to support the transition from Process 2 albiglutide (Phase 3 material) to Process 3 albiglutide (commercial formulation) during the ongoing Phase 3 program. The Process 2 drug product was formulated as a dual chamber cartridge (b) (4)

(b) (4). Process 3 included changes in (b) (4) and remains in a dual chamber pen injector.

The first phase of this study was conducted to evaluate the PK bioequivalence (BE) of Process 2 and Process 3 albiglutide following administration of a single dose of 30 mg albiglutide in subjects with T2DM. Subsequently, the subjects continued to be assessed as they progressed into the multiple-dose phase of the study, and additional subjects were randomized in the single- and multiple-dose phases of the study (Overall N=308).

This Part 2 of the study was performed at 41 clinical sites in the United States from July 26, 2011 to October 30, 2012. A total of 478 subjects were assessed for eligibility and enrolled into the Run-In Phase of the study. Of those 478 subjects, 170 subjects were classified as run-in failures. In all, 308 subjects were randomly assigned to 1 of the 2 treatment groups. The goal of the multiple-dose phase of the study was to compare Process 2 and Process 3 albiglutide with regard to efficacy of 12 additional weekly doses of 30 mg of albiglutide subcutaneously injected in subjects with type 2 diabetes mellitus. (i.e., glycemic effects on HbA1c, fasting plasma glucose [FPG], safety, tolerability, immunogenicity, and trough PK data).

i. **GLP114179** A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Liraglutide in Subjects With Type 2 Diabetes Mellitus

This study was conducted at 162 sites in 8 countries from May 5, 2010 to September 9, 2011. A total of 1764 subjects were screened; 443 subjects were classified as run-in failures. A total of 841 subjects were randomly assigned to one of the 2 treatment groups.

The primary objective of the study was to evaluate the efficacy of albiglutide as compared with liraglutide on the glycosylated hemoglobin (HbA1c) change from Baseline at Week 32.

For all Phase 3 studies, clinical laboratory tests, including HbA1c, were determined by a central laboratory (b) (4) Institutional Review Board (IRB) was the central IRB. The sponsor engaged an independent data monitoring committee, a clinical endpoint committee, and a pancreatitis adjudication committee for all studies.

There have been several issues regarding site implementation of the protocols that have been brought to the attention of the review team. These issues were also considered when deciding on site selection and what topics needed focus during the inspections.

➤ **Multiple Subject Enrollments**

As was noted in the application, in five of the eight studies there were 16 unique subjects who enrolled themselves in the same study at multiple sites or, in some instances, in a different study at multiple sites. Duplicate subjects were discovered either by the site staff, the contract research organization (b) (4) staff, or the (b) (4) Interactive Voice Response System (IVRS) through site by site comparisons of subject information, including initials, date of birth, and demography. At the time of discovery, all subjects were

immediately withdrawn from treatment and then assigned to one study site; those subjects who enrolled in multiple studies were assigned to a single site in one study for annual follow-up. In total, this represented 40 unique instances of “duplicate subjects” (GLP112753-20 subjects, GLP112754-13 subjects, GLP112756-4 subjects, GLP112757-1 subject, and GLP114130-2 subjects). These duplicate subjects were included in the primary integrated analysis for each of the treatment group(s) in which they were enrolled. All subjects who received study medication were included in the integrated safety analyses. (Study GLP114130 was not included in the integrated analysis of safety and efficacy).

#### ➤ **Malfunctioning Pen Injectors**

Details on malfunctioning pen injectors in the clinical program were not discussed in the clinical study reports but were summarized in the quality (CMC) section of the application in document P.2.4. Pharmaceutical Development Container Closure System Development, Section 3.7.9. The collated data is based on a cutoff date of May 11, 2012 for reporting defective pen injectors. For the eight Phase 3 studies, it was reported that a total of 16 (<0.01%) pen injectors have been returned to GSK as being potentially defective. Investigations identified that reasons for the failures were attributed to issues with the dual chamber cartridge (DCC).

**Table 25 Clinical Trial Returns due to Reports of Malfunctioning Pen Injectors:**

Study	Number of Pen Injectors Dispensed <sup>1</sup>	Number of Reported Pen Injector Malfunctions	Malfunctions as a Percentage of Total Pen Injectors Issued
GLP 112753	122,731	1	<0.01%
GLP 112754	65,379	3	<0.01%
GLP 112755	37,171	0	<0.01%
GLP 112756	37,216	3	0.01%
GLP 112757	79,411	4	0.01%
GLP 108486	19,382	3	0.02%
GLP 114179	17,547	2	0.01%
GLP 114130	27,216	0	<0.01%
<b>All</b>	<b>406,053</b>	<b>16</b>	<b>&lt;0.01%</b>

**Note:**

1. The number of pen injectors used included active and placebo

Of the 424,716 pen injectors dispensed in the albiglutide clinical studies, there were:

- 859 pen injector- related complaints;
- 68 product- (dual chamber cartridge) related complaints;
- 330 user errors identified with the pen injector

A review by the sponsor was undertaken of all patient complaints received from the Phase 3 clinical program between March 2009 and February 2012, in relation to the most common root

causes of identified complaints. The four major root causes identified were:

1. Timing of pen needle attachment (163 complaints/ 28.2% overall)
2. Frozen pen injector due to storage of pen injector below 2°C in refrigerator (106 complaints/ 20.6% overall)
3. Blocked needle (63 complaints/ 16.2% overall)
4. Pen injector not held upright during preparation (40 complaints/ 6.5% overall).

Summary conclusions drawn by the sponsor from the trending analysis of the Phase 3 clinical program complaints include the statement “*The commercial Instructions for Use (IFU) would require significant revisions from the Phase III clinical version to address the root causes identified in the clinical studies. The commercial IFU were revised and were included in commercial pen injector design validation.*”

➤ **Laboratory Issues**

In August 2009, the protocols for GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757 were amended to add amylase and lipase screening/baseline measurements and to add exclusion criteria for subjects with elevated amylase and/or lipase levels. For subjects enrolled into these five studies prior to August 2009, efforts were made to assess amylase and lipase from baseline samples collected for biomarker analysis; however, samples/assessments were not available for all subjects enrolled prior to the protocol amendment effective date for the respective country/site. *This is the extent of the discussion in the Pancreatitis Adjudication Committee Report.* In the Clinical Study Reports for GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757, the amylase and lipase were stated as being drawn on Visit 5 as baseline values but failed to mention that these were obtained from the previously drawn biomarker samples. The calcitonin level was reported as being obtained from the previously drawn biomarker sample in the GLP112753 report only.

➤ **Site Closures**

A request was made for a list of all sites terminated by the sponsor. Included in the submission were:

- Luis Sanchez Arriaga, Site 3005, Mexico
- Eric Wolfson, Wasatch Clinical Research, Site 1166, USA
- David Larsen, Wasatch Clinical Research, Site 1166, USA

*The complaints were evaluated by the OSI enforcement branch. The sponsor took appropriate steps; cases closed without inspection.*

There were three more sites closed after the application was submitted:

- Michelle Sewell, Site 1398, USA (for-cause inspection took place and results are being evaluated by the OSI enforcement team)
- John Pappas, Site 1078, USA (there are multiple complaints linked to this PI; they are being evaluated by the OSI enforcement team)
- Wilson Gallardo Rohas, Site 3302, Peru (closed by (b) (4) for all studies being done at the site; being evaluated by the OSI enforcement team)

➤ **On-going Masking of Studies**

The analyses of all safety data for the ongoing 3-year Phase 3 studies (GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757) were conducted in a masked fashion by the designated submission team. The sponsor document “Charter for Work Process Flow for Maintaining Blind: Albiglutide Phase III Studies” V2.0 dated December 21, 2011 defines the scope of the unblinded data review and reporting, the unblinding process and restrictions, and the system set up to maintain treatment blinding. Masked site/subject identification numbers (IDs) were generated for all data in the eCRFs, narratives, study reports, and summary documents included in the BLA. A listing that maps the masked subject and site IDs to the actual subject and site IDs had to be requested for each inspected site.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125431 in accordance with Compliance Program 7348.811 and 7348.810. General instructions were also provided with this assignment.

**NOTE:** The sponsor also submitted a marketing authorization application for albiglutide to the European Medicines Agency (EMA). A joint inspection occurred for one site (Dr. Babazadeh, as noted below).

## II. RESULTS (by Site)

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Pending Classification
Richard B. Stewart Site # 1200/3669	GLP108486 / 3 GLP112753 / 7 GLP112754 / 9 GLP112755 / 1 GLP112756 / 8 GLP114856 / 18 GLP112757 / 1 GLP114179 / 8	9/18/2013- 10/16/2013  (one week interrupted due to government furlough)	NAI
John-Louis Selam Site #1083/3442	GLP108486 / 9 GLP112754 / 20 GLP112755 / 0 GLP112757 / 0 GLP114179 / 19 GLP114856 / 16	7/10/2013- 7/25/2013	NAI
Simon Babazadeh Site # 1242/3601	GLP112753 / 10 GLP112756 / 1 GLP112757/ 14	8/5/2013- 8/9/2013	VAI
Opada Alzohaili Site # 1001/3460	GLP108486 / 9 GLP112753 / 4 GLP112754 / 5	7/18/2013- 8/14/2013	OAI

	GLP112755 / 5 GLP112756 / 4 GLP112757 / 6 GLP114130 / 0 GLP114179 / 16		
Gary Ruoff Site # 1294/3653	GLP108486 / 0 GLP112753 / 6 GLP112754 / 1 GLP112755 / 6 GLP112756 / 1 GLP112757 / 0 GLP114179 / 1	7/22- 29/2013	NAI
John Gabriel Site # 1325/3784	GLP108486 / 6 GLP112753 / 13 GLP112754 / 8 GLP112755 / 1 GLP112757 / 3 GLP114130 / 3 GLP114179 / 10	10/1- 22/2013	VAI
Cynthia Sadler/ John Lentz Site #1271/3630	GLP108486 / 3 GLP112753 / 12 GLP112754 / 11 GLP112755 / 2 GLP112756 / 5 GLP112757 / 4	8/19- 9/11/2013	NAI
Graham Ellis Site # 5604/7063	GLP108486 /15 GLP112753 / 23 GLP112754 / 28 GLP112755 / 2 GLP114130 / 8	9/16- 27/2013	NAI
GlaxoSmithKline LLC	GLP108486 GLP112753 GLP112754 GLP112755 GLP112756 GLP112757 GLP114130 GLP114179 GLP114856	8/1-23/2013	VAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication

with the field, and review of EIR; final classification is pending letter to site.

**1. Richard B. Stewart, M.D.**

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- a. What was inspected:** All informed consents for all studies, Institutional Review Board (IRB) approvals and the regulatory binders for all studies were reviewed. Subject selection, FDA 1572s, curriculum vitae, medical licenses, delegation logs, financial disclosure forms, training, and sponsor monitoring activities and communications were reviewed. Master investigational product (IP) accountability logs for all studies were reviewed.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 12	GLP112753- 7	GLP112753- 4
GLP112754-14	GLP112754- 9	GLP112754-4
GLP112755- 1	GLP112755- 1	GLP112755- 1
GLP112756- 11	GLP112756- 8	GLP112756- 4
GLP112757- 4	GLP112757- 1	GLP112757- 1
GLP108486- 5	GLP108486- 3	GLP108486- 2
GLP114179- 13	GLP114179- 8	GLP114179- 6
GLP114856- 30	GLP114856- 18	GLP114856- 14

Source documents and case report forms were reviewed for the following number of study records: GLP112753- 8, GLP112754- 9, GLP112755- 1, GLP112756- 5, GLP112757- 1, GLP108486- 5, GLP114179- 5 and GLP114856- 14.

- b. General observations/commentary:** All source records at Dr. Stewart's site were found to be adequate. Electronic case report forms (eCRFs) were used for all studies. All data were entered in a timely manner and the eCRFs were reviewed and signed by the principle investigator (PI) in a timely manner. Protocol deviations including out-of-window visits were appropriately reported and documented. There was no under-reporting of adverse events. Serious adverse events (SAEs) were appropriately reported. Monitoring by the contract research organization (CRO) (b)(4) was approximately every 6-12 weeks, although there was a lot of turnover of the monitoring staff.

Since five of the studies were still ongoing, the primary efficacy endpoint data was not available at the site. The FDA inspector requested and received from the sponsor a copy of the HbA1c results for all studies and the primary efficacy endpoint data was verifiable.

Repeat subjects were found in protocols GLP112754 (Subject 002) and GLP112756 (Subject 005). These subjects were found to be enrolled at other sites in the Atlanta area. This was discovered by the study coordinator when Subject 005 returned a pen that belonged to Site 1201. These subjects were withdrawn from active treatment at the site (and from the studies at the other sites) and assigned to the site for follow-up. There was one pen failure documented in Study GLP112754 (Subject 002).

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were a couple discussion items at close-out:

1. In the eight studies reviewed, there were four occurrences in which the subjects were re-consented late. Deviations were on file for all of these occurrences. Staff explained that in the past the informed consent forms were sent via United States Postal Service and there was often a delay in receiving. Recently the sponsor has put the informed consent forms available for use through an online portal.
2. Some of the subjects' visits were out-of-window due to personal obligations or forgetting about the scheduled appointment. The FDA inspector stressed the need for communication and reiterating to the subjects the importance of adhering to the study schedule.

**c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**2. Jean-Louis Selam, M.D.\***

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\*Name on consult was John-Louis Selam, but it was determined that the correct first name is Jean-Louis.

**a. What was inspected:** Records reviewed included 100% of the enrolled patients' signed informed consent forms for all four study protocols that randomized subjects, inclusion/exclusion criteria, recruitment and enrollment, subject case histories, IRB approvals and correspondences, case report forms,

monitoring logs and correspondences, regulatory documents, training documents, drug accountability logs, return shipment logs, master inventory lists, refrigeration temperature logs, curriculum vitae, delegation logs and other study documentation. The FDA inspector requested and received from the CRO the lists of Actual/Masked Key Subject ID Numbers.

Subjects screened	Subjects enrolled	Subjects completed
GLP112754-32	GLP112754-20	GLP112754-9
GLP108486- 21	GLP108486- 9	GLP108486- 6
GLP114179- 40	GLP114179- 19	GLP114179- 17
GLP114856- 49	GLP114856- 16	GLP114856- 15

The number of subject records reviewed during the inspection: GLP112754- 20, GLP108486- 9, GLP114179- 19, GLP114856- 6. Studies GLP112755 (two subjects screened) and GLP112757 (one subject screened) were not reviewed as there were no subjects randomized.

- b. General observations/commentary:** The firm maintained paper medical records, source documents, progress notes, and procedures/lab reports. Information was then captured into the eCRFs. There were no discrepancies noted. The regulatory binders, patients' CRFs binders and source documents were well-maintained, organized, in good condition, and complete for all four study protocols. There was no under-reporting of adverse events. The primary efficacy endpoint data was verifiable.

Subject 1083754005 enrolled in study GLP112754 was discovered by the monitor to be enrolled at another study site. The subject was withdrawn from the study and lost to follow-up.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were a couple discussion items at close-out:

1. There were frequent out-of-window visits documented/reported by the site for all four of the study protocols. The PI stated that they will start scheduling appointments at the beginning of the visit window to allow for more time.
2. Subject 1083754005 was discovered by the monitor to be enrolled at another study site. The PI stated that they will continue to remind patients and also add on the Appointment Card as well as the Study Visit Checklist "patients may not enroll in another study while in the current study".

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. **Simon Babazadeh, M.D.**

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- a. **What was inspected:** The inspection was a joint inspection with the European Medicines Agency (EMA). The European Union (EU) inspectors only focused their inspection on Study GLP 112757. The inspection included a comprehensive review of the informed consent process, institutional review board (IRB) review and approvals, drug accountability, protocol compliance, experience and training, adverse event reporting, monitoring, delegation of responsibilities, investigator oversight, study subject inclusion/exclusion criteria and study data verification/integrity. Due to time constraints and the fact that protocol GLP 112756 randomized only one subject at this site, this study did not undergo extensive review.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 15	GLP112753- 10	GLP112753- 10
GLP112756- 4	GLP112756- 1	GLP112756- 1
GLP112757- 25	GLP112757- 14	GLP112757- 14

All informed consent forms (ICF) for the 25 subjects screened in Study GLP 112757, 4 subjects screened in Study GLP 112756 and the 15 subjects screened in Study GLP 112753 were reviewed.

For Study GLP112753, the source records were reviewed for all 15 screened subjects (including the 5 screen failures). For Study GLP112756, the source records were reviewed for the one enrolled subject. For Study GLP112757, the source records were reviewed for 14 enrolled subjects and 2 screen failures.

- b. **General observations/commentary:** Studies GLP112753 and GLP112756 were completed but study GLP112757 was still on-going. The site was, therefore, blinded to efficacy results. The decode file had to be supplied to the agency inspectors upon request. The primary efficacy results were verifiable.

There were no duplicative enrolled subjects at the site.

The site considers the paper worksheets used as their source documents. These worksheets were not supplied by the sponsor but were created by the firm. In several

instances, these documents had missing signatures and dates of the person who had taken the notes on the visit worksheets. There was poor documentation concerning the diet and exercise advice, follow-up of glucose measurements by patients and no documented follow-up on metformin compliance. Data was entered into the eCRF system by the site coordinators.

The Investigational Supplies Assignment Logs were very difficult to review as there were many cross-outs and changes. Drug Accountability logs were reviewed and compared to subject records and e-CRF data. As noted previously by the site monitors, the blinded glimepiride container #50343701 was missing and container #5041140 assigned to Subject 53004 was not given to the subject but instead the subject received the #6025040 container. *[Since this incident, the policy of the site has been to have two site staff sign-off on the correctness of the dispensing].*

During the inspection, it was noted that there were pen failure discussions in the newsletters and that a Pen Failure Form was developed for the sites. One subject in Study GLP112753 (Subject 012) had a pen failure. It was requested to the sponsor that the report regarding pen failures for all the studies be submitted for review, as these had not been discussed in the final clinical study reports submitted to the agency with the application.

During the inspection of the source documents and data line listings, it was noticed that there were a number of laboratory tests reported by the sponsor in the line listings that did not have corresponding source documents. Upon further discussion, it was determined that prior to protocol amendment 1, the baseline calcitonin, amylase and lipase were retrospectively measured using an aliquot from a stored baseline serum sample that had been collected for future biomarker analyses. Therefore, there were no initial requests for these tests in the source documents and no reported results back to the site. These samples were also tested beyond the (b) (4) validated frozen serum sample stability period (28 days for calcitonin and 6 months for lipase and amylase).

During the inspection, it was noted that labels on the study medicines (investigational product and the active arms) did not contain any dosing instructions, and written instructions were not provided by any other means to the subjects. The labels also contained several protocol numbers (i.e., not specific for one study). Study staff was to circle the protocol number.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued to Dr. Babazadeh for the following deficiencies:

**OBSERVATION 1:** Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

For study GLP112753:

- a. Subject 002 was seen for scheduled Visit 13 on 12/4/09. Patient stated that she was hospitalized with a transient ischemic attack (TIA) on (b) (6)

- (b) (6) but this serious adverse event (SAE) was not reported to the IRB until four years after the event. There was an incomplete (b) (4) SAE Report Form in the subject's chart with no date and no signature. There was an initial report to (b) (4) IRB dated 1/29/13 and signed by the PI 1/30/13.
- b. Subject 004 was hospitalized (b) (6) with a large ulcer on the plantar aspect of the left foot, diffuse cellulitis, and osteomyelitis of the 3rd and 4th metatarsal heads. This SAE was not reported to the IRB until 1/29/13. There is a (b) (4) SAE Report Form that was filled out 2/2/10. Subject was discontinued from the study 11/4/10. However, this SAE was not reported to the IRB until 1/29/13.

The policy of the IRB is to have SAEs reported within 10 days. However, there must be at least a possible relationship to the study product. Unknown relationships were not to be submitted. The PI did not feel that the SAEs warranted submission. However, regardless of any IRB policy, the CRO (b) (4) wanted all serious adverse events (SAEs) to be reported to the IRB regardless of relationship.

**OSI Comment:** Lack of timely SAE reporting to the IRB is clearly a violation of GCP standards. However, these SAEs had been reported to the sponsor and have been reported to the agency. There was also conflicting policies regarding the IRB and the CRO concerning submissions.

**OBSERVATION 2:** Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

For study GLP112753:

- a. Subject 004 was hospitalized (b) (6) with a large ulcer on the plantar aspect of left foot, diffuse cellulitis, and osteomyelitis of left foot 3rd and 4th metatarsal heads. Hospital records also document previous toe amputations. Site records have a physical exam dated 1/8/10 as a normal exam and another physical exam dated 1/8/10 with "right 5th toe amputated; left 1st and 5th toe amputated". Furthermore, there was no recording of the large ulcer. On exam after hospitalization on (b) (6) it was recorded that there were no adverse events since the last visit. [*Note, the cellulitis and osteomyelitis are captured in the adverse event data line listings*]. Hospital discharge summary also stated that the subject is homeless. The site record had an address and no mention of homelessness. On 7/22/10, the albumin/creatinine ratio was 1033 mg/g. On 11/4/10 it increased to 2080 mg/g. This abnormal laboratory was not documented as an adverse event. In addition, there was a note in the subject's chart on a blank piece of paper dated 11/15/11 with no subject number or identification to link to the subject.

**OSI Comment:** In response, the PI acknowledged poor record-keeping regarding no identifiers on the records. He justified the repeat records with the same dates but different exams as a "staff error". The laboratory results were marked as "not

clinically significant” by the PI and, therefore, were not entered as adverse events. The PI stated that he felt the time lapse of 15 days between the physical at the site and the subject’s admission to the hospital was sufficient time for the ulcer to develop. The PI also stated that the subject never presented as being homeless and was always well-groomed. There is a possibility that the subject reported being homeless due to lack of medical insurance.

- b. Subject 002 was hospitalized with a transient ischemic attack (TIA) on (b) (6) and discharged (b) (6). Subject was seen at the site 12/4/09. The chart worksheet visit has recorded "No AE since last visit". *[Note, the TIA is captured in the adverse event data line listings].*

**OSI Comment:** In response, the PI acknowledged poor record-keeping and has instituted a Quality Assurance Plan with weekly chart reviews that he is hoping will reduce such incidences. Designated staff will review five subject charts at random per week for such items as proper consenting per the site’s SOP, patient laboratory results and physician’s review of the results, proper source document completion and data collection.

- c. Subject 014 chart has note of sudden loss of vision 7/1/12; seen by ophthalmologist 7/6/12 with diagnosis of occlusion of left retinal artery. Next visit note of 8/13/12 had that there were no adverse events since last visit. *[Note, the left retinal artery occlusion is NOT captured in the adverse event data line listings].* Furthermore, there were several abnormal laboratory values that were not recorded as an adverse event: +3 protein in urine noted 8/12/11; albumin/creatinine ratio 4466 mg/g. Creatinine laboratory results steadily deteriorated: on 7/2/09 it was 1.2 mg/dL; 8/10/11 it was 1.5 mg/dL; 5/23/12 it was 2.0 mg/dL. On 10/10/12, laboratory results showed creatinine 2.5 mg/dL, BUN 38 mg/dL, potassium 6.2 meq/L, calcium 8.1 mg/dL, hemoglobin 10.5 g/dL, hematocrit 31.5% (hemoglobin/hematocrit on 8/14/09 was 13 g/dL /38%).

**OSI Comment:** In response, the PI acknowledged poor record-keeping by not capturing the well-documented adverse event into the eCRF. Again, the abnormal laboratory results were marked as “not clinically significant” by the PI and, therefore, were not entered as adverse events. The PI also stated that he felt the laboratory changes were the result of long term diabetes.

- d. Subject 013 was screened on 7/2/09. The site medical history worksheet was blank and the physical exam page found in the chart was without any identification (no subject number, no subject initials, no date of birth, and no protocol number). However, it was signed and dated by the PI.

**OSI Comment:** In response, the PI acknowledged poor record-keeping and has instituted a Quality Assurance Plan that he believes will improve procedures.

- e. Subject 016 had a recorded potassium of 6.2 meq/L noted on 9/14/09. Lab sheet had note for subject to have test repeated. Blood testing was not repeated until 10/14/09. No adverse event was recorded. Potassium was again reported high (8.8 meq/L) on 12/10/09; uric acid was 8 meq/dL. It was reported on 4/21/10 that calcium was 6.2 mg/dL and potassium was 6.3 meq/L. Laboratory results on 5/12/11 had BUN 29 mg/dL; creatinine 1.5 mg/dL, calcium 8.2 mg/dL. None of the abnormal laboratory values were reported as adverse events. Visit 6 Baseline on 8/19/09 had several sections missing (information not filled out).

**OSI Comment:** In response, the PI acknowledged poor record-keeping and has instituted a Quality Assurance Plan with weekly chart reviews that he is hoping will reduce such incidences. Also, the newly created lab follow-up log is in response to the lack of adverse event capture.

- f. Subject 008 had several abnormal laboratory results not reported as adverse events including hemoglobin of 10.8 g/dL on 1/22/10 with a previous report of 11.8 g/dL on 8/14/09).

**OSI Comment:** Again, the abnormal laboratory results were marked as “not clinically significant” by the PI and, therefore, were not entered as adverse events.

For study GLP112757:

- g. For Subject 010, the source document for Visit 15 (Week 16), dated 10/6/09 records a subject complaint of fatigue with the question 2 "Were there any adverse events since the last visit?" A check mark answer of "Yes" was chosen and a note of "9/23/09 extremely fatigue [*sic*]" was listed. There was no documentation of grading of this adverse event, duration of this adverse event or resolution. Furthermore, this adverse event was not reported.

**OSI Comment:** In response, the PI acknowledged poor record-keeping and has instituted a Quality Assurance Plan with weekly chart reviews and staff training that he is hoping will reduce such incidences.

- h. For Subject 015, the eCRF as well as the data line listings note an AE of "left foot solar keratosis." with start date of 11/9/09 and end date of 11/23/09. However, in the source document, "Patient Progress Report", dated 11/19/09 this event was noted as a "small ulcer proximal to amputated big toe" and "open wound with slight light yellow discharge" diagnosed as "wound infection". Subject was given prescription for the antibiotic Bactrim DS. Furthermore, on the next visit, Visit 16 (Week 20) it is noted in the source document, Question #2, "Were there any adverse events since last visit" and it is checked "No."

**OSI Comment:** In response, the PI stated that the data managers could not code “left solar toe open sore” as listed in the source documents and the study

coordinator changed the term. PI acknowledged poor record-keeping and has instituted a Quality Assurance Plan with weekly chart reviews and staff training that he is hoping will reduce such incidences.

- i. For Subject 008, an abnormal finding under the gastrointestinal system was documented on the [REDACTED] <sup>(b) (4)</sup> sheet dated 2/4/10: "mild epigastric pain on palpation RUQ x3 days." This condition was not noted as a pre-existing condition and was not documented on the "Physical Exam" sheet at screening on 4/2/09. There was no documentation of any evaluation and grading of this adverse event. Furthermore, this adverse event was not reported. *[Note, the subject number was incorrectly recorded as 016 on the FDA 483. Therefore, the PI was unable to respond.]*

**OSI comment:** There has been definite under-reporting of adverse events at the site, most notably in Study GLP112753. The majority of these events are abnormal laboratory results. Although not listed as adverse events, they have been captured in the laboratory line listings. In response to the FDA 483, a tracking log has been created by the site (submitted with response) to track abnormal lab results and requested actions. The site will be engaged in further training of all staff on the importance and methods of querying subjects regarding adverse events.

**OBSERVATION 3:** An investigation was not conducted in accordance with the investigational plan.

For Study GLP112753:

- a. Per protocol, subjects had to be receiving at least 1500 mg of immediate release metformin daily for at least 3 months before Screening.
  - i. Subject 004 did not meet this inclusion criterion as this subject was started on metformin 850 mg BID on 4/1/09 and subject was screened on 6/4/09.
  - ii. Subject 008 did not meet this inclusion criterion as this subject's metformin was increased to 850 mg BID on 4/8/09 and subject was screened 6/22/09.

**OSI Comment:** These deviations were not reported by the sponsor in the line listings. PI acknowledged the deviations.

- b. Subject 012 was screened on 7/1/09. Randomization was not called in prior to Visit 6 Baseline as per protocol and, therefore, no drug was available for subject. Visit 6 had to be repeated on 7/20/09.

**OSI Comment:** This deviation was not reported by the sponsor in the line listings. PI acknowledged the deviations.

For study GLP112757:

- c. For Subject 022, [REDACTED] <sup>(b) (4)</sup> laboratory results dated 8/11/09 at

the Screening visit show an estimated creatinine clearance value of 58 ml/min. Per the protocol, subjects eligible for enrollment into the study must have a "creatinine clearance > 60 ml/min." A Protocol Inquiry Form was completed on 8/10/09 and states, "subject here for randomization V8; need override code; meets all inclusion criteria." The subject was enrolled in the study on 8/10/09.

**OSI Comment:** PI acknowledged the deviation.

- d. For studies GLP112753, GLP112756 and GLP112757, adherence to metformin was to be monitored as well as compliance with study medications. There was no documentation in the site records that subjects were queried at each visit for adherence and compliance to the study drugs.

**OSI Comment:** PI stated that when subjects were on existing metformin prior to study entry, the site's practice was to only capture non-compliance when the subjects were queried regarding metformin intake. As for the study drug itself, the dosing was captured in the subject's drug log but PI acknowledged that compliance was never captured in the source documentation. PI states that source documentation will be better written to capture verbal conversations and queries that take place in the clinical setting for research purposes.

In addition to the items in the FDA-483, discussion items at close-out included source documentation inadequacy, protocol compliance and understanding, and PI oversight. It was emphasized that communications with subjects needed to be documented in the study charts. There was also discussion regarding the capturing, assessment, and grading of adverse events, including those deemed to be abnormal laboratory results. It was emphasized that this is the responsibility of the investigator and not the research coordinator, sponsor or monitor.

The majority of the deviations were noted for Study GLP112753. The site appeared to have improved its processes and procedures in the subsequent studies. This may have been due to an IRB audit that took place which led to required increased GCP training, written SOPs for the site, and quality assurance activities to be put into place.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was available for review. The audit indicated deviations, the majority of which were noted with Study GLP 112753. Although deviations were noted, much of the missing information has been captured via other documentation. For example, many abnormal laboratory results were not reported as adverse events but were reported in the application as laboratory values. Therefore, the findings do not impact the overall validity or reliability of the submitted data.

**4. Opada Alzohaili, M.D.**

Alzohaili Medical Consultants\*  
1331 Monroe Street, Suite 100  
Dearborn, MI 48124

\*Subjects were initially seen at the previous research location: 4700 Greenfield Road, Dearborn, MI 48126. The site moved approximately August 2010.

- a. What was inspected:** The inspection included a comprehensive review of recruitment, informed consent process and documents (ICD), Institutional Review Board (IRB) review and approvals, inclusion/exclusion criteria, subject case histories, source documents, drug accountability records, site delegation forms, adverse event (AE) reports, electronic case report forms (eCRFs), monitoring records, training, staff background/experience, investigator oversight, financial disclosures, 1572s, and study data verification/integrity.

The inspection included 100% review of informed consents and complete review of all enrolled subjects.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 14 (EIR has 15)	GLP112753- 4	GLP112753- 3
GLP112754- 15	GLP112754- 5 (EIR has 7)	GLP112754- 5
GLP112755- 8	GLP112755- 5	GLP112755- 5
GLP112756- 8	GLP112756- 4	GLP112756- 4
GLP112757- 12	GLP112757- 6	GLP112757- 5
GLP108486- 21	GLP108486- 9*	GLP108486- 7
GLP114130- 2	GLP114130- 0	GLP114130- 0
GLP114179- 27 (EIR has 22)	GLP114179- 16 (EIR has 10)	GLP114179- 10

\*Email correspondence with the ORA investigator clarified that 9 subjects were enrolled in Protocol GLP108486 (12 subjects were reported in the EIR).

**b. General observations/commentary:**

The site was noted to be extremely busy. The PI delegated several study tasks to a study coordinator who does not have a scientific and/or medical background (was a former human resource administrator at a department store and court administrator). The study coordinator was also not listed as a sub-investigator, despite the number of clinical activities delegated to her (obtain informed consent, vitals and ECG, laboratory procedures, dispense investigational product, investigational product receipt/return,

essential documents, eCRF completion, query resolution). Duties listed for the study coordinator for on her curriculum vitae for Dr. Alzohaili:



Of note, this person was no longer employed at the site at the time of the inspection.

Protocol inquiry forms (PIFs) required a signature from the investigator attesting that he/she does not feel the change/deviation affects the rights, safety etc. of the subject(s). Several appeared to be signed by more than one person. The majority of the PIFs were signed by the study coordinator.

The PI stated that he had over 10,000 patients in his clinical practice and that recruitment was mainly done via selection from existing patients. Although the site has a diverse population (many from the Middle East), including individuals with limited English language capabilities, all of the signed consent forms were in English. Additionally, the handwriting and signature written by the study subjects were often difficult to read. Some subject informed consents were signed by two study coordinators, leading the FDA inspector to suspect that translations were being done, although this was denied by the current study coordinator.

The subject files were found to be bound in manila folders, organized and legible, although with little to no medical history source documentation. The site utilized a paper reporting system and transcribed information from worksheets directly into the electronic case report for (eCRF). There was no training log available at the site for study GLP114179. The majority of correspondences regarding IRB activity/approval were performed directly by the sponsor.

The site was "temporarily closed to screening" on 2/26/10 for study GLP108486 by the monitor <sup>(b) (4)</sup> and sponsor. As per the correspondence letters, there was lack of PI oversight noted, original source documents had been destroyed, and there were several clinical trial tasks that had not been completed in a timely manner including collection of past medical records for all active subjects, creation of a subject master log, weekly staff meetings, and investigational product accountability and compliance. For example, for Subject 1001486021, the monitoring visit of August 2-4, 2010 noted over 10 adverse events where there was no handwriting or notes documenting PI awareness, treatment and/or assessment of the AEs. There were several medication changes that were not written or signed off by the PI or a sub-PI. Laboratory reports were filed away prior to PI review/signing. The correspondence included issues noted across all of the other <sup>(b) (4)</sup> studies. The temporary screening hold was not reported to the IRB.

Review of the monitoring visit notes revealed that, although the site was originally approved with a locked refrigerator, on some occasions the refrigerator was found open and comingled with food/employee lunches. Monitor noted several times that the refrigerator had “access by many people uninvolved in the trial”. The clinic moved locations and discarded several pens due to “exposure”, although there was no documentation as to why or how they were damaged/exposed. One pen was replaced due to “water damage”; however, the site did not know how that occurred and there was no documentation of any issues. Subject 1001757007 was misdosed with incorrect pen #2039854 instead of #2038954 on October 30, 2009; this subject remained in the trial per sponsor. Subjects 1001486001 and 1001486006 were enrolled and did not meet inclusion criteria.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued to Dr. Alzohaili for the following deficiencies:

(b) (4)



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(b) (4)



**5. Gary Ruoff, M.D.**  
Westside Family Medical Center  
6565 West Main St  
Kalamazoo, MI 49009

**a. What was inspected:** Records for 100% of consented study subjects were reviewed. Inspection also included review of IRB approvals, medical records, inclusion/exclusion criteria, source documents, investigational product receipt, storage and dispensing, training, staff credentials, financial disclosure, and communications. The primary efficacy endpoint was compared to the sponsor data line listings.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 8	GLP112753- 6	GLP112753- 6
GLP112754- 2	GLP112754- 1	GLP112754- 1
GLP112755- 11	GLP112755- 6	GLP112755- 4
GLP112756- 1	GLP112756- 1	GLP112756- 1
GLP112757- 1	GLP112757- 0	GLP112757- 0
GLP108486- 4	GLP108486- 0	GLP108486- 0
GLP114179- 2	GLP114179- 1	GLP114179- 1

The original consult from the review division did not list GLP112756. Dr. Ruoff also served as PI for that study. One subject enrolled into this study. There are two site numbers that the sponsor gave to maintain blinding. The Ruoff Site is #1294 and also #3653.

- b. General observations/commentary:** The clinical site was a large private practice with over 50,000 patients. There were no issues noted regarding consenting of the subjects. Subject eligibility was first determined by the research nurse and then verified by the clinical investigator. There were no issues noted with drug accountability. There was adequate oversight and protocol compliance. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were a few discussion items at close-out:

- A physician in Dr. Ruoff's practice who was not identified in the Delegation of Authority (DOA) for GLP112755 performed two physical exams on two separate subjects, 1294755002 and 1294755005. However, the physician is a subinvestigator on protocol GLP114179, and did receive training to the requirements of protocol GLP112755 prior to the initiation of the protocol at the site.
- A physician in Dr. Ruoff's practice who is not identified in the Delegation of Authority for GLP112754 signed off on the clinical significance of laboratory values for the Visit 6 labs for subject 1294754001. Although not listed on the DOA, this physician did receive training on the protocol prior to the initiation of the protocol at the site.
- The site created a Delegation of Authority (DOA) that lists the principal investigator, the four subinvestigators that are on the 1572, and seven

additional physicians and one PA-C as “subinvestigators” for protocol GLP112753. However, these additional individuals are not listed on the 1572 and a Financial Disclosure was not completed for these individuals. It was explained that the site originally was planning on including all of these individuals as subinvestigators, but were discouraged to do so by the sponsor. The DOA was never updated to reflect this change.

- The site created their own Delegation of Authority (DOA) that failed to include all of the responsibilities of the principal investigator such as correspond with the IRB and/or sponsor. Also the DOA did not illustrate current staff and their responsibilities. Dr. Ruoff stated that in an attempt to document all of the protocol activities, his site inadvertently missed some. He stated that, in the future, the form will be revised or the site will use the DOA provided by the sponsor.
- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 6. John Gabriel

North Hills Family  
4351 Booth Calloway Road, Suite 105  
Practice, P.A. 76180

- a. What was inspected:** Due to time constraints, the focus of the inspection was studies GLP112753 and GLP112754. All 26 subject records for study GLP112753 were reviewed for informed consents, 13 were also reviewed for case report form and source documents. All 12 subject records for study GLP112754 were reviewed for informed consent; seven were also reviewed for case report forms and source documents. Institutional Review Board (IRB) approvals and the regulatory binders for all studies were reviewed. Subject selection, FDA 1572s, curriculum vitae, medical licenses, delegation logs, financial disclosure forms, training, and sponsor monitoring activities and communications were reviewed. Master investigational product (IP) accountability logs were reviewed.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 26	GLP112753- 13	GLP112753- 13
GLP112754- 12	GLP112754- 8	GLP112754- 8
GLP112755- 1	GLP112755- 1	GLP112755- 1
GLP112757- 15	GLP112757- 3	GLP112757- 3
GLP108486- 20	GLP108486- 6	GLP108486- 6
GLP114179- 30	GLP114179- 10	GLP114179- 10

GLP114130- 17

GLP114130- 3

GLP114130- 3

- b. General observations/commentary:** For study GLP112753, the first subject was screened at the study site on 04/13/09, the first subject enrolled 06/01/09 and the last subject completed the study on 12/14/12. For study GLP112754, the first subject was screened at the study site on 04/08/09, the first subject enrolled 05/22/09 and the last subject completed the study on 10/04/12. All FDA 1572 forms and Financial Disclosure forms were adequately completed, signed and were submitted to the sponsor.

Information was transcribed into the eCRF directly from the source documents by the Clinical Research Coordinators and loaded into an Oracle Clinical database. The Principal Investigator and Sub-Investigators electrically signed the eCRF's. Each user accessed the eCRF EDC data base using unique, individual passwords. All Serious Adverse Events (SEA's) and Adverse Events (AE's) were documented and were appropriately reported to the sponsor and IRB in a timely manner. There were no observations of the firm underreporting SAE's or AE's. The primary efficacy endpoint data was verifiable.

The test article was stored within the appropriate temperature and study site staff did appropriately record or document temperatures in the temperature log paper records. All temperature log paper records were legible, accurate and complete. A record review of the firm's Investigational Product Accountability/Disposition Records for studies GLP112753 and GLP112754 revealed that it could not be determined if the Investigational Product (GSK716155 Injector Pens) were returned to the sponsor.

Pen Failure records for Subject (b) (6) # 1325753003 and Subject (b) (6) # 1325754001 were reviewed. Both subjects prepared the injector pen correctly, inserted the injector pen into the abdomen and the plunger would not dispense or discharge. Both pen failures were reported to the sponsor and CRO.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following:

(b) (4)

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(b) (4)

**7. John D. Lentz, M.D.**

Georgia Clinical Research  
2121 Fountain Drive, Suite A  
Snellville, GA 30078

This inspection also focused on the previous PI at the site:  
Cynthia Sadler, MD, MPH, JD

- a. What was inspected:** All informed consents for all enrolled subjects were reviewed. Institutional Review Board (IRB) approvals and the regulatory binders for all studies were reviewed. Subject selection, FDA 1572s, curriculum vitae, medical licenses, delegation logs, financial disclosure forms, training, and sponsor monitoring activities and communications were reviewed. For Study **GLP108486**, complete records were reviewed for Subjects 486002, 486004, 486007, 486001 (screen failure), 486005 (screen failure), 486006 (screen failure); and 486007 (subject enrolled but lost to follow-up). For Study **GLP112755**, records were reviewed for Subjects 755001 (lost to follow up) and 755003 (lost to follow up); there were no amylase or lipase results reported at the screening visit for either subject. Records for two screen failures were also reviewed (755002 and 755004). For study **GLP112753**, records were reviewed for Subjects 753001, 753003, 753012 and 753027; there were no amylase or lipase results reported at the baseline visits. Additionally, the following subjects had data line listing results for amylase and lipase but no results were found in the source documents: 753008, 753016, 753017, 753019, 753022, and 753031. For study **GLP112754**, records were reviewed for Subjects 754001, 754002, and 754012. Data line listings had results for amylase and lipase but no results were found in the source documents for V6. For Subject 754017, amylase and lipase were not reported at baseline. For study **GLP112756**, records were reviewed for subjects 756002, 756003, 756006. For study **GLP112757**, records were reviewed for subjects 757001 and 757006.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 43	GLP112753- 12	GLP112753- 12
GLP112754- 18	GLP112754- 11	GLP112754- 11
GLP112755- 4	GLP112755- 2	GLP112755- 2
GLP112756- 7	GLP112756- 5	GLP112756- 5
GLP112757- 11	GLP112757- 4	GLP112757- 4
GLP108486- 7	GLP108486- 3	GLP108486- 3

- b. General observations/commentary:** This assignment was originally issued for clinical investigator Dr. Cynthia Sadler, M.D. Dr. Sadler was the principal investigator for a short time during the studies and it was reported to the Agency that Dr. Sadler had refused to sign financial disclosure forms for all studies. *(Sponsor inspection revealed that there was a Memo to File with documentation on 6/11/12 and 8/23/12 stating that no forwarding address was provided by Dr. Sadler and that she refused to sign the follow-up financial disclosure forms for the six Phase 3 studies; conveyed in a verbal conversation between the project assistant at (b) (4) and Dr. Sadler on 10/9/12).*

There were also concerns because the site was administrated by a site management organization (SMO) with multiple locations and multiple PI changes. This was investigated thoroughly. Originally the company was named Best Clinical Research and then became Georgia Clinical Research, LLC. The SMO had three locations: 3009 Rainbow Drive, Decatur, GA; 1116 East Ponce DeLeon Avenue, Decatur, GA and 2121 Fountain Drive, Snellville, GA. The first PI was Dr. Bonnie Ellenoff, who worked at the SMO for about 5 years.

(b) (4)

Dr. Sadler left the site and Dr. Goheer started work as the PI. The SMO was subsequently moved to Dr. Lentz's office in Snellville on Fountain Drive. Dr. Goheer did not move with the business. Dr. Lentz had overall responsibility for the study activities after he signed the 1572 on June 14, 2011 when he took over as principal investigator.

(b) (6)

As noted earlier, Dr. Sadler was the PI for only a few months at the SMO. Review of the records found signed financial disclosures for Dr. Sadler for all of the studies. There

(b) (4)



The sponsor reported that there were two duplicate subjects at this site. The duplicate subjects were Subject 754010 from study GLP112754 and Subject 756004 from study GLP112756. The site staff immediately knew the names of the two subjects identified as duplicate subjects by the sponsor. The site had been notified by the sponsor about the subjects who were subsequently discontinued from the study. Records for each subject were available. There were no other duplicate subjects at the site.

There was no evidence of pen failures recorded in the records reviewed during the inspection. Site staff all denied there were any pen failures reported or experienced at this site. Staff had seen a sponsor newsletter which addressed pen failures and ensured that the subjects were using the pen properly and reported any problems.

There were minor issues relating to poor documentation of events, such as lack of an explanation for an ECG that was not performed on a subject, and the lack of the PIs signature on a log. There did not appear to be any non- or under-reporting of adverse events at this site. The primary efficacy endpoint was verifiable. Due to time constraints, test article accountability was not reviewed for any of the studies. There did not appear to be any fraudulent activities taking place at the site.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 8. **Graham Ellis\***

Helderberg Clinical Trials Centre  
Sir Lowrys Pass Road  
7 G&H Arun Place  
Somerset West, South Africa 7129

\*A site in India had been originally selected by the review division but that site had recently been inspected. Therefore, this alternative site was chosen in consultation with the review division.

- a. **What was inspected:** Recruitment of subjects, Standard Operating Procedures, delegation of duties, informed consent process, financial disclosure, Ethics Committee review and approvals, training, and drug accountability were reviewed. For Study **GLP112753**, twelve subjects' records were randomly chosen and reviewed in detail to confirm compliance with the protocol: 004, 005, 006, 011, 014, 017, 019, 022, 023, 030, 034, and 038. Secondary efficacy endpoints were reviewed for a subset (6) of these subjects' records. For Study **GLP108486**, eight subjects' records were randomly chosen and reviewed in detail to confirm compliance with the protocol: 001, 005, 009, 011, 012, 013, 017, and 023. Secondary efficacy endpoints were reviewed for a subset (4) of these subjects' records. For Study **GLP112754**, 14 subjects' records were randomly chosen and reviewed in detail to confirm compliance with the protocol: 003, 004, 007, 017, 018, 020, 022, 023, 025, 030, 035, 038, 046, and 047. Secondary efficacy endpoints were reviewed for a subset (6) of these subjects' records. For Study **GLP112755**, full chart review was done for Subject 001. The other subject that was enrolled in this study was Subject 004. This subject was withdrawn after an SAE of renal failure. For Study GLP114130, a complete review of subjects' records was performed on seven of the eight subjects enrolled.

For all studies, there was 100% review of the subject records for informed consent, primary efficacy and adverse event reporting. The source documents and CRF's were compared against the sponsor line listings, specifically the following listings: Adverse Events, HbA1c, Protocol Deviations, Prior and Concomitant Medications, Weight, and Fasting Plasma Glucose.

Subjects screened	Subjects enrolled	Subjects completed
GLP112753- 40	GLP112753- 23	GLP112753- 22
GLP112754- 47	GLP112754- 28	GLP112754- 26
GLP112755- 7	GLP112755- 2	GLP112755- 1
GLP108486- 23	GLP108486- 15	GLP108486- 13
GLP114130- 25	GLP114130- 8	GLP114130- 8

- b. **General observations/commentary:** The site was very organized, staffed with experienced people, and overseen by the PI in a sufficient manner. Training operating procedures were in place. The firm has specific SOP's to cover general tasks, such as the informed consent process and test article accountability. Staff members are trained on these SOP's and they sign and date a form documenting this training. Each subject signed three informed consent forms during their screening visit: the Main ICF, the ICF for HIV-testing, and the ICF for the Pharmacogenetic Sub-Study. The majority of the subjects at this site are bilingual in English and Afrikaans. The ICFs were in both languages.

In GLP112754, the initial ICF, version 1.4, contained the following statement: "This is an open label study so both you and the study doctor will be able to pick which study group you are in." Sites were instructed by (b) (4) to inform the subject of this mistake and to correct the word "pick" to "know" by hand. Handwritten corrections were found to be made to the informed consents reviewed. This was not corrected until Version 2.1 of the ICF was released.

Review of the 12 subject records indicated that eligibility criteria for enrollment were met and that the procedures required by the protocol were followed. There were several Serious Adverse Events (SAE) reported during this study. Some of the SAEs were not found in the data listing as they occurred after Week 104 (data cut off). Adverse events (serious and non-serious) were accurately documented and reported; no evidence of under-reporting of adverse events was discovered. An SAE fax notification form was not sent within 24 hours for Subject 038, as was required by the protocol. However, the eCRF related to this event was completed within 24 hours. HbA1c values were verified against source documents for all 23 enrolled subjects; no discrepancies were noted. Primary efficacy endpoint data was verifiable.

No test article from this study was observed in the refrigerators or ambient storage as they have all been returned to the sponsor; the study is closed to

enrollment at this site. The site maintained a binder containing test article accountability log forms for the albiglutide pens. Confirmations of receipt forms were found in this file; no instances of test article receipt, with significant time/temperature deviations were noted.

The requirement for amylase/lipase testing, at Visit 5, was added in a protocol amendment for GLP112753 and GLP112754. Prior to this amendment, it was not on the laboratory requisition form. It was observed that there were some laboratory results which had a statement that serum samples submitted were reported beyond the documented frozen stability, at clients' request.

For study GLP114130, the site submitted frozen serum samples to the laboratory after a holiday season. The samples were deemed past the age of stability for calcitonin analysis. This rendered several subjects without a calcitonin value for the baseline visit. Also during the GLP114130 study, there were several subjects that did not receive their test article at their baseline study visit. They were told through the IVRS that there was not sufficient study drug on site. This occurred with at least three of the eight subjects enrolled. Usually the study drug was provided the following day.

At the beginning of the inspection, there were inquiries about pen failures. Dr. Ellis stated there were several patient/user errors but no device failures. Most of the time, it was the subject not using the pen properly and that this was often noted when the pens were returned with residual investigational product remaining. The site reported in the source documentation when there was a pen failure. Inquiries were also made regarding any instances of duplicate enrolled subjects. Dr. Ellis stated that at the time of screening, site staff would obtain a copy of each subject's photo identification. The staff stated that they were unaware of any subjects with duplicate enrollments. Subject initials and dates of birth were noted during review of the study source documents; no cases of duplicate enrollments occurred at this site.

An FDA 483, Inspectional Observations, was not issued to management during this inspection. The following verbal observations were discussed with management:

1. For the GLP112754 study, the site used the wrong version of the informed consent form with some subjects and re-consented subjects late;
2. The process to document when new protocols and informed consent forms were received and implemented was deficient;
3. The site did not keep records of which refrigerators the test article was stored in while the study was ongoing;
4. Amylase/ lipase testing was not performed, for one subject (protocol GLP112753), as was required by protocol amendment 1, prior to randomization;
5. An SAE fax notification form was not sent within 24 hours (only the eCRF was completed within this time frame) as was required by protocol

GLP112753.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**9. GlaxoSmithKline LLC\***

Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709

\*Inspection took place at mailing address: 709 Swedeland Rd., King of Prussia, PA 19406-2711. As of October 27, 2009 SmithKline Beecham Corporation has been re-domiciled from Pennsylvania to Delaware, converted into a limited liability company and re-named GlaxoSmith Kline LLC. The Registered Office for the US legal entity is: 2711 Centerville Road, Suite 400, Wilmington, DE 19808.

- a. What was inspected:** The inspection consisted of reviewing the organizational structure and responsibilities, credentials, contracts with CROs and vendors, training, investigational product, monitoring, 1572s, the Interactive Voice Response System (IVRS), financial disclosures, SOPs, Certificate of Analyses, selection criteria for members of the Independent Data Monitoring Committee (IDMC), the Cardiovascular Evaluation Committee (CEC) and the Pancreatitis Adjudication Committee (PAC), committee meeting minutes, as well as baseline and efficacy values of HbA1c for subjects at study Sites 1001, 1083, 1200, 1242, 1271, 1294, 1325, and 5604. Also reviewed were the firm's Corrective and Preventive Action (CAPA) for the non-compliant clinical investigators.
- b. General observations/commentary:** All studies were registered on Clinical Trials.gov. There were six amendments to the Master Clinical Services Agreement between (b) (4) (CRO) and GlaxoSmithKline, LLC. No discrepancies were observed. GSK provided the Task Order for each of the study protocols. The Standard Transfer of IND Sponsor Obligations was an attachment to Form FD 1571.

Company policy consisted of collecting financial interest information from investigators through questionnaires. Current and updated financial information were collected. Per SOP, due diligence process was followed whereby up to three documented attempts were conducted to collect the required information from investigators. After Dr. Sadler stopped working on the study trials, (b) (4) was unable to obtain the follow-up financial information. These were documented in a Memo to File dated 6/11/12 and 8/23/12. No forwarding address was supplied and there was verbal conversation of refusal to sign.

GSK and (b) (4) provided a list of the transfer dates for 2 years and the final electronic data for all nine studies.

Table 1: Date of last receipt of CDISC Datasets from (b) (4)

Study	Approval/load to GSK share	2-year lock datasets	Final datasets	Comments
112753	12/09/12	Y		BLA CDISC dataset delivery is based on 2-year database lock; Final CDISC dataset delivery , based on database freeze (3-year study), is ongoing
112754	12/10/12	Y		BLA CDISC dataset delivery is based on 2-year database lock; Final CDISC dataset delivery , based on database freeze (3-year study), is ongoing
112755	12/09/12	Y		BLA CDISC dataset delivery is based on 2-year database lock; Final CDISC dataset delivery , based on database freeze (3-year study), is ongoing
112756	12/09/12	Y		BLA CDISC dataset delivery is based on 2-year database lock; Final CDISC dataset delivery , based on database freeze (3-year study), is ongoing
112757	12/09/12	Y		BLA CDISC dataset delivery is based on 2-year database lock; Final CDISC dataset delivery , based on database freeze (3-year study), is ongoing
114130	12/05/12		Y	BLA CDISC dataset delivery is based on final database freeze.
114179	12/09/12		Y	BLA CDISC dataset delivery is based on final database freeze
108486	12/04/12		Y	BLA CDISC dataset delivery is based on final database freeze
114856	12/12/12		Y	BLA CDISC dataset delivery is based on final database freeze

(b) (4) provided the signed copies of the Database Finalization Form/ Final Database Lock for all studies:

Study	Approved / Date Signed
GLP112753	04/19/13
GLP112754	04/12/13
GLP112755	02/19/13
GLP112756	02/07/13
GLP112757	04/26/13
GLP114130	06/15/12
GLP114179	10/28/11
GLP108486	03/12/12
GLP114856	11/09/12

At the end of the study, the electronic copies of the CRFs were placed on a CD-ROM and provided to the study sites and to GSK. The table below represents the dates the CD-ROMs were received by GSK.

Phase III Study	Date Received BLA eCRF CD-ROM
GLP112753	6/11/2012
GLP112754	6/21/2012
GLP112755	6/18/2012
GLP112756	6/26/2012
GLP112757	7/02/2012
GLP114179	6/26/2012
GLP108486	6/26/2012
GLP114130	8/22/2012

A Working Practice Document WPD-CL-35 was provided which described the process for conducting and documenting a Pre-Study Visit. Pre-study visits were conducted at all locations where subjects were seen.

A log of temperature excursions for the albiglutide clinical trial program was provided for review. There were some falsely high readings in the packaging room due to misalignment of the unit measurement in the printout identified. Review of the actual temperature readings and scientific log were noted to be within the acceptable temperature ranges.

A report regarding all pen failures was requested. A technical memorandum entitled "Albiglutide GSK716155 Phase III Clinical study: Trend Report of Total Pen Injector Customer Complaints" was reviewed and shared with the review team. According to this report, there were a total of 859 complaints and 330 user errors received between February 2009 and April 2013. The report contained failure modes, root causes, user error, destroyed or lost pens, partial doses and substantiated complaints. The report failed to discuss if any of the complaints impacted the administration of the dose test article.

At the end of the inspection, a Form FDA-483 was presented with the following observations:



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### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of seven domestic sites and one foreign clinical site as well as the sponsor.

Observations noted above for all sites and the sponsor are based on the review of the Establishment Inspection Reports. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

One site, Dr. Opada Alzohaili (Site # 1001/3460) was issued a Form FDA 483 citing inspectional observations and pending classification is Official Action Indicated (OAI). The data from this site are deemed unreliable.

Two clinical sites inspected, Drs. Simon Babazadeh (Site #1242/3601) and John Gabriel (Site #1325/3784) and the sponsor were each issued a Form FDA 483 citing inspectional observations and pending classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above and discussed with the review division for the two sites and the sponsor inspected, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

Five clinical sites, Drs. Richard B. Stewart (Site #1200/3669), John-Louis Selam (Site #1083/3442), Gary Ruoff (Site #1294/3653), Cynthia Sadler/ John Lentz (Site #1271/3630), and Graham Ellis (Site #5604/7063) were not issued a Form FDA 483; pending classifications for each of these inspections are NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

In general, based on the inspections of the eight clinical study sites (representing 50 protocol sites) and the sponsor, the inspectional findings support validity of the data as reported by the sponsor under this NDA.

*{See appended electronic signature page}*

Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

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Janice Pohlman, M.D., M.P.H.  
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/s/  
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CYNTHIA F KLEPPINGER  
04/04/2014

JANICE K POHLMAN  
04/07/2014

KASSA AYALEW  
04/07/2014

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

**PATIENT LABELING REVIEW**

Date: April 4, 2014

To: Jean-Marc Guettier, MD  
Director (acting)  
**Division of Metabolism and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Kendra Y. Jones  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG),  
Instructions for Use (IFU)

Drug Name (established name): TANZEUM (albiglutide)

Dosage Form and Route: for injection, for subcutaneous use

Application Type/Number: BLA 125431

Applicant: GlaxoSmithKline LLC

## 1 INTRODUCTION

On January 11, 2013, GlaxoSmithKline submitted for the Agency's review a new Biologics License Application (BLA) for albiglutide, a glucagon-like peptide -1 receptor agonist, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Albiglutide is dispensed in a 30 mg or 50 mg prefilled pen supplied with a 29G 5-mm needle, to be patient self-administered subcutaneously once weekly.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on March 1, 2013, and March 1, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for albiglutide powder for solution for injection.

The Applicant submitted a major amendment to this BLA leading to the Agency invoking a 3 month review clock extension on July 30, 2013.

The proprietary name TANZEUM was approved on August 2, 2013.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the handling study and IFU was completed on October 24, 2013 and February 19, 2014.

## 2 MATERIAL REVIEWED

- Draft TANZEUM (albiglutide) for injection, for subcutaneous use MG and IFUs received on February 10, 2014, and received by DMPP on February 28, 2014
- Draft TANZEUM (albiglutide) for injection, for subcutaneous use MG and IFUs received on February 10, 2014, and received by OPDP on March 31, 2014
- Draft TANZEUM (albiglutide) for injection, for subcutaneous use Prescribing Information (PI) received on January 11, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on March 24, 2014
- Draft TANZEUM (albiglutide) for injection, for subcutaneous use Prescribing Information (PI) received on January 11, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on March 24, 2014
- Division of Medication Error Prevention and Analysis (DMEPA) review of the TANZEUM (albiglutide) for injection, for subcutaneous use handling study and IFUs dated October 24, 2013 and February 19, 2014
- Approved Novolog (insulin aspart [rDNA origin] injection) comparator labeling (for abbreviated MG format) dated October 31, 2013
- Approved Victoza (liraglutide [rDNA origin] injection) comparator labeling (for MG class labeling where applicable) dated June 13, 2013

### 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFUs, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, 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 10 and the IFU documents using the Verdana font, size 11.

In our collaborative review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable

### 4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

### 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/  
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ROBIN E DUER  
04/04/2014

KENDRA Y JONES  
04/04/2014

SHAWNA L HUTCHINS  
04/04/2014

LASHAWN M GRIFFITHS  
04/04/2014

# Internal Consult

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

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Joyce Weaver, Senior Risk Management Analyst, DRISK

From: Kendra Y. Jones, Regulatory Review Officer

CC: Kendra Y. Jones, Regulatory Review Officer, OPDP  
Adora Ndu, Acting Team Leader, OPDP  
Lyle Canida, SRPM, OSE  
Cynthia LaCivita, Team Leader, DRISK  
Joyce Weaver, Senior Risk Management Analyst, DRISK  
Kate Heinrich Oswell, Health Communications Analyst, DRISK  
Carole Broadnax  
CDER-OPDP-RPM  
Michael Wade, RPM, OPDP

Date: March 19, 2014

Re: BLA # 125431  
TANZEUM (albiglutide) for injection, for subcutaneous use  
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials (Submission date: December 18, 2013)

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## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for TANZEUM:

- Healthcare Provider (HCP) REMS Materials:
  - REMS letter for Healthcare Professional (print version)

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KENDRA Y JONES  
03/19/2014

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**Human Factors Study, LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** February 19, 2014  
**Requesting Office or Division:** Division of Metabolism and Endocrinology Products (DMEP)  
**Application Type and Number:** BLA 125431  
**Product Name and Strength:** Tanzeum (Albiglutide) for Injection, 30 mg and 50 mg  
**Product Type:** Single Ingredient Combination Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** GSK  
**Submission Date:** 01/28/2014  
**OSE RCM #:** 2013-278-1  
**DMEPA Primary Reviewer:** Yelena Maslov, Pharm.D.,  
**DMEPA Team Leader:** Yelena Maslov, Pharm.D.

---

## 1 REASON FOR REVIEW

This is a follow-up review to OSE Review #2013-278 and 2013-620 to evaluate Tanzeum’s labels and labeling based on the results from the re-test Human Factors (HF) Study conducted for Tanzeum Pen Injector Device. DMEPA requested the re-test HF study in their previous review.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A
Other	N/A
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	D

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The re-test Human Factors Study results submitted to the Agency on January 28, 2014 validated the safe and effective use of the pens containing 30 mg and 50 mg of Albiglutide as it relates to the regular method of reconstitution and the alternative method of reconstitution. More specifically, the study results demonstrated that both patients and healthcare practitioners can reconstitute the powder correctly and wait an appropriate amount of time for the product to dissolve because in the study no errors were made during this process. It appears that the revised IFU, package insert labeling, and carton labeling helped mitigate the previously seen errors with reconstitution (i.e., not waiting a sufficient amount of time for the product to dissolve).

Additionally, the Human Factors Study Results supported the addition of the alternate method of reconstitution for healthcare practitioners provided in the package insert labeling because all

healthcare practitioners were able to use the correct technique during product reconstitution and waited the appropriate amount of time for the product to dissolve.

#### **4 CONCLUSION & RECOMMENDATIONS**

The re-test Human Factors Study results submitted to the Agency on January 28, 2014 validated the safe and effective use of the pens containing 30 mg and 50 mg of Albiglutide as it relates to regular method of reconstitution and the alternative method of reconstitution.

Additionally, the proposed labels and labeling address all of DMEPA's previous recommendations, as a result, we have no additional recommendations at this time.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tanzeum (Albiglutide) that GSK submitted on January 28, 2014.

Table 2. Relevant Product Information for Albiglutide	
Active Ingredient	Albiglutide
Indication	GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus
Route of Administration	Subcutaneous injection
Dosage Form	Powder for injection
Strength	30 mg/0.5 mL and 50 mg/0.5 mL after reconstitution
Dose and Frequency	30 mg once weekly, may increase to 50 mg once weekly
How Supplied	30 mg single-dose pen (carton of 1 and carton of 4) 50 mg single-dose pen (carton of 1 and carton of 4)
Storage	Refrigerate at 36°F to 46° F (2° C to 8° C)

### APPENDIX B. PREVIOUS DMEPA REVIEWS

#### B.1 Methods

We searched the L:Drive on January 28, 2014 using the terms “ Albiglutide” to identify reviews previously performed by DMEPA.

#### B.2 Results

We identified previously completed review OSE Review #2013-278 and 2013-620 Albiglutide Human Factors, Label and Labeling Review that contains our previous recommendations regarding HF study re-test and improvements to the labels and labeling.

## **APPENDIX C. HUMAN FACTORS STUDY**

### **C.1 Study Design**

#### **Objective:**

The main objective of this study was to validate the saliency and clarity of the required wait times for the 30mg (15 minutes) and 50mg (30 minutes) doses, and to determine if users, once familiar with the wait time for the 30mg device, notice the different wait time for the 50mg device without any coaching. Another objective was to obtain additional data, beyond the recent summative testing, to validate that the GSK Albiglutide pen injector can be correctly, safely, and effectively used by the intended users (adult type 2 diabetes patients and the HCPs who will train patients), based on the proposed packaging and labeling (including the updated Instructions for Use - IFU). A third objective was to validate an alternate instructional procedure for use with Healthcare provider participants only. This procedure involves the HCP consistently swirling the pen to reconstitute the medication instead of placing the pen in a cup and waiting for a period of time.

#### **Participants:**

The study was conducted with a total of thirty (30) participants. Participants consisted of fifteen diabetes patients (eight (8) injection naïve and seven (7) injection experienced diabetic patients) and fifteen (15) Health Care Professionals (HCPs).

#### **Study design:**

All participants attended two sessions, one week apart from each other. After an introduction to the 30mg pen, participants were allowed to review the IFU and all associated materials in the manner they would normally do so at home/work prior to their first unaided use of the device. Participants then performed one unaided injection using the 30mg pen and provided subjective feedback on their experience. All participants returned one week later to perform only the reconstitution procedure using the 50mg dose (unbeknownst to them) to determine if the 30-minute wait time labeling was conspicuous and effective enough for users to distinguish the wait time differences between the 30mg and 50mg kits. Additionally, HCP participants performed an “alternate” reconstitution procedure while attempting to follow an additional instruction document.

## C.2 Results

### **Regular method of Reconstitution:**

#### **30mg Pen**

Across all participants: 100% (30/30) successfully noticed the 15-minute wait required for the reconstitution of the 30mg dose.

- The majority of participants (18/30, 60%) stated they located the wait time in the Instructions for Use.
- The remaining participants (12/30, 40%) stated they used the carton labeling to identify the 15-minute wait time.

#### **50mg Pen**

One week later, all participants successfully noticed the 30-minute wait time required for the 50mg pen 100% (30/30).

- With the 50mg pen, the majority of users (26/30, 80%) stated that they had first identified the 30-minute wait time based on the carton labeling. Of these participants, most (24/26, 92%) stated that they first identified the wait time on the outside of the carton (left image below), with two indicating they first identified the wait time on the inside of the carton (2/26, 8%).
- All participants 100% (30/30) also indicated that they noticed the different wait time in the IFU.

### **Alternate Method of Reconstitution:**

Across all HCP participants, 100% (15/15) successfully reconstituted a 30mg pen containing the active Albiglutide drug using the alternate Healthcare Provider Instructions. All participants correctly dialed the pen to #2, and swirled the pen gently (without inverting or shaking) for the appropriate amount of time until no particles were present. Upon visual inspection by the test team, no participant had any particles or unmixed drug left in their pen at the conclusion of their trial. Participants swirled the pen for an average time of three minutes and eight seconds (3:08).

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/s/  
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YELENA L MASLOV  
02/19/2014



Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** January 27, 2014

**From:** LCDR Keith Marin, Acting Combination Products Team Leader, WO66, RM 2567  
General Hospital Devices Branch, DAGRID, ODE, CDRH

**To:** Raymond Chiang, Regulatory Health Project Manager, WO 22, RM 3361  
OMPT/CDER/OND/ODEII/DMEP

**Subject:** CDRH Consult, ICC1300526, BLA 125431, Albiglutide Injection (Eperzan)

**Consultants:** Felicia Binion-Williams, Biocompatibility, ODE/DAGRID/ICDB

#### 1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125431. The device constituent of this combination product consists of an pen injector designed to deliver Albiglutide injection.

The original consult request from CDER states, "Please review the proposed device/pen injector and associated human factors study results (this was requested in pre-BLA meeting and submitted with the BLA"

The initial review was completed by CAPT Lana Shiu (ODE/DAGRID/GHDB) on September 4, 2013 (GEN1300149) where she identified the following deficiencies that were sent to CDER to be presented to the sponsor:

1. You claim compliance to ISO 11608-1 for your injector but yet you have not provided any performance testing in your submission per the ISO requirements to include your testing protocol, sample size, acceptance criteria and test results in order to demonstrate your compliance. In the same vein, if you comply with ISO 13926-1/11608-3glass cartridge then please provide the appropriate test results per the requirements in those ISO standards.
2. In your patient labeling, you have cautioned the patients that if the injector is to be stored for more than 4 weeks then it should be in the refrigerator between 2-8 degrees Celsius but you did not specify exactly how long the injector could be refrigerated. Please specify the maximum amount of time your combination product can be stored in the refrigerator and provide the test protocol/data using the final finished combination product (drug cartridge filled into the injector) to demonstrate that the performance of the combination product is not negatively impacted by the prolonged refrigeration in that the device is able to deliver the accurate drug dose w/o medication errors, leakage, device malfunctions or patient injuries.



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3. In your patient labeling, please include a caution statement to warn the patient that if the injector is pulled out of the skin before counting to 5, this can lead to significant under-dosing of the medication.
4. In the patient labeling, there should be an explanation why the medication should not be vigorously shaken when mixing (which will lead to foaming) and why foaming could negatively impact the medication delivery.
5. Please also provide a description of the device packaging and provide test protocol/data for Rough Handling Test- Shock Test Auto-Injector. Please specify if there were glass breakage. If yes, is there a corrective action plan?
6. What is the specified shelf life of your drug-device combination product? Please provide dose accuracy data to demonstrate that your combination product can achieve the same dose accuracy at the end of its shelf life as it would at the beginning of its shelf life.
7. The cartridge, needle and the injector device are device constituents of the combination product and thus should be included in the biocompatibility consideration. Per ISO 10993-1, your device constituents would be categorized as Tissue Contacting of Limited Duration (<24 hr). Please provide summarized test results of the recommended tests:
  - a. Cytotoxicity
  - b. Sensitization
  - c. Irritation

8. **Device Description**

The dual chamber cartridge (DCC) is constructed from Type 1 glass and each chamber is closed with (b) (4) rubber stoppers and a (b) (4) closure disc. (b) (4)

(b) (4)

(b) (4)

**Table 1 Materials of Construction for Dual Chamber Cartridge**

Component (Primary Packaging Materials)	Supplier	Material of Construction	Quality / Standard
(b) (4)	(b) (4)	(b) (4)	EP 3.2, USP <660>, JP 7.01
Middle stopper	(b) (4)	(b) (4)	EP 3.2.9, USP <381>
End stopper	(b) (4)	(b) (4)	EP 3.2.9, USP <381>
Assembled closure part	(b) (4)	(b) (4)	NA
Snap on cap	(b) (4)	(b) (4)	NA
Closure disc	(b) (4)	(b) (4)	EP 3.2.9, USP <381>

The following pen injector components are supplied to (b) (4)

1. Pen mechanics sub-assembly comprised of a plunger rod (b) (4)
2. Cartridge holder.

The (b) (4) components are manufactured by (b) (4). The cartridge holder is (b) (4). The (b) (4) and plunger rod are (b) (4)

(b) (4)

**Table 5 Materials of Construction for Pen Injector Components**

Component	Material	Typical Supplier and Grade
Cartridge Holder	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Plunger Rod	(b) (4)	(b) (4)

Item	Characteristic	Dimensions (Nominal in [mm])
(b) (4)		

The critical functional dimension is the (b) (4)

The pen injector has been designed to be (b) (4)

Manufacturing and controls information regarding the pen needles is provided in (b) (4)

To support usage of Albiglutide for injection patient will be supplied with a pen needle, (b) (4) pen needle.

#### **9. Documents Reviewed**

m1.11.1. Quality Information Amendment\_Filing Communication Dated September 6th 2013  
Summary Report and Biological Assessment of the (b) (4)  
P.2.4. Pharmaceutical Development\_Container Closure System Development

#### **10. CDRH Review and Comments**

The following deficiencies that were sent to CDER on September 4, 2013 by CAPT Lana Shiu as an IR response:

1. You claim compliance to ISO 11608-1 for your injector but yet you have not provided any performance testing in your submission per the ISO requirements to include your testing protocol, sample size, acceptance criteria and test results in order to demonstrate your compliance. In the same vein, if you comply with ISO 13926-1/11608-3glass cartridge then please provide the appropriate test results per the requirements in those ISO standards.

*Response: Summary of results from the testing to demonstrate compliance to ISO 11608-1 is available in Table 33 of P.2.4. Pharmaceutical Development – Container Closure System Development.*

Reference	Requirement	Pen Injector Feature	Conformance with Requirement	Justification for Non-conformance or Deviation from ISO 11608-1
ISO 11608-1 Chapter 5	<b>General Requirements</b>			
ISO 11608-1:2000 Chapter 5	When the pen-injector is ready for injection, the cartridge holder shall allow visibility of the deliverable volume.	Visibility of the drug is given by the clear viewing window of the cartridge holder	Yes	N/A
ISO 11608-1:2000 Chapter 5	The pen-injector shall be designed such that it is able to deliver the labelled volume from the cartridge for which it is designed.	Ability of the pen injector to deliver the labelled volume (= set dose)	Yes	N/A
ISO 11608-1:2000 Chapter 5	The pen-injector shall indicate the pre-set dose.	Indication of the pre-set dose = single fixed dose of the pen injector	N/A	Pen injector is labelled with the dose volume.
Reference	Requirement	Pen Injector Feature	Conformance with Requirement	Justification for Non-conformance or Deviation from ISO 11608-1
ISO 11608-1:2000 Chapter 5	The pen injector shall indicate, at least by visual means, that it is ready for injection.  There shall be an indication of the pre-setting procedure by tactile or audible means, or both.	Visual indication of the readiness for injection = locked position number in the state window in combination with the pushed out injection button  indication of the pre-setting procedure  = audible "clicks" indicate the completion of the mixing- and priming-steps	Yes	N/A
ISO 11608-1:2000 Chapter 5	The state of the pen-injector, when ready to deliver a dose, shall be different to its state when the dose has been delivered. The difference shall be visible.	Visible difference = the injection button is pushed out versus pushed in and locked	Yes	N/A
ISO 11608-1:2000 Chapter 5	The pen-injector shall be so designed that it does not allow a larger dose to be pre-set than is left in the cartridge.	The pen injector does not allow a larger dose to be set. It is designed as a single fixed dose.	N/A	Since this is a single fixed dose injection-pen, the corresponding test is not applicable.
ISO 11608-1:2000 Chapter 5	The pen-injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed.	Indication = injection button is pushed in and locked, audible "click"	Yes	N/A
ISO 11608-1:2000 Chapter 5	The pen-injector shall be designed to function with the needle fulfilling the specifications of ISO 11608-2.	The pen injector is designed to function with the pen needles according to standard ISO 11608-2.	Yes	N/A
ISO 11608-1 Chapters 9 + 10	<b>Determination of dose accuracy</b>			



Reference	Requirement	Pen Injector Feature	Conformance with Requirement	Justification for Non-conformance or Deviation from ISO 11608-1
ISO 11608-1:2000 Chapter 9.2.4	The requirements from Chapter 9.2.1 and Chapter 12 have to be proven after preconditioning according to Chapter 7.1. Preconditioning in dry heat atmosphere <ul style="list-style-type: none"> <li>- storage temperature: (70 +/- 2) °C;</li> <li>- storage relative humidity: (50 +/- 10) % RH;</li> <li>- storage time: minimum 96 h</li> <li>- tests are to be done in Standard atmosphere</li> </ul> Sample size - 60	There is no pen injector feature to control this requirement.  Has to be performed according to the standard	Yes	Performed with 30 mg and 50 mg doses using a 31G/8mm thin walled pen needle;  Deviations from standard: <ul style="list-style-type: none"> <li>- So injection time plus So holding time are applied</li> <li>- The preconditioning atmosphere is amended to 27 ± 3°C based on the maximum storage temperature of 30°C.</li> </ul>
ISO 11608-1:2000 Chapter 9.2.5	The requirements from Chapter 9.2.1 and Chapter 12 have to be proven after preconditioning according to Chapter 7.2. Preconditioning in cold storage atmosphere <ul style="list-style-type: none"> <li>- storage temperature: (-40 +/- 3) °C;</li> <li>- storage time: minimum 96 h</li> <li>- tests are to be done in Standard atmosphere</li> </ul> Sample size - 60	There is no pen injector feature to control this requirement.  Has to be performed according to the standard	Yes	Performed with 30mg and 50mg doses using a 31G/8mm thin walled pen needle;  Deviations from standard: <ul style="list-style-type: none"> <li>- So injection time plus So holding time are applied</li> <li>- The preconditioning atmosphere is amended to -2°C based on the minimum storage temperature of 5 ± 3°C.</li> </ul>

Reference	Requirement	Pen Injector Feature	Conformance with Requirement	Justification for Non-conformance or Deviation from ISO 11608-1
ISO 11608-1:2000 Chapter 10.3	The requirements from Chapter 9.2.1, Chapter 12 and Chapter 13 have to be proven after preconditioning according to Chapter 7.4. Preconditioning by free fall Pen-injectors with non-replaceable cartridges 1) Caplet the air; 2) Take off the needle and put on the cap; 3) Drop the pen-injectors by free fall from a height of 1 000 mm onto the test surface (see 8.3) in accordance with i), ii) and iii), as follows: i) Horizontal ii) Vertical A iii) Vertical B (180° from orientation i)) - tests are to be done in Standard atmosphere Sample size - 60	Is to be performed according to the standard in Position '0'.	Yes	Performed with 30 mg and 50 mg doses using a 31G/8mm thin walled pen needle;  Deviation from standard: <ul style="list-style-type: none"> <li>- So injection time plus So holding time are applied</li> </ul>
ISO 11608-1 Chapter 9#10	Inspection			
ISO 11608-1:2000 Chapter 9.2.4	None of the pen-injectors shall have visible defects after removal from the hot storage atmosphere when inspected in accordance with clause 12.	Visual assessment of the pen injector	Yes	NA
ISO 11608-1:2000 Chapter 9.2.5	None of the pen-injectors shall have visible defects after removal from the cold storage atmosphere when inspected in accordance with clause 12.	Visual assessment of the pen injector	Yes	NA

Reference	Requirement	Pen Injector Feature	Conformance with Requirement	Justification for Non-conformance or Deviation from ISO 11608-1
ISO 11608-1:2000 Chapter 10.3	None of the pen-injectors shall have visible defects after the free fall when inspected in accordance with clause 12.	Visual assessment of the pen injector	Yes	NA

The [REDACTED] (b) (4). The [REDACTED] (b) (4) are not designed according to ISO 11608-3 (Pen-injectors for medical use – Finished cartridges) and ISO 13926 (Pen systems) for Insulin cartridges/pens.

**The sponsor has provided a summary of the testing they have conducted based on ISO 11608-1. Based on the summary of testing, all testing conducted according to the standard passed. However, as mentioned in the original deficiency, the protocol, sample size, acceptance criteria and test results were not provided in order to demonstrate their compliance. The sponsor references table 33 of P.2.4 which is the same summary that was originally provided and reviewed. Additionally, they stated that they do not design their cartridges to ISO 11608-3 and ISO 13926 but have not provided complete test reports for the cartridges.**

**As a result, this response is not acceptable.**

2. In your patient labeling, you have cautioned the patients that if the injector is to be stored for more than 4 weeks then it should be in the refrigerator between 2-8 degrees Celsius but you did not specify exactly how long the injector could be refrigerated. Please specify the maximum amount of time your combination product can be stored in the refrigerator and provide the test protocol/data using the final finished combination product (drug cartridge filled into the injector) to demonstrate that the performance of the combination product is not negatively impacted by the prolonged refrigeration in that the device is able to deliver the accurate drug dose w/o medication errors, leakage, device malfunctions or patient injuries.

*Response: The sponsor has stated that the BLA contains 12 month supporting stability data. Eighteen month data can be provided upon request. Data submitted demonstrates that albiglutide for injection, 30 mg/DCC and 50 mg/DCC, made from the commercial process, retains its critical physical, chemical and biological quality attributes when stored at 2-8°C for up to 12 months. Stability data, for the 30 mg and 50 mg commercial image assembled pen injector, demonstrate that pen functionality is retained when stored at the recommended storage condition of 2-8°C for up to 12 months.*

*Additionally, the sponsor has proposed to revise their IFU changing it to the following: You may store your pens, in the box, at room temperature not to exceed 86°F (30°C) for up to 4 weeks prior to use.*

- (b) (4)  
*Product may be stored refrigerated until the expiration date. DO NOT FREEZE. If the liquid in the pen is frozen, discard the pen and use another pen.*
- *Keep (b) (4) out of the reach of children.*

**The sponsor has updated their instructions for use by stating that if the device can be store up to 4 weeks prior to use and that it can be stored up until its expiration date. In addition, the sponsor has specified that testing in P.8.3 supports that the device is not negatively impacted by prolonged refrigeration. Specifically, Tables 55-104 have summaries of the stability data demonstrating the volume delivered for 30mg of Albiglutide and 50mg of Albiglutide at different storage conditions. However, the sponsor has not provided complete tests reports to illustrate whether this testing was done according to the standard ISO 11608-1. The protocol, sample size, acceptance criteria and test results all need to be provided to us for review.**

**As a result, this response is not acceptable.**

3. In your patient labeling, please include a caution statement to warn the patient that if the injector is pulled out of the skin before counting to 5, this can lead to significant under-dosing of the medication.

*Response: In the sponsor's response, they have indicated that they propose to revise IFU text as follows: Under Step C, under the header 'Inject the Medicine', within the*

*graphic demonstrating injection of albiglutide, the caution text will be revised from ‘Inject slowly and steadily’ to ‘Inject slowly and steadily. After the ‘click’, count to 5 to deliver the full dose’.*

***The sponsor has made modifications to their labeling. The response is acceptable.***

4. In the patient labeling, there should be an explanation why the medication should not be vigorously shaken when mixing (which will leading to foaming) and why foaming could negatively impact the medication delivery.

*Response: The sponsor has proposed to revise IFU text under Step A, under the header ‘Twist Pen to Mix Your Medicine’, the 3rd bullet from: “*

*\_\_\_\_\_ (b) (4) to “Slowly and gently rock the pen to the side 5 times to mix the drug (like a windshield wiper). DO NOT shake the pen hard to avoid foaming which may affect your dose.”*

*Under Step B, under the header “Inspect Your Dissolved Medicine”, the 1st bullet will be revised from \_\_\_\_\_ (b) (4)*

*\_\_\_\_\_ to “Again, slowly and gently rock the pen to the side 5 times to re-mix the drug (like a windshield wiper). DO NOT shake the pen hard to avoid foaming which may affect your dose.”*

***The sponsor has made modifications to their labeling. The response is acceptable.***

5. Please also provide a description of the device packaging and provide test protocol/data for Rough Handling Test- Shock Test Auto-Injector. Please specify if there were glass breakage. If yes, is there a corrective action plan?

*Response: The Albiglutide device is available in two pack presentations (either a 4 pen pack or a single pen pack). The carton and tray are produced on a \_\_\_\_\_ (b) (4)*

*The carton is \_\_\_\_\_ (b) (4)*

*Shipping qualification was based on USP 1079 Good Storage and Shipping Practices and using ASTM D-4169-09 guidance, which consists of tests intended to simulate the physical hazards of shipping. All pack presentations on all strengths were tested.*

*The following tests were completed by \_\_\_\_\_ (b) (4)*

*\_\_\_\_\_ (b) (4)*

*The protocol identified the following defects:  
Broken or Damaged Pens (including glass) – 0 acceptable*

*Needle tabs removed from outer needle cap – 0 acceptable  
Number 1 not in viewing window on pen body – 0 acceptable  
Damage to cartons – Defects will be considered cosmetic*

***The sponsor has stated that they followed ISO 11608-1 to demonstrate compliance. Additionally, they have provided summary data for the packaging testing completed and have confirmed that there was no glass breakage in the rough handling testing. However, the sponsor has not provided complete test reports to evaluate the Rough Handling Test- Shock Testing for their device. Complete test reports (protocol, acceptance criteria, results, and conclusion) are needed to evaluate the testing that has been submitted.***

***The response is not acceptable.***

6. What is the specified shelf life of your drug-device combination product? Please provide dose accuracy data to demonstrate that your combination product can achieve the same dose accuracy at the end of its shelf life as it would at the beginning of its shelf life.

*Response: The sponsor has stated that the proposed shelf life for Abiglutide for Injection, 30 mg and 50 mg, is 12 months stored 2-8°C with up to 4 weeks at ≤30°C and provided. The sponsor has stated that the results of the dose accuracy data at the end of the shelf life can be found in table 85, 86, 90, 91, 93, 95, 96, 100, 101, 103, and 104 of P.8.3.*

***The sponsor has specified that testing in P.8.3 tables 55-104 have summaries of the stability data demonstrating the volume delivered for 30mg of Abiglutide and 50mg of Abiglutide at different time points up until the stated shelf life of 12 months. However, the sponsor has not provided complete tests reports to illustrate whether this testing was done according to the standard ISO 11608-1. The protocol, sample size, acceptance criteria and test results all need to be provided to us for review.***

***As a result, the sponsor's response is not acceptable.***

7. The cartridge, needle and the injector device are device constituents of the combination product and thus should be included in the biocompatibility consideration. Per ISO 10993-1, your device constituents would be categorized as Tissue Contacting of Limited Duration (b) (4). Please provide summarized test results of the recommended tests:
- Cytotoxicity
  - Sensitization
  - Irritation

*Response: The biocompatibility consideration for the pen injector was undertaken by (b) (4) the design authority for the pen injector. Following a risk assessment, the Abiglutide pen injector was classified as Tissue Contacting of Prolonged Duration (b) (4) which differed from the classification stated in the question, Tissue Contacting of Limited Duration (b) (4). This prolonged exposure is based upon a cumulative assessment of patient handling devices over an extended period due to the nature of type 2 diabetes.*

***The sponsor has provided biocompatibility testing for cytotoxicity, sensitization, and irritation testing for our review. The material was consulted out to Dr. Felicia Binion-Williams for review. Based on her comments, the response is not acceptable. The sponsor provided a summary report for the cytotoxicity data. No data was received for the sensitization test and intracutaneous or irritation test. In***

**addition, we need pyrogen testing and material safety data sheets. Revised sections were provided and not a complete statement. This information is needed to assess safety. As a result, the sponsor's response is not acceptable.**

On October 21, 2013, CDRH/ODE provided deficiencies to CDER that were asked of the BLA sponsor:

1. You claim compliance to ISO 11608-1 for your injector but yet you have not provided complete testing reports for your testing. A complete performance testing report in your submission per the ISO requirements includes your testing protocol, sample size, acceptance criteria test results, and conclusion in order to demonstrate your compliance. In addition, you have stated that the (b) (4) and it is not designed according to ISO 11608-3 and ISO 13926. However, you have not provided complete test reports to demonstrate the cartridge can fit properly in the injector, risk of cartridge cracking, seal integrity, etc.

**Response:** (b) (4)

(b) (4)  
A Performance Testing Summary Report has been produced to support the review. A copy of this report is in Attachment 1. The data supports compliance of the albiglutide pen injector to ISO 11608-1. GSK were responsible for the design validation of the albiglutide pen injector. The report is in the GSK Albiglutide Pen Injector: Human Factors Validation-Usability Test Report in 3.2.R. Container closure integrity testing (CCIT) was performed on several batches during the development phase of the pen assembly process and the associated qualification of the automated assembly equipment. All samples passed the CCIT testing.

**CDRH Response:** The sponsor has stated that that (b) (4)

(b) (4)  
A Performance Testing Summary Report has been produced to support the review. In the place of this testing, you have provide a summary of the testing which is not acceptable as it does not have enough information to evaluate the safety of the device. As a result, we need the sponsor to provide the complete performance test reports (protocol, acceptance criteria, results, and conclusion) **in English** so the Agency can evaluate the testing. **The response is not acceptable.**

2. You have specified that testing in P.8.3 supports your assertion that the device is not negatively impacted by different storage conditions. Specifically, Tables 55-104 have summaries of the stability data demonstrating the volume delivered for 30mg of Albiglutide and 50mg of Albiglutide at a variety of storage conditions. However, you have not provided complete tests reports to illustrate whether this testing was done according to the standard ISO 11608-1. A complete performance testing report in your submission per the ISO requirements includes your testing protocol, sample size, acceptance criteria test results, and conclusion in order to demonstrate your compliance. Please provide a complete testing report to demonstrate that your device functions adequately in different storage conditions.

**Response:** The injector was designed and verified in accordance with ISO 11608-1, as described in Response 1. Stability programs have been undertaken in accordance with protocols that specify samples sizes and acceptance criteria. A copy of the stability protocol provided in Attachment 4. The protocol references (b) (4) These are the albiglutide pen injector, there are project names, for internal purposes only, and maybe used in development documentation. (b) (4) is the albiglutide pen injector used in the clinical program and (b) (4) is the commercial albiglutide pen injector. The stability data presented in P.8.3. Stability Data is undertaken in accordance with the International

*Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Data has been reviewed and confirms that the albiglutide pen injector successfully functions following storage under different conditions. The stability summary and conclusions are presented in P.8.1. Stability Summary.*

**CDRH Response:** *The sponsor has provided complete stability testing data. Based on the testing provided, the pen injector functions appropriately. I do not have any additional questions or concerns related to the function of the device in different storage conditions. The response is acceptable.*

3. You have provided summary data for the packaging testing completed and have confirmed that there was no glass breakage in the rough handling testing. However, you have not provided complete test reports to evaluate the Rough Handling Test- Shock Testing for their device. A complete performance testing report in your submission per the ISO requirements includes your testing protocol, sample size, acceptance criteria test results, and conclusion in order to demonstrate your compliance to the standard. Please provide a complete testing report to demonstrate that your device functions adequately after the rough handling/shock testing.

*Response: The Albiglutide 30 mg and 50 mg shipping cases for both the commercial packs (4 pen injectors) and single (1 pen injector) sample and replacement packs were tested to evaluate the Rough Handling-Shock. The test protocol is based on USP 1079 Good Storage and Shipping Practices and uses ASTM D-4169-09 Standard Practice for Performance Testing of Shipping Containers and Systems. GSK uses ASTM D-4169-09 as it tests the shipping case ability to protect the product. The Albiglutide 30 mg and 50 mg protocol includes; the sampling plan, ASTM tests, container closure testing, and final product testing, and acceptance criteria for these tests. Summary of the results is presented in P.3.5. Process Validation and/or Evaluation, Section 4 Shipping Validation.*

**CDRH Response:** *The sponsor has provided a complete testing plan for the rough handling and shock testing of their device. The sponsor has stated that the testing follows USP 1079 and uses ASTM D-4169 standards to test the shipping case ability to protect the device. Review of the testing indicates that results meet acceptance criteria. The response is acceptable.*

On November 1, 2013, CDRH/ODE provided biocompatibility deficiencies to CDER that were asked of the BLA sponsor:

1. In ICC1300526, a summary of the cytotoxicity data was provided. However, the data for the sensitization and intracutaneous or irritation studies were not provided. We need full test studies and protocols for the cytotoxicity, sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO-10993-5 Cytotoxicity, ISO 10993-10 Irritation or intracutaneous and Sensitization.

*Response: For the primary pack and drug product, through a risk assessment and experimental studies, GSK has been able to establish that the risk of patient exposure to (b) (4) from albiglutide drug product and its associated manufacturing process are low, and that the levels of (b) (4) dosed pose no risk to patients. This is presented in P.2.4. Pharmaceutical Development – Container Closure System Development. The pen injector has been designed to be used in conjunction with pen needles, as defined by ISO 11608-2:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 2: Needles. Biocompatibility consideration information regarding the pen needles is provided in (b) (4)*

The biocompatibility consideration for the pen injector was undertaken by (b) (4) the design authority for the pen injector. Following a risk assessment, the Albiglutide pen injector was classified as Tissue Contacting of Prolonged Duration (24 hrs – 30 days), which differed from the classification stated in the question, Tissue Contacting of Limited Duration (<24 hr). This prolonged exposure is based upon a cumulative assessment of patient handling devices over an extended period due to the nature of type 2 diabetes.

The report concluded that the likelihood of a toxic effect from the pen injector is negligible. Based on the testing results and literature research, the pen injector is considered to have met the requirements of ISO 10993-1:2009 and ISO 14971:2007 for a device with prolonged contact duration (24 hours to 30 days) and can be considered safe and suitable for use as directed. The full report for this is provided as Attachment 1 of this response.

**CDRH Response:** The firm asserts that the risk assessment is sufficient to replace the biocompatibility testing. The risk assessment contained a narrative for the cytotoxicity study that was performed. No data was provided for the irritation and sensitization. The risk assessment cannot be used to assess the irritation and sensitization data. **The response is not adequate.**

2. Pyrogen testing should be completed because the device will have short contact with blood. Please submit a complete report for bacterial endotoxin estimation expressed in endotoxin units per milliliter, i.e., EU/mL, according to Limulus Amoebocytes Lysates (LAL) test for endotoxins per ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing.

**CDRH Response:** The needle that is being used by the sponsor is a cleared needle. No additional pyrogenicity testing will be needed for the needle that is in contact with the patient. **The response is adequate.**

3. During the review, we were unable to find the Material Safety Data Sheets for the materials listed in the tables under the Device Description. Provide additional information regarding the materials used to manufacture the device.

**Response:** No MSDS form were provided.

**CDRH Response:** We requested the material safety data sheets during the initial round of review. This information was not submitted. **The response is not adequate.**

On December 12, 2013, CDRH/ODE provided a performance deficiency to CDER that was asked of the BLA sponsor:

1. In our previous IR on October 21, 2013 we asked you for complete testing reports for the testing that you have conducted. However, you have stated that (b) (4)

(b) (4)

A Performance Testing Summary Report has been produced to support the review. In the place of this testing, you have provide a summary of the testing which is not acceptable as it does not have enough information to evaluate the safety of the device. As a result, please provide the complete performance test reports (protocol, acceptance criteria, results, and conclusion) **in English** so the Agency can evaluate your testing. Please provide this information by Wednesday COB December 18, 2013.

**Response:** "As promised, we provided the translated files for the complete test reports. We am providing one email with the 30 mg and a separate email with the 50

*mg translations. Since appendices 3-11 have few words these appendices were not translated but rather a translation guide is provided separately. I believe the translation firm took this approach because of the tight deadline and the Christmas holiday. We also have a certification of the translation from the translation firm and the original German reports. Please let me know if the reviewer would also like to receive these documents as well. During the translation a transcription error was discovered in the summary report submitted 22Nov2013 (sequence 0041) In section 1.3.3, Table 6: the humidity was indicated as  $75 \pm 10 \%RH$  but should have been  $50 \pm 10 \%RH$ . This correction has been made and will be submitted to replace the document previously submitted."*

**CDRH Response:** *The sponsor has provided a complete test report that has been translated in English so I can confirm that the dose accuracy testing met the acceptance criteria. Based on my evaluation of the testing, the sponsor has demonstrated that the device can deliver doses that meet the standard. Additionally, the the deviations in the pen injector testing in relation to testing temperatures is adequate based on the recommended drug storage temperatures. As a result, I have no further question related to device performance. **The response is adequate.***

On December 19, 2013, CDRH/ODE provided biocompatibility deficiencies to CDER that was asked of the BLA sponsor:

1. In BLA 125431, you have provided a risk assessment for the device. The risk assessment addressed the cytotoxicity test. We have no further questions regarding the cytotoxicity data. However, we requested the data for the sensitization and intracutaneous or irritation studies and this was not provided. We need full test studies and protocols for the sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO 10993-10 Irritation or intracutaneous and Sensitization.

*Response: On January 22, 2014, the sponsor updated their BLA and provide LOA for drug master files and device master files that contained the requested biocompatibility testing.*

**CDRH Response:** The sensitization study was found in MAF 0091 and the information was reviewed. Cytotoxicity and implantation testing was previously provided. Since implantation testing was shown to be normal, intracutaneous testing would not be necessary. As a result, we do not have any further questions regarding the proposed use of the surface device. **The response is adequate.**

2. During the initial review we requested the Material Safety Data Sheets. However, this information was not provided. You have stated that the materials identified within their table are in accordance with Title 21 Code of Federal Regulations, 21 CFR 177. Please provide the material safety data sheets for the materials listed in the tables under the Device Description. This information is needed to assess the safety of your device.

*Response: MSDS forms were provided in eCTD sequence 42 in attachment 8-10.*

**CDRH Response:** The sponsor provided the requested MSDS forms. We do not have any further questions. **The response is adequate.**

**8. CDRH Recommendation:**

**The sponsor has addressed both performance and biocompatibility concerns.  
CDRH/ODE does not have any additional questions.**

If you have any further questions, please contact LCDR Keith Marin at 301-796-2462.

<b>Digital Signature Concurrence Table</b>	
Reviewer Sign-Off	
Branch Chief Sign-Off	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAYMOND S CHIANG

01/29/2014

DMEP RPM checking in CDRH review for CDRH reviewer Keith Marin for BLA 125431

**MEMORANDUM**

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

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DATE: December 04, 2013

TO: Jean-Marc Guettier, M.D.  
Acting Director,  
Division of Metabolic and Endocrine Products  
Office of New Drugs

FROM: Ruben C. Ayala, Pharm.D.  
Pharmacologist  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

Xingfang Li, M.D., RAC  
Consumer Safety Officer  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

Michael F. Skelly, Ph.D.  
Pharmacologist  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director,  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: EIR covering BLA 125-431, Albiglutide, sponsored by  
GlaxoSmithKline (GSK), LLC

At the request of the Division of Metabolic and Endocrine Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the analytical portion of the following pharmacokinetic study:

**Study #:** GLP114856  
**Study Title:** "A Multi-Dose Study in Subjects with Type-2  
Diabetes Mellitus to Assess the Pharmacokinetics  
and Pharmacodynamics of Albiglutide:  
Bioequivalence Phase"

FDA investigators Marcelo Mangalindan (ORA), Ruben C. Ayala (OSI), Xingfang Li (OSI), and Michael F. Skelly (OSI) audited study records at the following bioanalytical site from August 19-21, 2013:

**Bioanalytical Site:** GlaxoSmithKline, LLC  
King of Prussia, PA

The audit included thorough reviews of study records, examination of facilities and equipment, and interviews and discussions with GSK's management and staff.

During the audit, FDA investigators observed the following two conditions, but did not issue Form FDA-483. The findings and DBGLPC's evaluations are discussed below.

**Inspectional findings:**

**1. GSK analysts engaged in analytical misconduct with four sample runs involving study GLP114856.**

Specifically, runs 24, 64, 67, and 90 failed the established acceptance criteria on the first chemiluminescence reading. The GSK analyst, with the approval of the team leader, re-read the plates until the runs passed the acceptance criteria. The study report and BE statistical analysis submitted to the Agency included data from these four runs.

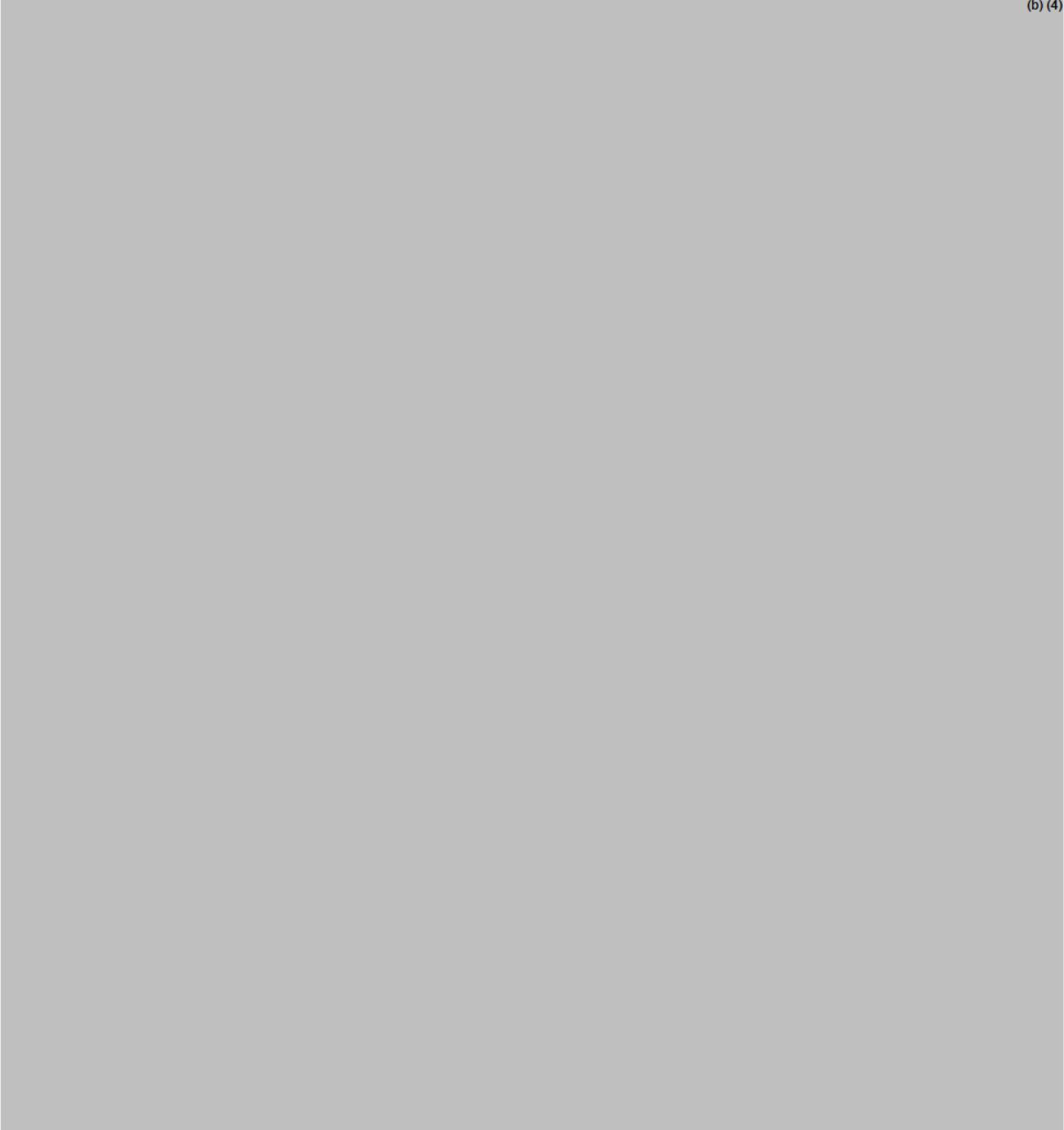
GSK discovered the analytical misconduct during a mock inspection of study records in May 2013. Shortly after the finding, GSK temporarily suspended the analyst, while the team leader retired. FDA investigators voiced concern about any other analytical work done by the two analysts. GSK provided a list of other albiglutide studies in which they participated (Attachment 1). According to GSK's investigation, these studies are clear of analytical misconduct involving run acceptance and rejection.

GSK voluntarily agreed to submit an updated study report and bioanalytical report that exclude data generated from the four analytical runs aforementioned.

GSK's analytical misconduct affects the results of study GLP114856. However, GSK voluntarily agreed to exclude the four analytical runs from the statistical analysis, and re-submit an updated study report to the Agency.

**2. GSK analysts modified acceptance/rejection criteria  
for Run 59, in order to make the run pass.**

(b) (4)



subjects: 1200856016, 1200856018, 1200856019, 1200856021,  
1222856006, and 1252856001.

**Conclusions:**

Following the above inspection, we recommend that the data for the analytical portions of study GLP114856 are acceptable for further Agency review. However, we suggest the following provisions:

1. GSK should submit an updated study report and bioanalytical report excluding results from runs 24, 64, 67, and 90. The updated study report should indicate the number of subjects excluded from the statistical bioequivalence analysis, and the reason for excluding them from the analysis.
2. GSK should exclude the original results for run 59, and replace them with the ISR reassay results. The original results are invalid because the process 2 mid-QCs failed the acceptance criteria.
3. GSK should exclude the reassay results for Run 59 samples from the ISR evaluation for the study.

Ruben C. Ayala, Pharm.D.  
Pharmacologist

Xingfang Li, M.D., RAC  
Consumer Safety Officer

Michael F. Skelly, Ph.D.  
Pharmacologist

**Final Classification:**

**VAI: GlaxoSmithKline, King of Prussia, PA**  
**FEI: 1000522100**

Note: The initial inspection classification was NAI because FDA inspectors did not issue a Form FDA-483 to GSK. However, Headquarters later changed the classification to VAI because GSK voluntarily agreed to submit an updated study report to the BLA.

**Attachments:**

1. GSK's list of albiglutide studies cleared of analytical misconduct

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Li/Ayala/Dejernett

OSI/DBGLPC/Choi/Bonapace/Mada

CDER/OTS/OCP/DCPII/Sahajwalla/Jain/Chiang

HFR-CE150/Campbell (DIB)

HFR-CE1515/Tammariello (BIMO)

HFR-CE3560/Mangalindan

Draft: RCA 11/6/2013; 12/04/2013

Edit: MFS 11/6/2013; XFL 11/7/2013; SRM 11/18/2013, WHT  
12/03/2013

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/ Inspections/BE

Program/Analytical Sites/GSK, King of Prussia, PA

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FACTS: 1512664

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RUBEN C AYALA  
12/04/2013

XINGFANG LI  
12/04/2013

MICHAEL F SKELLY  
12/04/2013

CHARLES R BONAPACE  
12/05/2013

WILLIAM H TAYLOR  
12/05/2013

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## HUMAN FACTOR, LABEL, AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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**Application Type and Number:** BLA 125431  
**Date of Submission:** March 7, 2013  
**Established Name and Strength:** (Albiglutide)  
For Injection  
30 mg and 50 mg single-dose pens  
**Product Type:** Single ingredient  
**Marketing Category:** Prescription  
**Applicant Name:** GlaxoSmithKline  
**OSE RCM #:** 2013-278 and 2013-620  
**Date of This Review:** October 24, 2013  
**Primary Reviewer:** Reasol Agustin, PharmD  
**Team Leader:** Yelena Maslov, PharmD

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### 1. REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested we evaluate the results of the Applicant's Human Factor Validation Study, as well as the proposed Prescribing Information, container label, carton labeling, and Instructions for Use (IFU) to ensure the intended population is able to use the proposed product (Albiglutide) safely.

### 2. CONCLUSION

The results of the Usability Study did not validate the safe and effective use of the pen containing the 50 mg dose because three participants failed to wait 30 minutes for the medication to dissolve. Failure to wait for the product to dissolve can result in delivery of an underdose. The wait time for the 50 mg dose should be the same as the 30 mg strength, or the wait time statement/diagram should be added to the container labels and carton labeling, and retested to validate users will wait for the product to dissolve before administering.

### 3. RECOMMENDATIONS

Based on our evaluation, we recommend the following revisions be implemented prior to approval of this product:

#### 3.1 Wait Time

- Revise the wait time for dissolving the medication to 30 minutes for both strengths (30 mg and 50 mg). Currently, the wait time is 15 minutes for the 30 mg strength and 30 minutes for the 50 mg strength. The Usability Study results demonstrated that three participants failed to wait 30 minutes because they assumed that the wait time for the 50 mg is the same as the 30 mg strength. Failure to wait 30 minutes for the 50 mg dose to dissolve can result in delivery of an underdose due to either low concentration dose volume or needle clogging. If this change is feasible, revise the Prescribing Information, IFU and carton labeling accordingly.
- If it is not feasible to revise the wait time to 30 minutes for both strengths, then add the wait time statement or diagram to the 30 mg and 50 mg container labels and carton labeling, and retest the wait time scenario with at least 15 patients and 15 HCPs to validate that users will wait for the product to dissolve before administering. Revising the labels and labeling may serve as an additional prompt for users who may not read the IFU or pay attention to the carton labeling - similar to the participants in the Usability Study who either skimmed or did not read the IFU for the 50 mg strength and assumed the wait time was the same as the 30 mg.

#### 3.2 Container Label

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.

#### 3.3 Carton Labeling

##### 3.3.1 Commercial Packaging

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other

printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.

- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Ensure that the image of the pen device accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.
- Remove the storage information on the primary display panel as this information is contained on the back panel. This will help reduce clutter and increase readability of other important information such as proprietary name, established name and strength.

### 3.3.2 Sample Packaging

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Relocate the statement “Sample- Not for Sale” to the primary display panel so that it is clear this package is not for commercial sale and it will differentiate it from the Replacement carton labeling.

### 3.3.3 Replacement

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.

- Use the same color scheme presentation used in the commercial carton labeling (i.e. strength presentation in color). As currently presented, the replacement carton is in (b) (4) making it difficult to differentiate between the two strengths.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Relocate the statement “Replacement Pen- Not for Sale” to the primary display panel so that it is well differentiated with the Sample carton labeling.

### 3.4 Instructions for Use (IFU)

- The IFU was revised to increase the prominence of the wait time (30 minutes) for the 50 mg dose. However, we did not receive results from another validation study that demonstrated this revision was effective. Therefore, we recommend retesting of the wait time scenario to ensure that the revisions to the IFU in addition to the container label changes are sufficient to mitigate or prevent the failure to correctly accomplish this critical task.

### 3.5 Prescribing Information (PI)

- Delete the section entitled “Alternate Method of Reconstitution (Healthcare Professional Use Only).” The information provided in this section conflicts with the information provided in the IFU and Human Factors Validation Test regarding wait times. Specifically, your (b) (4) on page 46 of the Human Factors Validation Test Report states that a user (b) (4)

(b) (4)

Additionally, you did not provide data to demonstrate the instructions for healthcare providers “Alternate Method of Reconstitution” are validated and that healthcare providers perform “appropriate swirling for one minute.”

If you have questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

## 4. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. Section 6 provides the methods and results for each material reviewed.

<b>Table 1. Materials considered for review of the Applicant’s Human Factors Validation Study, proposed Prescribing Information, container labels, and carton labeling</b>	
<b>Section</b>	<b>Material Reviewed</b>
6.1	Product Information/Prescribing Information
6.2	Human Factors/Usability Study
6.3	Container Label, Carton Labeling, and Instructions for Use

**5. OVERALL FINDINGS AND ASSESSMENT**

Although the Usability Study (see section 6.2) is acceptable in regards to attaching the needle and removing the inner needle cap, the study revealed wrong preparation technique errors (not waiting 30 minutes for the 50 mg to dissolve). We are concerned about the three failures that occurred with participants not waiting for 30 minutes for the medication to dissolve (b) (4)

These failures pose a risk of delivery of an underdose due to either low concentration dose volume or needle clogging. Although the Applicant stated that this risk has no immediate clinical impact, we disagree because this critical task can continue to occur each time a new device is initiated (i.e., once a week), resulting in an accumulation of underdose for a patient over the course of treatment. As a result, we do not find that the IFU or the carton labeling used in the study mitigated the wrong preparation technique error. Thus, we recommend that both doses have 30 minute wait time for the product dissolution or the IFU and labeling of the 50 mg dose is revised and re-tested in the same manner as in the provided study to validate the labeling changes.

We also acknowledge that the failures in Trial #1 occurred with the task of attaching the needle properly and removing the inner needle caps. We note that this failure is related to the needle and is not unique to this device. In fact, during our post-marketing surveillance we identified multiple medication errors involving incorrect attachment of the needle and not removing the inner needle cap. As a result, this failure does not affect the pen device itself. Furthermore, we acknowledge that these failures did not occur in Trial #2. Thus, the study is acceptable from that regard.

**6. METHODS AND RESULTS**

**6.1 Product Information**

The user must reconstitute Albiglutide before administering once weekly. Other GLP-1 receptor agonists such as Byetta (Exenatide) and Victoza (Liraglutide) do not require reconstitution, and Bydureon (Exenatide extended release) is available in a vial. Table 2 provides product information for Albiglutide.

<b>Table 2. Relevant Product Information for Albiglutide</b>	
<b>Active Ingredient</b>	Albiglutide
<b>Indication</b>	GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus
<b>Route of Administration</b>	Subcutaneous injection
<b>Dosage Form</b>	Powder for injection
<b>Strength</b>	30 mg/0.5 mL and 50 mg/0.5 mL after reconstitution
<b>Dose and Frequency</b>	30 mg once weekly, may increase to 50 mg once weekly
<b>How Supplied</b>	30 mg single-dose pen (carton of 1 and carton of 4) 50 mg single-dose pen (carton of 1 and carton of 4)
<b>Storage</b>	Refrigerate at 36°F to 46°F (2°C to 8°C)

## 6.2 Human Factors Validation Study

We reviewed the Human Factor validation study entitled, “GSK Albiglutide Pen Injector: Human Factors Validation-Usability Test Report,” dated December 5, 2012 that the Applicant submitted on March 7, 2013.

The Applicant originally submitted the Human Factors Validation Study Protocol on May 23, 2012 in IND 065177. In August 2012, we provided recommendations to the Human Factor Validation Study Protocol and Instructions for Use.<sup>1</sup> Subsequently, the Applicant submitted a revised protocol with the recommendations, and we provided final recommendations on October 24, 2012 via electronic mail.

### 6.2.1 Study Design

The study included two patient sessions and one HCP session:

<b>Patient Session Overview (2 Sessions)</b>		
<b>Session 1</b>	<b>Session 2 (Week 2)</b>	
<b>Injection #1</b>	<b>Injection #2</b>	<b>Injection #3</b>
Training/Supervised Injection: N=15 Self-Trained/Unaided Injection: N=30	Unaided Injection: N=45	Unaided Injection: N=45
<b>30 mg Dose</b>	<b>30 mg Dose</b>	<b>50 mg Dose</b>

HCP Session Overview (Single Session)	
Injection #1	Injection #2
Self-Trained/Unaided Injection: N=15	Unaided Injection: N=15
30 mg Dose	50 mg Dose

For the 30 mg pen, participants were tasked to perform the entire preparation and injection procedure and for the 50 mg dose, participants were tasked to demonstrate knowledge of the wait time while medication is dissolving during the initial set up process.

### 6.2.2 Study Results

#### 30 mg Pen

Of the 88 participants in the 30 mg trials, 97% of the participants (85/88) were successful in the preparation and administration tasks.

- **Trial 1**

Failures (n=3)	Close call (n=1)
<ol style="list-style-type: none"> <li>1. Failed to remove the inner needle cap</li> <li>2. Failed to fully twist the pen to 3 to prime the needle</li> <li>3. Failed to attach the needle correctly</li> </ol>	<ol style="list-style-type: none"> <li>1. Participant started her injection with the needle cap attached and realized that it was still attached and then removed the cap and performed the injection successfully</li> </ol>

- **Detailed Failures in Trial #1**

- P39 (Patient, Injection experienced, Untrained) failed to remove the needle cap resulting in no medication received. Patient removed the outer needle cap and injected the device into the pad. After 5 seconds, he realized that the inner cap was still on and noticed liquid on the surface of the pad.
- P43 (Patient, Injection experienced, Untrained) failed to fully twist the pen to 3 to prime the needle resulting no medication received. Patient proceeded with the injection but was unable to. Patient informed the moderator that she did not hear the click at the end, noting that this was something she was expecting. Patient further stated that in this situation, she would call her doctor. Patient successfully prepared and administered the full dose with the second pen.
- P52 (HCP, Injection experienced, Untrained) failed to attach the needle correctly resulting in no medication received. HCP was able to prime the needle but was unable to depress the plunger to administer the drug. HCP stated that she would

dispose of the needle and replace it with a new one and start over. HCP successfully prepared and administered the full dose with the second pen.

- During Trial #2 all participants were able to prepare, prime, and inject the medication from the pen correctly without any failures.

### **50 mg Pen**

Of the 58 participants in the 50 mg trial, 95% of the participants (55/58) was successful preparing the pen with 3 participants (2 patients and 1 HCP) failing to state the correct wait time.

- **Failures**
  - P28 (Patient, Injection naïve, Untrained) failed to identify the 30 minute wait time. The participant stated that he didn't read the IFU and assumed that the wait time is 15 minutes, similar to the 30 mg.
  - P60 (HCP, Injection experienced, Untrained) failed to identify the 30 minute wait time. HCP stated "I had read the 30 mg thoroughly and I made an assumption that it would be the same for the 50 mg."
  - P55 (HCP, Injection experienced, Untrained) failed to identify the 30 minute wait time. HCP was observed skimming through the instructions but did not spend very much time reading before preparing the dose.

### **6.3 Labels and Labeling Review**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarketing medication error data, we evaluated the following materials that the Applicant submitted on March 7, 2013:

- Albiglutide container labels (section 6.3.1)
- Albiglutide carton labeling (section 6.3.2)
- Albiglutide Instructions for Use (section 6.3.3)

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REASOL AGUSTIN  
10/24/2013

YELENA L MASLOV  
10/24/2013

CAROL A HOLQUIST  
10/24/2013



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**MEMORANDUM**

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: September 7, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Raymond Chiang, Regulator Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: BLA 125431  
Applicant: GSK  
Drug: Albiglutide  
Device: Peninjector  
Intended Use: to treat type 2 diabetes  
CTS Tracking: ICC1300081/CON134765

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Overview and Recommendation*

The Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a human factors consultative review of the human factors study report contained in BLA 125431 submitted by GSK. The device is peninjector that can be used to administer Albiglutide subcutaneously.

GSK performed a human factors validation study with 58 participants. Twenty participants were injection naïve patients with type 2 diabetes, and of these patients, 15 received representative training. Thirteen participants were injection experienced patients. Fifteen participants were healthcare professionals. The study included 13 participants (29% of patients) with neuropathy in their hands/arms and 27 participants (60% of patients) with retinopathy. In addition, 6 of the 45 patient participants (13%) were color-blind patients. The study results showed that for both 30 mg dose preparation and injections and the 50 mg drug preparation tasks, 11 different participants (3 different HCPs and 8 different patients) experienced 6 failures, 3 use errors, 1 unanticipated event, and 1 close call on the tasks for attaching the needle, priming the pen, removing inner and outer caps, waiting for 2 seconds after the click, and wait for 30 minutes for 50 mg pens. Subsequent to the study, GSK implemented three changes to the Instructions for Use to improve clarity of the steps associated with removal of inner and outer needle cap, and waiting for 30 minutes for 50mg pen.

The consultant finds that the human factors validation study results and GSK's explanation of the failures and errors acceptable. In addition, the consultant does not believe that the additional IFU changes require additional validation data to be submitted and reviewed.

### ***Summary of Human Factors Information***

GSK performed a human factors validation study with 58 participants. Twenty participants were injection naïve patients with type 2 diabetes, and of these patients, 15 received representative training. Thirteen participants were injection experienced patients. Fifteen participants were healthcare professionals. The study included 13 participants (29% of patients) with neuropathy in their hands/arms and 27 participants (60% of patients) with retinopathy. In addition, 6 of the 45 patient participants (13%) were color-blind patients.

The study tasks were identified based on use-related risks. These tasks include:

1. Knowledge of pen storage
2. Knowledge of dose frequency
3. Safe removal from packaging
4. Expire drug identification
5. Pen inspection
6. Identification of injection site
7. Twist pen to mix medicine
8. Rock pen
9. Wait time
10. Look for particles
11. Attach the needle
12. Prime needle
13. Remove inner and outer needle caps prior to injection
14. Insert needle
15. Inject full dose
16. Count after injecting full dose
17. Disposal of pen

The study results showed that for both 30 mg dose preparation and injections and the 50 mg drug preparation tasks, 11 different participants (3 different HCPs and 8 different patients) experienced 6 failures, 3 use errors, 1 unanticipated event, and 1 close call:

- Failure to correctly attach needle: 1 HCP attempted to attach needle and give injection but could not press down the injection button as the needle was not correctly attached. The root cause analysis indicated that the device prevented the participant from performing an injection with a miss-attached needle, thus preventing further errors or complications. Additionally, the participant knew that the device was not functioning properly and knew to discard it and start the procedure over with the new device.
- Failure to remove inner needle cap: 1 patient removed outer cap, but then started injection with inner cap still on. The participant realized their mistake, and performed the subsequent injection with no difficulty. A change in the IFU has been implemented to address this issue:

(b) (4)



### Figure 1: IFU Change to the Cap Removal Task

- Failure to fully turn to 3 to prime the needle: 1 Patient did not fully turn to number 3, then tried to inject even though injection button did not pop out. Patient was reported to be aware that she had not received her dose, stating that she did not hear a click at the end of the injection process. Patient noticed that there was still liquid inside. Subsequent injection was performed with no difficulty.
- Failures to wait for 30 minutes: 2 HCPs and 1 patient did not wait for 30 minutes for the 50 mg injection. A change in the IFU has been implemented to support user knowing how long the wait time for the 50mg injection.



Figure 2: IFU Change to the 30 Minute Wait Time Task

- Errors to wait less than 2 seconds after full dose administration: All three patients delivered a full dose. It was observed that one participant misinterpreted what they read when reading the instructions and counted to 5 upon depressing the plunger, rather than after hearing the click. Another participant counted up to 5 but did it at a faster rate and heard the click. The participant stated they thought the injection was complete when the plunger was all the way down. The participant received the click and lifted up rather than waiting to 5.
- Tried to remove air after priming (unanticipated event): 1 patient took off outer needle cap, primed to three and pressed syringe button down on table which resulted in some loss of drug. Patient knew that he did not receive all of his medication. It was determined that the amount of drug lost during this air removal was not significant enough to prevent the participant from receiving their full dose.
- Started injection with inner cap (close call): 1 patient started to depress plunger with inner cap on, realized mistake, removed cap and finished injection, knew she did not get full dose. A change in the IFU has been implemented.

## Appendix 1: Device Information

(b) (4)



Albiglutide is indicated for the treatment of type 2 diabetes and comes in 2 dose strengths pen injectors (30 mg and 50 mg) that are administered subcutaneously once a week. Initially patients start at a 30 mg dose and then over time may transition to the higher 50 mg dose if required. The only difference between the 30 mg and 50 mg pen was the wait time. For the 50 mg trial the protocol stated that the trial would end after the participant demonstrated knowledge of the wait time during the initial setup process.

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/s/  
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RAYMOND S CHIANG

09/23/2013

Uploaded into DARRTs on behalf of CDRH human factors reviewer Quynh Nhu Nguyen



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Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

CDRH Office of Device Evaluation Consult Review

BLA 125431/ GEN1300149

Date: September 4, 2013

To: Raymond Chiang (CDER/OND/DMEP)

From: Lana Shiu, M.D

Division: CDRH/ODE/DAGID/GHDB

Via: Richard Chapman, Branch Chief of GHDB

Keith Marin (Acting GHDB Combination Product Team Leader)

**Application Number:** BLA125431 / IND 65177

**Product Name:** Albiglutide Injection (Eperzan)

**Sponsor:** GSK (GlaxoSmithKline)

**Proposed Indication:**

(b) (4) is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1, 14)

**Important Limitations of Use:**

Not recommended as first-line therapy for patients inadequately controlled on diet and exercise,

(b) (4)  
(1)

Has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. (1)

Has not been studied in combination with prandial insulin. (1)

Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1)

**Material Reviewed by CDRH/ODE:**

1. Global Submit dated 1/14/2013 Section 3.2.P.7,
2. Drug labeling in section 1.14.1.2,
3. Patient labeling in section 1.14.1.3,
4. Albiglutide GSK716155 Phase III Clinical Study: Trend report of total pen injector customer complaints 7/9/2013

**RECOMMENDATION:** → Request for Additional Information

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**History:**

**Product Description**

The dual chamber cartridge (DCC) is constructed from Type 1 glass and each chamber is closed with (b) (4) rubber stoppers and a (b) (4) closure disc. (b) (4)



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(b) (4)

**Materials of Construction for Dual Chamber Cartridge**

Component (Primary Packaging Materials)	Supplier	Material of Construction	Quality / Standard
(b) (4)	(b) (4)	(b) (4)	EP 3.2, USP <660>, JP 7.01
Middle stopper	(b) (4)	(b) (4)	EP 3.2.9, USP <381>
End stopper	(b) (4)	(b) (4)	EP 3.2.9, USP <381>
Assembled closure part	(b) (4)	(b) (4)	NA
Snap on cap	(b) (4)	(b) (4)	NA
Closure disc	(b) (4)	(b) (4)	EP 3.2.9, USP <381>

The following pen injector components are supplied to (b) (4)

1. Pen mechanics sub-assembly comprised of a plunger rod (b) (4)
2. Cartridge holder.

The (b) (4) components are manufactured by (b) (4)



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(b) (4)

**Materials of Construction for Pen Injector Components**

Component	Material	Typical Supplier and Grade
Cartridge Holder		
 (b) (4)		
Plunger Rod		

(b) (4)



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Item	Characteristic	Dimensions (Nominal in [mm])
(b) (4)		

The critical functional dimension is the (b) (4) measurement (b) (4) Diagram in the submission showed the plunger rod (b) (4) that corresponds to the stroke length, which is monitored through Statistical Process Control (SPC) to ensure that the (b) (4)

The pen injector has been designed to be used in conjunction with pen needles as defined by ISO 11608-2:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 2: Needles.

Manufacturing and controls information regarding the pen needles is provided in (b) (4)

To support usage of Albiglutide for injection patient will be supplied with a pen needle, (b) (4) pen needle.

**CDRH/ODE Reviewer Comment:** (b) (4) was opened and compared with the information provided in this BLA regarding the injection needle. The needle dimension



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has not been modified since the clearance of the 510K and the needle device does comply with ISO 11608-2.

OPERATION OF THE AUTO-INJECTOR

Patient labeling was reviewed for the operation of the injector.

SPECIFICATIONS

No functional specs were listed in the submission reviewed.

Labeling -No product labeling was provided in the submission reviewed

Table with 2 columns: Required Elements, Provided. Rows include User Manual (for both types of devices), Labeling contains the prescribed statement from 21 CFR801.109, Device name/model/Specification, Description of the device, Intended Use/Indications for Use, Relevant contraindications, warnings, precautions, Device operating principles, functions, Instructions for use, If for Home use, a copy of patient instruction included, Cleaning instructions, Troubleshooting and explanations of all error messages.

Shelf Life - No Shelf life was mentioned in the PDF document received.

Biocompatibility -No information on biocompatibility in the submission reviewed by CDRH.

Performance Testing-Bench -No dose accuracy information and no performance testing per ISO 11608-1 requirements.

No performance testing on the glass cartridge ISO 13926/ISO 11608-3.

Albiglutide GSK716155 Phase III Clinical Study: Trend report of total pen injector customer complaints dated 7/9/2013 was reviewed. The sponsor's in-depth investigation and root cause analysis of the top 4 causes of device malfunction was well done and their subsequent corrective actions are congruent with the cause.

Performance Testing - Animal - No animal testing needed.



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**Performance Testing – Human Factors : Detailed Review of the simulated use testing will be addressed in a separate consult review memo by Quynh Nguyen of CDRH/ODE/DAGRID Human Factors Team.**

**Deficiencies**

1. You claim compliance to ISO 11608-1 for your injector but yet you have not provided any performance testing in your submission per the ISO requirements to include your testing protocol, sample size, acceptance criteria and test results in order to demonstrate your compliance. In the same vein, if you comply with ISO 13926-1/11608-3 glass cartridge then please provide the appropriate test results per the requirements in those ISO standards.
2. In your patient labeling, [REDACTED] (b) (4) [REDACTED] then it should be in the refrigerator between 2-8 degrees Celsius but you did not specify exactly how long the injector could be refrigerated. Please specify the maximum amount of time your combination product can be stored in the refrigerator and provide the test protocol/data using the final finished combination product (drug cartridge filled into the injector) to demonstrate that the performance of the combination product is not negatively impacted by the prolonged refrigeration in that the device is able to deliver the accurate drug dose w/o medication errors, leakage, device malfunctions or patient injuries.
3. In your patient labeling, please include a caution statement to warn the patient that if the injector is pulled out of the skin before counting to 5, this can lead to significant under-dosing of the medication.
4. In the patient labeling, there should be an explanation why the medication should not be vigorously shaken when mixing (which will lead to foaming) and why foaming could negatively impact the medication delivery.
5. Please also provide a description of the device packaging and provide test protocol/data for Rough Handling Test- Shock Test Auto-Injector. Please specify if there were glass breakage. If yes, is there a corrective action plan?
6. What is the specified shelf life of your drug-device combination product? Please provide dose accuracy data to demonstrate that your combination product can achieve the same dose accuracy at the end of its shelf life as it would at the beginning of its shelf life.
7. The cartridge, needle and the injector device are device constituents of the combination product and thus should be included in the biocompatibility consideration. Per ISO 10993-1, your device constituents would be categorized as Tissue Contacting of Limited Duration (<24 hr). Please provide summarized test results of the recommended tests:
  - Cytotoxicity
  - Sensitization
  - Irritation or Intracutaneous Reactivity



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Comments to CDER Project Manager: Please send consult to CDRH/Office of Compliance/General Hospital Device Branch (Branch Chief is Carl Fischer) for device manufacturing review and also their input into the device manufacturer's inspection if you have not already done so.**

**Recommendation –Request for Additional Information as outlined in the Deficiencies Section.**

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RAYMOND S CHIANG

09/20/2013

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

<b>BLA</b>	125431
<b>Generic Name</b>	Albiglutide
<b>Sponsor</b>	GlaxoSmithKline
<b>Indication</b>	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<b>Dosage Form</b>	Subcutaneous injection
<b>Drug Class</b>	GLP-1 agonist
<b>Therapeutic Dosing Regimen</b>	30 mg administered once weekly by subcutaneous injection with potential uptitration to 50 mg once weekly by subcutaneous injection
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not determined
<b>Submission Number and Date</b>	SDN 001 11 Jan 2013
<b>Review Division</b>	DMEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of albiglutide 30 mg and 50 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between albiglutide 30 mg and 50 mg 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  $\Delta\Delta\text{QTcI}$  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, double-blind, single-center, parallel, nested crossover study, 140 healthy subjects received albiglutide 30 mg and 50 mg, 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 Albiglutide 30 mg and 50 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Albiglutide 30 mg	1	0.5	(-1.2, 2.2)
Albiglutide 50 mg	1	1.5	(-0.2, 3.3)
Moxifloxacin 400 mg*	1	12.3	(10.2, 14.4)

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

Administration of 30 mg of albiglutide for 2 weeks followed by 50 mg for 4 weeks is adequate to represent therapeutic exposures. An increase in exposure by approximately 30%-40% is expected in patients with severe renal impairment compared to subjects with normal renal function. The studied dose does not cover this increased exposure scenario for renally impaired patients. However, since the exposure-response relationship is flat for the studied concentration range, large effects are not anticipated under the increased exposure scenario for renally impaired patients. The effects of hepatic impairment on the pharmacokinetics of albiglutide has not been studied because therapeutic proteins such as albiglutide are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide. Since albiglutide is catabolized by proteolytic enzymes, the effect of CYP3A4 inhibitors and inducers is not anticipated and drug-drug interaction studies for this have not been conducted.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

## 2 PROPOSED LABEL

### 2.1 SPONSOR’S PROPOSED LABEL

#### 12.2 Pharmacodynamics

(b) (4)

### 2.2 QT-IRT’S PROPOSED LABEL

*QT-IRT’s labeling recommendations are suggestions only. We defer final labeling decisions to the Division.*

(b) (4)

At doses up to the maximum recommended dose (50 mg), albiglutide does not prolong QTc to any clinically relevant extent.

### **3 BACKGROUND**

#### **3.1 PRODUCT INFORMATION**

Albiglutide is a recombinant fusion protein consisting of two copies of a 30-amino acid sequence of modified human glucagon-like peptide 1 (GLP-1, fragment 7-36) genetically fused in series to recombinant human albumin (rHA) and acts as a GLP-1 agonist. The molecular weight of albiglutide is approximately 73,000 Daltons.

#### **3.2 MARKET APPROVAL STATUS**

Albiglutide is not approved for marketing in any country.

#### **3.3 PRECLINICAL INFORMATION**

An hERG assay was not conducted for albiglutide.

#### **3.4 PREVIOUS CLINICAL EXPERIENCE**

Placebo subtracted HR increases after single dose of 30 mg albiglutide of up to 3 bpm and up to 6-8 bpm with 50 mg albiglutide were observed. An integrated analysis from more than 2800 participants in 5 phase 3 studies did not reveal any clinically meaningful change from baseline or in mean measures ECG parameters.

#### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of albiglutide's clinical pharmacology.

### **4 SPONSOR'S SUBMISSION**

#### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 65177 The sponsor submitted the study report GLP107085 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

#### **4.2 TQT STUDY**

##### **4.2.1 Title**

A Randomized, Double-blind, Parallel, Nested Crossover Study to Investigate the Effect of Albiglutide on Cardiac Repolarization (corrected QT Interval) Compared With Placebo in Healthy Male and Female Subjects: A Thorough ECG Study Employing Placebo, Albiglutide, and a Positive Control (Moxifloxacin).

##### **4.2.2 Protocol Number**

GLP107085

##### **4.2.3 Study Dates**

28-JUN-2011 -- 04-JAN-2012

##### **4.2.4 Objectives**

**Primary:**

The primary objective of the study was to determine the lack of effect of albiglutide as compared with placebo on cardiac repolarization corrected QT interval (QTc) (as determined by the QT correction method chosen for the primary analysis) after 6 weeks (Day 39) of treatment with albiglutide subcutaneously injected weekly.

**Secondary:**

- To determine the lack of effect of albiglutide as compared with placebo on cardiac repolarization QTc on Day 4 (as determined by the QT correction method chosen for the primary analysis)
- To determine the effect of albiglutide on cardiac repolarization on Days 4 and 39 as determined by QTc methods not included in the primary analysis
- To determine the effect of moxifloxacin on cardiac repolarization as determined by the QT interval corrected for individual heart rate (QTcI), QT interval corrected for heart rate by Fridericia's formula (QTcF), and QT interval corrected for heart rate by Bazett's formula (QTcB) after a single 400-mg dose on Days –1 or 40
- To characterize the pharmacokinetic (PK)/QT relationships for albiglutide
- To confirm exposures of albiglutide after weekly administration over 6 weeks
- To evaluate the safety and tolerability of albiglutide after 6 weeks of treatment

**4.2.5 Study Description**

**4.2.5.1 Design**

This is a Phase I, randomized, double-blind, single-center, parallel, nested crossover study.

**4.2.5.2 Controls**

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

**4.2.5.3 Blinding**

This is a double-blind study.

**4.2.6 Treatment Regimen**

**4.2.6.1 Treatment Arms**

Subjects will be assigned to 1 of 2 treatment groups to receive either albiglutide or albiglutide matching placebo. The albiglutide matching placebo treatment group will be split into 1 of 2 treatment schemes in accordance with the randomization schedule generated by (b) (4) prior to the start of the study, using validated internal software. Randomization will be implemented based on a sequestered fixed randomization schedule.

A description of each regimen is listed below:

Treatment Group	Moxifloxacin Day – 1	Albiglutide Days 1 and 8	Albiglutide Days 15, 22, 29, and 36	Moxifloxacin Day 40	Number of Subjects Analyzed
1. Albiglutide	Moxifloxacin placebo	Albiglutide 30 mg	Albiglutide 50 mg	Moxifloxacin placebo	70
2. Albiglutide matching placebo	a. Moxifloxacin 400 mg	Albiglutide matching placebo	Albiglutide matching placebo	a. Moxifloxacin matching placebo	35
	b. Moxifloxacin matching placebo			b. Moxifloxacin 400 mg	35

#### 4.2.6.2 Sponsor’s Justification for Doses

To minimize the potential for dose-limiting nausea and vomiting, and in consideration of the characteristics of albiglutide as a macromolecular protein (approximately 73 kDa), the assessment of a potential QT effect of albiglutide was determined at the maximum intended clinical dose of 50 mg (dose administered in the Phase III program). This is similar to the dose setting for the thorough QTc studies performed for liraglutide [Chatterjee, 2009] and exenatide [Linnebjerg, 2009]. To ensure that the dose-response and concentration-response relationship for QT/QTc prolongation were characterized, subjects received 2 weeks of treatment with 30 mg of albiglutide (or placebo) and 4 weeks of 50 mg of albiglutide (or placebo) for a total of 6 weeks of treatment.

*Source: Page 20 of study report*

*Reviewer’s Comment: Administration of 30 mg of albiglutide for 2 weeks followed by 50 mg for 4 weeks is adequate to represent therapeutic exposures. An increase in exposure by approximately 30%-40% is expected in patients with severe renal impairment compared to subjects with normal renal function. The studied dose does not cover this increased exposure scenario for renally impaired patients. The effects of hepatic impairment on the pharmacokinetics of albiglutide has not been studied because therapeutic proteins such as albiglutide are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of albiglutide. Since albiglutide is catabolized by proteolytic enzymes, the effect of CYP3A4 inhibitors and inducers is not anticipated and drug-drug interaction studies for this have not been conducted.*

#### 4.2.6.3 Instructions with Regard to Meals

Subjects had to fast overnight on days -21, -3, 1, 8, 15, 22, 29, 36. Fasting was defined as no food or drink except water for at least 8 hours before the blood draw. Days 1, 8, 15, 22, 29 and 36 correspond to the days of albiglutide administration.

*Source: Attachment 1, page 886 of study report*

*Reviewer’s Comment: This is a product for subcutaneous injection; hence, food effects are irrelevant.*

#### 4.2.6.4 ECG and PK Assessments

Pharmacodynamics: 12-lead ECGs were obtained using a Holter monitor at 10:00, 11:00, 12:00, 15:00, 21:00, and 09:00 (approximately 24 hours after dosing) on Days -2, -1, 4, 39 and 40. To provide additional data for concentration QT effect analysis, subjects returned to the study center at approximately 07:00 and wore a Holter monitor at approximately 08:00 for approximately 1 hour before dosing with albiglutide/albiglutide placebo on Days 8, 15, 22, 29, and 36. Subjects rested in a supine or semirecumbent position for at least 15 minutes before each time point when ECGs were obtained. The QT intervals were obtained approximately 30 minutes before the subject received study drug.

Pharmacokinetics: Blood samples for serial pharmacokinetic assessments were obtained on Days -2, -1, 4, 39, and 40. Pharmacokinetic samples were collected after the collection of ECGs at 10:00, 11:00, 12:00, 15:00, 21:00, and 09:00 (approximately 24 hours after dosing). Single blood samples for pharmacokinetic assessments for albiglutide were obtained after the collection of ECGs and before dosing on Days 8, 15, 22, 29, and 36.

*Source: Attachment 1, page 886 of study report*

*Reviewer's Comment: The ECG and PK sampling is reasonable as samples were collected at steady state.*

#### 4.2.6.5 Baseline

Two types of Baselines were used for the analyses of QTc:

- Primary Baseline: For albiglutide and albiglutide placebo parallel arms, the time-matched values on Day -2 were used as the Baseline for each postdose time point. For the crossover arm with moxifloxacin, the change from Baseline was computed based on the corresponding period Baseline. For example, if a subject received moxifloxacin or moxifloxacin placebo on Day -1, then Day -2 time-matched values were used as period Baseline. If a subject received moxifloxacin or moxifloxacin placebo on Day 40, the Day 39 time-matched values were used as period Baseline.
- Alternative Baseline (crossover arm): Baseline for subjects who received moxifloxacin on Day -1 was Day 40 and Baseline for placebo on Day 39 was Day -2. For subjects who received moxifloxacin on Day 40, Baseline for moxifloxacin was Day -1 and Baseline for placebo on Day -2 was Day 39. The analysis with Baseline defined previously was included as a sensitivity analysis.

#### 4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

## 4.2.8 Sponsor's Results

### 4.2.8.1 Study Subjects

Subject disposition and demographics for all subjects randomly assigned to treatment and for subjects who received at least 1 dose of abiglutide or abiglutide placebo (parallel arms) are summarized in Table 2. A total of 85 subjects were randomly assigned to receive abiglutide injected subcutaneously, with 78 subjects receiving all 6 doses of abiglutide: 2 weekly 30-mg doses of abiglutide on Days 1 and 8 and 4 weekly 50-mg doses of abiglutide on Days 15, 22, 29, and 36.

**Table 2: Summary of Subject Disposition and Demographic Characteristics – All Subjects and Parallel Arms (Safety Population)**

	All Subjects		Parallel Arms	
	Randomly Assigned to Abiglutide <sup>1,3</sup> N = 85	Randomly Assigned to Abiglutide Placebo <sup>2,3</sup> N = 89	Abiglutide Parallel Arm <sup>1,4</sup> N = 85	Abiglutide Placebo Parallel Arm <sup>2,4</sup> N = 88
<b>Number of Subjects</b>				
Number of subjects completed, n (%)	78 (91.8)	76 (85.4)	78 (91.8)	79 (89.8)
Number of subjects discontinued, n (%)	7 (8.2)	13 (14.6)	7 (8.2)	9 (10.2)
<b>Reasons for discontinuation, n (%)</b>				
Adverse event	1 (1.2)	3 (3.4)	1 (1.2)	2 (2.3)
Lost to follow-up	3 (3.5)	5 (5.6)	3 (3.5)	2 (2.3)
Protocol violation	1 (1.2)	0	1 (1.2)	0
Noncompliance with study visit schedule	2 (2.4)	2 (2.2)	2 (2.4)	2 (2.3)
Other	0	3 (3.4)	0	3 (3.4)
Number of subjects in Safety Population, n (%)	85 (100.0)	89 (100)	85 (100.0)	88 (100.0)
Number of subjects in Abiglutide PK Population, n (%)	85 (100.0)	NA	85 (100.0)	NA
Number of subjects in Abiglutide PK Concentration Population, n (%)	85 (100.0)	NA	85 (100.0)	NA
Number of subjects in PD Population, n (%)	85 (100.0)	88 (98.9)	85 (100.0)	88 (100.0)
<b>Demographics</b>				
Age in Years, Mean (Min, Max)	29.9 (18, 45)	28.9 (18, 45)	29.9 (18, 45)	29.0 (18, 45)
<b>Sex, n (%)</b>				
Male	57 (67.1)	45 (50.6)	57 (67.1)	44 (50.0)
Female	28 (32.9)	44 (49.4)	28 (32.9)	44 (50.0)
Females of childbearing potential, n (%)	24 (28.2)	35 (39.3)	24 (28.2)	35 (39.8)
BMI (kg/m <sup>2</sup> ), Mean (SD/Min, Max)	25.30 (2.908/19.4, 30.0)	25.19 (2.758/19.3, 30.0)	25.30 (2.908/19.4, 30.0)	25.17 (2.761/19.3, 30.0)
Height (cm), Mean (SD/Min, Max)	170.45 (9.793/ 152.3, 196.4)	167.75 (9.708/ 150.2, 195.0)	170.45 (9.793/ 152.3, 196.4)	167.64 (9.714/ 150.2, 195.0)
Weight (kg), Mean (SD/Min, Max)	73.68 (11.651/ 49.2, 106.6)	71.11 (11.487/ 52.1, 98.0)	73.68 (11.651/ 49.2, 106.6)	70.94 (11.433/ 52.1, 98.0)
<b>Ethnicity, n (%)</b>				
Hispanic or Latino	27 (31.8)	33 (37.1)	27 (31.8)	33 (37.5)
Not Hispanic or Latino	58 (68.2)	56 (62.9)	58 (68.2)	55 (62.5)

Source: CSR, Table 6

### 4.2.8.2 Statistical Analyses

#### 4.2.8.2.1 Primary Analysis

Mean change from Baseline in QTcI ( $\Delta$ QTcI) for abiglutide 30 mg (approximate  $C_{max}$  after a single 30-mg dose on Day 4) and abiglutide 50 mg (approximate  $C_{max}$  after repeat 50-mg doses on Day 39) was similar to the placebo response, whereas moxifloxacin caused a clear prolongation of  $\Delta$ QTcI. The resulting mean placebo-corrected  $\Delta$ QTcI ( $\Delta\Delta$ QTcI) was small for both abiglutide doses. On Day 4 (approximate  $C_{max}$  after a single 30-mg dose of abiglutide), the largest  $\Delta\Delta$ QTcI was 1.1 msec (upper bound of 90% CI: 3.8 msec) at 3 hours. On Day 39 (approximate  $C_{max}$  after repeat 50-mg doses of abiglutide), the largest effect on mean  $\Delta\Delta$ QTcI was  $-0.6$  msec (upper bound of CI: 1.8 msec) at 1 hour.

For albiglutide 30 mg, the largest  $\Delta\Delta\text{QTcI}$  was 3.3 msec (upper bound of 90% CI: 5.6 msec) on Day 4. For albiglutide 50 mg, the largest  $\Delta\Delta\text{QTcI}$  was 1.0 msec (upper bound of 90% CI: 3.4 msec) on Day 39.

#### **4.2.8.2.2 Assay Sensitivity**

Moxifloxacin caused a peak effect on  $\Delta\Delta\text{QTcI}$  of 10.9 msec at 2 hours after dosing and the lower bound of the CI was above 5 msec at all preselected time points, which demonstrated assay sensitivity.

When gender was included as an additional fixed effect in the statistical model, results were comparable and conclusions remained the same.

The peak mean  $\Delta\Delta\text{QTcI}$  effect of moxifloxacin was 11.1 msec and the lower bound of CI exceeded 5 msec at all 3 preselected time points.

#### **4.2.8.2.3 Categorical Analysis**

No subject who received albiglutide had a QTcI value exceeding 450 msec or a  $\Delta\text{QTcI}$  value exceeding 30 msec.

#### **4.2.8.2.4 Additional Analyses**

Mean changes from Baseline in PR ( $\Delta\text{PR}$ ) were similar for placebo and moxifloxacin. Mean change from Baseline in PR ( $\Delta\text{PR}$ ) was larger than placebo for both albiglutide doses and  $\Delta\Delta\text{PR}$  varied between approximately 1 and 4 msec for albiglutide 30 mg and between approximately 2 and 5 msec for albiglutide 50 mg.

Mean changes from Baseline in QRS ( $\Delta\text{QRS}$ ) were similar across all treatments and  $\Delta\Delta\text{QRS}$  for albiglutide was negligible with all values  $<1.1$  msec.

#### **4.2.8.3 Safety Analysis**

No deaths were reported in the study. Two serious adverse events were reported, none linked to albiglutide.

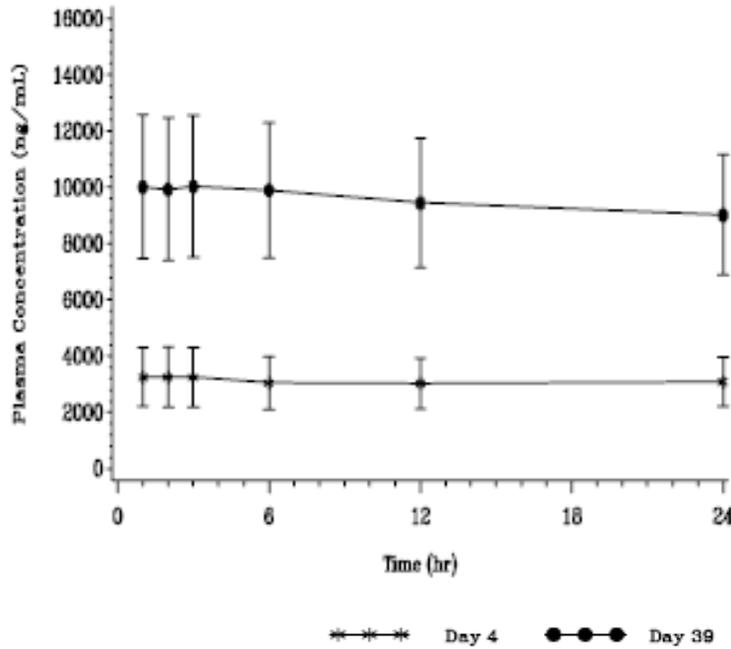
A total of 21 subjects (24.7%) and 19 subjects (21.6%) who received albiglutide and albiglutide placebo, respectively, reported at least 1 treatment-related TEAE during the study. The most commonly reported treatment-related TEAE with albiglutide was nausea (7 subjects, 8.2%) followed by vomiting (6 subjects, 7.1%) and headache and decreased appetite (5 subjects each, 5.9%). The most commonly reported treatment-related TEAEs with albiglutide placebo were nausea (9 subjects, 10.2%) and headache (8 subjects, 9.1%) followed by vomiting (5 subjects, 5.7%).

#### **4.2.8.4 Clinical Pharmacology**

##### **4.2.8.4.1 Pharmacokinetic Analysis**

The mean drug concentration-time profile is illustrated in Figure 1. The PK results are presented in Table 3.

**Figure 1: Mean plasma concentration-time profiles of Albiglutide on day 4 and day 39**



Source: Figure 4 on Page 69 of study report

**Table 3: Pharmacokinetic results of Albiglutide on day 4 and 39**

Day Parameter (unit)	Albiglutide N = 85
Day 4 <sup>1</sup>	
Cavg (ng/mL) <sup>2,3</sup>	2937 (33.7)
Day 39 <sup>4</sup>	
Cavg (ng/mL) <sup>3,5</sup>	9223 (25.7)

Data Source: Table 14.2.1.2

CV = coefficient of variation

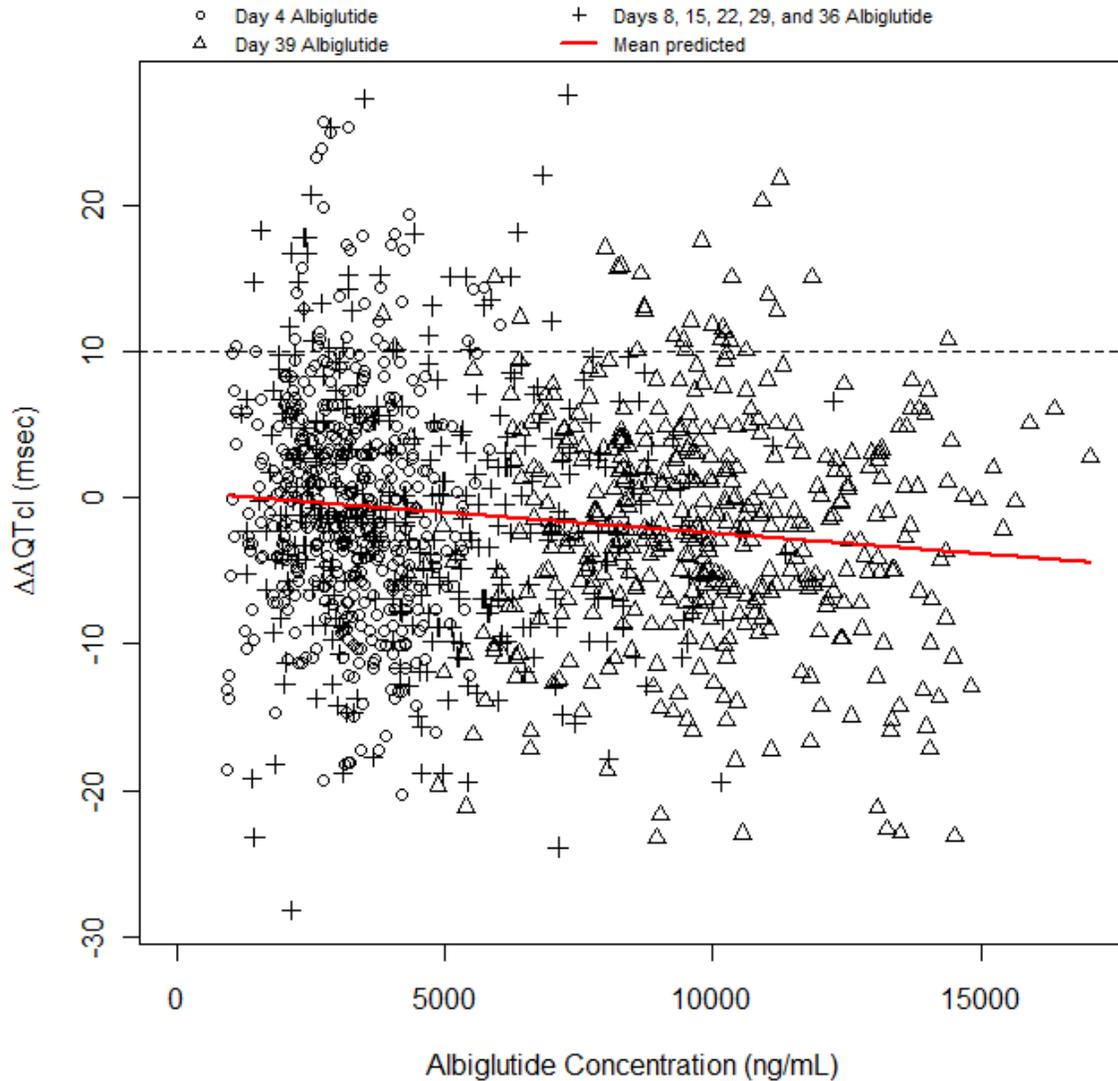
- Day 4 represents approximate Cmax after a single 30-mg dose
- N = 84. Although Subject 2907085067 on Day 4 qualified for inclusion in the Pharmacokinetic Population, the subject was excluded from the concentration and pharmacokinetic parameter summaries in order to match the Pharmacodynamic Population used for QT analyses.
- Cavg =  $AUC(1-t)/(t-1)$ , where t = time after hypothetical dosing at 09:00
- Day 39 represents approximate Cmax after repeat 50-mg doses
- N = 78

Source: Table 20 on Page 70 of study report

#### 4.2.8.4.2 Exposure-Response Analysis

Sponsor's  $\Delta\Delta QTcI$  vs. albiglutide plasma concentration plot is shown in Figure 2 **Error! Reference source not found.** Across the studied concentration range, there appeared to be no increase in  $QTcI$  duration.

**Figure 2: Sponsor's  $\Delta\Delta QTcI$  vs. Albiglutide Plasma Concentration**



Source: Figure 3 on Page 66 of study report

Reviewer's Analysis: A plot of  $\Delta\Delta QTcI$  vs. albiglutide concentrations is presented in Figure 5.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and 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 4, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

**Table 4: Comparison of QTcF and QTcI Using the Mixed Model**

Treatment Groups	Slope of QTcF	Slope of QTcI	diff_p_value
All	0.00784	0.00260	0.00000
Albiglutide	0.01136	0.00415	0.00000
Moxifloxacin	0.01630	0.01202	0.21736
Placebo	0.00205	0.00050	0.41687

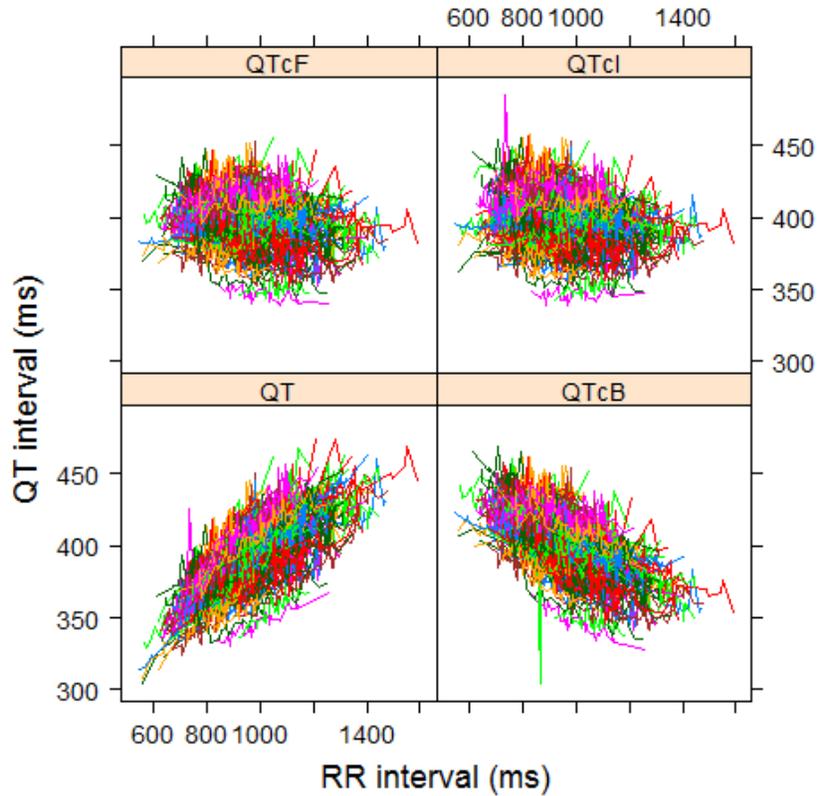
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

**Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

	Treatment							
	Albiglutide		Moxifloxacin		Placebo		All	
method	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	85	0.0041	84	0.0049	88	0.0048	173	0.0047
QTcF	85	0.0009	84	0.0037	88	0.0009	173	0.0009
QTcI	85	0.0004	84	0.0028	88	0.0004	173	0.0004

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

**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 Albiglutide

The statistical reviewer used lineal model to analyze the  $\Delta$ QTcI effect by time point. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 6: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group = Albiglutide 30 mg and Albiglutide 50 mg**

	Treatment Group							
	Albiglutide 30 mg				Albiglutide 50 mg			
	dQTcI	Placebo	ddQTcI		dQTcI	Placebo	ddQTcI	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-2.8	-3.3	0.5	(-1.2, 2.2)	-1.8	-3.3	1.5	(-0.2, 3.3)
2	-2.0	-1.7	-0.3	(-1.9, 1.4)	-1.2	-1.7	0.4	(-1.3, 2.1)
3	-1.1	-1.1	-0.0	(-1.8, 1.7)	-0.3	-1.1	0.8	(-1.0, 2.6)
6	-0.1	1.3	-1.4	(-3.2, 0.4)	1.0	1.3	-0.3	(-2.2, 1.5)
12	-1.5	0.7	-2.3	(-4.2, -0.3)	-1.5	0.7	-2.2	(-4.2, -0.2)
24	-0.6	-0.5	-0.1	(-1.9, 1.7)	0.6	-0.5	1.1	(-0.7, 3.0)

The largest upper bounds of the 2-sided 90% CI for the mean difference between albiglutide 30 mg and placebo, and between albiglutide 50 mg and placebo were 2.2 ms and 3.3 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. The largest unadjusted 90% lower confidence interval is 10.5 ms after considering Bonferroni multiple endpoint adjustment for 3 time points, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

**Table 7: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin**

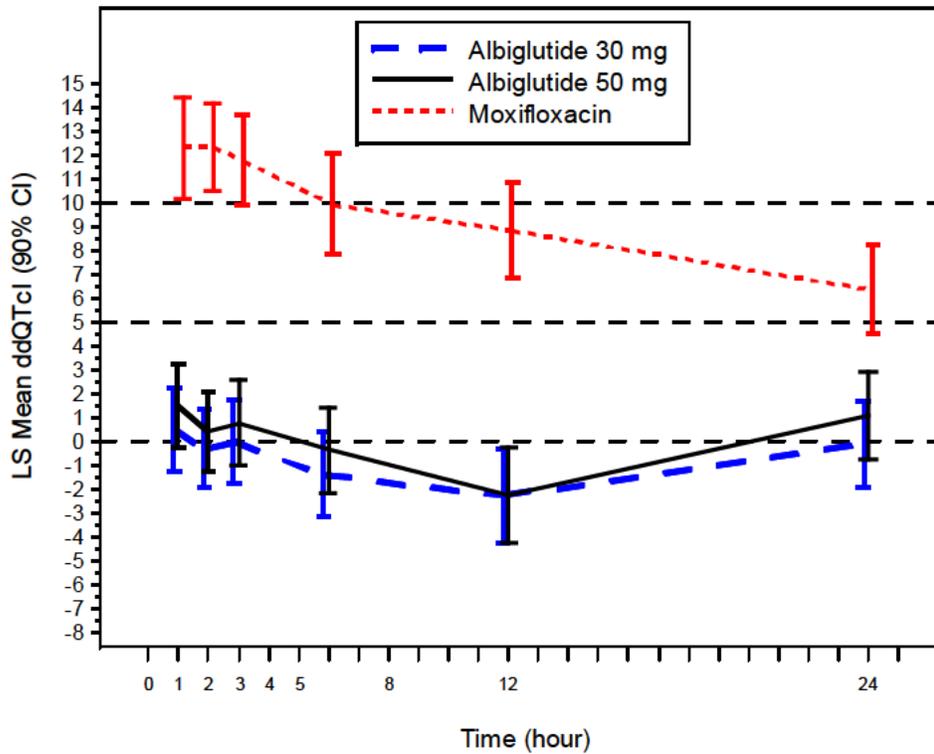
	Treatment Group			
	Moxifloxacin			
	dQTcI	Placebo	ddQTcI	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	7.8	-4.5	12.3	(10.2, 14.4)
2	10.8	-1.5	12.4	(10.5, 14.2)
3	11.7	-0.0	11.8	(9.9, 13.7)
6	10.0	0.0	10.0	(7.8, 12.1)
12	7.5	-1.4	8.9	(6.9, 10.9)
24	3.1	-3.3	6.4	(4.5, 8.2)

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

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

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

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



#### 5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcI was above 450 ms.

**Table 8: Categorical Analysis for QTcI**

Treatment Group	Total N		Value $\leq 450$ ms		Value $> 450$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Albiglutide 30 mg	84	502	84 (100%)	502 (100%)	0 (.%)	0 (0.0%)
Albiglutide 50 mg	78	453	78 (100%)	453 (100%)	0 (.%)	0 (0.0%)
Baseline	173	1015	173 (100%)	1015 (100%)	0 (.%)	0 (0.0%)
Placebo	88	528	88 (100%)	528 (100%)	0 (.%)	0 (0.0%)

Table 9 lists the categorical analysis results for  $\Delta$ QTcI. No subject's change from baseline was above 30 ms.

**Table 9: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq$ 30 ms		Value $>$ 30 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Albiglutide 30 mg	84	488	84 (100%)	488 (100%)	0 (.%)	0 (0.0%)
Albiglutide 50 mg	78	443	78 (100%)	443 (100%)	0 (.%)	0 (0.0%)
Placebo	88	519	88 (100%)	519 (100%)	0 (.%)	0 (0.0%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the HR mean differences between albiglutide 30 mg and placebo, and between albiglutide 50 mg and placebo were 6.7 bpm and 9.5 bpm, respectively. The outlier analysis results for PR are presented in Table 11.

**Table 10: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = Albiglutide 30 mg and Albiglutide 50 mg**

Time (hrs)	Treatment Group							
	Albiglutide 30 mg				Albiglutide 50 mg			
	dHR	Placebo	ddHR		dHR	Placebo	ddHR	
LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	
1	4.9	1.6	3.3	(1.9, 4.6)	9.7	1.6	8.0	(6.7, 9.4)
2	4.3	2.0	2.3	(0.9, 3.7)	10.1	2.0	8.1	(6.7, 9.5)
3	4.2	1.8	2.4	(1.1, 3.7)	9.3	1.8	7.5	(6.2, 8.8)
6	3.5	2.4	1.1	(-0.3, 2.5)	8.9	2.4	6.5	(5.1, 8.0)
12	4.4	3.0	1.4	(-0.1, 2.9)	9.5	3.0	6.5	(4.9, 8.1)
24	8.6	3.5	5.2	(3.6, 6.7)	9.3	3.5	5.9	(4.2, 7.5)

**Table 11: Categorical Analysis for HR**

Treatment Group	Total N		Value≤100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Albiglutide 30 mg	84	502	82 (97.6%)	499 (99.4%)	2 (2.4%)	3 (0.6%)
Albiglutide 50 mg	78	453	75 (96.2%)	449 (99.1%)	2 (2.5%)	4 (0.9%)
Placebo	88	528	88 (100%)	528 (100%)	0 (0.0%)	0 (0.0%)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the PR mean differences between albiglutide 30 mg and placebo, and between albiglutide 50 mg and placebo were 5.2 ms and 8.4 ms, respectively.

The outlier analysis results for PR are presented in Table 13.

**Table 12: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Albiglutide 30 mg and Albiglutide 50 mg**

	Treatment Group							
	Albiglutide 30 mg				Albiglutide 50 mg			
	dPR	Placebo	ddPR		dPR	Placebo	ddPR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	3.7	3.4	0.3	(-1.9, 2.4)	7.4	3.4	4.0	(1.8, 6.2)
2	3.4	3.2	0.2	(-2.0, 2.4)	7.2	3.2	4.0	(1.7, 6.2)
3	4.3	1.9	2.3	(-0.0, 4.6)	8.0	1.9	6.1	(3.7, 8.4)
6	4.5	1.2	3.3	(1.3, 5.2)	6.5	1.2	5.4	(3.3, 7.4)
12	3.9	1.8	2.1	(0.1, 4.1)	5.9	1.8	4.1	(2.0, 6.1)
24	3.5	2.1	1.4	(-1.0, 3.8)	6.7	2.1	4.6	(2.1, 7.1)

**Table 13: Categorical Analysis for PR**

Treatment Group	Total		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Albiglutide 30 mg	84	502	84 (100%)	502 (100%)	0 (0.0%)	0 (0.0%)
Albiglutide 50 mg	78	453	77 (98.7%)	451 (99.6%)	1 (1.3%)	2 (0.4%)
Placebo	88	528	87 (98.9%)	523 (99.1%)	1 (1.1%)	5 (0.9%)

**5.2.4 QRS Analysis**

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the QRS mean differences between albiglutide 30 mg and placebo, and between albiglutide 50 mg and placebo were 0.8 ms and 0.7 ms, respectively.

The outlier analysis results for QRS are presented in Table 15.

**Table 14: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Albiglutide 30 mg and Albiglutide 50 mg**

	Treatment Group							
	Albiglutide 30 mg				Albiglutide 50 mg			
	dqrs	Placebo	ddqrs		dqrs	Placebo	ddqrs	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.3	0.1	0.2	(-0.2, 0.7)	0.2	0.1	0.2	(-0.3, 0.6)
2	0.3	0.1	0.2	(-0.3, 0.6)	0.3	0.1	0.2	(-0.2, 0.7)
3	0.1	-0.0	0.1	(-0.4, 0.6)	0.2	-0.0	0.2	(-0.2, 0.7)
6	0.3	0.1	0.2	(-0.3, 0.7)	0.3	0.1	0.2	(-0.3, 0.7)
12	0.3	0.0	0.3	(-0.2, 0.8)	0.2	0.0	0.2	(-0.3, 0.7)
24	0.1	-0.1	0.2	(-0.3, 0.7)	0.0	-0.1	0.2	(-0.3, 0.7)

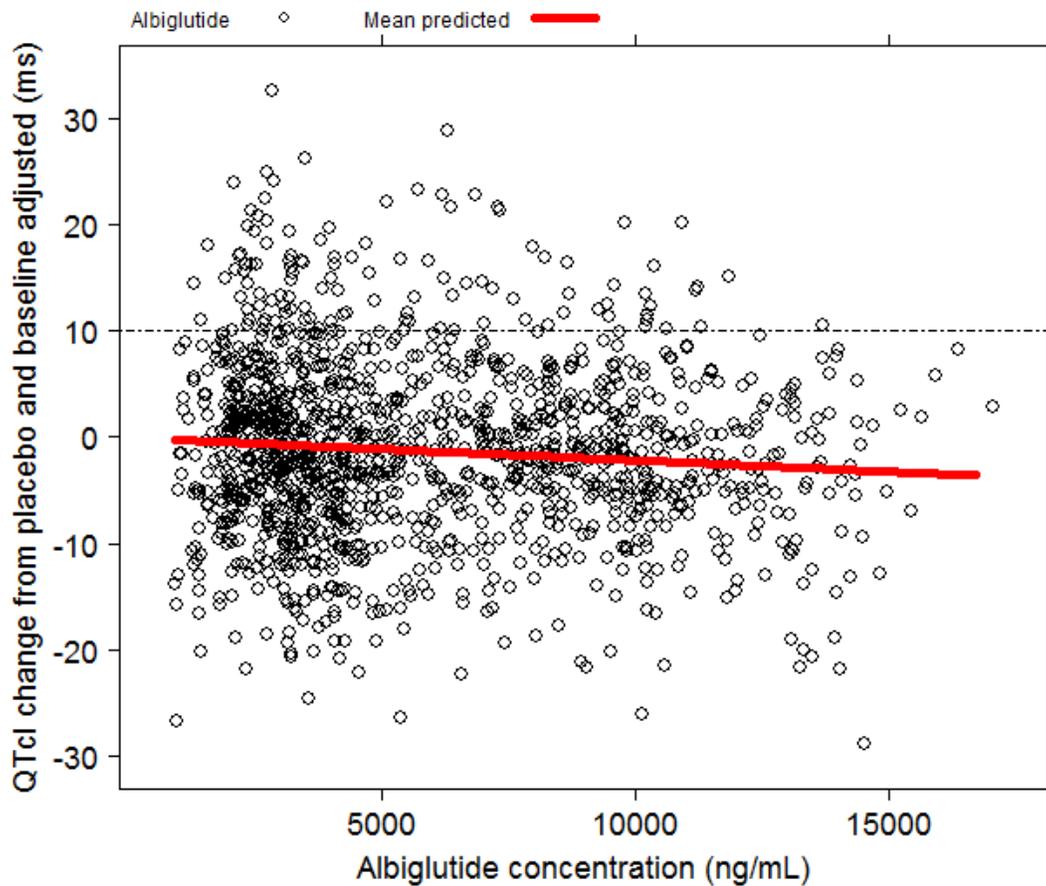
**Table 15: Categorical Analysis for QRS**

Treatment Group	Total		Value $\leq$ 100 ms		100 ms<Value $\leq$ 110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Albiglutide 30 mg	84	502	7 (8.3%)	57 (11.4%)	48 (57.1%)	299 (59.6%)	29 (34.5%)	146 (29.1%)
Albiglutide 50 mg	78	453	8 (10.3%)	66 (14.6%)	41 (52.6%)	240 (53.0%)	29 (37.2%)	147 (32.5%)
Placebo	88	528	17 (19.3%)	136 (25.8%)	52 (59.1%)	291 (55.1%)	19 (21.6%)	101 (19.1%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

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

**Figure 5:  $\Delta\Delta$  QTcI vs. Albiglutide 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.

An increase in HR was observed with the two doses of albiglutide. A placebo-subtracted mean increase of 3 and 8 bpm were reported for albiglutide 30 mg and 50 mg respectively at 1 hour postdose.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 98% of the ECGs were annotated in the primary lead II, with less than 0.2% 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 , QRS Interval and HR

One subject in the treatment group (50 mg dose) had PR greater than 200 ms but <205 ms. There were 29 subjects who experienced QRS interval greater than 110 ms in the both treatment groups. However, the majority had QRS > 110 ms at baseline. There were no postbaseline values > 120 ms. None of these reported values were clinically meaningful.

Three subjects in the treatment group had HR greater than 100 bpm, postbaseline values were <110 bpm.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	30 mg administered once weekly by subcutaneous injection with potential up-titration to 50 mg once weekly by subcutaneous injection					
Maximum tolerated dose	A maximum tolerated dose has not been identified for albiglutide.					
	NOAEL Exposures Relative to Estimated Steady-State Clinical Exposures					
	<b>Species</b>	<b>Dose</b>	<b>Population Mean Weekly AUC (µg h/mL)</b>	<b>Multiple of Human Exposure at Steady State<sup>4,5</sup></b>		
				<b>30 mg /wk</b>	<b>50 mg/wk</b>	
	Mouse	<1 mg/kg/day <sup>1</sup>	470.4 (67.2 <sup>3</sup> )	1.5	0.9	
		5 mg/kg/day <sup>2</sup>	2030 (290 <sup>3</sup> )	6.3	3.8	
		50 mg/kg/day	27063 (3866 <sup>3</sup> )	85	51	
	Monkey	15 mg/kg/week	13278	41	25	
	Human	30 mg/week	320	---		
		50 mg/week <sup>6</sup>	533	---		
	<ol style="list-style-type: none"> <li>1. NOAEL for F1 postnatal development and maternal toxicity in lactating dams</li> <li>2. NOAEL for female fertility and embryofetal development.</li> <li>3. Mouse AUC values in parentheses represent the daily AUC values. Fold-exposure is calculated from the AUC converted to weekly exposures.</li> <li>4. Based on population mean steady-state AUC for 30 mg and 50 mg weekly dosing.</li> <li>5. Note: Population PK analysis in a small population of Japanese subjects receiving albiglutide (n=32, GLP107865) indicates exposures ~37% higher than observed in study GLP110125.</li> <li>6. Observed data unavailable: predicted based on GLP110125 population PK.</li> </ol>					
Principal adverse events	GI events (nausea and vomiting) were the most common adverse events, and the rate of these events increased with increases in dose (Phase IIb data from GLP110125):					
	<b>Adverse Event</b>	<b>Albiglutide Treatment (N)</b>				
		30mg weekly (31)	30mg every other week (32)	50 mg every other week (35)	50 mg monthly (35)	100 mg monthly (34)

	<table border="1"> <tr> <td>Nausea (%)</td> <td>25.8</td> <td>25.0</td> <td>54.3</td> <td>37.1</td> <td>52.9</td> </tr> <tr> <td>Vomiting (%)</td> <td>12.9</td> <td>9.4</td> <td>28.6</td> <td>17.1</td> <td>41.2</td> </tr> </table> <p>Nausea and vomiting occurred in 40% and 17%, respectively, of the patients administered Byetta (N=35). Nausea and vomiting occurred in 11.8% and 2.0%, respectively, of the patients administered placebo (N=51).</p> <p>Local injection site reactions also were noted and occurred in approximately 10 – 20% of patients who were randomized to albiglutide in the Phase IIB study (GLP110125).</p>	Nausea (%)	25.8	25.0	54.3	37.1	52.9	Vomiting (%)	12.9	9.4	28.6	17.1	41.2								
Nausea (%)	25.8	25.0	54.3	37.1	52.9																
Vomiting (%)	12.9	9.4	28.6	17.1	41.2																
Maximum dose tested	Single Dose	<b>Maximum Single Doses</b> <ul style="list-style-type: none"> <li>80 mg single dose (Week 1) followed by a 104 mg single dose one week later (Week 2) (Study GLP105229)</li> </ul>																			
	Multiple Dose	<b>Maximum Multiple Doses Administered by Regimen To Date (Study GLP110125) *</b> <ul style="list-style-type: none"> <li>30 mg every week</li> <li>50 mg every 2 weeks</li> <li>100 mg every 4 weeks</li> </ul> <p>*Note: A 50 mg weekly dose is administered in Phase III studies (data unavailable).</p>																			
Exposures Achieved at Maximum Tested Doses	Single Dose	<b>Geometric Mean (CV%) Exposure Following Maximum Single Doses in Study GLP105229</b> <table border="1"> <thead> <tr> <th>Dose</th> <th>AUC(0-7days) (µg.h/mL)</th> <th>Cmax (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>80 mg Week 1</td> <td>1170 (33.5%)</td> <td>8920 (29.2%)</td> </tr> <tr> <td>104 mg Week 2</td> <td>3390 (22.4%)</td> <td>23300 (22.7%)</td> </tr> </tbody> </table>	Dose	AUC(0-7days) (µg.h/mL)	Cmax (ng/mL)	80 mg Week 1	1170 (33.5%)	8920 (29.2%)	104 mg Week 2	3390 (22.4%)	23300 (22.7%)										
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Multiple Dose	<b>Geometric Mean (CV%) Steady-State Exposure by Dosing Regimen<sup>+</sup></b> <table border="1"> <thead> <tr> <th>Regimen</th> <th>AUC(0-τ),ss µg h/mL</th> <th>AUC(0-28d),ss µg.h/mL</th> <th>Cmax ng/mL</th> </tr> </thead> <tbody> <tr> <td>30 mg Weekly</td> <td>320 (27%)</td> <td>1280 (27%)</td> <td>2148 (25%)</td> </tr> <tr> <td>50mg Weekly*</td> <td>533 (27%)</td> <td>2132 (27%)</td> <td>3580 (25%)</td> </tr> <tr> <td>50mg Biweekly</td> <td>548 (29%)</td> <td>1096 (29%)</td> <td>2330 (28%)</td> </tr> <tr> <td>100mg Monthly</td> <td>1149 (40%)</td> <td>1149 (40%)</td> <td>3887 (31%)</td> </tr> </tbody> </table> <p>*Predicted based on population PK from GLP110125  <sup>+</sup>For comparison across regimens, AUC is presented as exposure during a dosing interval [AUC(0-τ)] and monthly [AUC(0-28d)] at steady-state</p>	Regimen	AUC(0-τ),ss µg h/mL	AUC(0-28d),ss µg.h/mL	Cmax ng/mL	30 mg Weekly	320 (27%)	1280 (27%)	2148 (25%)	50mg Weekly*	533 (27%)	2132 (27%)	3580 (25%)	50mg Biweekly	548 (29%)	1096 (29%)	2330 (28%)	100mg Monthly	1149 (40%)	1149 (40%)	3887 (31%)
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100mg Monthly	1149 (40%)	1149 (40%)	3887 (31%)																		

Range of linear PK	<p><b>Range of Dose-Proportional Exposure:</b></p> <p>15 mg to 100 mg (based on population PK analysis of Study GLP110125)*</p> <p>*Increased estimates of CL/V and V/F were noted for the lowest (4mg weekly) dose level compared to the other doses evaluated.</p>															
Accumulation at steady state	<p><b>Geometric Mean Accumulation Ratio (CV%) for Maximum Doses in Study GLP110125</b></p> <table border="1" data-bbox="597 457 1182 716"> <thead> <tr> <th rowspan="2">Dose and Regimen</th> <th colspan="2">Geometric Mean Accumulation Ratio (CV%)</th> </tr> <tr> <th>AUC (0-<math>\tau</math>)</th> <th>C<sub>max</sub></th> </tr> </thead> <tbody> <tr> <td>30 mg Weekly</td> <td>2.2 (23%)</td> <td>2.0 (16%)</td> </tr> <tr> <td>50 mg BiWeekly</td> <td>1.3 (11%)</td> <td>1.3 (9%)</td> </tr> <tr> <td>100 mg Monthly</td> <td>1.05 (6%)</td> <td>1.05 (5%)</td> </tr> </tbody> </table> <p>*Based on population PK analysis of Study GLP110125 comparing</p>		Dose and Regimen	Geometric Mean Accumulation Ratio (CV%)		AUC (0- $\tau$ )	C <sub>max</sub>	30 mg Weekly	2.2 (23%)	2.0 (16%)	50 mg BiWeekly	1.3 (11%)	1.3 (9%)	100 mg Monthly	1.05 (6%)	1.05 (5%)
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100 mg Monthly	1.05 (6%)	1.05 (5%)														
Metabolites	<ul style="list-style-type: none"> <li>Traditional distribution, metabolism, and excretion studies common to small molecules have not been conducted with albiglutide.</li> <li>Precluded from such investigations in ICH Guidance S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals:</li> <li>Preliminary data indicate that the albiglutide molecule undergoes ‘normal’ protein catabolism during circulation and does not form any active ‘GLP-1-like’ peptides (i.e., peptides of at least 30 amino acids (b) (4)).</li> <li>Data suggest a progressive process over time with initial catabolism appearing in the first 20 amino acids with subsequent catabolism extending into the first 50 amino acids</li> </ul>															
Absorption	Absolute/Relative Bioavailability	<p>Absorption:</p> <ul style="list-style-type: none"> <li>Following SC injection, albiglutide is absorbed in a first-order manner with a half-life of ~1.5 days</li> <li>No absolute or relative bioavailability studies have been performed for albiglutide</li> </ul>														

	Tmax	<p><b>Median (minimum, maximum) of Tmax at steady-state based on Population PK analysis of Study GLP110125.</b></p> <table border="1"> <thead> <tr> <th>Dose and Regimen</th> <th>Tmax (days) at steady-state median (min, max)</th> </tr> </thead> <tbody> <tr> <td>30 mg Weekly</td> <td>2.5 (2, 3)</td> </tr> <tr> <td>50mg Weekly (predicted)</td> <td>2.5 (1, 3)</td> </tr> <tr> <td>50 mg Biweekly</td> <td>3.5 (2, 5)</td> </tr> <tr> <td>100 mg Monthly</td> <td>4 (2, 9)</td> </tr> </tbody> </table>	Dose and Regimen	Tmax (days) at steady-state median (min, max)	30 mg Weekly	2.5 (2, 3)	50mg Weekly (predicted)	2.5 (1, 3)	50 mg Biweekly	3.5 (2, 5)	100 mg Monthly	4 (2, 9)
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50 mg Biweekly	3.5 (2, 5)											
100 mg Monthly	4 (2, 9)											
Distribution	Vd/F or Vd	<p>Vd/F = 16.4 L (30.1% CV)*</p> <p>*Based on population PK analysis of GLP110125 for subjects with median age=54 and median body weight = 91Kg Population PK parameter estimates will be explored further based on Phase III data</p>										
	% bound	Not applicable										
Elimination	Route	<ul style="list-style-type: none"> <li>Formal human mass balance studies have not been performed for albiglutide</li> <li>Preliminary data indicate that the albiglutide molecule undergoes 'normal' protein catabolism during circulation and does not form any active 'GLP-1-like' peptides (i.e., peptides of at least 30 amino acids with an intact (b) (4).</li> </ul>										
	Terminal t <sub>1/2</sub>	~5 days (9.1% CV)										
	CL/F or CL	<p>CL/F = 94.2 (mL/hr) (34.1% CV)*</p> <p>*Based on population PK analysis of GLP110125 for subjects with median age=54 and median body weight = 91Kg Population PK parameter estimates will be explored further based on Phase III data</p>										
Intrinsic Factors	Age	<p>CL/F decreases by 0.607 mL/hr/year *</p> <p>*Based on population PK analysis of GLP110125 Effects of demographic covariates will be explored further during population PK analysis of Phase III studies</p>										
	Sex	<p>No observed effect of Sex on pharmacokinetics*</p> <p>*Based on population PK analysis of GLP110125 Effects of demographic covariates will be explored further during population PK analysis of Phase III studies</p>										
	Body Weight	<p>CL/F increases by 0.845 mL/hr/kg body weight*</p> <p>V/F increases by 0.119 L/kg*</p> <p>To explore the potential effect of demographic</p>										

		<p>scenarios on PK, exposures were simulated based on observed demographic characteristics in the PK population of study GLP110125:</p> <p>Age: Median=54 years, Range=20 – 75 years Weight: Median=91 Kg, Range =50 – 179 Kg</p> <p><b>Simulated effect of Demographic Variation on Exposure*</b></p> <table border="1" data-bbox="854 493 1385 772"> <thead> <tr> <th>Parameter</th> <th colspan="5">Simulated 30 mg Weekly at Steady-State</th> </tr> </thead> <tbody> <tr> <td>Body Weight (Kg)</td> <td>91</td> <td>179</td> <td>50</td> <td>179</td> <td>50</td> </tr> <tr> <td>Age (years)</td> <td>54</td> <td>20</td> <td>20</td> <td>75</td> <td>75</td> </tr> <tr> <td>AUC(weekly),ss µg,h/mL</td> <td>318</td> <td>158</td> <td>373</td> <td>192</td> <td>640</td> </tr> <tr> <td>Cmax, ss</td> <td>2129</td> <td>1086</td> <td>2559</td> <td>1289</td> <td>4147</td> </tr> </tbody> </table> <p>*Based on population PK and range of demographic characteristics in study GLP110125. Effects of demographic covariates will be explored further during population PK analysis of Phase 3 studies</p>	Parameter	Simulated 30 mg Weekly at Steady-State					Body Weight (Kg)	91	179	50	179	50	Age (years)	54	20	20	75	75	AUC(weekly),ss µg,h/mL	318	158	373	192	640	Cmax, ss	2129	1086	2559	1289	4147
Parameter	Simulated 30 mg Weekly at Steady-State																															
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Cmax, ss	2129	1086	2559	1289	4147																											
	Race	<p>No apparent effect of race on albiglutide pharmacokinetics has been noted*</p> <p>*Based on population PK from GLP110125. Effects of demographic covariates will be explored further during population PK analysis of Phase 3 studies</p>																														
	Hepatic & Renal Impairment	<p>The impact of <u>hepatic impairment</u> has not been evaluated for albiglutide.</p> <p>The impact of <u>renal impairment</u> is currently under investigation. Preliminary data indicate that clinically relevant alterations in albiglutide PK are not observed in subjects with moderate and severe renal impairment.</p>																														
Extrinsic Factors	Drug interactions	<p><b>“Victim” Interaction Potential:</b></p> <p>Inhibition and induction of cytochrome P450 enzymes and inhibition/induction of common small molecule drug transporters are not predicted to affect albiglutide exposures. As such, DDI studies have not been performed to assess the impact of co-administered drugs on albiglutide PK.</p> <p><b>“Perpetrator” Interaction Potential:</b></p> <p>The effect of albiglutide as a perpetrator of DDIs has been assessed for warfarin, digoxin, simvastatin, and an oral contraceptive (Brevicon). Preliminary data (final reports in progress) include:</p>																														

		<p>Summary of Perpetrator DDI studies</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Analyte</th> <th>Geometric Mean AUC Ratio*</th> <th>Geometric Mean Cmax Ratio</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Warfarin</td> <td>R-Warfarin</td> <td>1.02 (0.98 – 1.07)</td> <td>0.94 (0.89 – 0.99)</td> </tr> <tr> <td>S-Warfarin</td> <td>0.99 (0.95 – 1.03)</td> <td>0.93 (0.87 – 0.98)</td> </tr> <tr> <td>Digoxin</td> <td>Digoxin</td> <td>1.09 (1.01 – 1.18)</td> <td>1.11 (0.98 – 1.26)</td> </tr> <tr> <td rowspan="2">Simvastatin</td> <td>Simvastatin</td> <td>0.60 (0.52 – 0.69)</td> <td>1.18 (1.02 – 1.38)</td> </tr> <tr> <td>Simvastatin Acid</td> <td>1.36 (1.19 – 1.55)</td> <td>1.98 (1.75 – 2.25)</td> </tr> <tr> <td rowspan="2">Oral Contraceptive</td> <td>Norethindrone</td> <td>1.09 (1.06 – 1.14)</td> <td>1.20 (1.11 – 1.29)</td> </tr> <tr> <td>Ethinyl Estradiol</td> <td>1.00 (0.96 – 1.04)</td> <td>1.04 (0.98 – 1.10)</td> </tr> </tbody> </table> <p>*AUC= AUC(0-∞) for Warfarin, Digoxin and Simvastatin studies; AUC=AUC(0-24h) for Oral Contraceptive Study; Ratio represents combination/treatment alone</p>	Study	Analyte	Geometric Mean AUC Ratio*	Geometric Mean Cmax Ratio	Warfarin	R-Warfarin	1.02 (0.98 – 1.07)	0.94 (0.89 – 0.99)	S-Warfarin	0.99 (0.95 – 1.03)	0.93 (0.87 – 0.98)	Digoxin	Digoxin	1.09 (1.01 – 1.18)	1.11 (0.98 – 1.26)	Simvastatin	Simvastatin	0.60 (0.52 – 0.69)	1.18 (1.02 – 1.38)	Simvastatin Acid	1.36 (1.19 – 1.55)	1.98 (1.75 – 2.25)	Oral Contraceptive	Norethindrone	1.09 (1.06 – 1.14)	1.20 (1.11 – 1.29)	Ethinyl Estradiol	1.00 (0.96 – 1.04)	1.04 (0.98 – 1.10)
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	Food Effects	Not applicable for subcutaneous injection																													
Expected High Clinical Exposure Scenario	<p>Given the lack of “victim” interaction potential for albiglutide a worst-case high exposure scenario could be associated with mis-dosing rather than concomitant medications, such as multiple self-injection of 50 mg. However, given that albiglutide is only available as a single-dose pen (unlike other GLP-1 agonists), a scenario of high unintended clinical exposure is considered unlikely.</p> <p>Consider a possible worst-case exposure prediction based on administration of two 50 mg doses at steady-state during a 50 mg weekly dosing regimen:</p> <p><b>Simulated high exposure scenario*</b></p> <table border="1"> <thead> <tr> <th>Regimen</th> <th>Population Mean AUC(weekly) µg·h/mL</th> <th>Cmax ng/mL</th> </tr> </thead> <tbody> <tr> <td>50 mg Weekly at SS</td> <td>536</td> <td>3596</td> </tr> <tr> <td>Mis-dosing of 100 mg (2 x 50 mg) at SS during a 50 mg Weekly Regimen</td> <td>781</td> <td>5312</td> </tr> <tr> <td>% Increase in Exposure</td> <td>46%</td> <td>48%</td> </tr> </tbody> </table> <p>*Simulations based on population in study GLP110125</p>		Regimen	Population Mean AUC(weekly) µg·h/mL	Cmax ng/mL	50 mg Weekly at SS	536	3596	Mis-dosing of 100 mg (2 x 50 mg) at SS during a 50 mg Weekly Regimen	781	5312	% Increase in Exposure	46%	48%																	
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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QIANYU DANG  
08/05/2013

ANSHU MARATHE  
08/05/2013

KEVIN M KRUDYS  
08/05/2013

MONICA L FISZMAN  
08/05/2013

NORMAN L STOCKBRIDGE  
08/05/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # BLA# 125431	NDA Supplement #:S- BLA Supplement # 0.0	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: albiglutide Dosage Form: for injection Strengths: 30 mg, 50 mg		
Applicant: GlaxoSmithKline LLC Agent for Applicant (if applicable): Susan L. Watts, Ph.D.		
Date of Application: January 11, 2013 Date of Receipt: January 14, 2013 Date clock started after UN:		
PDUFA Goal Date: January 14, 2014		Action Goal Date (if different):
Filing Date: March 16, 2013		Date of Filing Meeting: February 27, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ): N/A				
List referenced IND Number(s): 065177				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			Tracking dates in RMS-BLA
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="#">0</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Tracked in RMS-BLA
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes</b> , explain in comment column.				
<b>If affected by AIP</b> , has OC/OMPQ been notified of the submission? <b>If yes</b> , date notified:				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<b>User Fee Status</b>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<b>Payment for this application:</b>  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		<b>Payment of other user fees:</b>  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
N/A					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?					
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].					
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?					
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug</b>			X		

<i>Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
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<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><b>If yes</b>, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			X	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>			X	
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?		<b>X</b>		
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		<b>X</b>		
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>			<b>X</b>	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?		<b>X</b>		
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?		<b>X</b>		
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?			X	
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?			X	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			waiver for albiglutide for the indication of type 2 diabetes mellitus in pediatric patients from birth to <10 years.
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>			X	This application also contains a PPSR. An inadequate PPSR letter will be issued.
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			Email sent to CDER OSI RMP mailbox
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>		X		
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK (Patient labeling)? ( <i>send WORD version if available</i> )	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Reviewer for OBP already assigned. He will review the carton and container labels.
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				Whether or not QT-IRT consult is necessary is still pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> October 21, 2008, November 22, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> November 15, 2012	X			Meeting comments sent out on August 10, 2011, July 6, 2012 for type C meeting.
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 27, 2013

**BLA/NDA/Supp #:** 125431

**PROPRIETARY NAME:** EPERZAN

**ESTABLISHED/PROPER NAME:** albiglutide

**DOSAGE FORM/STRENGTH:** for injection/30 mg, 50 mg

**APPLICANT:** GlaxoSmithKline LLC

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

**BACKGROUND:** EPERZAN (albiglutide) is a glucagon-like peptide-1 receptor (GLP-1R) agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). This licensing application is for a 30-mg and a 50-mg single-use prefilled pen, supplied with a 29G 5-mm needle, to be patient self-administered subcutaneously once weekly. For the BLA, the efficacy and safety of albiglutide are supported by results from 8 Phase III studies in adult patients with T2DM. At the time of this submission, five of these Phase III studies are ongoing to 3 years.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Y
	CPMS/TL:	Mehreen Hai	Y
Cross-Discipline Team Leader (CDTL)	Jean-Marc Guettier		Y
Clinical	Reviewer:	Kaveeta Vasisht	Y
	TL:	Jean-Marc Guettier	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Lokesh Jain	Y
Biostatistics	Reviewer:	Japobrata Choudhury	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ronald Wange	Y
	TL:	Karen Davis-Bruno	Y
Statistics (carcinogenicity) – see pharm tox filing review dated 2.27.13	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	Joao Pedras-Vasconcelos	Y
	TL:	Susan Kirshner	N
Product Quality (CMC)	Reviewer:	Joao Pedras-Vasconcelos (lead primary), Arulvathani Arudchandran (primary reviewer), Montserrat Puig (primary reviewer)	Y
	TL:	Susan Kirshner (secondary reviewer), Emanuela Lacana (tertiary reviewer)	
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Lakshmi Narasimhan (DS), Bo Chi (DP)	Y
	TL:	Patricia Hughes	
CMC Labeling Review	Reviewer:	See Product Quality Reviewers	
	TL:	See Product Quality Reviewers	
Facility Review/Inspection	Reviewer:	Lakshmi Narasimhan (DS), Bo Chi (DP)	Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Sarah Vee (TradeName); Reasol Agustin (C&C label)	Y
	TL:	Lena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	N
	TL:	Cynthia LaCivita	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Bo Li (DB7 stats), MatSoukup (DB7 stats TL)		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> No comments</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> No comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <ul style="list-style-type: none"> <li>Reason: this drug/biologic is not the first in its class <b>and the application did not raise</b></li> </ul>

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p><b>significant safety</b></p>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> No comments for 74-day letter. Comments in Clinical Pharmacology filing review already sent and respond to by sponsor (eCTD 005)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> No comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> No comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b> Joao Pedras Vasconcel reviewed the immunogenicity assays during the IND phase.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> No comments for the 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Environmental Assessment</p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> See also CMC reviewer's filing review dated 2.28.13</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> submitted by Lakshmi Rani Narasimhan</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b> No comments for 74-day letter</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> CV stats had no comments for the 74-day letter.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Dr. Curt Rosebraugh</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): June 19, 2013</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). N/A</p>

<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. N/A
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAYMOND S CHIANG  
04/03/2013

# Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

## INSTRUCTIONS FOR COMPLETING THE SRPI

There is one drop-down menu and one comment field for each item.

Drop-Down Menu: “NO” is the default option. For each SRPI item, click on the word “NO” and choose one of three following options:

- NO: The PI does not meet the requirement for this item (deficiency).
- YES: The PI meets the requirement for this item (no deficiency).
- N/A (not applicable): This item does not apply to the specific PI under review.

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word “Comment” and insert your comment.

## INSTRUCTIONS FOR COPYING ITEMS FROM SRPI TO 74-DAY OR ADVICE LETTER:

The SRPI is “protected” (or “locked”) to allow use of the drop-down menus. However, the “protection” mode does not allow you to directly copy the SRPI item into the 74-day or advice letter.

To copy SRPI items in the letter, after completion of the 48-item SRPI checklist, unprotect (or unlock) the document:

### Microsoft Word 2003

(1) Click on the “Tools” tab, then (2) click on “Unprotect Document.”

### Microsoft Word 2007

(1) Click the “Review” tab, (2) click on “Protect Document”, (3) on “Restrict Formatting and Editing” window click “Stop Protection” at the bottom of the window, and (3) click “OK” (leave the password box blank).

If you need to switch from the “unprotected” mode back to the “protected” mode to allow use of the drop-down menus:

### Microsoft Word 2003

(1) Click the “Tools” tab (2) click on “Protect Document”, (3) click on “Yes, Start Enforcing Protection” in the right-sided task pane, and (4) click “OK” (leave the password box blank).

### Microsoft Word 2007

(1) Click the “Review” tab, (2) click on “Protect Document” tab, (3) click on “Restrict Formatting and Editing”, (4) click on “Yes, Start Enforcing Protection”, and (5) click “OK” (leave the password box blank).

END INSTRUCTION: DELETE ALL INSTRUCTIONS BEFORE DARRTS CHECK-IN.]

# Selected Requirements of Prescribing Information (SRPI)

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## Highlights (HL)

### GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI

## Selected Requirements of Prescribing Information (SRPI)

• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

- YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

- YES** 12. All text must be **bolded**.

**Comment:**

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

### Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

### Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

### Comment:

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

### Comment:

**N/A**

## Selected Requirements of Prescribing Information (SRPI)

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: TOC states (b) (4) whereas the HL and FPI state “Warning”.

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
Comment:

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>

## Selected Requirements of Prescribing Information (SRPI)

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

### Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

### Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

### Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

### Comment:

## FULL PRESCRIBING INFORMATION DETAILS

### Boxed Warning

- YES** 42. All text is **bolded**.

### Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

### Comment:

### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

### Comment:

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information (SRPI)

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### **Patient Counseling Information**

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:** *Only mentions the Medication Guide*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAYMOND S CHIANG  
03/19/2013