

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209803Orig1s000

209805Orig1s000

209806Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209803 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Steglatro Established/Proper Name: ertugliflozin Dosage Form: tablet		Applicant: Merck Sharpe & Dohme Corporation Agent for Applicant (if applicable):
RPM: Elizabeth Godwin		Division: Metabolism and Endocrinology Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>December 19, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date Approval, December 19, 2017
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included (refer to labels attached to approval letter)
❖ Proprietary Name - Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	Conditionally Acceptable 3/27/2017 Reviews 3/22/2017
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☒ 3/1/2017 DMEPA: ☒ 11/1/2017, 5/4/2017 DMPP/PLT (DRISK): ☒ 11/17/2017 OPDP: ☒ 11/16/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ DPMH: 8/25/2017
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM: 3/1/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>11/01/2017</u> If PeRC review not necessary, explain: _____	11/1/2017
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 9/6/2016
EOP2 meeting (<i>indicate date of mtg</i>)	☒ 12/17/2012
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ 6/5/2017
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ 9/18/2017
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ No separate review
Division Director Summary Review (<i>indicate date for each review</i>)	☒ No separate review
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 12/13/2017
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ 2
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		☒ No separate review
• Clinical review(s) (indicate date for each review)		12/4/2017; 2/16/2017
• Social scientist review(s) (if OTC drug) (indicate date for each review)		☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)		See page 55 of clinical review dated December 4, 2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵		☒ QT/IRT: 6/14/2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		☒ N/A
❖ Risk Management		
• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))		N/A
• REMS Memo(s) and letter(s) (indicate date(s))		N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)		☒ 8/24/2017
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		☒ 8/18/2017
Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)		☐ None
Biostatistics		☐ None
❖ Statistical Division Director Review(s) (indicate date for each review)		☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)		☒ No separate review
Statistical Review(s) (indicate date for each review)		☒ 8/25/2017; 8/15/2017; 2/17/2017; 2/6/2017
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)		☒ 8/18/2017; 2/6/2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		☒ 2/17/2017; 2/16/2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ 12/11/2017
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☒ 8/17/2017; 1/4/2017; 8/5/2016; 10/7/2013; 8/29/2011; 5/23/2011; 10/30/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ 6/29/2017
❖ ECAC/CAC report/memo of meeting	☒ 5/26/2017
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ Not applicable
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ Not applicable
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☒ 8/18/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	8/18/2017
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ N/A ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☐ N/A
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ N/A <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	Done

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

/s/

ELIZABETH R GODWIN
12/21/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209805 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Steglujan Established/Proper Name: ertugliflozin and sitagliptin Dosage Form: tablet		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Elizabeth Godwin		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>December 19, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1 and 4
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval, December 19, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	☒ Included (refer to labels attached to approval letter)
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>)	02/15/2017 02/10/2017; 10/06/2016
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ 03/01/2017 DMEPA: ☒ 11/01/2017; 05/04/2017 DMPP/PLT (DRISK): ☒ 12/01/2017 OPDP: ☒ 11/21/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ DPMH 08/25/2017
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	RPM: 03/01/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>11/01/2017</u> If PeRC review not necessary, explain: _____	11/1/2017
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Not applicable
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 09/06/2016
EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ 06/05/2017
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ 09/18/2017
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ No separate review
Division Director Summary Review (<i>indicate date for each review</i>)	☒ No separate review
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 12/13/2017
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		☒ No separate review
• Clinical review(s) (indicate date for each review)		12/04/2017; 02/16/2017
• Social scientist review(s) (if OTC drug) (indicate date for each review)		☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)		See page 55 of clinical review dated December 4, 2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵		☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)		☒ None 08/25/2017
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		☒ 08/18/2017
Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)		☐ None
Biostatistics		☐ None
❖ Statistical Division Director Review(s) (indicate date for each review)		☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)		☒ No separate review
Statistical Review(s) (indicate date for each review)		☒ 08/28/2017; 08/25/2017; 02/17/2017
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)		☒ 08/18/2017; 08/07/2017; 02/07/2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		☒ 04/17/2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ 12/11/2017
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☒ 12/14/2017; 08/17/2017; 01/05/2017; 08/05/2016; 12/03/2015; 08/28/2014; 10/07/2013; 08/29/2011; 05/23/2011; 10/30/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ 05/26/2017 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☒ 11/06/2017; 08/18/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	08/18/2017
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ N/A ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☐ N/A
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ N/A <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	Done

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/s/

ELIZABETH R GODWIN
12/21/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209806 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)
Proprietary Name: Segluromet Established/Proper Name: ertugliflozin and metformin hydrochloride Dosage Form: tablets		Applicant: Merck Sharpe & Dohme Corp Agent for Applicant (if applicable):
RPM: Elizabeth Godwin		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity (notify CDER OND IO) Date of check: December 19, 2017 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>December 19, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions (specify type and date for each action taken)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1 and 4
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval, December 19, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (refer to labeling attached to approval letter)
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	☒ Included (refer to labeling attached to approval letter)
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>)	02/15/2017 02/10/2017; 11/08/2016
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ 03/01/2017 DMEPA: ☒ 11/01/2017; 05/04/2017 DMPP/PLT (DRISK): ☒ 12/01/2017 OPDP: ☒ 11/21/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ DPMH 08/25/2017
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	03/01/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Cleared: 11/20/2017
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>11/01/2017</u> If PeRC review not necessary, explain: _____	11/1/2017
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Not applicable
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 09/06/2016
EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ 06/05/2017
Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ 09/18/2017
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ 12/13/2017
Division Director Summary Review (<i>indicate date for each review</i>)	☒ 12/13/2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 12/13/2017
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ 1
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	12/04/2017; 02/16/2017
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None Not applicable
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	See page 55 of clinical review dated December 4, 2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None 08/24/2017
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ 08/18/2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☒ 08/28/2017; 08/25/2017; 02/22/2017
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☒ 08/18/2017; 08/07/2017; 02/07/2017
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☐ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ 12/11/2017
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☒ 08/31/2017; 01/05/2017; 08/05/2016; 12/03/2015; 09/05/2014; 10/07/2013; 08/29/2011; 05/23/2011; 10/30/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ 05/26/2017 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☒ 08/18/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	08/18/2017
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ N/A <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	Done
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	Done

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/s/

ELIZABETH R GODWIN
12/21/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin) - Round 6 FDA Labeling Comments
Date: Monday, December 18, 2017 3:41:15 PM
Attachments: [image002.png](#)

Thanks Liz.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, December 18, 2017 3:23 PM
To: Fuh, Vivian
Subject: NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin) - Round 6 FDA Labeling Comments
Importance: High

Hi Vivian,

Attached is the sixth round of Agency edits of the proposed labeling and Medication Guides for NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin). We remind you that portions of labeling are still under review and consideration, and therefore the recommended revisions do not reflect a final regulatory decision for this application.

In the revised labeling for all three NDAs, only use the 'tracked changes' and 'comment bubble' features of Microsoft Word. Please accept all Agency edits that you agree with. The documents that you return to us should only show in tracked changes of: (1) any new edits you have made to our prior edits; and (2) any new edits unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations. When you add a comment bubble, please state "Applicant response to FDA change" or "Applicant comment."

We ask the you complete your review and return comments as soon as possible.

Please confirm receipt of this email, and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

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Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
12/18/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin) - Round 5 FDA Labeling Comments
Date: Friday, December 15, 2017 1:28:14 PM
Attachments: [NDA 209803 ertugliflozin PI FDA Comments 15Dec2017.doc](#)
[NDA 209803 ertugliflozin MG FDA Comments 15Dec2017.docx](#)
[NDA 209805 ertugliflozin and sitagliptin PI FDA Comments 15Dec2017.doc](#)
[NDA 209805 ertugliflozin and sitagliptin MG FDA Comments 15Dec2017.docx](#)
[NDA 209806 ertugliflozin and metformin PI FDA Comments 15Dec2017.doc](#)
[NDA 209806 ertugliflozin and metformin MG FDA Comments 15Dec2017.docx](#)
[image001.png](#)

Hi Vivian,

Attached is the fifth round of Agency edits of the proposed labeling and Medication Guides for NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin). We remind you that portions of labeling are still under review and consideration, and therefore the recommended revisions do not reflect a final regulatory decision for this application.

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We ask the you complete your review and return comments by **noon on Monday, December 18, 2017**.

Please confirm receipt of this email, and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
12/15/2017

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To: [Fuh, Vivian](#)
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[NDA 209805 ertugliflozin and sitagliptin MG FDA Comments 15Dec2017.docx](#)
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Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

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/s/

ELIZABETH R GODWIN
12/15/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin) - Round 5 FDA Labeling Comments
Date: Friday, December 15, 2017 1:28:14 PM
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[NDA 209805 ertugliflozin and sitagliptin MG FDA Comments 15Dec2017.docx](#)
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[NDA 209806 ertugliflozin and metformin MG FDA Comments 15Dec2017.docx](#)
[image001.png](#)

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Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

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ELIZABETH R GODWIN
12/15/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 and 209806 - ertugliflozin and ertugliflozin/metformin - PMR Description Information Request - Response
Date: Friday, December 15, 2017 8:32:16 AM
Attachments: [image007.png](#)

Hi Liz, the highlighted change is acceptable. Regards, Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Thursday, December 14, 2017 10:16 AM
To: Fuh, Vivian
Subject: NDA 209803 and 209805 - ertugliflozin and ertugliflozin/metformin - PMR Description Information Request

Hello Vivian,

We propose the following change to the description of your deferred pediatric study required under the PREA:

Conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, and pharmacokinetics (PK) of ertugliflozin **as add-on to metformin background therapy** for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 30-week double-blind, controlled extension. Patients will be randomized to receive one of two doses of ertugliflozin or placebo once daily. The ertugliflozin doses will be determined using a population PK model derived from the Phase 3 program (in adult subjects) for ertugliflozin. As part of the pediatric study, sparse blood samples for population PK and exposures-response analysis will be collected. An interim analysis of the PK data will be performed during this study to confirm acceptable exposure to ertugliflozin with the selected doses.

Final Protocol Submission:	October 2018
Study Completion:	March 2026
Final Report Submission:	September 2026

This change is intended to improve clarity and consistency with your Agreed PSPs. In addition, please note that this PMR will apply to both NDA 209803 and NDA 209806, consistent with your Agreed PSP for each product.

Please confirm receipt of this email and provide your concurrence with the above by noon on Friday, December 15.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
12/15/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin) - Round 4 FDA Labeling Comments
Date: Friday, December 08, 2017 4:45:32 PM
Attachments: [image001.png](#)
[NDA 209803 ertugliflozin MG FDA Comments 08Dec2017.docx](#)
[NDA 209803 ertugliflozin PI FDA Comments 08Dec2017.docx](#)
[NDA 209805 ertugliflozin and sitagliptin PI FDA Comments 08Dec2017.docx](#)
[NDA 209805 ertugliflozin sitagliptin MG FDA Comments 08Dec 2017.doc](#)
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[NDA 209806 ertugliflozin metformin MG FDA Comments 08Dec2017.doc](#)
[FDA Proposal for Labeling in Section 14.docx](#)

Hi Vivian,

Attached is the fourth round of Agency edits of the proposed labeling and Medication Guides for NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin). We remind you that portions of labeling are still under review and consideration, and therefore the recommended revisions do not reflect a final regulatory decision for this application. In addition to the labels, we have included a Word document with our proposals for labeling in Section 14.

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We ask the you complete your review and return comments by noon on Tuesday, December 12, 2017.

Please confirm receipt of this email, and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
12/08/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
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ELIZABETH R GODWIN
12/08/2017

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To: [Fuh, Vivian](#)
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ELIZABETH R GODWIN
12/08/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - PMR/PMC Draft List
Date: Wednesday, December 06, 2017 2:25:39 PM
Attachments: [image002.png](#)

Hi Liz, we agree with the additional edits. Thanks, Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, December 04, 2017 3:23 PM
To: Fuh, Vivian
Subject: RE: NDA 209803 - ertugliflozin - PMR/PMC Draft List

Hi Vivian,

Please find attached the PMR/PMC list for NDA 209803 ertugliflozin tablets with some additional edits. Please let us know if you agree with the edits by Wednesday, December 6, 2017.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Wednesday, November 15, 2017 3:32 PM
To: Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>
Subject: RE: NDA 209803 - ertugliflozin - PMR/PMC Draft List

Thanks Liz, confirming receipt.

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, November 15, 2017 3:20 PM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - PMR/PMC Draft List

Hello Vivian,

Please see the attached draft PMR/PMC list for NDA 209803 ertugliflozin tablets. Instructions are included in the first part of the document. The submission can be sent back either via email or as a formal submission to the application. Please respond by close of business on **Wednesday, November 22, 2017**, with any edits marked via tracked changes.

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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PMR list for NDA 209803
STEGLATRO (ertugliflozin) tablets

While review of your application continues, we are sending you a draft list of PMRs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR studies/trials to us with the milestone dates indicated below.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

- 1) Conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, and pharmacokinetics (PK) of ertugliflozin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 30-week double-blind, controlled extension. Patients will be randomized to receive one of two doses of ertugliflozin or placebo once daily. The ertugliflozin doses will be determined using a population PK model derived from the Phase 3 program (in adult subjects) for ertugliflozin. As part of the pediatric study, sparse blood samples for population PK and exposures-response analysis will be collected. An interim analysis of the PK data will be performed during this study to confirm acceptable exposure to ertugliflozin with the selected doses.

~~Draft Protocol Submission:~~

Final Protocol Submission: October, 2018

Trial Completion: March, 2026

Final Report Submission: September, 2026

Comment: The Sponsor proposes that the draft protocol submission date not be included as a milestone for the PMR. We are currently anticipating submission of a draft protocol by February, 2018. We propose a final protocol submission of October, 2018 to allow time for input from FDA and EMA.

FDA Response: Your proposal is acceptable.

- 2) Conduct a randomized, double blind, placebo-controlled trial evaluating the effect of ertugliflozin on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. 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 ertugliflozin to that observed in the placebo group is less than 1.3. This trial must also assess pregnancy outcomes and the following adverse events: amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, and malignancies, and pregnancy outcomes. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess effects on renal function.

Trial Completion: October, 2019

Final Report Submission: December, 2020

Comment: The study is an event-driven study. The proposed trial completion date of October, 2019 is the estimated accrual date of the final CV death event. Last Patient Last Visit to occur sometime thereafter.

FDA Response: Your proposed milestones are acceptable. Please note our minor clarifying edit made in the PMR description above.

Additional Information

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of 5 years from the U.S. approval date, you submit all cases of ketoacidosis reported with STEGLATRO (ertugliflozin) tablets as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of events of ketoacidosis reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of STEGLATRO (ertugliflozin) tablets as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of ketoacidosis reported with STEGLATRO (ertugliflozin) tablets should also be provided in the periodic safety report.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C PBRER format, you will need to submit a formal waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs. You should ensure that your proposal does not result in any gaps in reporting.

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ELIZABETH R GODWIN
12/06/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request: Sponsor Clarification Request
Date: Thursday, November 30, 2017 5:01:02 PM
Attachments: [image007.png](#)

Hi Vivian,

Please find our responses in bold.

1. What is the meaning of the “*” and “***” symbols in the column headers?

FDA Response: It’s a typo-please disregard

2. A review of several products in the Drugs Trial Snapshots website did not result in any examples of other products that have subgroup analyses with relative risk and forest plots for a safety endpoint. We think a table summarizing the absolute risk for each treatment group, without comparative analyses would provide a simpler display and be more easily understood by the general public. Please confirm if a simpler table providing incidence rates by subgroup (columns A-E of the spreadsheet) can be provided for this purpose. In this case, no forest plot would be created.

FDA response: While absolute risk is indeed a simpler display, we also aim for more informative way of assessing the demographic differences for drug safety (e.g. Kengreal, Tremfya, Fasenra, Vabomere snapshots) using RR with or without plots.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Tuesday, November 28, 2017 2:43 PM
To: Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>
Subject: RE: NDA 209803 - ertugliflozin - Information Request: Sponsor Clarification Request

Thanks Liz. We have the following questions:

- 1) What is the meaning of the “*” and “***” symbols in the column headers?
- 2) A review of several products in the Drugs Trial Snapshots website did not result in any examples of other products that have subgroup analyses with relative risk and forest plots for a safety endpoint. We think a table summarizing the absolute risk for each treatment group, without comparative analyses would provide a simpler display and be more easily understood by the general public. Please confirm if a simpler table providing incidence rates by subgroup (columns A-E of the spreadsheet) can be provided for this purpose. In this case, no forest plot would be created.

Thanks for the clarifications.

Regards,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Tuesday, November 28, 2017 11:00 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request

Hello Vivian,

We are requesting your assistance in populating the attached table and producing a forest plot for safety subgroup analyses for your New Molecular Entity, ertugliflozin, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on Drugs Trial Snapshots webpage.

We are requesting you submit this information no later than December 4, 2017.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Please confirm receipt.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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your system.

APPEARS THIS WAY ON ORIGINAL

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/s/

ELIZABETH R GODWIN
12/01/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803 - ertugliflozin - Information Request
Date: Tuesday, November 28, 2017 10:59:57 AM
Attachments: [safety subgroup analysis \(002\).xlsx](#)
[image001.png](#)

Hello Vivian,

We are requesting your assistance in populating the attached table and producing a forest plot for safety subgroup analyses for your New Molecular Entity, ertugliflozin, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on Drugs Trial Snapshots webpage.

We are requesting you submit this information no later than December 4, 2017.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Please confirm receipt.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



Table 7.5.3-a. Subgroup Analysis of Genital Mycotic Infections

Subgroup	TRADEMARK (N=1029)	Total, n	Placebo (N=515)	Total, n	Relative Risk***	95% CI	
	n(%) x (%)**		n(%) x (%)**			LL	UL
Overall Genital Mycotic Infection							
Sex							
Men							
Women							
Age Group							
<17 years							
17 - 64 years							
>=65 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Source:							

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ELIZABETH R GODWIN
11/28/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803, 209805, and 209806 - ertugliflozin; ertug/sitagliptin; ertug/metformin - Round 3 Labeling FDA Comments
Date: Friday, November 24, 2017 11:49:03 AM
Attachments: [image001.png](#)
[NDA 209803 ertugliflozin PI FDA Comments 24Nov2017.doc](#)
[NDA 209805 ertugliflozin and sitagliptin PI FDA Comments 24Nov2017.doc](#)
[NDA 209806 ertugliflozin and metformin PI FDA Comments 24Nov2017.doc](#)
[NDA 209803 ertugliflozin MedGuide FDA Comments 24Nov2017.doc](#)

Hello Vivian,

Attached is the third round of Agency edits of the proposed labeling for NDA 209803 (ertugliflozin), NDA 209805 (ertugliflozin and sitagliptin), and NDA 209806 (ertugliflozin and metformin). We remind you that portions of labeling are still under review and consideration, and therefore the recommended revisions do not reflect a final regulatory decision for this application. The Medication Guide for NDA 209803 (ertugliflozin) is also attached, the Medication Guides for NDAs 209805 and 209806 will be sent at a later date.

In the revised labeling for all three NDAs, only use the 'tracked changes' and 'comment bubble' features of Microsoft Word. Please accept all Agency edits that you agree with. The documents that you return to us should only show in tracked changes of: (1) any new edits you have made to our prior edits; and (2) any new edits unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations. When you add a comment bubble, please state "Applicant response to FDA change" or "Applicant comment."

We ask the you complete your review and return comments by November 29, 2017.

Please confirm receipt of this email, and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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Tel: 240-402-3438

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

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ELIZABETH R GODWIN
11/24/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 8, 2017

Application Number: NDA 209803

Product Name: ertugliflozin tablets

Applicant Name: Merck Sharpe & Dohme Corp.

Subject: Discussion of including amputations in the ertugliflozin label

FDA Participants

Mary T. Thanh Hai, MD, Deputy Director, ODE II

William Chong, MD, Clinical Team Lead, DMEP

Frank Pucino, PharmD, MPH, Clinical Reviewer, DMEP

Eugenio Andraca-Carrera, PhD, Lead Mathematical Statistician, Office of Translational Sciences (OTS), Office of Biostatistics (OB), Division of Biometrics VII (DBVII)

Elande Baro, PhD, Statistical Reviewer, OTS, OB, DBVII

Liz Godwin, MSHS, CCRP, Regulatory Project Manager

Applicant Participants

Merck

Vivian Fuh, Executive Director, Global Regulatory Affairs

Leslie Lipka, Senior Director, Clinical Safety and Risk Management

Jose Vega, VP Regulatory Affairs (Global Safety)

Sandra Milligan, SVP Regulatory Affairs

Yale Mitchel, Scientific AVP, Clinical Research, GCD Atherosclerosis

Steven Bird, Senior Principal Scientist, Biostatistics

Raymond Bain, VP Biostatistics

Pfizer

Kenneth Verburg SVP Global Medicines Development

Richard Anziano, VP Global Statistics

1.0 BACKGROUND:

On December 19, 2016, Merck Sharpe & Dohme Corp. submitted a New Drug Application (NDA) for ertugliflozin tablets (NDA 209803). During the review, it was noted that there were concerns with the observed numeric imbalance in lower limb amputations in the ertugliflozin Phase 3 program that suggested an increased risk for these events.

The Division notified the Applicant of this concern during the June 5, 2017, Mid-Cycle Communication and the September 18, 2017, Late Cycle Meeting.

To further assess this potential safety signal the Division issued an information request (IR) to the firewalled team on September 26, 2017, asking for additional information on amputations from the ongoing blinded cardiovascular outcomes trial (CVOT). In response to the IR, the Applicant submitted a response on October 12, 2017.

On November 2, 2017, the Division provided the second round of ertugliflozin labeling edits, which included proposed language on the risk of lower limb amputation in Section 5 (Warnings & Precautions).

On November 3, 2017, the Applicant requested a teleconference with the Division to discuss amputations with the firewalled team.

A teleconference was arranged for November 8, 2017.

2.0 DISCUSSION:

Representatives from the firewalled team at Merck provided their thoughts (b) (4)

The Applicant acknowledged an imbalance in lower limb amputations in their Phase 3 program, but noted that there were only a small number of events (11 events in the ertugliflozin arm vs. 1 event in the comparator arm). Further, they felt that the information submitted from their ongoing CVOT did not support differences in event rates between ertugliflozin and placebo also noting that there was no evidence of dose response for these events. Therefore, their preference would be to wait until additional data from the completed CVOT were available (b) (4)

The Division expressed continued concerns as there were more events in the ertugliflozin treated patients in the CVOT. Given a suggestion of increased risk from two different sources of data and a finding of increased risk from another member of the class, the Division feels that this risk should be communicated to prescribers and patients in labeling. Based on available data, the Division acknowledged that there does not appear to be a dose-response relationship (i.e., the amputation event rate was higher in the ertugliflozin 5 mg vs. 15 mg arm). However, the absence of dose response is not necessarily reassuring as it remains unclear whether a dose response would be expected for amputation events.

The Applicant expressed concerns with the proposed amputation language provided in the Agency's labeling comments (dated November 2, 2017) as similar language is included in canagliflozin labeling, albeit without the Boxed Warning. The Division stated that this was the initial proposal and that the Division was open to considering alternative language. The Division suggested that the Applicant propose alternative language, which should include a rationale for the revised language.

To maintain the data integrity of the ongoing CVOT, the Division and Applicant agreed that it may be best to not to include data from this ongoing trial in the prescribing information. The

Division proposed that the rationale supporting the Applicant's proposed language be submitted separately to the Regulatory Project Manager to minimize the potential for blinded team members becoming aware of unblinded data from the CVOT.

3.0 ACTION ITEMS:

- Merck agreed to provide revised labeling with proposed amputation language and their rationale on Tuesday, November 14, 2017.

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/s/

ELIZABETH R GODWIN
11/20/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - PMR/PMC Draft List
Date: Wednesday, November 15, 2017 3:33:09 PM
Attachments: [image007.png](#)

Thanks Liz, confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, November 15, 2017 3:20 PM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - PMR/PMC Draft List

Hello Vivian,

Please see the attached draft PMR/PMC list for NDA 209803 ertugliflozin tablets. Instructions are included in the first part of the document. The submission can be sent back either via email or as a formal submission to the application. Please respond by close of business on **Wednesday, November 22, 2017**, with any edits marked via tracked changes.

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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PMR list for NDA 209803
STEGLATRO (ertugliflozin) tablets

While review of your application continues, we are sending you a draft list of PMRs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR studies/trials to us with the milestone dates indicated below.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

- 1) Conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, and pharmacokinetics (PK) of ertugliflozin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 30-week double-blind, controlled extension. Patients will be randomized to receive one of two doses of ertugliflozin or placebo once daily. The ertugliflozin doses will be determined using a population PK model derived from the Phase 3 program (in adult subjects) for ertugliflozin. As part of the pediatric study, sparse blood samples for population PK and exposures-response analysis will be collected. An interim analysis of the PK data will be performed during this study to confirm acceptable exposure to ertugliflozin with the selected doses.

Draft Protocol Submission:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

- 2) Conduct a randomized, double blind, placebo-controlled trial evaluating the effect of ertugliflozin on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. 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 ertugliflozin to that observed in the placebo group is less than 1.3. This trial must also assess the following adverse events: amputations, ketoacidosis, complicated genital infections, complicated urinary tract infections, fractures, pancreatitis, serious hypersensitivity events, malignancies, and pregnancy outcomes. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess effects on renal function.

Trial Completion:

Final Report Submission:

Additional Information

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of 5 years from the U.S. approval date, you submit all cases of ketoacidosis reported with STEGLATRO (ertugliflozin) tablets as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of events of ketoacidosis reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of STEGLATRO (ertugliflozin) tablets as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of ketoacidosis reported with STEGLATRO (ertugliflozin) tablets should also be provided in the periodic safety report.

Please note that if your product is approved and you wish to submit the periodic safety report in the ICH E2C PBRER format, you will need to submit a formal waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs. You should ensure that your proposal does not result in any gaps in reporting.

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/s/

ELIZABETH R GODWIN
11/15/2017

PeRC Meeting Minutes
November 1, 2017

PeRC Members Attending:

Lynne Yao
George Greeley
Meshaun Payne
Gerri Baer
Jacqueline Yancy
Shrikant Pagay
Susan McCune
Lily Mulugeta
Greg Reaman
Raquel Tapia
Thomas Smith
Daiva Shetty
Donna Snyder
Barbara Buch
Adrienne Hornatko-Munoz
Robert "Skip" Nelson
Susan Mccune
Julia Pinto
Jingjeng Ye
Dionna Greene
Victor Baum

Agenda

9:00	NON-RESPONSIVE				
9:15	NDA's 209803; 209805; 209806	Ertugliflozin Tablets; Sitagliptin and Ertugliflozin Tablets; Ertugliflozin and Metformin Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP	DMEP	Liz Godwin	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
9:25	NON-RESPONSIVE				
9:40					
9:50					
10:05					
10:25					
10:35					
10:45					

NON-RESPONSIVE

11:00

NON-RESPONSIVE

Ertugliflozin Tablets (Partial Waiver/Deferral/Plan); Sitagliptin and Ertugliflozin Tablets (Full Waiver); Ertugliflozin and Metformin Tablets (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Indication – Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- These product triggers PREA as a new active ingredient and have a PDUFA goal date of December 19, 2017.
- The division clarified that the studies planned for this product are consistent with other T2DM products, including semaglutide (see discussion above). The PeRC agreed with the studies planned for this product.
- The division also clarified that the PREA requirements for ertugliflozin as monotherapy and ertugliflozin in combination with metformin will be completed with the same studies.
- A plan for a full waiver for the sitagliptin and ertugliflozin combination product will be acceptable because studies are impossible or highly impracticable. T2DM pediatric patients rarely require triple drug therapy (this drug would be added on to metformin therapy).
- *PeRC Recommendations:*
 - The PeRC concurred with the sponsor's plan for waivers and deferrals for these 3 products (see discussion above).
 - The PeRC recommended that the division try to harmonize the language in the PREA PMR for this product and the other T2DM products so that it is clear the requirements for T2DM products are generally aligned.

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
11/14/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Round 2 Labeling FDA Comments
Date: Thursday, November 02, 2017 5:57:28 PM
Attachments: [image007.png](#)

Hi Liz, thanks, confirming receipt. I had a few questions. Please let me know when is a good time for me to call you, or please try my cell (b) (6) (I'm at an offsite meeting on Friday Nov 2).
Thanks, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, November 02, 2017 4:29 PM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Round 2 Labeling FDA Comments

Hello Vivian,

Attached is the second round of Agency edits of the proposed labeling for NDA 209803 (ertugliflozin). We remind you that portions of labeling are still under review and consideration, and therefore the recommended revisions do not reflect a final regulatory decision for this application.

Additionally, revise the prescribing information for NDA 209805 (ertugliflozin and sitagliptin) and NDA 209806 (ertugliflozin and metformin hydrochloride) to be consistent with our labeling recommendations for NDA 209803. Please note, we do not recommend the use of ertugliflozin and ertugliflozin fixed combination drug products (FCDPs) in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.72 m². (b) (4)

(b) (4)

In the revised labeling for all three NDAs, only use the 'tracked changes' and 'comment bubble' features of Microsoft Word, and remove all additional text boxes and associated formatting. Please accept all Agency edits that you agree with. The documents that you return to us should only show in tracked changes of: (1) any new edits you have made to our prior edits; and (2) any new edits unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations. When you add a comment bubble, please state "Applicant response to FDA change" or "Applicant comment."

We ask that you complete your review and return comments by November 9, 2017.

Please confirm receipt of this email, and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
11/03/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Cc: [Lalmansingh, Anika](#)
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request
Date: Wednesday, November 01, 2017 2:46:11 PM
Attachments: [image002.png](#)

Thanks Liz!

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, November 01, 2017 2:37 PM
To: Fuh, Vivian
Cc: Lalmansingh, Anika
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Hi Vivian,

Based on updated information, the sitagliptin manufacturer (b) (4) can remain on the FDA 356h form.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Thursday, October 26, 2017 10:58 AM
To: Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>
Cc: Lalmansingh, Anika <Anika.Lalmansingh@fda.hhs.gov>
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Thanks Liz, confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, October 26, 2017 10:37 AM
To: Fuh, Vivian
Cc: Lalmansingh, Anika
Subject: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Hi Vivian,

We note that as of the October 20, 2017, amendment to NDA 209805 ertugliflozin/sitagliptin tablets, the deficient sitagliptin manufacturer (b) (4) is still on the FDA 356h form. We request that you submit an amendment to remove this site from the NDA **no later than November 15, 2017**, in order to not impact the final recommendation, unless the deficiencies at this site are resolved prior to this date.

Please confirm receipt.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

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ELIZABETH R GODWIN
11/01/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209806 - ertugliflozin/metformin - Information Request
Date: Wednesday, November 01, 2017 12:47:18 PM
Attachments: [image007.png](#)

Hi Liz,

Thanks for pointing this out. The statement was inadvertently left out of the original application and will be submitted to the NDA later today.

Please confirm receipt.

Regards,
Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, November 01, 2017 9:35 AM
To: Fuh, Vivian
Subject: NDA 209806 - ertugliflozin/metformin - Information Request

Hi Vivian,

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 020357 for Glucophage (metformin hydrochloride) tablets, but does not contain a patent certification or statement for the listed drug upon which you rely. Please submit an appropriate patent certification or statement.

Please confirm receipt and submit your response by November 8, 2017.

Thanks,
Liz

Liz Godwin, MSHS, CCRP
Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
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/s/

ELIZABETH R GODWIN
11/01/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Cc: [Lalmansingh, Anika](#)
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request
Date: Thursday, October 26, 2017 11:00:32 AM
Attachments: [image007.png](#)

Thanks Liz, confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, October 26, 2017 10:37 AM
To: Fuh, Vivian
Cc: Lalmansingh, Anika
Subject: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Hi Vivian,

We note that as of the October 20, 2017, amendment to NDA 209805 ertugliflozin/sitagliptin tablets, the deficient sitagliptin manufacturer (b) (4) is still on the FDA 356h form. We request that you submit an amendment to remove this site from the NDA **no later than November 15, 2017**, in order to not impact the final recommendation, unless the deficiencies at this site are resolved prior to this date.

Please confirm receipt.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
10/26/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDAs 209805 (ertugliflozin and sitagliptin) 209806 (ertugliflozin and metformin) - Information Request
Date: Tuesday, October 03, 2017 1:06:01 PM
Attachments: [image001.png](#)

Thanks Liz. Confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Tuesday, October 03, 2017 12:51 PM
To: Fuh, Vivian
Subject: NDAs 209805 (ertugliflozin and sitagliptin) 209806 (ertugliflozin and metformin) - Information Request

Hi Vivian,

We have the following information request for NDA 209805 (ertugliflozin and sitagliptin) tablets and NDA 209806 (ertugliflozin and metformin hydrochloride) tablets, please submit your response by Wednesday, October 11, 2017.

- For all packaging labels of NDA 209805 and NDA 209806, replace “/” by “and” in the dosage strengths (for example, revise “(ertugliflozin and metformin HCl) tablets 7.5 mg/500 mg” to “(ertugliflozin and metformin HCl) tablets 7.5 mg and 500 mg”.

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
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ELIZABETH R GODWIN
10/03/2017

From: CappelLynch, Callie
To: ["vivian_fuh@merck.com"](mailto:vivian_fuh@merck.com)
Cc: [Godwin, Elizabeth](#)
Subject: NDA 209803, 209805, 209806
Date: Tuesday, September 26, 2017 11:43:56 AM
Importance: High

Hi Vivian,

Please see the information request below for the above mentioned NDAs.

As discussed at the late cycle meeting, we have concerns with the observed numeric imbalance in lower limb amputations in the ertugliflozin Phase 3 program that suggested an increased risk for these events with ertugliflozin. To assist us in assessing this safety concern, please provide us with a count of the total number of amputation events to date in the CVOT (Trial P004/1021) and basic estimates of risk for these events in the ongoing trial. To maintain the CVOT data integrity and limit the potential for further unblinding we recommend, to the extent possible, that you do not further unblind yourselves for this request. In this light, we suggest you request these data from the DMC and that they present these counts and analyses as Treatment A vs. Treatment B.

We request that you send response as soon as possible. Please let us know the earliest feasible date for your response. Liz will return tomorrow, but please direct any communications to both of us for the remainder of today.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/26/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDAs 209803, 209805, and 209806 - ertugliflozin, ertugliflozin and sitagliptin, and ertugliflozin and metformin - Information Request
Date: Wednesday, September 13, 2017 11:49:16 AM
Attachments: [image001.png](#)

Hi Liz, Confirming receipt of this email. Regards, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, September 13, 2017 10:59 AM
To: Fuh, Vivian
Subject: NDAs 209803, 209805, and 209806 - ertugliflozin, ertugliflozin and sitagliptin, and ertugliflozin and metformin - Information Request

Hi Vivian,

We acknowledge receipt of your response to our information request for subgroup by treatment interaction analyses results for ertugliflozin on September 11, 2017. We now have a follow-up request.

Please provide a forest plot for each set of subgroup analyses:

- 1) Factorial study P005 and non-inferiority study P002 individually.
- 2) Studies P003, P006, P007 and P005 combined.

An example forest plot may be found at:

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm464098.htm> under the MORE INFO section of the question addressing whether there were any differences in how well the drug worked in clinical trials among sex, race and age.

Please submit your response by **Friday, September 15, 2017**.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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ELIZABETH R GODWIN
09/13/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Round 1 FDA Comments on Labeling
Date: Wednesday, August 30, 2017 2:19:19 PM
Attachments: [image001.png](#)

Thanks Liz. Confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, August 30, 2017 2:06 PM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Round 1 FDA Comments on Labeling

Hi Vivian,

Please refer to your New Drug Application (NDA 209803), dated and received December 19, 2016, for ertugliflozin tablets.

We also refer to our March 1, 2017, letter in which we notified you of our target date of August 26, 2017, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

Attached are the initial round of FDA edits of the draft labeling for the Prescribing Information (PI) for NDA 209803. These are preliminary edits and may be subject to change. We remind you that these edits do not reflect on the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "Merck response to FDA change" or "Merck comment." Only use Word document tracked changes and comments. The resubmitted labeling will be used for further labeling discussions.

We ask the you complete your review and return comments by close of business on Friday, September 15, 2017.

Please confirm receipt.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ELIZABETH R GODWIN
08/30/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Round 1 FDA Comments on Labeling
Date: Wednesday, August 30, 2017 2:18:53 PM
Attachments: [image001.png](#)

Thanks Liz, confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, August 30, 2017 2:06 PM
To: Fuh, Vivian
Subject: NDA 209805 - ertugliflozin/sitagliptin - Round 1 FDA Comments on Labeling

Hi Vivian,

Please refer to your New Drug Application (NDA 209805), dated and received December 19, 2016, for ertugliflozin and sitagliptin tablets.

We also refer to our March 2, 2017, letter in which we notified you of our target date of August 26, 2017, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

Attached are the initial round of FDA edits of the draft labeling for the Prescribing Information (PI) for NDA 209805. These are preliminary edits and may be subject to change. We remind you that these edits do not reflect on the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "Merck response to FDA change" or "Merck comment." Only use Word document tracked changes and comments. The resubmitted labeling will be used for further labeling discussions.

We ask the you complete your review and return comments by close of business on Friday, September 15, 2017.

Please confirm receipt.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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ELIZABETH R GODWIN
08/30/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209806 - ertugliflozin and metformin - Round 1 FDA Comments on Labeling
Date: Wednesday, August 30, 2017 2:12:11 PM
Attachments: [image001.png](#)

Hi Liz, confirming receipt. Thanks, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, August 30, 2017 2:06 PM
To: Fuh, Vivian
Subject: NDA 209806 - ertugliflozin and metformin - Round 1 FDA Comments on Labeling

Hi Vivian,

Please refer to your New Drug Application (NDA 209806), dated and received December 19, 2016, for ertugliflozin and metformin tablets.

We also refer to our March 2, 2017, letter in which we notified you of our target date of August 26, 2017, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

Attached are the initial round of FDA edits of the draft labeling for the Prescribing Information (PI) for NDA 209806. These are preliminary edits and may be subject to change. We remind you that these edits do not reflect on the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "Merck response to FDA change" or "Merck comment." Only use Word document tracked changes and comments. The resubmitted labeling will be used for further labeling discussions.

We ask that you complete your review and return comments by close of business on Friday, September 15, 2017.

Please confirm receipt.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
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ELIZABETH R GODWIN
08/30/2017

From: [Korn, Scott H.](#)
To: [Godwin, Elizabeth](#); [Fuh, Vivian](#)
Subject: RE: NDAs 209803, 209805, and 209806 - ertugliflozin; ertug/sitagliptin; ertug/metformin - Information Request
Date: Friday, August 25, 2017 11:19:30 AM
Attachments: [image001.png](#)

Proprietary

Liz,

Receipt confirmed. Will have our folks get started on request.

Scott

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Friday, August 25, 2017 11:16 AM
To: Fuh, Vivian; Korn, Scott H.
Subject: NDAs 209803, 209805, and 209806 - ertugliflozin; ertug/sitagliptin; ertug/metformin - Information Request

Hi Vivian and Scott,

Please complete the shell table for HbA1c results by subgroup based on analyses in each of the studies or combinations of studies listed below, using the return to baseline (RTB) multiple imputation method. For the individual active-controlled studies, estimate the treatment effect of ertugliflozin relative to the active comparator within subgroups and test for the difference in overall treatment effect across subgroups. For the analysis involving the combination of studies (first bullet below), estimate the treatment effect of ertugliflozin relative to the placebo within subgroups and test for the difference in overall treatment effect across subgroups by combining the estimates from the individual studies inversely weighted by their variances. For all analyses, please report least square means rather than raw means.

- Studies P003, P006, P007 and P005, combined:
 - For factorial study P005, only include comparisons involving Ertugliflozin + Sitagliptin + Metformin vs. Sitagliptin + Metformin (Sitagliptin + Metformin form the placebo).
- Active-controlled Factorial Study P005:
 - Only include comparisons involving Ertugliflozin + Sitagliptin + Metformin vs. Sitagliptin + Metformin.
- Active-controlled Non-Inferiority Study P002: Ertugliflozin versus Glimepiride.

With respect to the interaction tests of the treatment effect by race: for an individual study the ANCOVA model should include the factors/terms

- race (as a categorical factor)
- treatment

- treatment by race interaction term
- the covariates used in the primary analysis

When performing an interaction test of the treatment effect by race for a combination of studies, additionally include the factors/terms

- race by study interaction term
- treatment by study interaction term
- interaction terms with study for each covariate used in the primary analysis

Please provide the code and a description of the statistical methods used to generate these analyses.

Please confirm receipt of this email and submit your response by September 8, 2017.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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Table X. Effect of ertugliflozin on HbA1c by subgroup (see special instructions in Word docu

Demographic Parameters		Ertugliflozin
	N	Mean HbA1c at baseline
Sex		
Male		
Female		
Age Group		
below 65 years		
65 years and above		
Race		
White		
Black or African American		
Asian		
Other		
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		

ment)

		Control
Mean Change from Baseline to End of Study in HbA1c	N	Mean HbA1c at baseline

	Difference (95% Confidence Interval) in Mean Change from Baseline to End of Study in HbA1c (Ertugliflozin minus Control)
Mean Change from Baseline to End of Study in HbA1c	

Test for Treatment by Subgroup Interaction (p-value)
insert
insert
insert
insert

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ELIZABETH R GODWIN
08/25/2017

From: [Godwin, Elizabeth](#)
To: scott_korn@merck.com; [Fuh, Vivian](#)
Subject: NDAs 209803, 209805, and 209806 - information request
Date: Tuesday, August 22, 2017 8:40:18 AM
Attachments: [image001.png](#)

Hi Vivian and Scott,

In reviewing your New Drug Applications (NDAs) dated and received December 19, 2016, submitted under section 505(b) and pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin, ertugliflozin and sitagliptin, and ertugliflozin and metformin tablets. We have the following information request:

- We also refer to your submission dated February 24, 2017, Attachment 1 title, “Tenth Annual Report on Exposure during Pregnancy from the Merck Pregnancy Surveillance Program (previously called the Merck Pregnancy Registry) for JANUVIA® (sitagliptin phosphate) and JANUMET® (sitagliptin phosphate/metformin hydrochloride)”
 - Has the pregnancy registry been converted to a pregnancy surveillance program?
Your website still has this program listed as a registry.
 - If so, will data also be collected under this surveillance program for your other marketed products?

Please submit your response by Wednesday, August 23, 2017.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

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U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
08/22/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: Re: NDA 209803 209805 209806 May 11 2017 Information Requests
Date: Friday, August 11, 2017 3:50:56 PM

Hi Liz, confirming receipt.
Regards, Vivian

From: Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>
Sent: Friday, August 11, 2017 3:46:17 PM
To: Fuh, Vivian
Subject: RE: NDA 209803 209805 209806 May 11 2017 Information Requests

Hi Vivian,

We have reviewed your July 31, 2017, submission containing revised carton and container labels for NDAs 209803 (ertugliflozin), 209805 (ertugliflozin and sitagliptin), and 209806 (ertugliflozin and metformin), in response to our May 11, 2017, information request. We have no additional comments at this time and request you submit all of the carton and container labels officially to the three NDAs.

Please submit your response by August 28, 2017.

Please confirm receipt of this email.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Tuesday, August 01, 2017 12:49 PM
To: Godwin, Elizabeth
Subject: NDA 209803 209805 209806 May 11 2017 Information Requests

Hi Liz,

Responses to the May 11, 2017 information requests were submitted yesterday through the gateway.

Due to the large number of packaging components associated with these 3 concurrent NDA filings, Merck has submitted representative samples. This includes one full collection of one strength for NDA 209803 (to use as a basis for review), and one component for one strength to present for each of NDA 209805 and NDA 209806. As there are many similarities among the components the goal is for maximizing efficiency for both creation and subsequent review of the revisions. Once confirmed that, tentatively, there are no additional comments to the representative samples, Merck will supply all other packaging to the agency to complete the submission.

Please confirm receipt

Kind regards,
Vivian

Vivian L. Fuh, M.D., F.A.C.P.
Executive Director
Global Regulatory Affairs
Merck Sharp and Dohme, Corp.
126 East Lincoln Avenue, RY34-B188
Rahway, NJ 07065
phone: 732 594-0374

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ELIZABETH R GODWIN
08/11/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request
Date: Friday, August 04, 2017 3:44:21 PM
Attachments: [image001.png](#)

Liz, thanks very much. Confirming receipt. Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Friday, August 04, 2017 3:24 PM
To: Fuh, Vivian
Subject: RE: NDA 209803 - ertugliflozin - Information Request

Hi Vivian,

Please find attached the code for the ANCOVA model for non-inferiority study P002 for HbA1c (%).

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Tuesday, August 01, 2017 2:09 PM
To: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - Information Request
Importance: High

Hi Liz, regarding the questions below, we have the following clarification request:

Regarding the observed differences in results for the P002 J2R analyses, please clarify if you are using same base code that we used, ie the DIA Missing Data Working Group '5 macros'. Would you share your SAS program code with us so that we can examine the differences?

Thanks,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Tuesday, August 01, 2017 9:01 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request

Hi Vivian,

We acknowledge your response to our June 16, 2017, statistical information request, received Friday, July 21, 2017. Below are our follow-up requests, along with a request for information related to database lock for two of the studies (#4 below). Please submit your response by August 9, 2017.

- 1) We performed an ANCOVA analysis (using no intermediate measures) where missing final assessments on all arms were imputed based on the reference arm. For the non-inferiority Study P002 only, a 0.3 penalty for the experimental arms was included for the imputed values. On all studies, results using this approach were fairly close to your jump-to-reference (J2R) analysis - except for the P002 study. For this study, the 95% CI for my ANCOVA analysis was (0.01 0.26). On your J2R analysis for the same study, the 95% CI was (0.35, 0.66), a difference of 0.34 to 0.4. This seems odd.

Also your return to baseline analysis (RTB) analysis for P002, which appears to use RTB on the experimental arms and missing at random (MAR) on the glimepiride arm (see # 2 below), has 95% CI of (0.086, 0.34). These results also appear to be at odds with your J2R analysis for P002. Your J2R analysis for P002 also assumes MAR on the Glimepiride arm, and has only a 0.3 penalty on the experimental arms. Yet it has more extreme results than your RTB analysis.

Please check your J2R analysis for Study P002.

- 2) It appears from your report that your RTB analysis for HbA1c for P002 uses RTB on the ertugliflozin arms and MAR for the Glimepiride arm; see underlined bold statements (added for clarity) below from your report. We did ask for this analysis. However, please provide or point to the location of the RTB analysis that uses RTB on all arms. The relevant section from your report is included below:

Two missing data imputation approaches were used for continuous endpoints: return to baseline (RTB) and jump-to-reference (J2R). The RTB multiple imputations assumes subjects who discontinued study medication experienced a 'washout' of any potential effect of the assigned study medication and therefore returned to their baseline value following discontinuation. **For the RTB imputation, missing Week 52 values in the ertugliflozin arms were imputed from a normal distribution with the expected value set to the subject's baseline value** and the standard deviation estimated from the RMSE estimated from an ANCOVA model that used the observed data where the dependent variable was the Week 52 change from baseline for the parameter of interest, the independent variables included treatment, baseline eGFR, baseline value of the parameter of interest and prior antihyperglycemic medication (monotherapy or dual therapy). The random seed used in the RTB imputation was 89331. **Missing Week 52 values in the glimepiride arm were imputed assuming a MAR mechanism with PROC MI and random seed=59348.** The J2R multiple imputation used the same general approach as for the other ertugliflozin studies with K=100 imputations for each endpoint, random seed 12345 for the Markov chain Monte Carlo (MCMC) simulation and seed 834416 for the missing at random (MAR) model that imputed intermittent missings; with the exception that for the analysis of the primary A1C endpoint, a penalty shift of 0.3% was added to the ertugliflozin arms for each imputed Week 52 value.

- 3) For the P002 RTB output, there was no pairwise comparison in the results files. There was this output from the Log:

“WARNING: Variable PAHANUM already exists on file WORK.A1C2_TRANS2.

NOTE: Invalid string.
NOTE: Invalid argument to function INPUT. Missing values may be generated.
NOTE: Table WORK.A1C2_TRANS2 created, with 1324 rows and 9 columns.”

Then further down:

“ERROR: Cannot find level Glimepiride for effect TREAT. ”

This error was repeated several times. Can you help resolve this for us?

- 4) For studies P003 and P007, please provide or point to the location of the date of database lock.

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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please notify us immediately by reply e-mail and then delete it from your system.

Below is the code for the ANCOVA model for non-inferiority study P002 for HbA1c (%). No intermediate measures are used. Missing data on both the Glimepiride arm and the Ertugliflozin arms are imputed based on non-missing data on the Glimepiride arm. Then a 0.3 penalty is added for the Ertugliflozin arms.

For the non-inferiority study, the results are very different from your Jump-to-Reference (J2R) analysis. The difference between confidence intervals is about 0.35 to 0.4 in the non-inferiority study (95% CI 0.01, 0.25) for this method compared to (0.35, 0.66) for the J2R. The differences in results for the two methods are much closer in the other studies (always less than 0.1). **We recognize that these two methods of analysis are different and are not expected to have the same results. However, do you have any insights as to why the results of the two methods are so much more different from each other in the non-inferiority study compared to the other studies?**

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ELIZABETH R GODWIN
08/04/2017



NDA 209803

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000, Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by **Friday, July 28, 2017**, in order to continue our evaluation of your NDA.

1.

2.

3.

4.

5.

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

16.

(b) (4)

17.

If you have any questions, please contact Anika Lalmansingh, Regulatory Business Process Manager at (240) 402-0356.

Sincerely,

Suong Tran, PhD
Application Technical Lead
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

SUONG T TRAN
06/29/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request: Sponsor Response and Requests for Further Clarification
Date: Monday, June 26, 2017 9:11:04 AM
Attachments: [image001.png](#)

Thanks Liz. Confirming receipt.

Regards, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, June 26, 2017 8:50 AM
To: Fuh, Vivian
Subject: RE: NDA 209803 - ertugliflozin - Information Request: Sponsor Response and Requests for Further Clarification

Hi Vivian,

Your requests, received by the Agency on Thursday, June 22, 2017, are followed by Agency responses in bold.

1. We acknowledge FDA's request for supplemental analyses related to efficacy. Given the scope of this request and required run time for the programs, the Sponsor proposes to submit the requested analyses and analysis packages by July 14, 2017. Please confirm that this date is acceptable.

FDA Response: Submission of the requested analyses and analysis packages by July 14, 2017, is acceptable.

2. The Agency has specified a +/- 4-week window for the Week 26 superiority study assessments and the Week 52 non-inferiority study assessments. Due to the longer time period, we request that a +/- 8-week window be applied to the Week 52 non-inferiority study assessments. Please confirm that this is acceptable.

FDA Response: Your proposed +/- 8-week window for the Week 52 non-inferiority study assessments is acceptable.

3. To avoid multiple measures within a visit window, we propose an alternative method to that described in General Comments 4.c. We propose to use the method that was specified in our SAPs which selects the last multiple measure. Please confirm that this is acceptable.

FDA Response: Your alternative method which selects the last multiple measure to avoid multiple measures is acceptable.

4. According to Carpenter and Kenward *Multiple Imputation and Its Application* (Chichester,

West Sussex: Wiley, 2013; pp 54-55) 100 imputations provide accurate β and p-value estimation. We propose to use 100 imputations in our RTB and J2R analyses. Please confirm that this is acceptable.

FDA Response: We prefer 1000 imputations to increase precision for confidence intervals, however your proposal to use 100 imputations is acceptable.

5. Please clarify - is the analysis of the categorical endpoint of achievement of HbA1C < 7% (Specified Analysis 3) to use the imputation results for the Return to Baseline imputation or for the J2R imputation?

FDA Response: Please provide analysis results for both Return to Baseline and Jump to Reference imputation results.

6. Finally, the Sponsor would like to better understand the Agency's rationale for this request and current thinking on how these supplemental analyses (vs. analyses provided to date) contribute to the understanding of treatment effect and inform labeling. As discussed at the pre-NDA meeting, the inclusion of post-rescue data in the summary estimates of treatment conflates responses to trial treatment with responses to rescue treatment. Using this representation of a clinical trial finding confounds clinical interpretation of treatment effect and does not supply the information a provider needs in making informed treatment decisions. We acknowledge that the fact that rescue occurred is important to recognize in the analysis but do not agree with inclusion of the actual values in the primary description of the treatment effect. FDA also acknowledged that parity with other SGLT2 inhibitor labeling is a consideration for the labeling of ertugliflozin and the combination products.

FDA Response: Please refer to our "General Statistical Comments" in response to Question 13, found in the meeting minutes for the September 6, 2016 pre-NDA meeting. These are partially reprinted below:

FDA Response to Question 13:

General Statistical Comments: A. We are interested in estimating the treatment effect based on the intent-to-treat (de facto) estimand, which considers the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy, including use of glycemic rescue therapy, bariatric surgery, or bone mineral density rescue therapy...

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]

Sent: Thursday, June 22, 2017 11:19 AM

To: Godwin, Elizabeth

Subject: RE: NDA 209803 - ertugliflozin - Information Request: Sponsor Response and Requests for Further Clarification

Hi Liz,

We acknowledge FDA's request for supplemental analyses related to efficacy. Given the scope of this request and required run time for the programs, the Sponsor proposes to submit the requested analyses and analysis packages by July 14, 2017. **Please confirm that this date is acceptable.**

The Agency has specified a +/- 4-week window for the Week 26 superiority study assessments and the Week 52 non-inferiority study assessments. Due to the longer time period, we request that a +/- 8-week window be applied to the Week 52 non-inferiority study assessments. **Please confirm that this is acceptable.**

To avoid multiple measures within a visit window, we propose an alternative method to that described in **General Comments 4.c**. We propose to use the method that was specified in our SAPs which selects the last multiple measure. **Please confirm that this is acceptable.**

According to Carpenter and Kenward *Multiple Imputation and Its Application* (Chichester, West Sussex: Wiley, 2013; pp 54-55) 100 imputations provide accurate β and p-value estimation. We propose to use 100 imputations in our RTB and J2R analyses. **Please confirm that this is acceptable.**

Please clarify - is the analysis of the categorical endpoint of achievement of HbA1C < 7% (**Specified Analysis 3**) to use the imputation results for the Return to Baseline imputation or for the J2R imputation?

Finally, the Sponsor would like to better understand the Agency's rationale for this request and current thinking on how these supplemental analyses (vs. analyses provided to date) contribute to the understanding of treatment effect and inform labeling. As discussed at the pre-NDA meeting, the inclusion of post-rescue data in the summary estimates of treatment conflates responses to trial treatment with responses to rescue treatment. Using this representation of a clinical trial finding confounds clinical interpretation of treatment effect and does not supply the information a provider needs in making informed treatment decisions. We acknowledge that the fact that rescue occurred is important to recognize in the analysis but do not agree with inclusion of the actual values in the primary description of the treatment effect. FDA also acknowledged that parity with other SGLT2 inhibitor labeling is a consideration for the labeling of ertugliflozin and the combination products.

Please confirm receipt of this response and requests for further clarification.

Kind regards,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Friday, June 16, 2017 11:11 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request

Hello Vivian,

We appreciate your response to our previous requests for information and sensitivity analyses. After further review, including further review of use of variable AVISITN, we are requesting the following additional analyses.

Please perform the specified analyses and submit the results and code.

General Comments – these comments apply to all the analyses found in the “Specified Analyses” section further below except where indicated

1. Please provide the specified analyses for every primary and secondary endpoint that you plan to include in the label.
2. Each analysis should include all randomized subjects who have a baseline measurement and have been exposed to treatment, regardless of whether they have a post-baseline measurement.
3. All observed data, including measurements after initiation of rescue therapy or treatment discontinuation, should be used.
4. The final assessment for each of the analyses should fall within the following window:
 - a. The final assessment should fall within a 26 +/- 4 week window for the 26 –Week studies as determined by the “Analysis Relative Day” (ADY) variable. This criterion applies regardless of the value of visit number (regardless of the value of AVISITN for that record).
 - b. For the 52 week non-inferiority study, the final assessment should fall within a 52 +/- 4 week window as determined by the ADY variable. Again, this criterion applies regardless of the value of visit number (regardless of the value of AVISITN for that record).
 - c. If needed, to avoid multiple measurements for a subject, the measurement that is closest to 26 weeks (52 weeks for the non-inferiority study) may be chosen. If there are still multiple measurements for a subject due to two measurements being equally close to the target number of weeks, the last of the remaining measurements may be chosen. You may also propose an alternative method of avoiding multiple measurements for a subject.
5. If there is no assessment for the endpoint that falls within the window specified in #4 above, the final assessment for a patient should be treated as missing. It will then need to be imputed for each of the analyses.
6. For each of the analyses (except the non-responder analysis), generate 1000 data sets and apply Rubin’s rule to obtain LS Means and difference in LS Means, along with standard errors and confidence intervals. For Study P005 Jump to Reference (J2R) Analyses, the number of generated data sets may be the same as was used in your previously submitted J2R analyses to avoid unduly lengthening the time needed to run the program.
7. “All studies” refers to studies P001, P002 (the non-inferiority study), P003, P005 (the factorial study), P006, P007, and P017.

Specified Analyses

1. For all studies, for the continuous endpoints, please provide an ANCOVA “Return to Baseline” (RTB) analysis for each arm. The variance for imputed values can be based on variance of the endpoint at 26 weeks (52 weeks for the non-inferiority study) and can be conditional on baseline covariates included in the primary analysis (i.e. based on residual standard deviation). You may also propose an alternative method to specify variance for imputed values.
 - a. In addition, for the non-inferiority study, conduct an ANCOVA analysis using RTB on the experimental arms, and missing at random on the control arm.

2. Conduct a J2R analysis for each study with the criteria specified above (under “General Comments”). For the non-inferiority study, include a 0.3 penalty for the HbA1c (%) assessment for the experimental arms.
3. For the categorical endpoint of achievement of HbA1c < 7%, the imputation results from the corresponding HbA1c (%) analysis may be used to calculate proportion of responders for each treatment group. For each data set please count the proportion of patients with HbA1c < 7% at week 26/52 and compute the average of these proportions across the 1,000 data sets (for each treatment group). In addition please conduct a logistic regression analysis using Rubin’s rule for significance testing.
4. For the categorical endpoint of achievement of HbA1c < 7%, conduct a non-responder analysis, which assumes patients with HbA1c at week 26/52 missing are non-responders. Include number and proportion of responders for each treatment group.

Please confirm receipt and submit the response no later than June 30, 2017.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
06/26/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDAs 209803, 209805, and 209806 - ertugliflozin, ertugliflozin/sitagliptin, ertugliflozin/metformin - Information Request
Date: Monday, June 12, 2017 10:18:54 AM
Attachments: [image001.png](#)

Hi Liz, confirming email receipt.

Regards,

Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, June 12, 2017 9:16 AM
To: Fuh, Vivian
Subject: NDAs 209803, 209805, and 209806 - ertugliflozin, ertugliflozin/sitagliptin, ertugliflozin/metformin - Information Request

Hello Vivian,

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin tablets.

We have the following comments and information requests. We request a prompt written response by Wednesday, June 14, 2017, in order to continue our evaluation of your NDA.

During recent inspections at Dr. Fragosos site in Houston last week and is now at Dr. Akright's office. It's been brought to our attention an issue with the OSI BIMO data line listings and the subject numbering. The sponsor data line listings provide the correct study site name and number but a non-identifiable 7 digit participant number (and the site has a 5 digit number). The only matching participant numbers with the documents supplied by the sponsor has been with the inclusion exclusion criteria for both the 003 and 007 protocols. All the laboratory testing participant numbers aren't matching. And, similarly the participant ID numbers for the protocol deviations aren't matching the subject IDs either.

Please explain why the subject numbers are different and what is to be used to link the source records to the data line listings?

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
06/12/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209803

NDA 209805

NDA 209806

MID-CYCLE COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Product Name
209803	ertugliflozin tablets
209805	ertugliflozin and sitagliptin tablets
209806	ertugliflozin and metformin hydrochloride tablets

We also refer to the teleconference between representatives of your firm and the FDA on June 5, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Liz Godwin, Regulatory Project Manager at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

William Chong, MD
Medical Officer, Clinical Team Lead
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Mid-Cycle Communication
Slides presented by applicant during teleconference



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: June 5, 2017 at 12:00 pm ET

Application Numbers: NDA 209803
NDA 209805
NDA 209806

Product Names: NDA 209803: ertugliflozin tablets
NDA 209805: ertugliflozin and sitagliptin tablets
NDA 209806: ertugliflozin and metformin hydrochloride tablets

Proposed Indications: NDA 209803: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
NDA 209805: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate
NDA 209806: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

Applicant Name: Merck Sharpe and Dohme Corp.

Meeting Chair: William Chong, MD, Clinical Team Lead

Meeting Recorder: Liz Godwin, MSHS, CCRP, Regulatory Project Manager

FDA ATTENDEES

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

William Chong, MD, Clinical Team Lead, DMEP

Frank Pucino, PharmD, MPH, Clinical Reviewer, DMEP

Yun Wang, PhD, Acting Statistical Team Lead, Office of Biometrics II, Division of Biometrics II

Alexander Cambon, PhD, Statistical Reviewer, Office of Biometrics II, Division of Biometrics II

Julie Van der Waag, MPH, Chief, Project Management Staff, DMEP

Liz Godwin, MSHS, CCRP, Regulatory Project Manager, DMEP

APPLICANT ATTENDEES

Merck

Vivian Fuh, MD, Executive Director, Global Regulatory Affairs

Scott Korn, MD, Vice President, Global Regulatory Affairs

Lina AlJuburi Director, Regulatory Policy

Brett Lauring, MD, PhD, Distinguished Scientist, Clinical Research, Late Stage Development, Diabetes & Endocrinology

Sam Engel, MD, Scientific AVP, Clinical Research, Late Stage Development, Diabetes & Endocrinology

Keith Kaufman, MD, VP, Clinical Research, Late Stage Development, Diabetes & Endocrinology

Shrita Patel, MD, MSCE, Senior Director, Clinical Safety and Risk Management

Susan Huyck, DrPh, Director, Biostatistics

Gregory Golm, PhD, Executive Director, Biostatistics

Pfizer

Karen Cox, BSc Director, Global Regulatory Lead

Susan DeCorte, RPh, RAC, MBA, JD Asset Team Leader

Susan McCann BS Senior Director, Global Project Manager

Steven Terra, PharmD Senior Director, Global Clinical Lead

Anne Hickman, DVM, PhD Senior Director, Safety Risk Lead

James Mancuso, PhD Director, Biostatistics

Douglas Lee, PhD Executive Director, Biostatistics

Joe Arena, PhD Vice President, Regulatory

Esther Nougier, MSc Pharm Eng, MSc Reg Aff, MBA Senior Director, Regulatory

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

Chemistry, Manufacturing, and Controls (CMC):

- a. We are evaluating the CMC information to be submitted as discussed in NDA 209803 amendment dated March 21, 2017, NDA 209805 amendments dated March 21 and May 8, 2017, and NDA 209806 amendment dated March 21, 2017. In addition, we are evaluating

your responses to the information requests that we sent you on May 23, 2017. We do not have additional CMC information requests at this time.

Clinical:

- b. In your dedicated moderate renal impairment trial (P001), the primary efficacy endpoint (i.e., mean hemoglobin A1c [HbA1c] change from baseline to Week 26) for both the 5 mg and the 15 mg ertugliflozin treatment arms were not statistically different than the placebo-control arm. You note that the pre-specified analysis of glycemic efficacy was confounded by concomitant use of metformin, which was a prohibited medication, and that a ‘post-hoc’ analysis excluding these subjects resulted in a significant placebo-corrected reduction in HbA1c in the ertugliflozin 15 mg treatment arm. However, it appears that possible metformin use (based on measurable metformin concentrations) was similar and relatively consistent across treatment arms during the trial. For Study P001, even though use of metformin was prohibited by the protocol inclusion criteria, there appears to be nothing prohibiting metformin use in practice in this patient population. In addition, the post-hoc subgroup analysis in Section 14.4 of the label (Moderate Renal Impairment) appears to include a post-baseline covariate. Therefore it may not be meaningful. Preliminary review of the safety data from subjects with an eGFR between 45 to <60 mL/min/1.73 m² in Trial P001 and those included in the 4-Month Safety Update (4-MSU), suggests that the combined ertugliflozin treatment arms (5 mg plus the 15 mg groups) had higher proportions of clinically relevant adverse events (e.g., fatal, serious and severe adverse events and/or discontinuations due to severe/serious adverse events) compared to the comparator arms. Please provide your rationale for why the use of ertugliflozin in this patient subset would have a favorable benefit-risk profile.

Discussion: The applicant’s attached slides provided additional information in response to this comment. The FDA acknowledged that the post-hoc analyses suggested a different conclusion than the primary analysis. Whether this explains the observed findings in study P001 remains unclear and the FDA stated that we will continue to consider what the available data support in terms of dosing recommendations. We acknowledge the information provided and have no additional comments at this time.

- c. A numerical imbalance in lower limb amputations and/or peripheral revascularization procedures has been noted in your NDA(s). You state that cases of non-traumatic limb amputations were identified based on a search of adverse events and procedures using a Custom MedDRA Query (CMQ) and through a search of the serious adverse event comment field for the term amputation. Cases of peripheral revascularization were identified based on a search of adverse events and procedures using a separate CMQ. Please confirm that this was the approach used to identify these cases and clarify if there are concerns that events may have been missed using this approach.

Additionally, please describe the approach you plan to use to identify potential amputation and peripheral revascularization events once your cardiovascular outcomes trial (P004) is COMPLETED and UNBLINDED. Further, we refer you to the FDA Safety Communication for another SGLT-2 inhibitor (<https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm>) dated May 16, 2017. Clarify if this information will be provided to investigators and study subjects.

Discussion: The applicant's attached slides provided clarification and additional information in response to this issue. We acknowledge the information provided and have no additional comments at this time.

Statistical:

- d. We acknowledge receipt of your program containing J2R or jump to reference (t-e201b-v2) and tipping point analysis code. To run the program in our environment, we created the LPTDA library, set the location for the LPTDA library, and included the input ADEFF data set in that library. For P005 we also specified the location for the lst and log output files.

The software version we use is SAS Version 9.4, Windows 7 operating system.

The tipping point code for study P006 appears to have executed without errors. The J2R program executed well past the point where the ADEFF data set was loaded. However the code did not complete running, and the .lst file (or output for P006) with the results was incomplete. The log files are included for both P005 and P006. The lst file is also included for P005 – the P006 output goes to the SAS output, and was incomplete. The P005 lst file contains the table outline and names, but does not include any output.

This is some output toward the end of the P005 J2R log. The complete log is also provided.

PRINT(M_TE201B): * Calling the Five macros

*****;

MPRINT(M_TE201B):

*****;

MPRINT(PART1A): * Additional quit and run to flush any existing data

step or proc;

MPRINT(PART1A): quit;

MPRINT(PART1A): run;

MPRINT(PART1A): * Now put error message and stop macro;

ERROR:

ERROR: In macro Part1A with Jobname= P005

ERROR: This macro requires SAS version 9.2 Level 2M3 or later

ERROR:

ERROR:

MPRINT(M_TE201B): ;

MPRINT(PART1B): * Additional quit and run to flush any existing data

step or proc;

MPRINT(PART1B): quit;

MPRINT(PART1B): run;

```
MPRINT(PART1B): ods select all;
MPRINT(PART1B): * Now put error message and stop macro;
ERROR:
ERROR: In macro Part1B with Jobname= P005
ERROR: Master Data set does not exist with name <P005_master>
ERROR:
ERROR:
MPRINT(M_TE201B): ;
MPRINT(M_TE201B): ***** MAR method - for checking
```

Below is some of the output log for P006. The complete log output is also provided.

```
MPRINT(PART1A): * Additional quit and run to flush any existing data
step or proc;
MPRINT(PART1A): quit;
MPRINT(PART1A): run;
MPRINT(PART1A): * Now put error message and stop macro;
MLOGIC(PART1A): %PUT _ERR_OR:
ERROR:
MLOGIC(PART1A): %PUT _ERR_OR: In macro &macname with Jobname= &jobname
ERROR: In macro Part1A with Jobname= P006
MLOGIC(PART1A): %PUT _ERR_OR: &errtext1
ERROR: This macro requires SAS version 9.2 Level 2M3 or later
```

- e. The J2R analysis population appears to be the subset of “randomized subjects who took at least 1 dose of study medication and had baseline and at least one assessment after baseline.” However the primary analysis population will be the set of all randomized subjects. Can this be accomplished in your macro by substituting the appropriate flag (RANDFL) in place of ANL04FL?
- f. Please provide the J2R program for studies P001 and P002.

Discussion: The applicant’s attached slides addressed the statistical information requests. If further issues persist with running the code(s) we will request additional clarification.

The applicant will provide the J2R program for study P001. We will discuss internally the need for the applicant to provide the J2R program for study P002 and will send a separate information request to the applicant if necessary.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Please refer to Comment #4c under section 3.0, Information Requests.

5.0 ADVISORY COMMITTEE MEETING

There is no advisory committee meeting planned at this time.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Late Cycle Meeting tentatively scheduled September 18, 2017.

27 Page have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM H CHONG
06/27/2017

Executive CAC Final Study Minutes

Date of Meeting: 5/23/2017

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abby Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Todd Bourcier, PhD, DMEP, Alternate Member
Ron Wange, PhD, DMEP, Pharm Tox Supervisor
Jessica Hawes, PhD, DMEP, Presenting Reviewer

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

IND/NDA/BLA #209803

Drug Name: Ertugliflozin

Sponsor: Merck Sharpe and Dohme Corp.

Background

Ertugliflozin is a selective SGLT2 inhibitor being developed for the treatment of type 2 diabetes mellitus as a monotherapy and as two separate combination therapies. Other members of this class have been associated with tumors of the adrenal gland, testes, vasculature, kidney, thyroid, and bladder.

Mouse Carcinogenicity Study

Male and female Crl:CD1(ICR) mice were administered 5, 15 or 40 mg/kg/day ertugliflozin daily via oral gavage for up to 102 weeks. These doses were in accordance with ECAC recommendations. Three concurrent control groups were included, wherein group 1 was administered 0.5% methylcellulose (MC) alone and groups 2 and 3 were administered 0.5% MC + 10% PEG 400 vehicle. All male groups were terminated during Week 97 and all female groups were terminated during Week 102 due to low survival. In both males and females, there were no dose-dependent, statistically significant dose-response relationships, or statistically significant pairwise comparisons in incidences of neoplasms in any tissues with drug treatment compared to concurrent control groups. There were no statistically significant increases in incidences of combined neoplasm data for any specific tissue or in blood malignancies. Overall, there were no significant drug-related neoplastic findings in male or female mice at any of the doses examined.

Rat Carcinogenicity Study

Male and female Sprague Dawley rats were administered 1.5, 5, or 15 mg/kg/day ertugliflozin daily via oral gavage for up to 104 weeks. These doses were in accordance with ECAC recommendations. One concurrent 0.5% MC + 10% PEG 400 vehicle control group was included; however, a saline/water control group, which was recommended by ECAC after review of the protocol, was not implemented. Females were terminated during Week 92 due to low

survival of control animals. In female rats, there were no statistically significant increases in incidences of benign or malignant neoplasms in any tissues. In male rats, dose-dependent increases in benign Pheochromocytoma (PCC) and combined benign + malignant PCC in the adrenal medulla were statistically significant for a dose-response relationship (p value <0.005). At 15 mg/kg/day in male rats, statistical significance was achieved for pairwise comparisons of incidences of adrenal medulla benign PCC (p value = 0.0010) and combined benign + malignant PCC (p value = 0.0042) neoplasms.

Table 1: Male Rat Tumor Types with Statistically Significant Incidence Rate Differences

Organ name	Tumor name	Ertugliflozin			
		0 mg/kg	1.5 mg/g	5 mg/kg	15 mg/kg
Adrenal, Medulla	Benign Pheochromocytoma	2/70 (46) p = 0.0018*	6/60 (40) p = 0.0925	9/60 (42) p = 0.0167@	15/69 (51) p = 0.0010*
	Malignant Pheochromocytoma	3/70 (47) p = 0.2862	2/60 (39) p = 0.4112	1/60 (40) p = 0.6285	4/69 (49) p = 0.5235
	Benign + Malignant Pheochromocytoma	5/70 (47) p = 0.0039*	8/60 (40) p = 0.1791	10/60 (42) p = 0.0846	18/69 (52) p = 0.0042*

X/YY (ZZ): X = number of tumor bearing animals; YY = unweighted total number of animals observed; ZZ = mortality weighted total number of animals

* = Statistically significant in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons

@ = Not statistically significant at 0.01 level in common tumor for test of pairwise comparisons

Executive CAC Conclusions

Rat

- The Committee concurred that the study was suboptimal but adequate, noting prior approval of the protocol but the lack of inclusion of a saline or water control group and early sacrifice of females.
- The Committee concurred that there were drug-related benign and malignant adrenal medulla pheochromocytoma in males at 15 mg/kg/day by both trend and pairwise statistical analyses.

Mouse

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females.

Karen Davis Bruno, PhD
Chair, Executive CAC

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/s/

STEPHANIE J QUINN
05/26/2017

KAREN L DAVIS BRUNO
05/26/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - information request
Date: Thursday, May 11, 2017 9:13:15 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt.

Thanks, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, May 11, 2017 8:22 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - information request

Hello Vivian,

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin tablets.

We recommend the following be implemented prior to approval of this NDA 209803:

A. Trade and Hospital Unit Dose Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4)-shaped rather than the proposed triangular-shape. In addition, the featured color for the tablets is (b) (4) rather than the proposed pink for 5 mg tablet, and red for 15 mg tablet as stated in the PI. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.^a
2. Replace "Trademark" with conditionally acceptable Proprietary Name, Steglatro, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the Carton Labeling. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry^a, where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to

drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

1. We note your intention to include a 30 count sample of the 5 mg and 15 mg tablet. Please include the carton labeling for the 30 count 5 mg and 15 mg tablet.
2. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(j).
3. Please include the expiration date on sample carton labeling if possible.
4. Please include the NDC on sample carton labeling if possible.
5. Please increase the font size of the statement "Sample Not for Sale" as currently presented it is small making it difficult to read.
6. See. A.4.

D. Trade and Sample Container Labels

1. See A.1. through A.4.

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet]. FDA. April 2013 [cited 2017 April 13]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
05/11/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - CVMA information request
Date: Thursday, May 11, 2017 9:18:52 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt and the reminder to discuss this only with the unblinded team member.
Best, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, May 11, 2017 9:00 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - CVMA information request

Hello Vivian,

The following information request concerns some patients from the ongoing trial P004/B1521021. In order to maintain the integrity of this trial, please discuss this request only with personnel who have been previously identified and authorized to access unblinded data.

Clarify why the following subjects discontinued study due to death but are not counted as having a death event in the analysis of all-cause mortality. (b) (4)

flagged as having either a discontinuation from study (TRDREAS='DEATH') or a discontinuation from study medication (SMDREAS='DEATH') due to death in the file adslcv.xpt. However, these subjects are censored in the analysis of all-cause mortality, with CNSR=1 under PARAMCD='DEATH' in the file adcvtte.xpt.

Please submit your response by Thursday, May 25, 2017.

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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Tel: 240-402-3438

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ELIZABETH R GODWIN
05/11/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209805 - ertugliflozin and sitagliptin - information request
Date: Thursday, May 11, 2017 9:13:41 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt.

Thanks, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, May 11, 2017 8:24 AM
To: Fuh, Vivian
Subject: NDA 209805 - ertugliflozin and sitagliptin - information request

Hello Vivian,

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin and sitagliptin tablets.

We recommend the following be implemented prior to approval of this NDA 209805:

A. Trade and Hospital Unit Dose Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4)-shaped rather than the proposed almond-shape. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.^a
2. Replace the word "Trademark" with conditionally acceptable Proprietary Name, Steglujan, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the HUD and Trade Carton Labels. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry^a, where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to

drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

1. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(i).
2. Please include the expiration date on sample carton labeling if possible.
3. Please include the NDC on sample carton labeling if possible.
4. Please increase the font size of the statement "Sample Not for Sale" as currently presented it is small making it difficult to read.
5. See. A.4.

D. Trade and Sample Container Labels

1. See A.1 through A.4.

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet].FDA. April 2013 [cited 2017 April 13]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
05/11/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209806 - ertugliflozin and metformin - information request
Date: Thursday, May 11, 2017 9:13:11 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt.
Thanks, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, May 11, 2017 8:25 AM
To: Fuh, Vivian
Subject: NDA 209806 - ertugliflozin and metformin - information request

Hello Vivian,

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin and metformin tablets.

We recommend the following be implemented prior to approval of this NDA 209806:

A. Trade and Hospital Unit Dose (HUD) Carton Labeling

1. We note the image of a tablet is present on the Principal Display Panel (PDP) for the carton labeling. The featured tablets are (b) (4)-shaped rather than the proposed oval-shape. We are concerned that the images do not represent the actual tablets with respect to size, color and imprint which may hinder healthcare providers' ability to confirm the correct medication. If an image of a tablet will be included on the labeling, the image should reflect the true size, color, and imprint for the corresponding product. Schematic or computer-generated images should not be used.^a
2. Replace the word "Trademark" with conditionally acceptable Proprietary Name, Segluromet, throughout all labels and labeling.
3. We note the space allotted for the expiration date and lot number on the HUD and Trade Carton Labels. Ensure the expiration date conforms with the standard format outlined in 21 CFR 201.10(i) and Draft Guidance for Industry^a, where the expiration date must be written as either 3-letter text for month with 4-digit numerals for year MMMYYYY (e.g. FEB2020), or 3-letter text for month, with 2-digit numerals for day, and 4-digit numerals for the year MMMDDYYYY (e.g. FEB012020).
4. In the storage section, add the temperature unit after each numerical temperature reading. For example: "Store at 20°C to 25°C (68°F to 77°F)".

B. Trade and Hospital Unit Dose Blister Container Label

1. See A.2.
2. As currently presented, the NDC number is located at the bottom of the container label above the bar code. Since NDC number is often used as an additional verification prior to

drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

C. Professional Sample Carton Labeling

1. We note the absence of the lot or control number on the sample carton labeling. Please include the lot number per 21 CFR 201.10(i).
2. Please include the expiration date on sample carton labeling if possible.
3. Please include the NDC on sample carton labeling if possible.
4. Please increase the font size of the statement "Sample Not for Sale" as currently presented it is small making it difficult to read.
5. See A.4.

D. Trade and Sample Container Labels

1. See A.1 through A.4.

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication errors. Draft Guidance [Internet].FDA. April 2013 [cited 2017 April 13]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

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ELIZABETH R GODWIN
05/11/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Cc: [Lalmansingh, Anika](#)
Subject: RE: NDA 209803 - Information Request, 5/4/2017
Date: Monday, May 08, 2017 3:25:43 PM
Attachments: [image001.png](#)
[image007.png](#)

Thanks Liz/Anika, confirming receipt. Regards, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, May 08, 2017 3:23 PM
To: Fuh, Vivian
Cc: Lalmansingh, Anika
Subject: RE: NDA 209803 - Information Request, 5/4/2017

Hi Vivian,

We acknowledge your communication dated 5/5/2017 in response to our Quality Information request dated 5/4/2017. We have the following additional questions and request a prompt written response in order to continue our evaluation of the Nonclinical section of your application:

1. Submit in Module 4 Nonclinical Study Reports a copy of the certificate of analysis or any signed and dated documentation that provides evidence of the (b) (4) % of (b) (4) in the drug batch used in the nonclinical study 13GR318.
2. Clarify the testing facility and test method used in quantitating (b) (4) in this specific drug bat

Please submit your response by **COB, Wednesday, May 10, 2017.**

Please confirm receipt.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



From: Fuh, Vivian [mailto:vivian_fuh@merck.com]

Sent: Friday, May 05, 2017 2:07 PM
To: Lalmansingh, Anika
Cc: Godwin, Elizabeth
Subject: RE: NDA 209803 - Information Request, 5/4/2017

Hi Anika

Please see our response below; we will formally submit this to the NDA early next week:

The Agency is correct in their observation of differences in reporting methods of impurity content between the original certificate of analysis of Lot 705847-91-10, as presented in Sec. 4.2.3.7.7, and the batch analysis data found in Sec. 3.2.S.4.4. In the certificate of analysis, the applicant has reported the presence of all impurities in accordance with the principles described in ICH Q3A in which the maximum dose is less than 2 grams/day. That is, only those impurities which are present at levels exceeding 0.05% were reported and summed as part of the total impurities calculation.

Thus, a level of (b) (4) % of this impurity, which was detected at the time of release of lot 705847-91-10, was not necessary to report. The applicant does note that the level of (b) (4) % is within the quantification limit of the analytical method used to analyze ertugliflozin L-PGA.

As a result of subsequent process development work however, it was determined that process-related impurity (b) (4) would require an individual specification, and the proposed limit for this impurity is presented in Sec. 3.2.S.4.1. In support of our justification of the specification of this impurity, additional details on the impurity profile of lot 705847-91-10 were provided in Sec. 3.2.S.4.4 which were not originally presented in the certificate of analysis.

The Applicant can confirm that impurity (b) (4) was present at a level of (b) (4) % in the batch used to support the toxicological study referenced above. We refer the Agency to Sec. 3.2.S.4.5 wherein details of this study are presented, with conclusions regarding impurity qualification and justified safety thresholds.

Best,
Vivian

Please confirm receipt of this email.

From: Lalmansingh, Anika [<mailto:Anika.Lalmansingh@fda.hhs.gov>]
Sent: Thursday, May 04, 2017 4:29 PM
To: Fuh, Vivian
Cc: Godwin, Elizabeth
Subject: NDA 209803 - Information Request, 5/4/2017

Information Request – CMC only

NDA 209803

Hello Vivian,

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by COB **Friday, May 5, 2017** in order to continue our evaluation of your NDA.

In Table 3.2.S.4.4-14 of Section 3.2.S.4.4, you report a content of (b) (4) % for the impurity (b) (4) for batch 705847-91-10. However, the original Pfizer certificate of analysis for this batch in Section 4.2.3.7.7 does not have this impurity listed and does not have the amount of (b) (4) % for any impurity. Explain this discrepancy. If this impurity was not qualified in the nonclinical study 13GR318, indicate the NDA section where the nonclinical study of this impurity qualification and the original Pfizer certificate of analysis can be found.

-

Kindly acknowledge receipt of this email.

Regards.

-*Anika*

Anika Lalmansingh, PhD

Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)

Office of Pharmaceutical Quality (OPQ)

U.S. Food and Drug Administration

Tel: 240-402-0356

anika.lalmansingh@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
05/08/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request
Date: Thursday, April 27, 2017 10:59:04 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt.
Regards, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, April 27, 2017 10:43 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request

Hi Vivian,

We thank you for your presentation on Thursday, February 16, 2017, to address our questions and requests. Your presentation and responses were very helpful. Below are three follow-up requests. Again, these requests are made so that we can reproduce your analysis and characterize the data.
Please submit your response by Friday, May 5, 2017.

1. The pdf named "t-e201c.pdf" which you reference in your response to question 6a (for Jump to Reference, or J2R code) has the following comment in the 6'th line of the pdf:

"Program Name: t-e201b;"

Therefore we are not sure which pdf to use for code per your instructions in response to Question 6a (see below):

"...Jump-to-Reference – program code **t-e201c.pdf** calls and executes macro in **m-te201b.pdf**;"

Please provide code and comments with corrected file/code names to avoid confusion.

2. Using the program t-e201c.pdf above (labeled t-e201b on line 6), the J2R Program Code for P005 (file m-te201b.pdf) references 5 macros ("SAS Macros Used: Merck macro J2R TheFiveMacros m_printto") that are needed to execute the program. The relevant output from the log is:

```
MPRINT(M_TE201B):
*****
****,
MPRINT(M_TE201B): * Calling the Five macros
*****,
MPRINT(M_TE201B):
*****
****,
WARNING: Apparent invocation of macro PART1A not resolved.
NOTE: Line generated by the invoked macro "M_TE201B".
```


Please provide or point to the location of these macros. If there is any other code needed to execute the J2R or tipping point code for study P005 or any of the other studies, please provide those as well.

3. You indicated in your response to question 6a that subgroup analysis code has not been provided to us. Please provide the code for the pooled subgroup analyses for sex, race, ethnicity, region, baseline BMI, and baseline A1C.

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
04/27/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request
Date: Thursday, April 27, 2017 11:35:40 AM
Attachments: [image001.png](#)
[image002.png](#)
[image003.png](#)

Thanks confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, April 27, 2017 11:32 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request

Hi Vivian,

We have the following information requests for NDA 209803. Please submit your response by COB, Friday, April 28, 2017.

1. Please identify a treatment-emergent flag or the variables used to identify treatment-emergent adverse events in the ISS and ISS Broad datasets.
2. Please identify the datasets and the variable names used to derive the numbers presented in the following tables (i.e., Tables 20 and 21) of your Summary of Clinical Safety:

ISS: Table 20, page 68 of 372.

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	515		519		510		1,029	
with one or more adverse events	263	(51.1)	236	(45.5)	257	(50.4)	493	(47.9)
with no adverse event	252	(48.9)	283	(54.5)	253	(49.6)	536	(52.1)
with drug-related [†] adverse events	48	(9.3)	74	(14.3)	75	(14.7)	149	(14.5)
with serious adverse events	15	(2.9)	17	(3.3)	12	(2.4)	29	(2.8)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued [‡] due to an adverse event	9	(1.7)	12	(2.3)	7	(1.4)	19	(1.8)
discontinued due to a drug-related adverse event	5	(1.0)	5	(1.0)	3	(0.6)	8	(0.8)
discontinued due to a serious adverse event	2	(0.4)	1	(0.2)	0	(0.0)	1	(0.1)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
[†] Determined by the investigator to be related to the drug. [‡] Study medication withdrawn. One subject in Ertugliflozin 5 mg group with an AE started in Phase A and later discontinued the study medication due to the AE after the completion of Phase A and during Phase B.								

ISS Broad: Table 21, page 69 of 372.

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,450		1,716		1,693		3,409	
with one or more adverse events	940	(64.8)	1,074	(62.6)	1,049	(62.0)	2,123	(62.3)
with no adverse event	510	(35.2)	642	(37.4)	644	(38.0)	1,286	(37.7)
with drug-related [†] adverse events	239	(16.5)	316	(18.4)	325	(19.2)	641	(18.8)
with serious adverse events	80	(5.5)	110	(6.4)	98	(5.8)	208	(6.1)
with serious drug-related adverse events	3	(0.2)	3	(0.2)	3	(0.2)	6	(0.2)
who died	3	(0.2)	10	(0.6)	8	(0.5)	18	(0.5)
discontinued [‡] due to an adverse event	60	(4.1)	70	(4.1)	74	(4.4)	144	(4.2)
discontinued due to a drug-related adverse event	32	(2.2)	35	(2.0)	42	(2.5)	77	(2.3)
discontinued due to a serious adverse event	10	(0.7)	17	(1.0)	15	(0.9)	32	(0.9)
discontinued due to a serious drug-related adverse event	3	(0.2)	2	(0.1)	3	(0.2)	5	(0.1)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
One subject in Ertugliflozin 5 mg group with an AE started in Phase A and later discontinued the study medication due to the AE after the completion of Phase A and during Phase B.

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
04/27/2017

M E M O R A N D U M

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

DATE: 4/17/2017

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209805

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Pfizer New Haven CRU	One Howe Street, New Haven, CT
Analytical	(b) (4)	
Analytical		

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/s/

SHILA S NKAH
04/17/2017

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

DATE: 4/17/2017

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209806

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Pfizer New Haven CRU	One Howe Street, New Haven, CT
Analytical	(b) (4)	

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/s/

SHILA S NKAH
04/17/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - information request- Sponsor Response
Date: Wednesday, April 05, 2017 11:58:00 AM
Attachments: [image001.png](#)

Thanks Liz, confirming receipt. We'll look into this and get back to you as soon as possible. Regards,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, April 05, 2017 11:55 AM
To: Fuh, Vivian
Subject: RE: NDA 209803 - ertugliflozin - information request- Sponsor Response

Hi Vivian,

Thanks for your prompt response. After examining the data, one discrepancy was found. In ecg.xpt, Subject ID=10021034 COLLDATE=31JUL2014 EGACTTM=17:35:00, although they were identified as EGSEQ 2 and 3, identical observations were found after transposed. One entry (TIME= 31JUL2014:17:33:27 PIMS ID= 229964) in the ECG warehouse had no corresponding observations in ecg.xpt. It looked like to be the replicate 2. Please verify the findings and update the dataset accordingly.

Please confirm receipt.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Wednesday, April 05, 2017 11:19 AM
To: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - information request- Sponsor Response

Hi Liz, this will be submitted today.
Regards, Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Tuesday, April 04, 2017 3:47 PM
To: Fuh, Vivian
Subject: RE: NDA 209803 - ertugliflozin - information request- Sponsor Response

Thanks, Vivian. Yes, please formally submit through the gateway.

Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Tuesday, April 04, 2017 3:45 PM
To: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - information request- Sponsor Response

Hi Liz,

Please see below. Do you need me to formally submit this information through the gateway?

Regards, Vivian

Please confirm receipt.

Subject ID	PIMS ID
10021001	218893
10021002	223193
10021003	228722
10021004	227327
10021005	209906
10021006	215355
10021007	220733
10021008	219196
10021009	227479
10021010	219648
10021011	220807
10021012	201102
10021013	211564
10021014	210427
10021015	227204
10021016	227842
10021017	222223
10021018	200274
10021019	221646
10021020	211490
10021021	209150
10021022	218827
10021023	205652
10021024	221243
10021025	222380
10021026	211139
10021027	200701
10021028	209262
10021029	228449

10021030	208840
10021031	210343
10021032	225441
10021033	222499
10021034	229964
10021035	230011
10021036	229894
10021037	221432
10021038	217262
10021039	229889
10021040	220337
10021041	219906
10021042	219497

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Tuesday, April 04, 2017 2:01 PM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - information request

Hi Vivian,

We have the following information request since receiving the upload of your ECG waveforms to the ECG warehouse.

- Please submit the subject map between the PT of the clinical dataset (DEMOG) and the SUBJECT ID of the ECG Warehouse for Study MK-8835-010/B1521025.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
04/05/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Cc: [Lalmansingh, Anika](#)
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request
Date: Monday, April 03, 2017 11:17:28 AM
Attachments: [image001.png](#)

Hi Liz, confirming receipt of this email.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, April 03, 2017 11:16 AM
To: Fuh, Vivian
Cc: Lalmansingh, Anika
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Hello Vivian,

We are denying your request for a teleconference. We acknowledge that, in response to our comment in the February 21, 2017 letter, you updated the NDA to add the sitagliptin drug substance manufacturer (MSD International GmbH, Singapore). However, your response did not include any Quality information on the drug product manufactured with the sitagliptin drug substance from MSD International GmbH, Singapore. Therefore, the new information is incomplete at this time.

Please confirm receipt.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Monday, April 03, 2017 9:44 AM
To: Godwin, Elizabeth
Cc: Lalmansingh, Anika
Subject: RE: NDA 209805 - ertugliflozin/sitagliptin - Information Request
Importance: High

Hi Liz,

The team seeks further clarification and would like a teleconference with FDA to discuss this request.

As noted by FDA in the February 21, 2017 letter, Section 3.2.S.2.1 in the original NDA listed (b) (4)

(b) (4) as the only commercial drug substance manufacturer for sitagliptin. In response to FDA's query as to whether there will be additional manufacturing sites and to provide business sourcing flexibility, the Sponsor followed the Agency's advice to "Update the NDA [at this time] with this information if applicable" to include the sitagliptin drug substance manufacturer (MSD International GmbH, Singapore), a sitagliptin drug substance stability tester (Merck Sharp & Dohme Corp., Wilson NC), (b) (4)

(b) (4). As noted in the March 21, 2017 Sponsor's response, these 3 sites are already approved for their respective activity in (b) (4).

We also note that (b) (4) is now the subject of 2 FDA Import Alerts.

Therefore, the Sponsor would like to meet with the Agency at your earliest convenience to ensure an approvable supply chain in the NDA.

Regards,
Vivian

Please confirm receipt of this email.

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Friday, March 31, 2017 9:46 AM
To: Fuh, Vivian
Subject: NDA 209805 - ertugliflozin/sitagliptin - Information Request

Hi Vivian,

We received your amendment dated March 21, 2017, that includes a request to add a sitagliptin drug substance manufacturer (MSD International GmbH, Singapore), a sitagliptin drug substance stability tester (Merck Sharp & Dohme Corp., Wilson NC), (b) (4)

(b) (4) An application is expected to be complete at the time of original submission. Your amendment would be considered a major amendment, review of which may be deferred to a subsequent review cycle. We recommend that you submit a correspondence to this NDA withdrawing these requests.

Please submit your response by COB, Monday, April 3, 2017.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov





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/s/

ELIZABETH R GODWIN
04/04/2017



NDA 209803

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated and received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin Tablets, 5 mg and 15 mg.

We also refer to your correspondence, dated and received January 4, 2017, requesting review of your proposed proprietary name, Steglatro.

We have completed our review of the proposed proprietary name, Steglatro and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Elizabeth Godwin, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/27/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: RE: NDAs 209803 question regarding 30 count sample bottles
Date: Monday, March 20, 2017 4:09:20 PM
Attachments: [image001.png](#)

Hi Vivian,

Yes, please submit the draft labeling now.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Monday, March 20, 2017 12:28 PM
To: Godwin, Elizabeth
Subject: NDAs 209803 question regarding 30 count sample bottles

Hi Liz,

The team would want to have 30 ct sample bottles for ertugliflozin 5mg and 15mg. This is in addition to the 30 ct trade bottles already proposed in the filing. Only variation would be the bottle labels. Should we amend the NDA now with label artwork to support the sample bottles? If not, when do you suggest?

Please confirm receipt of this request and thanks for your advice,
Vivian

Vivian L. Fuh, M.D., F.A.C.P.

Director

Global Regulatory Affairs

Merck Sharp and Dohme, Corp.

126 East Lincoln Avenue, RY34-B188

Rahway, NJ 07065

phone: 732 594-0374

fax: 732-594-1030

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/s/

ELIZABETH R GODWIN
03/21/2017



NDA 209805

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ertugliflozin and sitagliptin, (b) (4) 5/100 mg; and 15/100 mg, tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 19, 2017**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 26, 2017**. In addition, the planned date for our internal mid-cycle review meeting is **May 23, 2017**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
03/02/2017



NDA 209806

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ertugliflozin and metformin hydrochloride, 2.5/500 mg, 2.5/1000 mg, 7.5/500 mg, and 7.5/1000 mg, tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 19, 2017**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 26, 2017**. In addition, the planned date for our internal mid-cycle review meeting is **May 23, 2017**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied

If you have any questions, call Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
03/02/2017



NDA 209803

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ertugliflozin, 5 mg and 15 mg, tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 19, 2017**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 26, 2017**. In addition, the planned date for our internal mid-cycle review meeting is **May 23, 2017**. We are not currently planning to hold an advisory committee meeting to discuss this application.

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- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
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- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied

If you have any questions, call Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
03/01/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request
Date: Monday, February 27, 2017 8:51:34 AM
Attachments: [image001.png](#)

Thanks Liz. Confirming receipt.

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, February 27, 2017 8:46 AM
To: Fuh, Vivian
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Vivian,

To assist in reviewing your February 24, 2017, submission containing nonclinical and clinical information to support the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling for NDAs 209803, 209805 and 209806, please provide the references that were cited or direct us to where we may find the references in the submission.

Please submit your response by Monday, March 6, 2017.

Please confirm receipt of this email.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Friday, February 24, 2017 11:37 AM
To: Godwin, Elizabeth
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Liz, responses to this information request have been submitted through the gateway today to the 3 NDAs.
Best, Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, January 30, 2017 12:59 PM
To: Fuh, Vivian
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Vivian,

In reviewing your request, we have the following revised information request.

During our preliminary review of your submitted labeling for NDAs 209803, 209805 and 209806 on December 19, 2016, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Submit the following information by [February 24, 2017](#):

- a review and summary of available nonclinical information, including published literature regarding sitagliptin and metformin use in pregnant and lactating animals and the effects of sitagliptin and metformin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding metformin use in pregnant and lactating women and the effects metformin on male and female fertility (include search parameters),
- a review and summary of all available published literature regarding sitagliptin and sitagliptin/metformin use in pregnant and lactating women and the effects sitagliptin and sitagliptin/metformin on male and female fertility (from 8/3/2015 to present, include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from 8/3/2015 through present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidance.

If you have any questions, please let me know.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]

Sent: Friday, January 27, 2017 4:49 PM

To: Godwin, Elizabeth

Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Liz,

(b) (4)

Thanks for your clarification,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Thursday, January 26, 2017 10:57 AM
To: Fuh, Vivian
Subject: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Vivian,

During our preliminary review of your submitted labeling for NDAs 209803, 209805 and 209806 on December 19, 2016, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Submit the following information by February 24, 2017:

- a review and summary of available nonclinical information, including published literature regarding sitagliptin and metformin use in pregnant and lactating animals and the effects of sitagliptin and metformin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding sitagliptin and metformin use in pregnant and lactating women and the effects sitagliptin and metformin on male and female fertility (include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please confirm receipt of this email and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (2000 Galloping Hill Road, Kenilworth, New Jersey, USA 07033), and/or its affiliates Direct contact information for affiliates is available at <http://www.merck.com/contact/contacts.html>) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (2000 Galloping Hill Road, Kenilworth, New Jersey, USA 07033), and/or its affiliates Direct contact information for affiliates is available at <http://www.merck.com/contact/contacts.html>) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

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/s/

ELIZABETH R GODWIN
02/27/2017

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

DATE: 2/13/2017

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209803

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Pfizer New Haven Clinical Research Unit	One Howe Street, New Haven, CT

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/s/

SHILA S NKAH
02/16/2017



NDA 209805

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated and received December 19, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin and Sitagliptin Oral Tablets, (b) (4) 5 mg/100 mg, and 15 mg/100 mg.

We also refer to your correspondence, dated and received January 4, 2017, requesting review of your proposed proprietary name, Steglujan.

We have completed our review of the proposed proprietary name, Steglujan and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Elizabeth Godwin, Regulatory Project Manager in the Office of New Drugs, at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/15/2017



NDA 209806

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated and received December 19, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin/Metformin Oral Tablets, 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg.

We also refer to your correspondence, dated and received January 4, 2017, requesting review of your proposed proprietary name, Segluromet.

We have completed our review of the proposed proprietary name, Segluromet and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

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Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/15/2017



NDA 209806

**INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION**

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated and received December 19, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ertugliflozin and metformin hydrochloride tablets.

We also refer to your amendments dated January 13 and 20, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either: 1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verifies that the proposed change described in the amendment is not one of the types of

amendments described in 21 CFR 314.60(f)(1), as appropriate. Your response to this information request must clearly reference your amendments dated January 13 and 20, 2017.

If you have any questions, contact me at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Liz Godwin, MSHS, CCRP
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R GODWIN
02/14/2017

From: [Fuh, Vivian](#)
To: [Petrucelli, Marisa](#)
Cc: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803, 209805, and 209806 - Application Orientation Presentation T-Con Request
Date: Thursday, February 09, 2017 4:45:25 PM
Attachments: [image002.png](#)
[image009.png](#)

Thanks very much. Confirming receipt.

From: Petrucelli, Marisa [mailto:Marisa.Petrucelli@fda.hhs.gov]
Sent: Thursday, February 09, 2017 3:23 PM
To: Fuh, Vivian
Cc: Godwin, Elizabeth
Subject: RE: NDA 209803, 209805, and 209806 - Application Orientation Presentation T-Con Request

Hi Vivian,

On behalf of Liz Godwin, I am providing the following requests for the February 16 application orientation presentation.

We need to reproduce your analysis and to characterize the data, including missing data and rescue data. The following questions/requests are presented with these tasks in mind. Requests 1 through 5 concern variables, and requests 6 through 8 concern code/analyses. Note that some requests have phrases like “such as”, which means that there might be other pertinent variables/quantities beyond those specifically requested.

Please provide your presentation slides in advance of the meeting so that we can be better prepared.

1. We note that Tables 3 through 7 in your ISE report provide helpful cross-study characteristics, including a general overview of each study and its endpoints. As well, we note Section 3.2 (titled “Core Variables”), of Analysis Data Reviewers Guide for study P005. With that in mind, we have the following questions/requests in the paragraph directly below.

In the studies P002, P003, P005, P006, P007, P017, as well as P001, are there any differences in names for core variables (variables used in primary and sensitivity analyses, including demographic variables, and flag variables)? Please provide a table showing across-study comparisons, including any differences in analysis approach, any differences in core variable names, or any differences in variables included in primary or sensitivity analyses. Also point out any special issues that came up for any of the studies.

2. We note your helpful Section 3.3 of Analysis Data Reviewers Guide for study P005. We also note, in “Analysis Dataset Definition” file for study P005, variable TRTEDY – “Day of Last Exposure to Treatment”, and TR01SDT – “Date of First Exposure in Phase A.” With that in mind, we have the following requests below.

Please provide clarification on timeline variables such as treatment start time (probably TR01SDT), planned treatment end time, actual treatment end time (probably TRTEDY), time of initiation of rescue therapy (including glycemic, bariatric, and, if applicable, therapy related to bone mineral density evaluation), and, if applicable, time of completion /discontinuation of rescue therapy. Also please explain how, for example, to find the last assessment before

treatment discontinuation (or last assessment prior to initiation of rescue medication if applicable). A chart with time on x axis depicting these quantities with respect to time would be helpful.

Also note any differences in these variables (names, definitions, etc) between studies.

3. Did you perform any visit reallocation? If so please clarify the approach.
4. We note the description in the Analysis Dataset Reviewer's Guide for variable "FSACFL41": "... For the A1C analysis, subjects are included in the cLDA population excluding rescue approach if FSACFL11='Y', in the cLDA population including rescue approach if FSACFL41='Y', in the ANCOVA population, excluding rescue approach if FSACFL21='Y' and in the ANCOVA population, including rescue approach if FSACFL51='Y'." There is also a definition in the Analysis Dataset Definition File. With this as background, we have the following request below.

Please elaborate on flag/variable "FSACFL41" - used in "including rescue" analysis for study P005. Also are there any differences in this variable between studies?

5. In study P005, file ADEFF, please explain why are there some values missing for variable RACIGR1 ("Pooled Race Group 1, IR") that are not missing for variable RACGR1 ("Pooled Race Group 1, ER").
6. We note your ISE Report which includes subgroup analyses, sensitivity analyses, and rational for why certain studies are grouped or not grouped for the subgroup analyses. With this in mind we have the following request below.

Please provide or point to the location of the code for the subgroup analyses, the tipping point analysis, and for the Jump-to-Reference analysis (both excluding and including rescue). Also please provide the code with comments.

7. Please elaborate on the primary analysis code for P005 (for example) – for both including and excluding rescue. The code is commented, and the code does produce output, but we would appreciate at least a brief step by step explanation of the code, including flags used, and reasons why each manipulation step is needed.
Also please point out any differences in the approach/code for any of the other studies.
8. For the “including rescue” analysis for study P005 for the primary endpoint, boxplots, histograms, residual plots, etc. show up in a word document “t-e201-a1c-ir-diag.rtf”. Then in a SAS log file, table results for table “14.2.1.1.1 A1C” show up in a SAS lst file in C:\temp named “t-e-201- a1c-ir.lst”. Is there any other output we should be seeing from this code?
9. Please explain the differences between the p001 and p001v01 datasets; the p002 and p002v01 datasets; the p003 and p003v01 datasets; the p006 and p006v01 datasets, and the p007 and p007v01 datasets.
10. In addition to SI units, please clarify whether laboratory units in the lb.xpt datasets are also provided as conventional units in the tabulation datasets.

Please let me know if there are any questions.

Thank you,
Marisa

Marisa Petruccelli

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-6147

Marisa.Petruccelli@fda.hhs.gov



From: Fuh, Vivian [mailto:vivian_fuh@merck.com]

Sent: Tuesday, January 31, 2017 2:40 PM

To: Godwin, Elizabeth

Subject: RE: NDA 209803, 209805, and 209806 - Application Orientation Presentation T-Con Request

Thanks Liz. Look forward to the feedback.

Let's plan to have this meeting on Thursday, February 16, 11:00 -12:00pm ET

Would this be planned as a tcon with WebEx? Or just teleconference?

Regards,

Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]

Sent: Monday, January 30, 2017 1:39 PM

To: Fuh, Vivian

Subject: NDA 209803, 209805, and 209806 - Application Orientation Presentation T-Con Request

Importance: High

Hello Vivian,

We would like to arrange a teleconference with Merck to orient the review team (clinical, statistical, and clin pharm) with the datasets and application for the ertugliflozin NDAs (NDA 209803, 209805, and 209806).

Please let me know if any of the following dates work and your preferred date/time by tomorrow, January 31.

Monday, February 6 12:00 – 1:00pm ET

Tuesday, February 7, 11:00 – 12:00pm ET

Thursday, February 16, 10:00 – 11:00 am or 11:00 -12:00pm ET

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
02/13/2017

From: [Fuh, Vivian](#)
To: [Petrucelli, Marisa](#)
Cc: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803 - ertugliflozin - Information Request for SimCYP
Date: Thursday, February 09, 2017 10:55:44 AM
Attachments: [image001.png](#)
[image007.png](#)

Hi Marisa,
Thanks for the quick response.
Vivian

From: Petrucelli, Marisa [<mailto:Marisa.Petrucelli@fda.hhs.gov>]
Sent: Thursday, February 09, 2017 10:47 AM
To: Fuh, Vivian
Cc: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - Information Request for SimCYP

Hi Vivian,

We are in the process of being upgraded to the newer SimCYP version, so no further action there is needed.

Regarding your second question, please submit both PE files.

Thank you,
Marisa

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Thursday, February 09, 2017 10:03 AM
To: Petrucelli, Marisa
Cc: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - Information Request for SimCYP

Hi Marisa,
The reviewer should have all the files needed to replicate the analyses provided, but will require the later SimCYP version 15.1 to execute. Can you please confirm whether the reviewer still has questions, or that no further action will be needed from our end on this issue.

I did have one more request for clarification.

Regarding the request for parameter estimation data file as MS Excel files, please confirm whether the reviewer would want just the .xml files (created in MS Excel) that are used as executable inputs in the PE module, the MS Excel outputs from the PE module, or both?

Regards,
Vivian

From: Petrucelli, Marisa [<mailto:Marisa.Petrucelli@fda.hhs.gov>]

Sent: Thursday, February 09, 2017 8:52 AM
To: Fuh, Vivian
Cc: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - Information Request for SimCYP

Hi Vivian,

Liz is out of the office today and tomorrow so I am responding on her behalf. The reviewer is using SymCYP version 14 and wants to ensure that your submission has all the files needed to replicate your analysis.

Please let me know if there are any other questions or issues.

Thank you,

Marisa Petruccelli

Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-6147
Marisa.Petruccelli@fda.hhs.gov



From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Wednesday, February 08, 2017 6:10 PM
To: Godwin, Elizabeth
Subject: RE: NDA 209803 - ertugliflozin - Information Request for SimCYP

Hi Liz,
Confirming receipt. Sorry to hear about the difficulty.

SimCYP version v15.1 was used for the PBPK modeling. Can you please confirm whether simCYP version v15.1 was used to open the .wksz files, or please clarify which simCYP version was used by the reviewer? These files (.wksz) are fully executable when accessed using v15.1.

Thanks for the clarification,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]

Sent: Wednesday, February 08, 2017 9:18 AM
To: Fuh, Vivian
Subject: NDA 209803 - ertugliflozin - Information Request for SimCYP

Hello Vivian,

We acknowledge receiving SimCYP data files for the above mentioned study in the eCTD module “..m4\datasets\pk059mk8835\misc\simcyp” directory of the Original NDA 209803 submission and non-eCTD format.

We are unable to execute the files submitted in non-eCTD format that have a .wksz extension.

Submit the model files in their native format that were used to generate the final results in your PBPK report [i.e., drug model files, population files, and workspace files (.cmpx, .lbrx, and .wksx)]. Please ensure that these files are executable by the FDA reviewers using SimCYP. In addition, submit the any parameter estimation data file as MS Excel files.

We request you to submit these files by COB February 15, 2017.

Please confirm receipt of this email.

If you have any questions, please let me know.

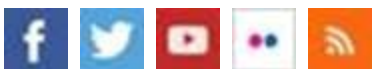
Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
02/13/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: NDA 209803 - ertugliflozin - Information Request for SimCYP
Date: Wednesday, February 08, 2017 9:17:37 AM
Attachments: [image001.png](#)

Hello Vivian,

We acknowledge receiving SimCYP data files for the above mentioned study in the eCTD module “..m4\datasets\pk059mk8835\misc\simcyp” directory of the Original NDA 209803 submission and non-eCTD format.

We are unable to execute the files submitted in non-eCTD format that have a .wksz extension.

Submit the model files in their native format that were used to generate the final results in your PBPK report [i.e., drug model files, population files, and workspace files (.cmpx, .lbrx, and .wksx)]. Please ensure that these files are executable by the FDA reviewers using SimCYP. In addition, submit the any parameter estimation data file as MS Excel files.

We request you to submit these files by COB February 15, 2017.

Please confirm receipt of this email.

If you have any questions, please let me know.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
02/08/2017

From: [Godwin, Elizabeth](#)
To: [Fuh, Vivian](#)
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request
Date: Monday, January 30, 2017 12:58:35 PM
Attachments: [image001.png](#)

Hi Vivian,

In reviewing your request, we have the following revised information request.

During our preliminary review of your submitted labeling for NDAs 209803, 209805 and 209806 on December 19, 2016, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Submit the following information by [February 24, 2017](#):

- a review and summary of available nonclinical information, including published literature regarding sitagliptin and metformin use in pregnant and lactating animals and the effects of sitagliptin and metformin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding metformin use in pregnant and lactating women and the effects metformin on male and female fertility (include search parameters),
- a review and summary of all available published literature regarding sitagliptin and sitagliptin/metformin use in pregnant and lactating women and the effects sitagliptin and sitagliptin/metformin on male and female fertility (from 8/3/2015 to present, include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from 8/3/2015 through present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidance.

If you have any questions, please let me know.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Friday, January 27, 2017 4:49 PM
To: Godwin, Elizabeth
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Liz,

(b) (4)

Thanks for your clarification,
Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Thursday, January 26, 2017 10:57 AM
To: Fuh, Vivian
Subject: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Vivian,

During our preliminary review of your submitted labeling for NDAs 209803, 209805 and 209806 on December 19, 2016, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Submit the following information by February 24, 2017:

- a review and summary of available nonclinical information, including published literature regarding sitagliptin and metformin use in pregnant and lactating animals and the effects of sitagliptin and metformin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding sitagliptin and metformin use in pregnant and lactating women and the effects sitagliptin and metformin on male and female fertility (include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>

). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please confirm receipt of this email and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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ELIZABETH R GODWIN
01/30/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request
Date: Thursday, January 26, 2017 12:49:08 PM
Attachments: [image001.png](#)

Hi Liz, confirming receipt of this request.

Regards, Vivian

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, January 26, 2017 10:57 AM
To: Fuh, Vivian
Subject: NDAs 209803, 209805 and 209806 - ertugliflozin; ertugliflozin-sitagliptin; ertugliflozin-metformin - Information Request

Hi Vivian,

During our preliminary review of your submitted labeling for NDAs 209803, 209805 and 209806 on December 19, 2016, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Submit the following information by February 24, 2017:

- a review and summary of available nonclinical information, including published literature regarding sitagliptin and metformin use in pregnant and lactating animals and the effects of sitagliptin and metformin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding sitagliptin and metformin use in pregnant and lactating women and the effects sitagliptin and metformin on male and female fertility (include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please confirm receipt of this email and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

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Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
01/26/2017



NDA 209803

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B-188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin Tablets, 5 mg and 15 mg.

We acknowledge receipt of your January 4, 2017, correspondence, received January 4, 2017, requesting a review of your proposed proprietary name, Steglatro.

If the application is filed, the user fee goal date will be April 4, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Elizabeth Godwin, Regulatory Project Manager in the Office of New Drugs, at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
01/19/2017



NDA 209805

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B-188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin and Sitagliptin Tablets, (b) (4) 5mg/100mg, and 15mg/100 mg.

We acknowledge receipt of your January 4, 2017, correspondence, received January 4, 2017, requesting a review of your proposed proprietary name, Steglujan.

If the application is filed, the user fee goal date will be April 4, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Elizabeth Godwin, Regulatory Project Manager, in the Office of New Drugs at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
01/19/2017



NDA 209806

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Merck Sharp & Dohme Corp
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B-188
Rahway, NJ 07065

Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) dated December 19, 2016, received December 19, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ertugliflozin/Metformin Tablets, 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg.

We acknowledge receipt of your January 4, 2017, correspondence, received January 4, 2017, requesting a review of your proposed proprietary name, Segluromet.

If the application is filed, the user fee goal date will be April 4, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Elizabeth Godwin, Regulatory Project Manager in the Office of New Drugs, at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
01/19/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request
Date: Wednesday, January 18, 2017 2:58:38 PM
Attachments: [image001.png](#)

Hi Liz, Confirming receipt. Thanks.

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Wednesday, January 18, 2017 2:42 PM
To: Fuh, Vivian
Subject: RE: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request

Hello Vivian,

We have the following additional requests for information in addition to your January 13, 2017, response to our January 9, 2017, information request for NDAs 209803, 209805, and 209806.

Please submit your response no later than Friday, January 20, 2017.

Provide the timelines of the following:

1. Manufacture of the drug products of NDAs 209803 and 209806 (specify dosage strengths) using ertugliflozin L-PGA manufactured at the drug substance commercial facility in Ringaskiddy, and submission of release data of these batches to the NDAs
2. Manufacture of the drug product of NDA 209805 (specify dosage strengths) at the drug product commercial facility in (b) (4) using ertugliflozin L-PGA manufactured at the drug substance commercial facility in Ringaskiddy, and submission of release data of these batches to the application

Please confirm receipt of this email.

Thanks,
Liz

From: Fuh, Vivian [mailto:vivian_fuh@merck.com]
Sent: Friday, January 13, 2017 2:20 PM
To: Godwin, Elizabeth
Subject: RE: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request

Hi Liz, a heads up that responses to this request should have/should be going through the gateway today.

Have a good weekend. Regards, Vivian

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Monday, January 09, 2017 2:56 PM
To: Fuh, Vivian

Subject: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request

Hello Vivian,

In reviewing your December 19, 2016, submission for NDA 209803, NDA 209805, and NDA 209806, we have the following information requests. Please submit your response to the NDAs no later than Friday, January 13, 2017.

1. In NDAs 209803, 209805, and 209806, provide the location of Quality data (i.e., batch release, stability) for the ertugliflozin drug substance manufactured at the proposed commercial site “Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland” and for the drug product manufactured with the ertugliflozin drug substance from this Pfizer Ireland site.
2. Clarify the identity of “Pfizer Ltd Sandwich” listed in the stability sections of NDA 209803.
3. Clarify the identity of “Pfizer, Inc., United Kingdom” listed in the drug product stability section of NDA 209805.
4. In NDA 209805, provide the location of Quality data (i.e., batch release, stability) for the ertugliflozin/sitagliptin drug product manufactured at the proposed commercial site
(b) (4)
5. In NDA 209806, provide the location of the proposed master batch records for the drug product, or confirm that the submitted executed records are the same as the actual master records.

Please confirm receipt of this email.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Office of Drug Evaluation II

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
01/18/2017

From: [Fuh, Vivian](#)
To: [Godwin, Elizabeth](#)
Subject: RE: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request
Date: Monday, January 09, 2017 2:58:46 PM
Attachments: [image001.png](#)

Hi Liz, confirming receipt.

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Monday, January 09, 2017 2:56 PM
To: Fuh, Vivian
Subject: NDA 209803, NDA 209805, and NDA 209806 - ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin - Information Request

Hello Vivian,

In reviewing your December 19, 2016, submission for NDA 209803, NDA 209805, and NDA 209806, we have the following information requests. Please submit your response to the NDAs no later than Friday, January 13, 2017.

1. In NDAs 209803, 209805, and 209806, provide the location of Quality data (i.e., batch release, stability) for the ertugliflozin drug substance manufactured at the proposed commercial site "Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland" and for the drug product manufactured with the ertugliflozin drug substance from this Pfizer Ireland site.
2. Clarify the identity of "Pfizer Ltd Sandwich" listed in the stability sections of NDA 209803.
3. Clarify the identity of "Pfizer, Inc., United Kingdom" listed in the drug product stability section of NDA 209805.
4. In NDA 209805, provide the location of Quality data (i.e., batch release, stability) for the ertugliflozin/sitagliptin drug product manufactured at the proposed commercial site
(b) (4)
5. In NDA 209806, provide the location of the proposed master batch records for the drug product, or confirm that the submitted executed records are the same as the actual master records.

Please confirm receipt of this email.

Thanks,
Liz

Liz Godwin, MSHS, CCRP
Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
01/09/2017



NDA 209803

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ertugliflozin tablets; 5 mg and 15 mg

Date of Application: December 19, 2016

Date of Receipt: December 19, 2016

Our Reference Number: NDA 209803

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **February 17, 2017**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Liz Godwin, MSHS, CCRP
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R GODWIN
12/21/2016



NDA 209805

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ertugliflozin and sitagliptin tablets; (b) (4) 5/100mg, and 15/100 mg

Date of Application: December 19, 2016

Date of Receipt: December 19, 2016

Our Reference Number: NDA 209805

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **February 17, 2017**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Liz Godwin, MSHS, CCRP
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ELIZABETH R GODWIN
12/21/2016



NDA 209806

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ertugliflozin and metformin hydrochloride tablets; 2.5/500 mg, 2.5/1000 mg, 7.5/500 mg, and 7.5/1000 mg

Date of Application: December 19, 2016

Date of Receipt: December 19, 2016

Our Reference Number: NDA 209806

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **February 17, 2017**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Liz Godwin, MSHS, CCRP
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELIZABETH R GODWIN
12/21/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106447
IND 122329
IND 122330

MEETING MINUTES

Merck Sharp & Dohme Corporation
Attention: Vivian Fuh, MD, FACP
Director, Global Regulatory Affairs
126 East Lincoln Avenue
PO Box 2000
Mail Drop: RY34 – B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ertugliflozin (MK-8835/PF-04971729) tablets, ertugliflozin and metformin HCl (MK-8835B) tablets, and sitagliptin and ertugliflozin (MK-8835A) tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 6, 2016. The purpose of the meeting was to discuss the upcoming NDA submissions, the proposed indications, the content and format of the applications, and related regulatory deliverables.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Liz Godwin, Regulatory Project Manager at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 6, 2016, 2:00pm – 4:00pm ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 106447
IND 122329
IND 122330

Product Name: ertugliflozin (MK-8835/PF-04971729) tablets
ertugliflozin and metformin HCl (MK-8835B) tablets
sitagliptin and ertugliflozin (MK-8835A) tablets

Indication: IND 106447: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
IND 122329: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
IND 122330: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate

Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Jean-Marc Guettier, MD, Director, Division of Metabolism and Endocrinology Products

Meeting Recorder: Liz Godwin, MSHS, CCRP, Regulatory Project Manager

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD	Director
Jennifer Rodriguez Pippins, MD, MPH	Deputy Director of Safety
Frank Pucino, PharmD, MPH	Clinical Reviewer
Lisa Yanoff, MD	Clinical Team Leader
Jessica Hawes, PhD	Nonclinical Reviewer

Ron Wange, PhD	Nonclinical Team Leader
Liz Godwin, MSHS, CCRP	Regulatory Project Manager
Julie Van der Waag, MPH	Chief, Project Management Staff

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics II

Alexander Cambon, PhD	Statistical Reviewer
Mark Rothmann, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics VII

Shanti Gomatam, PhD	Statistical Reviewer
Mat Soukup, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Clinical Pharmacology

Sury Sista, PhD	Clinical Pharmacology Reviewer
Manoj Khurana, PhD	Clinical Pharmacology Team Leader

Office of Pharmaceutical Quality, Division of Biopharmaceutics

Poonam Delvadia, PhD	Biopharmaceutical Reviewer
Kimberly Raines, PhD	Biopharmaceutical Team Lead

Office of Scientific Investigations

Cynthia Kleppinger, MD	Senior Medical Officer

Office of Surveillance and Epidemiology, Division of Risk Management

Mei-Yean Chen, PharmD, BCOP	Risk Management Analyst
Amarilys Vega,	Risk Management Analyst

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein	Independent Assessor

SPONSOR ATTENDEES

Merck:

Vivian Fuh, MD	Director, Global Regulatory Affairs
Scott Korn, MD	Vice President, Global Regulatory Affairs
Lina AlJuburi	Director, Regulatory Policy
Shrita Patel, MD, MSCE	Director, Clinical Safety and Risk Management
Nagaraja Muniappa, DVM, PhD	Sr. Principal Scientist, Global Pathology
Paul Fackler, PhD	Executive Director Biopharmaceutics, Translational Pharmacology
Zexun (Susan) Zhou, PhD	Principal Scientist, Pharmacokinetics Pharmacodynamics Drug Metabolism
Susan Huyck, DrPh	Director, Biostatistics
Greg Golm, PhD	Exec. Director, Biostatistics

Brett Lauring, MD, PhD	Distinguished Scientist, Clinical Research, Diabetes and Endocrinology
Sam Engel, MD	Scientific AVP, Clinical Research, LSD Diabetes & Endocrinology
Peter Stein, MD	Vice President, Clinical Research
Shrinivas (Cheenu) Murti, PhD, MBA	Director, Global CMC Regulatory Affairs

Pfizer:

Karen Cox, BSc	Director, Global Regulatory Lead
Anne Hickman, DVM, PhD	Senior Director, Safety Risk Lead
John Pettersen, PhD, DABT	Research Fellow, Toxicology
Vaishali Sahasrabudhe, PhD	Senior Director, Clinical Pharmacology
Vikas Kumar, MBA, PhD	Director, Clinical Pharmacology
James Mancuso, PhD	Director, Biostatistics
Steve Terra, PharmD	Senior Director, Clinical Development, Global Clinical Lead
Susan Johnson, MD	Director, Clinical Development
Susan DeCorte, RPh, RAC, MBA, JD	Asset Team Leader, Global Product Development

1.0 BACKGROUND

Ertugliflozin is an oral, selective inhibitor of sodium glucose co-transporter-2 (SGLT2), thereby inhibiting renal glucose reabsorption resulting in urinary glucose excretion and reducing plasma glucose and hemoglobin A1c (A1C) in patients with type 2 diabetes mellitus (T2DM). Ertugliflozin is being developed as an adjunct to diet and exercise for the treatment of T2DM.

IND 106447 for ertugliflozin was submitted by Pfizer Inc. on September 28, 2009. Sponsorship of IND 106447 was transferred from Pfizer Inc. to Merck Sharp & Dohme Corp. (Merck) on June 21, 2013. IND 122329 for the ertugliflozin and metformin HCl fixed combination drug product (FCDP) was submitted on August 13, 2014. IND 122330 for the ertugliflozin and sitagliptin FCDP was submitted on July 30, 2014. (Note: The sponsor's use of the term "fixed-dose combination" (FDC) is equivalent to the term FCDP, but the latter is now preferred.)

Merck plans to submit New Drug Applications (NDAs) for their proposed products, ertugliflozin and ertugliflozin-containing FCDPs with metformin HCl and sitagliptin, in December 2016.

On July 6, 2016, Merck submitted Type-B Pre-NDA meeting requests for each product. On July 27, 2016, the meetings were granted.

The purpose of the pre-NDA meetings was to gain feedback from FDA related to the upcoming NDA submissions, the proposed indications, the content and format of the applications, and related regulatory deliverables.

The briefing document received July 6, 2016, provided the background and the questions to be addressed at the September 6, 2016, meeting. The questions included in the briefing document

were the same for all three applications; therefore this document includes responses for all three applications.

FDA sent Preliminary Comments to Merck on September 1, 2016.

2. DISCUSSION

2.1. Non-Clinical Development

Question 1: Does the Agency agree that the nonclinical safety package as outlined is adequate to allow review of the NDAs to support filing and approval of ertugliflozin and the two FDC products?

FDA Response to Question 1:

The nonclinical safety package is considered to be adequate to support filing and allow review of the NDAs for ertugliflozin and the two FCDPs.

Discussion to Question 1: No discussion occurred.

Question 2: Does the Agency agree that additional experimental data addressing the mode of development for ertugliflozin-related adrenal medulla pheochromocytomas and their relevance to human risk is not necessary?

FDA Response to Question 2:

Conclusions regarding the carcinogenicity findings and the necessity of follow-up studies are a matter of review.

Discussion to Question 2: No discussion occurred.

2.2. Clinical Pharmacology and Biopharmaceutics

Question 3: Does the Agency agree that the clinical pharmacology and biopharmaceutics package is sufficient to support the review of the ertugliflozin, ertugliflozin/sitagliptin FDC and ertugliflozin/metformin FDC NDAs?

FDA Response to Question 3:

Clinical Pharmacology: Yes, the clinical pharmacology package seems sufficient to support the review of ertugliflozin and the two FCDP NDAs.

We have following general comments:

- A. You indicated in the briefing document that (a) a population pharmacokinetic (PK) analysis will be conducted using data from nine Phase 1, two Phase 2, and four Phase 3 studies, (b) an exposure/dose-efficacy analysis will be conducted using data from one Phase 2 study P016/1006 and Phase 3 studies with both A1C**

and PK data. Note that the following are general expectations for submitting the pharmacometric data and models:

- i. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
 - ii. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**
 - iii. A model development decision tree and/or table which gives an overview of modeling steps should be submitted.**
 - iv. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**
 - v. In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ct1.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file, and if necessary a pdf file (e.g., "revieweraid.pdf") to explain the flow of running the code. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.**
- B. Submit all relevant datasets and model codes for your exposure-response analysis. For clinical pharmacology studies containing pharmacokinetic and pharmacodynamic data please submit datasets preferably as SAS transport (.xpt) files. Please ensure that the pharmacokinetic (concentration and parameters) and pharmacodynamic data sets include treatment, period, sequence information, as applicable. We also recommend the inclusion of SAS code used to merge datasets used in the final analysis.**

We acknowledge your plan to assess the safety from a DDI perspective for subjects receiving ertugliflozin in combination with loop diuretics from a pooled

safety analysis of Phase 3 trials. We recommend you submit necessary SimCYP model files and associated input and output data related to your model based DDI evaluation for UGT1A9 inhibitor. Clarify if you intend to make any labeling claims based on this analysis. Whether this information forms sufficient basis for any labeling claims is a review issue.

Biopharmaceutics: Yes, the biopharmaceutics package seems sufficient to support the review of ertugliflozin NDA; however, we have the following additional comments:

You are reminded of previous communications - written responses dated Oct 9, 2014, and May 6, 2016, - on disintegration and dissolution testing, and application of dissolution for bridging formulation/manufacturing changes.

If submitting a biowaiver request for the lower strength, 5 mg, provide supportive data in Module 1.12.15. *Request for Waiver of In Vivo Bioavailability Studies*, subject to the biowaiver approach used [e.g., based on 21 CFR 320.22 (d)(2), refer to [21 CFR 320.22\(d\)\(2\)](#) and [FDA's Draft Guidance for Industry – Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs- General Considerations](#)].

We acknowledge that data on absolute bioavailability, solubility, and dissolution supporting classification of ertugliflozin as a biopharmaceutics classification system (BCS) class 1 drug will be provided in the NDA. It is encouraged to reference [FDA's Draft Guidance for Industry on BCS](#) for recommendations on data submission.

The biopharmaceutics package seems sufficient to support the review of ertugliflozin and metformin FCDP NDA; however, we have the following additional comment:

We acknowledge that *in vivo* BE studies comparing ertugliflozin and metformin FCDP with individual components at lowest (2.5 mg/500 mg) and highest (7.5 mg/1000 mg) strengths, and *in vitro* dissolution reports supporting middle strengths (2.5 mg/1000 mg and 7.5 mg/500mg) will be submitted in the NDA. Submit a biowaiver request in Module 1.12.15. *Request for Waiver of In Vivo Bioavailability Studies*, for the middle strengths supported by data recommended in written responses dated June 08, 2015. Reference is also made to written responses dated July 3, 2014, that provided recommendations on dissolution method development and setting of dissolution acceptance criterion.

The biopharmaceutics package seems sufficient to support the review of sitagliptin and ertugliflozin FCDP NDA; however, we have the following additional comment:

We acknowledge that *in vivo* BE studies on the proposed four strengths of ertugliflozin and metformin FCDP will be submitted in the NDA and therefore biowaiver is not applicable. For dissolution testing, reference is made to the written responses dated June 12, 2014, that provided recommendations on dissolution method development and setting of acceptance criterion.

Discussion to Question 3: No discussion occurred.

2.3. Clinical Development

Question 4: Does the Agency agree that the efficacy and safety data package from the seven Phase 3 clinical trials is adequate to support the review of the ertugliflozin, ertugliflozin/sitagliptin FDC and ertugliflozin/metformin FDC NDAs for the proposed indications and dose strengths?

FDA Response to Question 4:

The proposed data package from the seven Phase 3 clinical trials will be sufficient to submit your NDAs for ertugliflozin, sitagliptin and ertugliflozin FDCP, and ertugliflozin and metformin FDCP, provided you are able to achieve the anticipated exposures described in Table 6 (page 33) of your briefing document.

The proposed indication for your ertugliflozin and metformin FDCP is “as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)” Since all of the clinical trials you plan to submit in support of this FDCP (i.e., P007/1017, P002/1013, P005/1019, and P006/1015) were designed as add-on to background metformin, you did not study the HbA1c lowering effect of starting two drugs at once. Therefore, this may need to be reflected in the labeled indication (i.e., as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients already being treated with both ertugliflozin and metformin).

Discussion to Question 4: No discussion occurred.

Question 5: Does the Agency agree that the only data from the CVOT (P004/1021) to be provided is that related to the CVMA, as described below?

FDA Response to Question 5:

We agree that, for the purpose of preservation of data integrity and in light of the accumulated experience with this class of drug, the only data provided from your cardiovascular outcome trial (CVOT) relates to the cardiovascular meta-analysis (CVMA). We note however from experience with other members of the class, that certain drug-related adverse reactions related to the drug’s mechanism of action (i.e., see Warnings and Precautions for approved members of the class) were observed more frequently in populations of patients enriched for comorbid conditions prevalent in the CV outcomes trial. We note that adverse reactions data for these patients will not be included in your original submission and reported prevalence of adverse reactions found in your program will be interpreted in that light. Note that comments sent on July 29, 2016, should be addressed to protect the integrity of the ongoing CVOT.

Discussion to Question 5: No discussion occurred.

Question 6: Does the Agency agree with:

- a. a single (common), self-contained, comprehensive ISE (Section 5.3.5.3.2) for the three NDAs as described below?
- b. the draft tables of contents (TOCs) for the three SCEs and a common ISE?

FDA Response to Question 6:

This is acceptable. Additionally, the inclusion of a copy of Module 2 (Section 2.7.3) from the ertugliflozin NDA in Module 2 of the FCDP NDAs, and the proposed TOCs, with a clear leaf title of each document and unique headers, will be acceptable.

Discussion to Question 6: No discussion occurred.

Question 7: Does the Agency agree that the updates to the ISS SAP made in response to Agency requests adequately address the Agency's concerns?

FDA Response to Question 7:

- A. The additional updates to the ISS SAP (i.e., inclusion of measurements after initiation of glycemic rescue, and inclusion of additional safety endpoints) are adequate.**
- B. Utilizing study as a stratification factor in the statistical analyses (i.e., stratified Miettinen & Nurminen for adverse events [AEs] and predefined limits of change [PDL]), and tabulation of AEs using an exposure-adjusted incidence approach will be acceptable.**
- C. We agree that data from the CVOT is not to be included in the ISS.**
- D. On May 18, 2016, FDA issued a Drug Safety Communication (DSC) regarding another member of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor class, and the risk of foot and leg amputations, mostly affecting the toes. Therefore amputations and revascularization procedures should be considered adverse events of special interest (AESI), and clinical narratives should be provided for these events. Additionally, for your ongoing CVOT and Phase 3 trials, we recommend that amputations and revascularization procedures be designated as AESI and evaluated prospectively. The case report forms should also be revised to capture these events. Please refer to the FDA Drug Safety Communication (dated 05/18/2016), available at:
<http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm>.**

Discussion to Question 7: No discussion occurred.

Question 8: Does the Agency agree with:

- a. the proposed distribution of content between the three SCSs (Module 2, Section 2.7.4) and a common ISS (Module 5, Section 5.3.5.3.3) as described below?
- b. the tables of contents (TOCs) for the three SCSs and the common ISS?

FDA Response to Question 8:

The inclusion of a Summary of Clinical Safety (SCS), specific to each NDA, in Module 2 (i.e., Section 2.7.4), and a common set of referenced documents, including the ISS, in Module 5 (Section 5.3.5.3) for each NDA will be acceptable. We also concur with the placement of a copy of Module 2 (Section 2.7.4) from the ertugliflozin NDA in Module 2 of the FCDP NDAs, and with the proposed TOCs.

Discussion to Question 8: No discussion occurred.

Question 9: Does the Agency agree with the Sponsor's proposed case ascertainment strategy and case definitions for events of ketoacidosis?

FDA Response to Question 9:

The proposed ascertainment strategy (case identification by Custom MedDRA queries, laboratory criteria, and narrative text string searches) and case definitions, with adjudication of events by an Internal Case Review Committee, consisting of three independent experienced clinicians blinded to treatment allocations, are adequate. We also recommend that you consider the following:

- A. Broaden your Custom MedDRA Query (CMQ) to include the following additional MedDRA PTs: Acetonaemia; Acid-base balance disorder mixed; Anion gap; Anion gap abnormal; Anion gap increased; Blood bicarbonate decreased; Blood ketone body; Blood pH abnormal; Blood pH decreased; Coma acidotic; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Diabetic metabolic decompensation; Diabetes with hyperosmolarity; Hyperglycemic seizure; Hyperosmolar hyperglycemic state; Hyperosmolar state; Kussmaul respiration; Organic acid analysis abnormal; Respiratory alkalosis; and Urine ketone body.
- B. Include anion gap in your laboratory search criteria and possibly your Case Definition.
- C. Since a diagnosis may not always be definitive, consider the use of the term 'confirmed' in lieu of 'certain' for your Case Definition.
- D. Consider inclusion of associated symptoms in the Case Definition.
- E. Known potential triggers for ketoacidosis will be captured in your Case Review Form and included in your clinical narrative. Any precipitating events which may be associated with investigational product (e.g., complicated urinary tract

infections/urosepsis, reduction/discontinuation in insulin therapy) should be assessed for relatedness.

Discussion to Question 9: No discussion occurred.

Question 10: Does the Agency agree with the proposed timetable for submission of a common 4-month Safety Update Report for the 3 NDA submissions and with the proposed content of the report?

FDA Response to Question 10:

At the time of the four-month Safety Update (4MSU) Report, you propose to submit the same update report for all three NDA submissions, “as the new safety data in the Broad Pool will be applicable to all three submissions, and individual study Phase B safety updates will satisfy the unique needs of each individual submission.” This may be reasonable.

You also plan to submit additional safety datasets for trials P003/1022, P005/10198, P006/1015, and P001/1016, updated tables for the Broad Pool population, and revised listings of SAEs, deaths, and discontinuations due to AEs obtained after the NDA cut-off date for studies contributing safety information to the FCDP submissions (i.e., P002/1013, P005/1019, P006/1015, and P007/1017). The submission will also include the 52-week bone mineral density data for study P007/1017, completed eCRFs, and safety narratives. Your updated tables should include a side-by-side comparison of the safety findings in the original submission with those including the updated data. Any notable differences should be highlighted.

In addition, please clarify the extent of additional exposure that will contribute to the data submitted for the 4MSU. The Agency generally assumes that when an original application is submitted for review, the applicant believes that the Agency can approve the application as submitted (21 CFR 314.60). Therefore, the clinical data necessary to support the safety of your three NDAs for the proposed indications should be provided at the time these NDAs are originally submitted.

Discussion to Question 10: Refer to the sponsor’s response in attached Slide #3. The sponsor agreed to submit additional Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) data sets to support the 4MSU report. The sponsor will also provide associated Define files, if updated from the original submission, and side-by-side tables with notable differences highlighted for comparison.

2.4. Multidisciplinary Questions

Question 11: Does the Agency agree with the proposed content and format of the New Drug Applications for ertugliflozin, ertugliflozin/sitagliptin FDC and ertugliflozin/metformin FDC as described in the respective Table of Contents (TOC)?

FDA Response to Question 11:

From a technical standpoint (not content related) yes, the proposed format for the planned NDAs is acceptable. However, please see additional comments below:-

- A. Providing Table of Contents in 3.1 and 4.1 is not necessary in the eCTD structure. Instead, it will be helpful to reviewers if you can provide a linked reviewer's aid/ reviewer's guide to briefly describe where information can be found throughout the application and place the document in m1.2.
- B. List of investigators should reside in m5 (not m5.2), under the specific study tagging file (STF) and tagged as "list-description-investigator-site"
- C. Do not create additional nodes (e.g. m2.7.1.1 – m2.7.1.5; m2.7.2.1 - m2.7.2.6, etc.,) in the eCTD structure beyond what is in the specifications. Please make sure your approach fits the DTD and the "Granularity Annex", located at:-
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf>
- D. The summary level clinical site information should be submitted in m5.3.5.4 (not m5.2), in the format described in the "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning."
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ucm332466.pdf>
- E. Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form".

Discussion to Question 11: No discussion occurred.

Question 12: Does the Agency require additional information to facilitate the review of the CRT deliverables?

FDA Response to Question 12:

Based on the information provided in your background package, the submission of sample legacy SAS transport, and Study Data Tabulation Model (SDTM) datasets (dated August 22, 2016), the proposed Case Report Tabulation (CRT) deliverables appear reasonable.

At the time of your NDA submission, please provide the following for the tabulation datasets:

- A. Include actual treatment arm (ACTARM) in the DM and LB domains.

- B. In the DM domain, also include Death, Death Date (DTHDTC), and a Death Flag (DTHFL).**
- C. For efficiency, accuracy, and proper interpretation of clinical laboratory test results, provide the results in both U.S. conventional units and SI units in the LB domain.**
- D. Incorporate MedDRA hierarchy within the AE domain.**

Discussion to Question 12: Refer to the sponsor's response in Slides #4 and #5. The Agency acknowledges the previous waiver request to use SDTM IG v.3.1.1 standard and agrees that the listed variables, proposed in the attached slides, are acceptable.

Question 13: Does the Agency agree with the scope and high-level content of the Analysis Package described in the Background Package?

FDA Response to Question 13:
General Statistical Comments:

- A. We are interested in estimating the treatment effect based on the intent-to-treat (de facto) estimand, which considers the actual measurements of subjects regardless of adherence to treatment or use of subsequent therapy, including use of glycemic rescue therapy, bariatric surgery, or bone mineral density rescue therapy. The corresponding analyses should account for missing data in the primary endpoint in a fashion consistent with what the measurement would have been, had it been measured and should address missing data based on that information most relevant to what the measurement would have been had it been measured. The cLDA (constrained Longitudinal Data Analysis) method likely does not appropriately address missing data as they both treat the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm. We would recommend addressing missing data on the primary endpoint by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement for the primary endpoint. Analysis results based on the de facto estimand will likely be the results put on the product label.**
- B. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.**

- C. The analysis dataset documentation (Define.pdf) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables.**
- D. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.**
- E. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.**
- F. In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).**
- G. Based on the sample datasets you submitted on August 16, 2016, for the completed Phase 3 trial (i.e., P006) and the Phase 3 Integrated Summary of Safety (ISS) we also recommend that you provide the following at the time your NDA is submitted:**
 - i. Provide the results in both U.S. conventional units and SI units for the ADLB datasets for the Phase 3 trials and ISS, as well as the LB domain in the tabulation datasets.**
 - ii. For the Phase 3 trials, include the relative study day for any AE-related date variable in the ADAE datasets, and any CM-related dates in the ADCM datasets.**
 - iii. For the Phase 3 ISS, include the relative day for all AE-related date variables in ADAE dataset.**
 - iv. Include adjudicated events of ketoacidosis in the Adjudicated AE Analysis dataset for the ISS.**
 - v. We acknowledge the use of predefined limits of change (PDLc) for clinical laboratory parameters in the ADLB datasets. To further assist with the review of clinical laboratory changes, include a post-baseline flag for both the ADLB and ADVS datasets for the Phase 3 trials and ISS. For estimated glomerular filtration rate (eGFR), also include baseline and post-baseline categories using the Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria (i.e., eGFR ≥ 90 , 60-89, 30-59, 15-29, and <15 mL/min/1.73 m²).¹**

Comments on information to be submitted for your cardiovascular meta-analysis (CVMA) to evaluate the 1.8 risk margin:

- A. Integrated data sets:** For your CVMA, The following integrated data sets should be submitted to the NDA. Note that a) The trials included in each of these integrated data sets should be the same set of trials for which you plan to evaluate cardiovascular risk; b) All datasets requested should contain a unique identifier (e.g. USUBJID) for every subject and unique identifier (e.g. STUDYID) for each trial. The subject and trial identifiers should be consistent across all submitted datasets; c) The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report.
- i. **Demographics:** This dataset should contain, at minimum, demography, population flags, treatment group, trial dates (e.g. randomization date, start of treatment date, etc.), and measured baseline subject characteristics (e.g. smoking status, history of CV disease, baseline use of anti-hyperglycemic agents, baseline use of CV medications, etc.).
 - ii. **Subject Disposition:** This dataset should contain all subject disposition information (e.g. screened, enrolled, treated, discontinued treatment or trial and reasons for discontinuation), as well as key dates which are used to derive the disposition variables.
 - iii. **Adverse Events:** This dataset should contain information (including dates) relevant to all adverse events, including CV events, collected during the respective trials. Include the verbatim term for each adverse event, the MedDRA lower level term, the preferred term to which it was coded and all other levels of the MedDRA hierarchy.
 - iv. **Cardiovascular Event Committee Findings:** This dataset should contain information (including dates) for all event triggers sent for adjudication. Include whether the event was positively adjudicated for inclusion in the CV meta-analysis.
 - v. **Concomitant Medications:** This dataset should contain information about all medications administered, including study treatments. The dataset should also contain data collected about medications taken after discontinuation from randomized treatment until trial completion.
 - vi. **Time to CV Event Analysis Dataset:** This dataset should contain all information relevant for the planned time-to-CV event analyses, for example, subject and trial identification, demographics, risk factor,

¹ National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.

treatment group, population flags, cardiovascular composite endpoint(s), individual component, censoring flag, censoring date and event date. All composite endpoints specified in the meta-analysis protocol (e.g. primary and secondary), and respective components, as well as all-cause mortality, should be accounted for in this dataset. This dataset should also contain any variable relevant for protocol-specified subgroup CV analyses. The structure of this dataset should be one record per subject per analysis population per censoring scheme per event.

B. Data Specification

- i. We encourage the use of standardized data structures as this enhances our ability to review the data. See the following link for more information:
<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>**
- ii. Submit all requested datasets in SAS transport (.xpt) format.**

C. Submission Content

- i. Submit the statistical analysis plan (SAP) for your CVMA and all amendments.**
- ii. Submit ALL protocol versions and protocol amendments with track changes. Include a summary document that describes the changes to this document.**
- iii. Submit all DMC and Steering Committee meeting minutes. Summarize recommendations made for each meeting and changes (nature, rationale etc.) implemented as a result of these input.**
- iv. Submit all charters (steering, executive, clinical endpoint committee) and changes made to these charters with a document summarizing changes to these charters and the reason for making the change.**
- v. In your CVMA study report, list in one table the following information for each trial:**
 - 1) Date of first subject visit and date of last subject visit**
 - 2) Date of database lock**
 - 3) Date of interim analysis, if applicable**
 - 4) Date of initial protocol and all revisions (with a hyperlink to the protocol and each revision).**

vi. Submit all adjudication packages exactly and completely as seen by the adjudicators.

Discussion of Question 13:

Discussion Related to General Statistical Comments

Comment A: Refer to the sponsor's response in attached Slide #16. The sponsor agreed to submit the Jump to Reference (J2R) program, one of the analytical approaches they propose for handling missing data, for Agency review prior to submitting the NDA.

Comment B: The Agency agrees with the plan proposed in the attached slides to provide a separate SAS transport file that would identify the unique individual and the subject IDs used across the multiple randomizations. Refer to the sponsor's Slide #6.

Comment C: The sponsor agreed to provide the analysis dataset documentation in both a define.PDF and define.XML formatted file. Refer to the sponsor's Slide #7.

Comment E: The Agency agrees that what the sponsor proposes to provide for datasets and programs will be acceptable. Refer to the sponsor's Slide #8.

Comment G: See sponsor's response in attached Slide #9. The sponsor agreed to submit a separate SAS transport file for adjudicated events of ketoacidosis. They propose to include text, summary, and datasets with the associated Define file. The sponsor confirmed adjudicated events of ketoacidosis will not include events from the CVOT.

Discussion Related to Comments on Information to be Submitted for your Cardiovascular Meta-Analysis (CVMA) to Evaluate the 1.8 risk Margin

Comment A.iii: Refer to the sponsor's response in attached Slide #11. The Agency confirmed the sponsor may disregard this comment.

Comment A.v.: Refer to the sponsor's response in attached Slide #12. The sponsor reiterated that concomitant medication summaries were not planned to be included in the CVMA as they were not pre-specified in the meta-analysis. The Agency requested that the sponsor provide a list of all datasets along with content/variable listings that they plan to be submitted in the NDA to allow for requests of additional data/information to be submitted if needed. The sponsor agreed to provide this information prior to NDA submission.

Comment C.iii: The Agency agrees with the sponsor's DMC meeting minutes proposed in the attached slides for NDA submission. Refer to Slide #13.

Post-Meeting Comment: On September 13, 2016, the Agency received the sponsor's programs supporting jump-to-reference sensitivity analyses and list of datasets along with content/variable listings that they plan to submit in the NDA for the Agency's review. On September 20, 2016, the Agency received the sponsor's by-study listings of

A1C measurements collected after study medication discontinuation. The Agency will provide comment, if necessary, under separate cover.

Question 14: Does the Agency agree with the Sponsor's proposed format for submission of summary level clinical site datasets and proposed method for estimation of within-site treatment effect size to aid OSI data integrity review and inspection planning? Per FDA request, interim information from the CVOT is used only to evaluate pre-market CV-risk, and general safety information from the CVOT or efficacy sub-studies embedded in the CVOT will not be analyzed at interim. Access to the CVMA will be limited to a specified group of Sponsor individuals, as per the Data Access Plan. Therefore, the Sponsor does not plan to provide unblinded data listings or unblinded summary level clinical site datasets for the ongoing cardiovascular safety study, P004/1021 to OSI.

FDA Response to Question 14:

- A. You have stated that Financial Disclosure information will not be included in the summary site level dataset. This is acceptable.**
- B. You have stated that estimates for the primary efficacy endpoint (change from baseline in A1C) were calculated using a last-observation-carried-forward imputation approach. This differs from the primary statistical method used in the clinical study reports. You should clarify your rationale for this approach at the meeting.**
- C. You should define the approach used in either the define.xml file that accompanies the clinsite.xpt, or in the BIMO Reviewer Guide if one will be included in the submission.**
- D. You have stated that Study P005/1015 had 3 reference groups. We have confirmed that you are referring to study P005/1019. For the Summary Level Clinical Site Data file, a single reference group was chosen, and it was the group used in the first statistical hypothesis tested. You will need to include in your define file for the clinsite.xpt, and/or in your BIMO Reviewer Guide, what you are using for your site effect calculation.**
- E. You have stated that you do not plan to provide unblinded data listings or unblinded summary level clinical site datasets for Study P004/1021 to OSI. This is acceptable to OSI. If the review team anticipates requesting clinical site inspections for this study during the original NDA submission review, then the firewalled group preparing the submission should also prepare a separate clinsite.xpt file for just Study P004/1021 alone that can be submitted in the firewalled amendment to the NDA. If all the data for this study is remaining blinded to the review division, then it could likewise remain blinded in the clinsite.xpt (would then be reported as a single arm study with total number CVOT events reported by site for TRTEFFE). OSI would then have the option of presenting data from this study in a separate tool or recombining it with the**

clinsite.xpt data in the original NDA submission that included data for the other studies.

Discussion to Question 14:

Discussion of OSI Comment B: The sponsor agrees to utilize a dual approach to estimate TRTEFFE, with estimates provided using arithmetic means on non-imputed values to calculate one endpoint value and the LOCF approach for the second endpoint value. Refer to Slide #15.

Discussion of OSI Comment E: The Agency agrees with the sponsor's proposal that the estimate be based on all CV events as reported in the CRF's and described in the attached slides. Refer to Slide #14.

Post-Meeting Comment: On September 9, 2016, the sponsor submitted the following post-meeting clarification request regarding the OSI deliverable (referencing the Pre-NDA meeting discussions related to FDA response B to Question 14 in the Meeting Preliminary Comments): Please confirm whether FDA is requesting that the Sponsor provides TRTEFFE estimates using both LOCF and the primary analysis (cLDA) approaches, or would FDA prefer a single approach using arithmetic means on non-imputed values?

FDA Response to the September 9, 2016, clarification request: We would prefer that you submit using two approaches (i.e. as two endpoints):

1. Using LOCF
2. Using arithmetic means on non-imputed values.

Question 15: Please confirm that the list of trials for which we will provide financial disclosure information is acceptable. If the Agency desires financial disclosure information for any other trials, please identify the trials.

FDA Response to Question 15:

We note that you do not plan to provide financial disclosure information for your ongoing CVOT (i.e., P004/1021), trial P012/1045 (the add-on to metformin, Asia-Pacific region), or the following clinical pharmacology/biopharmaceutics studies: P036/1001, P037/1002, P038/1003, P040/1007, P035/1051, P010/1025, P009/1023, P014/1024, P041/1009, P019/1032, P022/1033, P032/1044, P030/1036, P021/1040, P020/1043, P024/1048, P011/1034, P022/1033, P026/1050, P019/1032, P028/1049. Disclosure of financial interests and arrangements is required for covered clinical studies, specifically, those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). Should any of the trials/studies mentioned above be considered covered clinical studies, financial disclosure information will need to be provided. Please refer to the *Guidance for Clinical Investigators, Industry and FDA Staff. Financial Disclosure by Clinical Investigators*,

available at:

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf>

Discussion to Question 15: No discussion occurred.

Additional Clinical Comments:

In Appendix 2b (Statistical Analysis Plan for Integrated Summary of Safety Data of MK-8835/PF-04971729) of your background package, you plan to identify AESI using the Standard MedDRA Queries (SMQ) and Custom MedDRA Queries (CMQ), as described on pages 31-42. To assist with identification of these events, consider broadening your SMQ/CMQ searches by including the following additional MedDRA PTs (Note: it would be helpful if the PTs for complicated genital and urinary tract infections are also included in the more general genital mycotic infection and urinary tract infection SMQs/CMQs, respectively):

- **Embolic and Thrombotic Events, Venous:** Axillary vein thrombosis; Thrombosis
- **Genital Mycotic Infection:** Acquired phimosis; Bartholin's abscess; Bartholinitis; Cellulitis of male external genital organ; Circumcision; Clitoris abscess; Escherichia vaginitis; Genital burning sensation; Genital discharge; Genital infection bacterial; Genital rash; Phimosis; Pruritus genital; Urogenital infection fungal; Vaginal abscess; Vaginal cellulitis; Vaginal discharge; Vaginal erosion; Vaginal exfoliation; Vaginal hemorrhage; Vaginal lesion; Vaginal odour; Vaginal swelling; Vaginitis bacterial; Vulval abscess; Vulval cellulitis; Vulval disorder; Vulval edema; Vulvovaginal burning sensation; Vulvovaginal discomfort; Vulvovaginal disorder; Vulvovaginal dryness; Vulvovaginal erythema; Vulvovaginal pain; Vulvovaginal pruritus; Vulvovaginitis Streptococcal; Vulvovaginal burning sensation; Vulvovaginal ulceration; Vulvovaginitis
- **Hypersensitivity:** Atopy; Blepharitis allergic; Blood immunoglobulin E abnormal; Blood immunoglobulin E increased; Bronchospasm; Chronic eosinophilic rhinosinusitis; Chronic hyperplastic eosinophilic sinusitis; Circulatory collapse; Conjunctival oedema; Corneal oedema; Cutaneous vasculitis; Dermatitis; Dermatitis acneiform; Dermatitis allergic; Dermatitis atopic; Dermatitis bullous; Dermatitis contact; Dermatitis exfoliative; Dermatitis exfoliative generalised; Dermatitis herpetiformis; Dermatitis infected; Dermatitis psoriasiform; Distributive shock; Documented hypersensitivity to administered product; Drug eruption; Drug hypersensitivity; Drug reaction with eosinophilia and systemic symptoms; Eczema nummular; Eczema vesicular;
- **Osmotic Diuresis:** Dry mouth; Dry throat; Micturition urgency; Thirst; Tongue dry
- **Volume Depletion:** Blood osmolarity increased; Blood pressure ambulatory decreased; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure immeasurable; Blood pressure orthostatic abnormal; Blood pressure systolic decreased; Blood pressure systolic inspiratory decreased; Blood urea nitrogen/creatinine ratio

increased; Capillary nail refill test abnormal; Central venous pressure decreased; Decreased ventricular preload; Femoral pulse decreased; Hypoperfusion; Hypotension; Left ventricular end-diastolic pressure decreased; Mean arterial pressure decreased; Orthostatic heart rate response increased; Peripheral circulatory failure; Pulmonary arterial pressure decreased; Pulmonary arterial wedge pressure decreased; Pulse volume decreased; Radial pulse decreased; Renal ischemia; Urine flow decreased; Venous pressure decreased; Venous pressure jugular decreased; Volume blood decreased

- **Urinary Tract Infection:** Acute focal bacterial nephritis; Asymptomatic bacteriuria; Bacterial prostatitis; Bacteriuria; Candiduria; Costovertebral angle tenderness; Culture urine positive; Cystitis glandularis; Cystitis gonococcal; Cystitis interstitial; Cystitis pseudomonas; Cystitis-like symptom; Leukocyturia; Malacoplakia vesicae; Nitrite urine present; Nitrituria; Prostatitis; Prostatovesiculitis; Pyelonephrosis; Pyuria; Trigonitis; Ureteritis; Urethral carbuncle; Urinary tract infection enterococcal; Urinary tract infection fungal; Urinary tract inflammation; Urine leukocyte esterase positive; White blood cells urine positive

Additional Discussion Comments:

(b) (4)

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 27, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

4.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was not held. We will notify you during the review cycle if it is determined that a REMS is necessary.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There are no agreements for late submission of application components.

5.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at

301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

6.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

7.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

8.0 505(b)(2) REGULATORY PATHWAY - For ertugliflozin and metformin HCl FCDP tablets

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its

October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

9.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

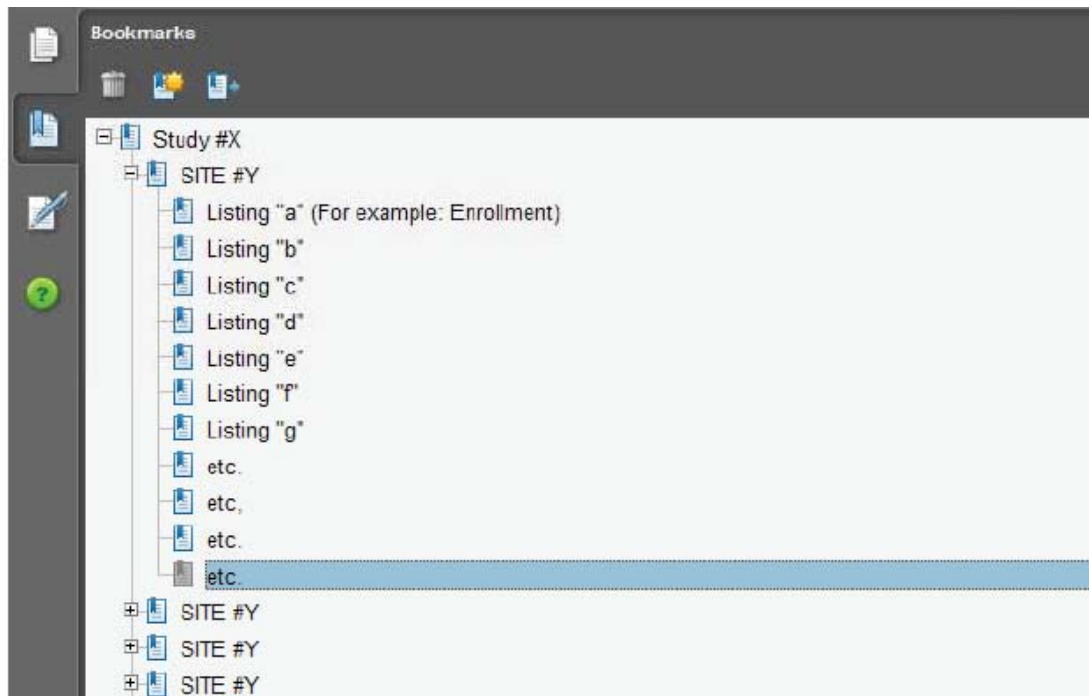
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

10.0 ISSUES REQUIRING FURTHER DISCUSSION

Discussions on how to integrate concomitant medication datasets into the CVOT is ongoing.

11.0 ACTION ITEMS

There were no action items identified at the meeting.

12.0 ATTACHMENTS AND HANDOUTS

Attached are the slides presented by Merck during the September 6, 2016, meeting.

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

/s/

JEAN-MARC P GUETTIER
09/30/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106447

MEETING MINUTES

Pfizer Inc.
Attention: Marsa D. Hatfield
Director, Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06430

Dear Dr. Hatfield:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-04971729 Oral.

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to gain agreement and feedback on your proposed Phase 3 developmental plan, toxicology studies, and pediatric plan.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: December 17, 2012
Meeting Location: 10903 New Hampshire Avenue
Building 22, Conference Room 1419
Silver Spring, MD 20993

Application Number: IND 106447
Product Name: PF-04971729
Indication: Treatment of Type 2 Diabetes Mellitus (SGLT2 inhibitor)
Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Mary H. Parks, MD
Meeting Recorder: Abolade (Bola) Adeolu, RPh, MS, MBA

FDA ATTENDEES

Mary H. Parks, MD – Director, Division of Metabolism & Endocrinology Products
Jean-Marc Guettier, MDCM – Clinical Team Lead
Frank Pucino, PharmD, MPH – Clinical Reviewer
Todd Bourcier, PhD – Pharmacology/Toxicology Supervisor
Jeffrey Quinn, PhD – Pharmacology/Toxicology Reviewer
Todd Sahlroot, PhD – Deputy Director, Division of Biometrics II (DBII)
Wei Liu, PhD – Statistical Reviewer (DBII)
Lokesh Jain, PhD – Clinical Pharmacology Team Lead
Sang Chung – Clinical Pharmacology Reviewer
Donna Snyder, MD – Reviewer, Pediatric and Maternal Health Staff
Matthew Bacho – Senior Regulatory Health Project Manager
Abolade (Bola) Adeolu, RPh, MS, MBA – Regulatory Project Manager



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

SPONSOR ATTENDEES

Pfizer Attendees

Ken Sprenger, MD, MBBCh – Medicine Team Leader, Executive Director, Primary Care

Beth Anne Piper, MD – Clinical Sciences, Executive Director, Primary Care

Steven Terra, PharmD – Clinical Lead Senior Director, Primary Care

Neeta Amin, PharmD – Clinical Lead, Senior Director, Research

James Mancuso, PhD – Director, Biostatistics

Enayet Talukder, PhD – Senior Director, Biostatistics

Anne Hickman, DVM, PhD – Director, Safety Risk Lead

Vaishali Sahasrabudhe, PhD – Director, Clinical Pharmacology

John Pettersen, PhD, DABT – Research Fellow, Toxicology

Marsa Hatfield, PhD – Global Regulatory Lead, Director, Regulatory Strategy

Esther Nougier, Msc, MBA – Portfolio Lead, Senior Director, Regulatory Strategy

Susan McCann – Director, Global Project Manager for Diabetes

Merck Attendees

Manu Chakravarthy, MD, PhD – Senior Principal Scientist, Clinical Research, Clinical Pharmacology

Sam Engel, MD – Executive Director, Clinical Research, Diabetes & Endocrinology

Vivian Fuh, MD – Director, Worldwide Regulatory Affairs

Barry Goldstein, MD, PhD – Vice President, Clinical Research, Diabetes & Endocrinology

Keith Kaufman, MD – Vice President, Project Leadership and Management, Diabetes & Endocrinology

Eseng Lai, MD, PhD – Executive Director, Project Leadership and Management, Diabetes Endocrinology

Nagaraja Muniappa, DVM, PhD – Senior Principal Scientist, Global Pathology

Bret Musser, PhD – Senior Principal Scientist, Informatics & Analytics, Modeling & Simulation

Robert Silverman, MD, PhD – Executive Director, Worldwide Regulatory Affairs

1.0 BACKGROUND

Pfizer Inc. submitted an End of Phase 2 Meeting (EOP2) meeting request on September 13, 2012. The purpose for the EOP2 meeting was to gain agreement and feedback on their proposed Phase 3 developmental plan, toxicology studies, and pediatric plan.

Pfizer Inc. plans to develop PF 04971729 as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 Diabetes Mellitus (T2DM). According to the sponsor, PF-04971729 is a highly potent and selective inhibitor of the sodium/glucose co-transporter type 2 (SGLT2) and possesses a high selectivity for SGLT2 versus SGLT1 and several other glucose transporters (GLUT1-4)

The Division agreed to a face-to-face meeting which was scheduled for Monday, December 17, 2012. The background package was received on November 16, 2012. Preliminary meeting comments were issued, and an email copy was sent to the sponsor the same day, on December 13, 2012. The sponsor responded on December 14, 2012, requesting a telecommunication meeting in lieu of a face-to-face meeting, and also provided a list of specific questions to be discussed at the meeting.

2. DISCUSSION

FDA's preliminary responses to the questions enclosed in the November 6, 2012, meeting package were sent to the sponsor via email on December 13, 2012. On December 14, 2012, the Sponsor emailed their plan to discuss the following questions in more detail: Questions 4, 12, 5, 16, 19, 18, and 2 in this order. The Sponsor's questions appear below, followed by our preliminary responses in **bold**. A summary of the discussion at the meeting is shown in *italics*. Post-meeting comments are shown in underlined regular font.

Nonclinical

Question 1: The sponsor has conducted an extensive toxicology package including up to 6-month rat and 9-month dog studies to date and concludes that the completed nonclinical safety study package supports initiation of Phase 3 clinical studies. Does the Agency agree?

FDA Preliminary Response:

The completed toxicology package appears to be sufficient in scope to support the Phase 3 clinical studies. Please note that the chronic toxicity study in dogs has not been submitted for review, so our current toxicology assessment is based only on the non-clinical data already submitted to and reviewed by the Division.

Please also note that additional studies may be needed, as appropriate, if the formulation changes in purity, composition, or degradant profile or if there are unexpected results in the clinical or nonclinical studies that merit further preclinical investigation.

Discussion: No discussion occurred.

Question 2: Does the Agency agree that the completed and planned, including assessment of potential carcinogenicity using the 2-year rat and 6-month mouse rasH2 (Taconic model 00178-T) models, nonclinical safety study package support registration of PF-04971729?

FDA Preliminary Response:

We will provide a more informed answer to this question at the preNDA stage of development. However, the following comments are currently pertinent:

Carcinogenicity Studies

Emerging carcinogenicity data with SGLT2 inhibitors have identified potential class-related tumor findings in the kidney, testicular, and adrenal tissues of rats. Carbohydrate malabsorption and disrupted calcium homeostasis subsequent to SGLT1 inhibition have been invoked as a potential mode of carcinogenic action. However, this mode of action currently remains hypothetical. Should tumor signals arise in the rodent bioassays at clinically relevant exposure, it is recommended that experimental data addressing potential modes of action and their relevance to human risk be discussed with the Division prior to submitting the registration package for PF-04971729.

Reproductive/Developmental Studies

Kidneys of juvenile rats are target organs of toxicity for SGLT2 inhibitors. There is an increased incidence of dilatation of the renal tubules and pelvi with increased kidney weights in juvenile animals that have not reversed during a recovery period. These adverse effects have occurred without a safety margin to clinical exposure, and are considered secondary to the pharmacological action of SGLT2 inhibition. Due to differences in timing of kidney development/maturation between rats and humans,¹ these adverse effects seen in the kidneys of juvenile rats are considered relevant to the assessment of reproductive and developmental risk for communication in the drug label.

Standard reproductive toxicology studies with some other SGLT2 inhibitors have reported morphological effects in the kidneys, but the findings have not been considered indicative of increased human risk based on considerations of incidence, severity, or safety margin to the clinical dose. The substantial difference in the toxicity profile for effects on the kidney between the standard reproductive toxicology studies and juvenile animal studies may reflect exposure to the test-article during a “critical window” of renal development. The presence of an SGLT2 inhibitor in fetal tissues and/or in maternal milk of rats is considered sufficient evidence of potential human risk, which would be conveyed in drug labeling.

As a result, determination of placental transfer of drug to fetal tissues and presence of drug in maternal milk in lactating rats is considered necessary to identify risk and to support

appropriate drug labeling. This data must be included as part of the registration package for PF-04971729.

Your meeting background package notes that a one-month juvenile toxicity study is planned. The drug distribution data requested above is considered a sufficient substitute for a juvenile animal study to assess for this toxicity in support of the adult indication. The Division has specific study design recommendations that can be shared should you choose to conduct a juvenile animal study with PF-04971729.

¹Suzuki, M (2009) J Toxicol Sci 34; SP267-271 and Zoetis T and Hurtt ME (2003) Birth Defects Res 68; 111-120.

Discussion: The sponsor asked and the Division agreed that a 2-year rat and 6-month transgenic mouse study would be an acceptable strategy for assessing carcinogenic risk of PF-04971729.

Question 3: In support of the registration of the two FDCs [fixed-dose combinations], the sponsor plans on conducting two 3-month repeat dose toxicity studies in rats. One study will include a combination of PF-04971729 and metformin, whereas the second study will include a combination of PF-04971729 and Sitagliptin. Does the Agency agree?

FDA Preliminary Response:

We tentatively agree but will defer a definitive answer following submission of the relevant INDs for these FDC products.

Discussion: No discussion occurred.

Clinical

Question 4: Does the Agency agree with the proposed dose of PF-04971729 for the Phase 3 studies?

FDA Preliminary Response:

No, we do not agree. Data from your Phase 2 studies in T2DM subjects show that the 10 mg daily dose does not appear to provide any additional benefit over the 5 mg daily dose for reduction in baseline HbA1c; although, we acknowledge that the fasting plasma glucose data for the 10 mg daily dose appear numerically better than these data for the 5 mg daily dose.

We strongly encourage you to study at least two doses in your Phase 3 program so that the risk-benefit profile can be evaluated at more than one dose level and for a longer exposure duration. Evaluating two doses in Phase 3 would also be useful should an unforeseen, potentially dose-dependent, safety issue arise, or should an alternative dose be needed for a selected patient population.

Discussion: Based on the Division's response, the sponsor proposed a 5 mg once daily oral dose as the single dose to be evaluated in their Phase 3 program. The sponsor was informed that the Division is not in a position to determine the most appropriate dose for the pivotal clinical trials. However, the sponsor was advised that it may be in their best interest to study at least two doses (e.g., the 5mg and 10mg doses) based on preliminary experience with this class of drugs and the potential for a dose-response relationship for volume depletion and renal adverse events. The Agency reiterated its position that, evaluating only a single dose in Phase 3 may be risky. Sponsor was asked to consider evaluating dose strengths at select studies, as appropriate.

Question 5: Does the Agency agree that the proposed Phase 3 clinical studies (i.e., study designs, study population, primary and secondary endpoints, control groups, duration, exposure, statistical methodology) described in this Briefing Document support the indications for improved glycemic control as stated above, for PF-04971729, PF-04971729/metformin FDC and PF-04971729/sitagliptin FDC?

FDA Preliminary Response:

You propose to conduct placebo-controlled and active-controlled Phase 3 glycemic efficacy studies with the primary endpoint of HbA1c change from baseline to Weeks 26 or 52.

We remind you that the two proposed combination products will need to be submitted under separate INDs. We defer comments related to these products until that time.

With regards to PF-04971729 only:

At this time and based only on the limited synopsis information provided in your background package, your proposed Phase 3 program appears reasonable to support an indication for improved glycemic control. Note however that a final determination will be made after review of each of the complete protocol and statistical analysis plans and we recommend that you submit these for review and comments.

We have the following comments based on your synopses:

Clarify what eGFR entry criteria will be used in the pivotal glycemic efficacy trials.

For the purpose of hypoglycemia reporting we do not agree with your plan to pool different categories of hypoglycemic episodes.

We note that you plan to conduct

(b) (4)

Sulfonylurea is a commonly used first line agent and populations of patients using sulfonylurea monotherapy (e.g., renally impaired) may be at increased risk for certain adverse events (i.e., hypoglycemia). Please clarify how you intend to evaluate the efficacy

and safety of co-administration of PF-04971729 with sulfonylurea monotherapy in your clinical program.

We note that you do not plan to carry out dedicated add-on to PPAR-gamma or add-on to GLP-1 agonist safety and efficacy studies. While these trials are not required for filing you should consider whether PF-04971729 should or should not be used in combination with these or other anti-diabetic classes in light of potential shared safety issues (e.g., bone safety issues associated with PPAR-gamma use and renal safety issues associated with GLP-1 agonist use).

You state that you intend to use the “near-to-commercial formulation” of PF-04971729 in your “pivotal Phase 3 studies.” We strongly recommend that you use the ‘to-be-marketed’ formulation in your pivotal trials.

Further, we note that the primary analysis population for the superiority efficacy analyses will be the Full Analysis Set, which includes all randomized subjects who have a baseline and at least one post-baseline observation of HbA1c. For your non-inferiority studies, you plan to use the Per Protocol Analysis Set (i.e., all randomized subjects who have a baseline HbA1c, at least one post-baseline observation of HbA1c, at least 50% compliance with study medication, and no important protocol deviations). For your adequate and well-controlled trials (i.e., both the superiority and non-inferiority studies) we recommend that you use the Full Analysis Set.

Discussion: The Division questioned how the sponsor intended to evaluate efficacy and safety of co-administration of PF-04971729 with sulfonylurea (SU) monotherapy. The sponsor stated that they plan to evaluate the safety of their product with SUs, including the risk for hypoglycemia, in Studies (b) (4), B1521016, and B1521021, and will have efficacy data with SU monotherapy from Studies B1521016 and B1521021. Sponsor believes that these studies, for which no minimum dose of SU will be required for study entry, should provide adequate safety data to evaluate the potential risk for hypoglycemia, as well as provide sufficient efficacy data for use of PF-04971729 as add-on therapy to SU monotherapy. The Division recommended that the sponsor enroll patients receiving at least 50% of the maximum labeled SU dose into these studies, and that anti-diabetic medications be held constant for all patients. Further, it was recommended that the Sponsor conduct a pre-specified glycemic subgroup study within Studies B1521016 and B1521021 to evaluate PF-04971729 as add-on to SU monotherapy, similar to what is proposed for the add-on to insulin therapy subgroup study in Study B1521018.

The sponsor clarified that except for the moderate renal insufficiency (i.e., Study B1521016) and CV outcome (i.e., Study B1521021) clinical trials, they intend to exclude subjects with an eGFR <60 mL/min/1.73m² for their pivotal glycemic efficacy trials. The sponsor and the Division agreed that the 4-variable MDRD would be acceptable to use to estimate glomerular filtration rate for determining subject eligibility across the clinical program. However, the Division did

not agree with the Sponsor regarding the exclusion of subjects with an eGFR <60 mL/min/1.73m². This is further detailed in the discussion for Question 12.

Question 6: Does the Agency agree that [REDACTED] (b) (4) along with a study demonstrating bioequivalence of the single tablet of PF-04971729/sitagliptin to the individual tablets used in Phase 3 would provide the pivotal data to support the approval for the PF-04971729/sitagliptin FDC?

FDA Preliminary Response:

Again, it is premature for us to comment on this combination product. However, we remind you that for approval of a new molecular entity as a combination product, you will need to provide adequate evidence that the individual components each contribute to the overall efficacy of the product and that the risk-benefit profile is acceptable. While designing the drug development program for your FDC, we also recommend that you consider the following in addition to the proposed bioequivalence study:

- address the potential for a drug interaction between individual components of the FDC formulation
- address how the dosing adjustments for the FDC will be made based on intrinsic and extrinsic factors if the recommended dose adjustments are not similar for individual component drugs

Discussion: No discussion occurred.

Question 7: [REDACTED] (b) (4)

FDA Preliminary Response:

We refer you to our responses to Questions 5 and 6.

Discussion: No discussion occurred.

Question 8: Does the Agency agree that the pre-specified glycemic sub-study of the cardiovascular outcome trial provides sufficient efficacy and safety data to support the proposed use of PF-04971729 as an add-on to insulin in subjects with type 2 diabetes mellitus?

FDA Preliminary Response:

You propose to demonstrate superiority of PF-04971729 over placebo as add-on therapy to insulin using HbA1c change from baseline to Week 18 as your primary efficacy endpoint.

Although we prefer an analysis based on at least 24 weeks of data, the proposed pre-specified glycemic sub-study included in your cardiovascular outcome trial is reasonable for evaluating the safety and efficacy of PF-04971729 as an add-on to insulin therapy. We agree that HbA1c at baseline should fully reflect baseline, stable, insulin doses (i.e., $\leq 10\%$ change in insulin dose for ~ 120 days prior to baseline HbA1c). We recommend that insulin regimen reflect regimens used in the diabetic population likely to use the combination of PF-04971729 and insulin. We agree that no dose changes to glucose lowering agent should be allowed during the 18-week glycemic assessment phase. We recommend you submit the complete study protocol for review and comments.

Discussion: No discussion occurred.

Cardiovascular Study

Question 9: Does the agency agree with the Sponsor's proposal to satisfy the cardiovascular safety data requirements for the NDA submission by providing data from the completed Phase 2/3 efficacy studies (including extensions to the pivotal HbA1c efficacy studies) plus data from the planned interim analysis of the ongoing cardiovascular safety study (B1521021)?

FDA Preliminary Response:

Study B1521021 is a randomized, prospective, placebo-controlled, double-blind, parallel group, event-driven cardiovascular outcome trial in which T2DM patients with established atherosclerotic disease will be randomized to PF-04971729 or placebo as add-on therapy to standard of care. You plan to combine interim data from this study with data from completed Phase 2/3 efficacy studies to exclude a hazard ratio of 1.8 when 122 primary cardiovascular events, based on a four component major adverse cardiac event (MACE) composite endpoint (i.e., MACE + hospitalization for unstable angina), are accrued. Please clarify how many events, from the total of 122, will be derived from Study B1521021.

In your synopsis, you plan a single analysis (at 122 events) to rule out 1.8. You should consider pre-specifying an additional analysis for assessing the 1.8 margin with appropriate type-1 error adjustment in case you do not exclude a hazard ratio of 1.8 on the first analysis.

Although the plan synopsis appears reasonable, we will not make a final acceptability determination until we review and agree with your protocol and detailed statistical analysis plan. Furthermore, we will not be able to comment on whether the data fulfills the requirements for NDA filing until we have seen and reviewed the result of the planned analysis(es) to rule out a hazard ratio of 1.8.

Discussion: No discussion occurred.

Question 10: Does the Agency agree with the Sponsor's proposed primary endpoints for ruling out the 1.8 and 1.3 upper confidence limits?

FDA Preliminary Response:

You propose to use the four component composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke and hospitalization for unstable angina (MACE+) to exclude 1.8 and a the three component composite endpoint of CV death, non-fatal MI, and non-fatal stroke to exclude 1.3. The proposed endpoints for ruling out the 1.8 and 1.3 are acceptable.

Discussion: No discussion occurred.

Question 11: The Sponsor plans to perform a formal sample size re-estimation based on an interim analysis of study B1521021 and potentially to increase the study sample size for the purpose of testing for superiority (i.e., a statistically significant reduction of the primary composite cardiovascular endpoint) (b) (4)

Does the Agency agree with this plan (including proposal for interim analysis) (b) (4)

FDA Preliminary Response:

Your overall plan to use interim, unblinded data to potentially increase the sample size (number of primary CV events, i.e., MACE) to test for superiority is, in principle, satisfactory. The Division's final acceptance of this adaptive design will depend on the details of the statistical plan, including adequate control of type 1 error. Both the protocol and detailed statistical analysis plan must be submitted, reviewed and accepted by the Division prior to the conduct of this study. (b) (4)

Discussion: No discussion occurred.

Renal Study

Question 12: Does the Agency agree that study B1521016 (i.e., study design, study population [including eGFR inclusion criterion], primary and secondary endpoints, control group, duration, exposure, statistical methodology) is adequate to support dosing and safety in subjects with type 2 diabetes mellitus and moderate renal impairment?

FDA Preliminary Response:

You propose to conduct a dedicated efficacy and safety trial (i.e., B1521016) in subjects with moderate renal insufficiency (i.e., estimated glomerular filtration rate [eGFR] of 30-59 mL/min/1.73m²) receiving background anti-diabetic therapy. Subjects will be randomized

to PF-04971729 or placebo for 26 weeks, and continued to be followed in a controlled extension phase for an additional 26 weeks. Further, you plan to conduct a Phase 1 clinical pharmacology study to assess the pharmacokinetics, pharmacodynamics and tolerability of PF-04971729 in subjects with varying degrees of renal dysfunction, including subjects with an eGFR of $<30 \text{ mL/min/1.73m}^2$ using the MDRD 4-variable equation.

We do not agree with your proposal to conduct a Phase 1 renal PK study and Phase 3 efficacy and safety study in parallel. We recommend that you first complete the Phase 1 clinical pharmacology study in patients with renal impairment and use the data from this study, such as pharmacodynamic data, to inform and support the clinical evaluation of efficacy and safety for PF-04971729 in patients with varying degrees of renal dysfunction. We can not provide meaningful comments to your proposal for the Phase 3 efficacy and safety study without first reviewing the results from Phase 1 renal PK study.

To ensure adequate representation of the entire moderate renal impairment population, we recommend that your recruitment procedures ensure that at least 50% of patients in the moderate renal impairment cohort have an eGFR of $\leq 45 \text{ mL/min/1.73m}^2$.

A key objective of this study should be to evaluate the renal safety of PF-04971729. We expect renal function changes due to the mechanism of action of the drug. You should propose a plan to thoroughly characterize the renal function changes in this population and evaluate for acute kidney injury. As part of this plan you should document the reversibility, by means of a washout, of the observed on therapy eGFR changes. We recommend you submit the protocol for review and approval prior to initiating this study.

Based on your existing toxicological and clinical data, we note that you do not intend to measure other markers of renal injury. However, we encourage you to consider measuring translational biomarkers of renal injury (e.g., urinary beta-2 microglobulin, urinary cystatin C). For more information on renal biomarkers, the Sponsor can contact Bill Mattes at C-PATH through <http://c-path.org/>.

Finally, we recommend that you enroll patients with moderate renal impairment into your general Phase 2/3 clinical development program, and request that you provide an estimate of the anticipated number of PF-04971729-treated patients with mild (e.g., eGFR assessed by MDRD formula $60\text{-}89 \text{ mL/min/1.73m}^2$) and moderate (e.g., eGFR $30\text{-}59 \text{ mL/min/1.73m}^2$) renal impairment who may be exposed to study drug for at least one, two and three years in your Phase 2/3 program.

Discussion: Since glucuronidation is the primary mode of drug metabolism for PF-0497129, with less than 2% eliminated renally as parent compound, the sponsor stated that they plan to use the same dose for both normal and renally impaired patients. Further, the sponsor does not expect that the pharmacokinetic and pharmacodynamic data from the Phase 1 clinical trial will inform dosing for patients enrolled in Study B1521016. The sponsor stated that the intent of the Phase 1 clinical trial was to provide pharmacokinetic and pharmacodynamic (i.e., urinary

glucose excretion) data from subjects with varying degrees of renal dysfunction to inform product labeling, while the Phase 3 trial was expected to provide renal safety data for the population at risk (i.e., patients with moderate renal insufficiency). The sponsor inquired why the Division considered Phase 1 study results necessary prior to initiation of Phase 3 study. The Division acknowledged that the single-dose pharmacokinetic data derived from the proposed Phase 1 study would not likely yield relevant exposure data to inform dosing for the Phase 3 program. However, it is possible that the Phase 1 study could provide pharmacodynamic data that may be useful for determining the patient population and study design for the multiple-dose Phase 3 efficacy studies. The Division stated that it is up to the sponsor to design their program but repeated the recommendation to conduct the Phase 1 study prior to initiating the Phase 3 study citing the experience from other drugs in this class of drugs.

The Division suggested that the sponsor enrich their Phase 3 study populations to include patients with moderate renal impairment. The sponsor raised some concerns about including patients with moderate renal insufficiency who are receiving metformin, since many of their studies include metformin as background anti-diabetic therapy. The Division noted that other development programs have allowed enrollment of metformin-treated subjects with eGFR of 50 mL/min/1.73m². Further, current metformin product labeling only contraindicates use based on serum creatinine concentrations (i.e., ≥ 1.5 mg/dL males and ≥ 1.4 mg/dL females) and not eGFRs; which would suggest that some patients with eGFRs < 60 mL/min/1.73m² could be allowed to participate. Inclusion of these patients could also provide useful information for determining tolerability of PF-0497129 as add-on to metformin therapy in patients with moderate renal insufficiency who initially tolerated metformin monotherapy.

Post-meeting comment:

For subjects with moderate renal impairment on metformin at baseline you should capture and characterize the number of patients who discontinue metformin as a result of renal function changes elicited by PF-0497129.

It was also noted that a sample size of only 100 patients exposed to PF-0497129 in Study B1521016 would not be sufficient to determine the renal safety of this product in patients with moderate renal insufficiency. The Agency is concerned that the risk benefit profile for this drug class differs across categories of renal function. The design of your Phase 3 program should allow adequate characterization of the efficacy and safety of PF-0497129 in patients with moderate renal impairment. The sponsor proposed to also include the interim data from their CV outcomes trial (i.e., Study B1521021) at the time of their NDA submission. This would then provide one-year exposure data for approximately 244 patients with moderate renal impairment. The Division felt that this could be reasonable, provided no efficacy issues or safety signals are observed in this patient population during the Phase 3 program. As the CV outcome trial will be ongoing at the time of NDA submission, the sponsor and Division agreed that it would be acceptable for the sponsor to provide 3-year renal safety data post-approval. It was also agreed that the proposed safety monitoring plan in the renal safety study B1521016 (i.e., change from baseline in eGFR, creatinine clearance, serum creatinine, BUN, albuminuria, and follow-up visit

approximately 2 weeks following discontinuation of dosing to assess reversibility of any changes in eGFR and related endpoints) was reasonable. The Division recommended that the sponsor work with the Agency to finalize their plan to address efficacy and safety evaluation of PF-04971729 in the subpopulation of diabetes and moderate renal impairment.

Question 13: Does the Agency agree that SGLT2 inhibitors would not be suitable for use in subjects with severe renal impairment (eGFR <30 mL/min) or in patients receiving hemodialysis and that an efficacy and safety study in this population would not be required to support the NDA?

FDA Preliminary Response:

See our response to question 12.

Discussion: No discussion occurred.

Bone Study

Question 14: Does the Agency agree that study B1521017 (i.e., study design, study population, primary and secondary endpoints, control group, duration, exposure, statistical methodology) described in this Briefing Document is adequate to assess any effects of PF-04971729 on bone mineral density (measured via DXA) and bone biomarkers?

FDA Preliminary Response:

You propose to conduct a clinical trial (i.e., B1521017) to assess the effects of exposure of PF-04971729 in patients for up to two years (i.e., 26 weeks followed by a 78-week extension) on bone mineral density (BMD) and biomarkers of bone resorption and formation. Although patients with osteoporosis will be excluded from participation, patients with osteopenia may be enrolled, but will not be offered calcium and vitamin D supplementation, and medications affecting bone turnover will be prohibited. We also note that across your Phase 3 program, all spontaneously reported fractures will be evaluated by an independent blinded adjudication panel.

In general, we acknowledge that Study B1521017 may provide supportive data for assessing the effects of PF-04971729 on BMD and bone biomarkers. However, we will need to review the complete protocol and consult the Division of Reproductive and Urologic Products (DRUP) to determine the acceptability of the proposed patient population and clinical trial design.

Discussion: No discussion occurred.

Clinical Safety Assessments

Question 15: Does the Agency agree with the proposed monitoring for both urinary tract infections and genital fungal infections throughout the Phase 3 program?

FDA Preliminary Response:

At the time of screening for your clinical trials, you propose to exclude subjects at risk for either urinary tract infections (UTI) or genital fungal infections (GFI). During the study, urine samples and dipstick analysis (as well as culture and sensitivity when positive) will be performed by a central lab, and subjects will be encouraged to promptly report clinical signs and symptoms consistent with a UTI or GFI. Additionally, genital swabs will be collected and analyzed by a central lab when clinically indicated, and patients diagnosed with either a UTI or GFI treated empirically or based on the laboratory results by the investigator or treating physician.

At face, without review of the actual study protocols, the proposed monitoring plan for urinary tract infections and genital fungal infections for your Phase 3 clinical development program appears reasonable.

Discussion: No discussion occurred.

Question 16: Does the Agency agree with the Sponsor's proposed exclusion criteria for hematuria and the proposed monitoring during the conduct of the Phase 3 studies for any subject who develops clinically significant hematuria?

FDA Preliminary Response:

You propose to exclude subjects with a prior history of malignancy or hematuria defined as $\geq 1+$ on urinary dipstick or visible hematuria (i.e., unless the presence of significant urologic disease has been ruled out). Urine samples for dipstick assessment and microscopy (when indicated) will also be collected at frequent intervals during the study, and subjects presenting with microscopic hematuria (i.e., ≥ 3 or more red blood cells per high powered field on one properly collected, non-contaminated urinalysis without evidence of infection) will be referred to a urologist for consultation and appropriate diagnostic workup. Additionally, all reported malignancies in your Phase 3 clinical development program will be adjudicated by an independent and blinded external panel.

In general, the proposed monitoring plan appears to be acceptable. However, it is unclear why you plan to exclude participants with a treated, past, genitourinary tract malignancy or with baseline microscopic hematuria from your phase three trials. Please clarify whether you intend to use these criteria as a condition of use of the product if marketed.

We recommend that participants who screen positive for baseline microscopic hematuria be referred for an appropriate work-up to document the cause of the hematuria and be allowed to continue in the study. Source documents including laboratory, imaging and pathological results used to establish the final diagnosis should be captured in your safety database and should be available for review should the need arise. We recommend that

subjects with a past history of malignancy that have completely recovered be included in your studies.

Discussion: The sponsor stated that the protocols will allow subjects with a history of any malignancy that has been recurrence free for ≥ 10 years (5 years for squamous cell carcinoma) to participate in their clinical trials. Additionally, subjects with dipstick or visible hematuria at screening will be eligible if they have undergone an evaluation within 6 months of screening to rule out clinically significant urologic disease. The Division stated that most patients with hematuria defined as $\geq 1+$ on urinary dipstick would have benign disease, and that these patients should be allowed to participate as long as appropriate follow-up and standard of care is provided. Also it was acknowledged that exclusion of these patients could result in restricted labeling, with a requirement for baseline assessment for hematuria in all patients prescribed this product. The sponsor clarified that they intended to include screening for hematuria only to exclude patients with undiagnosed bladder cancer or clinically significant urologic disease. The Division stated that the nonclinical data for SLGT2 products does not suggest a risk for bladder cancer, and that the occurrence of bladder cancer in the proposed population would be rare. The sponsor further clarified that as part of due diligence they plan to evaluate all patients with hematuria, and allow them to enroll into their clinical trials if significant urologic disease can be ruled out. The Division acknowledged that this approach would be acceptable.

Clinical Pharmacology Plan

Question 17: Does the Agency agree that the completed and proposed Phase 1 clinical pharmacology studies adequately support labeling and registration?

FDA Preliminary Response:

In general, based on the results summarized in your briefing package, the proposed clinical pharmacology program seems adequate.

However, with respect to DDI, you should provide detailed assessment for cases where you do not plan to conduct in vivo studies because DDI is not anticipated (if any), following the decision trees from the recent FDA guidance on evaluation of DDI

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>). We do not have sufficient information to comment on the registration and labeling.

Furthermore, it is not clear from your background package whether you have evaluated the potential for in vivo chiral conversion of PF-04971729. Note that this issue would need to be addressed before NDA submission as it may have implications in determining the adequacy of preclinical studies. For further information, refer to the FDA guidance on *Development of New Stereoisomeric Drugs*, available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm>.

In addition, to facilitate the review, we encourage you to evaluate the impact of PF-04971729 on renal function by performing analysis such as baseline eGFR vs. change in eGFR and longitudinal change in eGFR for data from Phase 2 and Phase 3 trials representing different treatment durations and treatment arms.

Discussion: No discussion occurred.

Pediatric Plan

Question 18: The Sponsor intends to request a deferral of a pediatric study in children between the ages of 10 to 17 years inclusive, and a waiver of pediatric studies for children below the age of 10 years at the time the NDA is filed. Does the Agency agree with this proposal?

FDA Preliminary Response:

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. Applicants are required to submit a pediatric plan no later than 60 days from the Phase 2 meeting. Although you may request a deferral as part of that plan, you still must submit an initial pediatric plan. That plan must include an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver under this section, if applicable, along with any supporting information.

If you plan to request a full or partial waiver, you must include a rationale or justification to support a waiver, including epidemiologic and/or drug use data when applicable. Studies may be waived, for all pediatric age groups or certain pediatric age groups in specifically described situations. Reasons for full waiver include:

- Necessary studies are impossible or highly impracticable;
- There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups (If a waiver is granted for this reason, labeling must reflect the safety concern and/or lack of efficacy.);
- The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients. Under this last condition, both criteria must be met to receive a pediatric waiver.

Discussion: The sponsor asked if the Agency would allow a 6-month extension from the date of EOP2 meeting to submit the Pediatric Study Plan. The sponsor was informed that the law (i.e., the Food and Drug Administration Safety and Innovation Act of 2012) does not allow for any extension, and therefore the Pediatric Study Plan will need to be submitted within 60 days after this meeting.

Post-meeting Comment:

A template will be available in the first quarter of 2013 to aid sponsors in formulating a Pediatric Study Plan (PSP). Should the sponsor elect to move forward without the template, the PSP should include (but is not limited to) the following:

- a. Overview of the disease in the pediatric population and the product under development
- b. Potential plans and justification for use of extrapolation
- c. Plans and justification for full or partial waiver for pediatric studies
- d. Plans for pediatric specific formulation development
- e. Nonclinical data, complete or planned, to support studies in children
- f. Synopsis/summary of all clinical studies planned
- g. Timeline for the Pediatric Study Plan
- h. Provide any agreements with other Health authorities (e.g., Pediatric Investigation Plan for EMA)

Secondary Endpoints

Question 19: Two of the Phase 3 studies will assess seated systolic and diastolic blood pressure as pre-specified secondary endpoints using Sponsor-provided standardized, automated equipment. The remaining Phase 3 studies will also assess systolic and diastolic blood pressure as secondary endpoints based on routine clinical measurements.

Assuming statistically significant decreases compared to placebo, does the Agency agree that these data will permit inclusion of the blood pressure change from baseline in the clinical studies section of the label?

FDA Preliminary Response:

No. In general, to support inclusion in the clinical studies section of product labeling, efficacy for blood pressure reduction must be demonstrated in at least one dedicated ambulatory blood pressure monitoring study, powered to detect pre-specified, clinically meaningful differences between treatment arms. The final decision regarding labeling will be made after review of the data.

Discussion: The sponsor asked if the Agency agrees that body weight and blood pressure data could be included in Section 14 of product labeling, assuming statistically significant effects are observed based on a pre-specified statistical methodology. The Division reiterated that without

review of the complete study protocols, detailed statistical analysis plan and actual clinical trial data to determine whether pre-specified, clinically meaningful differences were observed, it was premature to provide further comment.

Question 20: Assuming statistically significant effects, does the Agency agree that inclusion of weight loss as a pre-specified secondary endpoint in several Phase 3 studies permit inclusion of the weight change from baseline results with PF-04971729, placebo and any active comparator in the clinical studies section of the label?

FDA Preliminary Response:

No. Similar to our response to Question 20, to support inclusion of a beneficial effect of PF-04971729 on weight reduction in the clinical studies section of product labeling, you will need to provide adequate evidence from at least one dedicated adequate and well-controlled clinical trial powered to detect pre-specified, clinically meaningful differences in weight loss between treatment arms. Again, whether a description of the study and the results may be included in product labeling will be made only after review of the data.

Discussion: Refer to the discussion for Question 19.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion

5.0 ACTION ITEMS

No action items

6.0 ATTACHMENTS AND HANDOUTS

See attachment

17 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MARY H PARKS
01/15/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209803
NDA 209805
NDA 209806

LATE-CYCLE MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Applications (NDAs) dated December 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Product Name
209803	ertugliflozin tablets
209805	ertugliflozin and sitagliptin tablets
209806	ertugliflozin and metformin hydrochloride tablets

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 18, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Liz Godwin, Regulatory Project Manager at (240) 402-3438

Sincerely,

{See appended electronic signature page}

William Chong, MD
Clinical Team Lead
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 18, 2017 at 12:00pm ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Numbers: NDA 209803
NDA 209805
NDA 209806

Product Names: NDA 209803: ertugliflozin tablets
NDA 209805: ertugliflozin and sitagliptin tablets
NDA 209806: ertugliflozin and metformin hydrochloride tablets

Applicant Name: Merck Sharpe and Dohme Corp.

Meeting Chair: William Chong, MD
Meeting Recorder: Liz Godwin, MSHS, CCRP

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD	Director
Frank Pucino, PharmD, MPH	Clinical Reviewer
William Chong, MD	Clinical Team Leader
Jessica Hawes, PhD	Pharmacology/Toxicology Reviewer
Ron Wange, PhD	Pharmacology/Toxicology Supervisor
Julie Van der Waag, MPH	Chief, Project Management Staff
Peter Franks, MS	Regulatory Project Manager
Liz Godwin, MSHS, CCRP	Regulatory Project Manager

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics II

Alexander Cambon, PhD	Statistical Reviewer
Yun Wang, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics VII

Elande Baro, PhD	Statistical Reviewer
Eugenio Andraca-Carrera, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Clinical Pharmacology

Lei He, PhD	Clinical Pharmacology Reviewer

APPLICANT ATTENDEES

Merck:

Vivian Fuh, MD, Executive Director, Global Regulatory Affairs
Scott Korn, MD, Vice President, Global Regulatory Affairs
Lina AlJuburi Director, Regulatory Policy
Brett Luring, MD, PhD, Distinguished Scientist, Clinical Research, Late Stage Development, Diabetes & Endocrinology
Sam Engel, MD, Scientific AVP, Clinical Research, Late Stage Development, Diabetes & Endocrinology
Keith Kaufman, MD, VP, Clinical Research, Late Stage Development, Diabetes & Endocrinology
Shrita Patel, MD, MSCE, Senior Director, Clinical Safety and Risk Management
Susan Huyck, DrPh, Director, Biostatistics
Gregory Golm, PhD, Executive Director, Biostatistics
Tongtong Wang, BMed PhD, Senior Principal Scientist, CORE-Pharmacoepidemiology

Pfizer:

Karen Cox, BSc Director, Global Regulatory Lead
Susan DeCorte, RPh, RAC, MBA, JD, Executive Director, Asset Team Leader
Susan McCann BS Senior Director, Global Project Manager
Steven Terra, PharmD Senior Director, Global Clinical Lead
Anne Hickman, DVM, PhD Senior Director, Safety Risk Lead
James Mancuso, PhD Director, Biostatistics
Douglas Lee, PhD Executive Director, Biostatistics
Vaishali Sahasrabudhe, PhD, Executive Director, Clinical Pharmacology Lead
Vikas Kumar, PhD, MBA, Director, Clinical Pharmacology

1.0 BACKGROUND

NDA 209803 was submitted on December 19, 2016, for ertugliflozin tablets.
NDA 209805 was submitted on December 19, 2016, for ertugliflozin and sitagliptin tablets.
NDA 209806 was submitted on December 19, 2016, for ertugliflozin and metformin hydrochloride tablets.

Proposed indications: **NDA 209803:** an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
NDA 209805: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate
NDA 209806: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

PDUFA goal date: December 19, 2017

FDA issued a Background Package in preparation for this meeting on September 11, 2017.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion: *No discussion occurred.*

2. Discussion of Substantive Review Issues

Clinical

- Risk:benefit in moderate renal impairment

○

(b) (4)

As discussed at the Mid-Cycle Meeting, your dedicated moderate renal impairment trial (P001/1016) failed to show superiority over placebo for both the ertugliflozin 5 mg and the 15 mg treatment arms for the primary efficacy endpoint (change from baseline in HbA1c at Week 26) in subjects with a baseline eGFR ≥ 30 to < 60 mL/min/1.73 m². The secondary analysis of this endpoint in the subset of subjects with a baseline eGFR ≥ 45 to < 60 mL/min/1.73 m² also was not significant. Further, for Trial P001/1016, as well as across the ertugliflozin Phase 3 development program, there were numerically more adverse outcomes (deaths, serious adverse events, and discontinuations due to adverse events) in ertugliflozin-treated subjects with a baseline eGFR ≥ 45 to < 60 mL/min/1.73 m². While we acknowledge that these differences were limited, the totality of the data does not support a favorable risk:benefit profile with the use of ertugliflozin at this level of renal function.

- Imbalance in amputations

- We note that the observed numeric imbalance of lower limb amputations in ertugliflozin-treated subjects (i.e., 11 [0.32%] vs. 1 [0.07%] in the non-ertugliflozin treatment arm), of which one subject had a second amputation and a second also required a peripheral revascularization procedure. We are continuing to consider this finding and the significance of this finding particularly since an increased risk of lower limb amputations has already been observed with another SGLT2 inhibitor.

Discussion:

Risk:benefit in moderate renal impairment

The Division reiterated its concern with the use of ertugliflozin in patients with moderate renal impairment. Merck referred the Division to their July 21, 2017, submission containing a response to an information request, in which Merck proposed revised posology for patients with Stage 3A Chronic Kidney Disease (CKD) that does not recommend initiation of ertugliflozin in patients with an eGFR <60 mL/min/1.73 m² but would allow for continued use in patients tolerating ertugliflozin until the eGFR falls persistently below 45 mL/min/1.73 m². Merck believes that the revised posology provides an acceptable risk:benefit profile for patients whose eGFR falls between 45 to <60 mL/min/1.73 m², predicated on the patient's prior experience with ertugliflozin (acceptable tolerability with evidence of improved glycemic control). Though the HbA1c results did not support efficacy, Merck felt that the other findings such as urinary glucose excretion, fasting plasma glucose, and body weight support a conclusion that ertugliflozin is exerting pharmacodynamic activity.

Based on review of the safety profile of subjects with moderate renal impairment across their development program, Merck considers ertugliflozin to have a safety profile that is similar to other members of the SGLT2 inhibitor drug class. They request that the Division consider the totality of the data, in regards to the use of ertugliflozin in this patient population, and not just the findings from their dedicated moderate renal impairment study (Trial P001/1016), which failed on its primary efficacy endpoint. The Division stated that in the absence of benefit it becomes difficult to justify drug-related risks. The Division agreed to consider the revised posology and the additional data submitted on July 1, 2017, and the data for the non-HbA1c findings in determining whether the benefit:risk is favorable for this population.

Merck indicated that they do not agree with the proposed Limitation of Use (LOU) statement included in the Division's labeling revisions provided on August 30, 2017, as they felt that the safety profile of ertugliflozin is similar to other drugs in the class for which product labeling does not include a LOU statement. The Division stated that the version of the label sent on August 30, 2017, reflected initial thoughts for the prescribing information. The Division noted that labeling negotiations are ongoing, and stated that they would review Merck's response to that iteration of the label.

Imbalance in amputations

The Division expressed a concern with the observed numeric imbalance of lower limb amputations in ertugliflozin-treated subjects, particularly since an increased risk for these events has been observed with another product in the SGLT2 inhibitor class.

Merck acknowledged the Division's concerns and referred back to the June 5, 2017, Mid-Cycle Communication teleconference in which they clarified their search strategy used to identify amputation events. They noted that the potential mechanisms for why amputations occur remain unclear, as there did not appear to be an association with hemoconcentration, volume depletion or potential adverse events (AEs) that preceded surgery. They also noted that the amputation event rate appears to be similar to incidence

rates reported for adult patients with type 2 diabetes mellitus. The Division acknowledged the thoroughness of the event identification and that this contributes to the level of concern. Merck asked whether the Division views this as a class-related risk and if other members of the class will be labeled with a risk for amputation. The Division stated that while all members of the SGLT2 inhibitor class are being evaluated for this risk, the Division is not currently considering class labeling.

The Division stated that consideration of this signal is challenging given the small number of events available for consideration and noted that the ongoing blinded CVOT which might provide more data for consideration. Merck indicated that although an additional 60 amputations have been reported in the CVOT, the Data Monitoring Committee (DMC) did not express concerns for an imbalance between treatment arms. The Division stated that this additional data may be informative but that the integrity of the ongoing trial should not be compromised. The Division stated that they will consider requesting additional data from the firewalled team. To maintain the integrity of this ongoing trial, no additional discussion between Merck and the DMC occurred.

3. Discussion of Minor Review Issues

Statistical

- a. The cLDA primary analysis does not adequately address missing data and should not be the analysis used for labeling purposes. The Return to Baseline (RTB) analysis results are what we will be putting in the label.

Discussion: Merck expressed concern that if only the RTB analysis results are included in labeling, the results will not be comparable to the labels of other products in the same class. The Division stated that cross-label comparison should generally not be done due to differences in study design and statistical analyses. The Division stated that we are interested in presenting the de facto estimand, which represents the treatment effect of a product mostly likely seen in clinical practice, in the product label. (b) (4)

All data including data obtained after initiation of rescue therapy or treatment discontinuation should be used in estimating treatment effect. Missing values should be imputed using the method most appropriately addressing the potential bias caused by missing values.

Merck requested if the Division would be willing to include an analysis that does not include data collected after initiation of rescue therapy. The Division suggested Merck provide a detailed proposal on how they propose to present these data in the label along with the rationale for this approach for the Division to review and consider.

4. Additional Applicant Data

Discussion: *No discussion occurred..*

5. Information Requests

The following Information Requests (IRs) have been communicated by the project manager, but are pending a response to FDA at the time the Late Cycle Meeting Background Package was generated.

Date IR Sent	Discipline Sending IR	Date Response Expected
August 11, 2017	Division of Medication Error Prevention and Analysis	September 11, 2017
August 25, 2017	Statistics	September 8, 2017

Discussion: *The responses to the above information requests were received by the Division and are currently under review.*

6. Postmarketing Requirements/Postmarketing Commitments

The Division is continuing to consider postmarketing requirements/commitments.

Discussion: *No discussion occurred.*

7. Major Labeling Issues

Initial labeling was sent on August 30, 2017. Labeling negotiations are ongoing.

Discussion: [REDACTED] (b) (4)

Merck expressed the following concerns with the labeling revisions provided by the Division on August 30, 2017.

- [REDACTED] (b) (4)
- [REDACTED]
- *Merck does not agree with removal of the fasting plasma glucose (FPG) [REDACTED] from the tables, as these endpoints were prespecified.*

The Division acknowledged Merck's comments on the labeling. The Division stated that the initial labeling recommendations were proposed to provide prescribers with the data

that support the indication of glycemic control, and also noted that labeling discussions are generally an iterative process. The Division acknowledged that other labels contain additional endpoints other than HbA1c. The Division will review the rationale provided by Merck in their revised labeling submitted on September 15, 2017, and provide additional labeling comments later in the review cycle.

8. Review Plans

FDA will continue review of these NDAs and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal date.

Discussion: The Division indicated that the majority of primary reviews are completed and additional analyses are ongoing. The Division intends to take an action by the PDUFA goal date of December 19, 2017.

9. Wrap-up and Action Items

Discussion: The following action items are pending:

- ***The Division will continue internal discussions on how to address the observed imbalance of lower limb amputations.***
- ***Merck will provide, within a month, their rationale for the analytical approach used to support the primary efficacy analyses intended for product labeling.***

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

WILLIAM H CHONG
10/17/2017



NDA 209803
NDA 209805
NDA 209806

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Merck Sharp & Dohme Corp.
Attention: Vivian Fuh, M.D., F.A.C.P.
Executive Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Mail Drop: RY34-B188
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Product Name
209803	ertugliflozin tablets
209805	ertugliflozin and sitagliptin tablets
209806	ertugliflozin and metformin hydrochloride tablets

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 18, 2017.
Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Elizabeth.Godwin@fda.hhs.gov, at least one week prior to the meeting.

For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least one week prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

NDA 209803
NDA 209805
NDA 209806
Late-Cycle Meeting Background Package
Page 2

If you have any questions, call Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 18, 2017 at 12:00pm ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Numbers: NDA 209803
NDA 209805
NDA 209806

Product Names: NDA 209803: ertugliflozin tablets
NDA 209805: ertugliflozin and sitagliptin tablets
NDA 209806: ertugliflozin and metformin hydrochloride tablets

Proposed Indications: **NDA 209803:** an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
NDA 209805: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate
NDA 209806: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

Applicant Name: Merck Sharpe and Dohme Corp.

FDA ATTENDEES (tentative)

Office of Drug Evaluation II

Curtis Rosebraugh, MD, MPH

Mary Thanh Hai, MD

Sara Stradley, MS

Director

Deputy Director

Associate Director for Regulatory Affairs

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD

Frank Pucino, PharmD, MPH

William Chong, MD

Jessica Hawes, PhD

Ron Wange, PhD

Elisabeth Hanan, MS

Julie Van der Waag, MPH

Liz Godwin, MSHS, CCRP

Director

Clinical Reviewer

Clinical Team Leader

Pharmacology/Toxicology Reviewer

Pharmacology/Toxicology Supervisor

Safety Regulatory Project Manager

Chief, Project Management Staff

Regulatory Project Manager

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics II

Alexander Cambon, PhD	Statistical Reviewer
Yun Wang, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Biostatistics, Division of Biometrics VII

Elande Baro, PhD	Statistical Reviewer
Eugenio Andraca-Carrera, PhD	Lead Mathematical Statistician

Office of Translational Sciences, Office of Clinical Pharmacology

Sury Sista, PhD	Clinical Pharmacology Reviewer
Lei He, PhD	Clinical Pharmacology Reviewer
Lian Ma, PhD	Clinical Pharmacology Reviewer
Yaning Wang, PhD	Clinical Pharmacology Reviewer
Manoj Khurana, PhD	Clinical Pharmacology Team Leader

Office of Pharmaceutical Quality

Suong Tran, PhD	CMC Lead
Anika Lalmansingh	Regulatory Project Manager

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The applications have not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for these applications. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical

1. (b) (4)

As discussed at the Mid-Cycle Meeting, your dedicated moderate renal impairment trial (P001/1016) failed to show superiority over placebo for both the ertugliflozin 5 mg and the 15 mg treatment arms for the primary efficacy endpoint (change from baseline in HbA1c at Week 26) in subjects with a baseline eGFR ≥ 30 to < 60 mL/min/1.73 m². The secondary analysis of this endpoint in the subset of subjects with a baseline eGFR ≥ 45 to < 60 mL/min/1.73 m² also was not significant. Further, for Trial P001/1016, as well as across the ertugliflozin Phase 3 development program, there were numerically more adverse outcomes (deaths, serious adverse events, and discontinuations due to adverse events) in ertugliflozin-treated subjects with a baseline eGFR ≥ 45 to < 60 mL/min/1.73 m². While we acknowledge that these differences were limited, the totality of the data does not support a favorable risk:benefit profile with the use of ertugliflozin at this level of renal function.
2. We note that the observed numeric imbalance of lower limb amputations in ertugliflozin-treated subjects (i.e., 11 [0.32%] vs. 1 [0.07%] in the non-ertugliflozin treatment arm), of which one subject had a second amputation and a second also required a peripheral revascularization procedure. We are continuing to consider this finding and the significance of this finding particularly since an increased risk of lower limb amputations has already been observed with another SGLT2 inhibitor.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Clinical
 - Risk:benefit in moderate renal impairment
 - Imbalance in amputations

3. Discussion of Minor Review Issues – 5 minutes

- Statistical
 - The cLDA primary analysis does not adequately address missing data and should not be the analysis used for labeling purposes. The Return to Baseline (RTB) analysis results are what we will be putting in the label.

4. Additional Applicant Data – 15 minutes (Applicant)

5. Information Requests – 5 minutes

The following Information Requests (IRs) have been communicated by the project manager, but are pending a response to FDA at the time the Late Cycle Meeting Background Package was generated.

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August 11, 2017	Division of Medication Error Prevention and Analysis	September 11, 2017
August 25, 2017	Statistics	September 8, 2017

6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

The Division is continuing to consider postmarketing requirements/commitments.

7. Major labeling issues – 5 minutes

Initial labeling was sent on August 30, 2017. Labeling negotiations are ongoing.

8. Review Plans – 5 minutes

FDA will continue review of these NDAs and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal date.

9. Wrap-up and Action Items – 5 minutes



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FOREIGN VISITORS DATA REQUEST FORM

VISITOR'S FULL NAME	First	Middle	Last
GENDER		DATE OF BIRTH (MM/DD/YYYY)	
COUNTRY OF ORIGIN / CITIZENSHIP			
PLACE OF BIRTH (CITY AND COUNTRY)			
PASSPORT NUMBER			
ISSUING COUNTRY			
ISSUANCE DATE			
EXPIRATION DATE (MM/DD/YYYY)			
VISITOR'S ORGANIZATION/EMPLOYER			
MEETING START (DATE/TIME)	September 18, 2017, 12:00 p.m.		
MEETING ENDING (DATE/TIME)	September 18, 2017, 2:00 p.m.		
PURPOSE OF MEETING	Late Cycle Meeting		
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22, Room 1419		
BUILDING ENTRANCE	Building 22		
FDA LABORATORIES T O BE VISITED	No		
HOSTING FDA CENTER	CDER		
HOSTING OFFICIAL	Name: Elizabeth Godwin		
	Title: Regulatory Project Manger		
	Office/Bldg.: 3361/22		
	Email: elizabeth.godwin@fda.hhs.gov	Phone: 240-402-3438	
ESCORT INFORMATION (If different from Hosting Official)	Name:		
	Title:		
	Office/Bldg.:		
	Email:	Phone:	

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/s/

JEAN-MARC P GUETTIER
09/11/2017