CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210598Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: September 14, 2018

To: Nina Ton, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Taylor Burnett, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC
Team Leader
OPDP

Subject: OPDP Labeling Comments for YUPELRI (revefenacin) inhalation solution, for oral inhalation

NDA: 210598

In response to DPARP's consult request dated December 20, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for YUPELRI (revefenacin) inhalation solution, for oral inhalation (Yupelri).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on August 30, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide, and IFU were sent under separate cover on September 14, 2018.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 10, 2017, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Taylor Burnett at (240) 402-1349 or Taylor.Burnett@fda.hhs.gov.

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/s/

TAYLOR B BURNETT
09/14/2018

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

PATIENT LABELING REVIEW

Date:	September 14, 2018
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	YUPELRI (revefenacin)
Dosage Form and Route:	inhalation solution, for oral inhalation
Application Type/Number:	NDA 210598
Applicant:	Theravance Biopharma US, Inc.

1 INTRODUCTION

On November 10, 2017, Theravance Biopharma US, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210598 for YUPELRI (revefenacin) inhalation solution, for oral inhalation. The proposed indication for YUPELRI (revefenacin) inhalation solution, for oral inhalation is for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on December 20, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for YUPELRI (revefenacin) inhalation solution, for oral inhalation.

2 MATERIAL REVIEWED

- Draft YUPELRI (revefenacin) inhalation solution, for oral inhalation MG and IFU received on November 10, 2017 and received by DMPP and OPDP on September 6, 2018.
- Draft YUPELRI (revefenacin) inhalation solution, for oral inhalation Prescribing Information (PI) received on November 10, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 30, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Arial font, size 10 and 11 respectively.

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

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
09/14/2018

TAYLOR B BURNETT
09/14/2018

SHARON W WILLIAMS
09/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 7, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210598
Product Name and Strength:	Yupelri (revefenacin) Inhalation Solution, 175 mcg/3 mL
Applicant/Sponsor Name:	Theravance Biopharma Ireland Limited
FDA Received Date:	September 5, 2018
OSE RCM #:	2017-2337-1
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised professional sample carton labeling for Yupelri (Appendix A) to determine if it is acceptable from a medication error perspective. The Applicant relocated the National Drug Code (NDC) and the 'Rx Only' statement to the opposite side of the principal display panel and revised the placeholder of 'Tradename' to 'Yupelri'.

2 CONCLUSION

The revised professional sample carton labeling for Yupelri is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 5, 2018

Carton labeling

(b) (4)

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/s/

LISSA C OWENS
09/07/2018

SARAH K VEE
09/07/2018

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: August 9, 2018

TO: Sally Seymour, M.D.
Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of New Drugs (OND)

FROM: Zhou Chen, M.D., Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [redacted] (b) (4)
covering NDA 210598.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of **Studies 0126, 0127** and **0135** (**NDA 210598**), [redacted] (b) (4) (**not yet submitted**) conducted at [redacted] (b) (4)

[redacted] (b) (4)

After reviewing the inspectional findings, we conclude the analytical data from **Studies 0126, 0127** and **0135** (**NDA 210598**), [redacted] (**not yet submitted**) are reliable. Thus, the analytical data from the current audited studies and other studies conducted by [redacted] using similar methods (**Attachment 1**) should be reliable for review by the Agency without an inspection.

Inspected Studies

NDA 210598

Study #1: 0126
Study Title: "A Phase 3, 12-week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease"
Dates of Bioanalyses Conduct: [redacted]

Study #2: 0127
Study Title: "A Phase 3, 12-week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease"
Dates of Bioanalyses Conduct: [redacted]

Study #3: 0135
Study Title: "The Effect of Severe Renal Impairment on the Pharmacokinetics Following Single-Dose Inhaled Administration of TD-4208"
Dates of Bioanalyses Conduct: [redacted]

Study not yet submitted to the Agency

[redacted]

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[redacted]

Conclusion:

After reviewing the inspectional findings, we conclude the [redacted] for **Studies 0126, 0127** and **0135 (NDA 210598),** [redacted] **(not yet submitted)** are reliable.

However, the exhibits collected from [redacted] **(Attachments 2-5)** suggest several issues with [redacted] The review division should evaluate the enclosed attachments, and if needed, request additional information from the Sponsor to determine if the affected samples are reliable for further review.

Based on the inspectional findings, [redacted] and the

end of the current surveillance interval should be reliable for review by the Agency without an inspection.

Zhou Chen, M.D., Ph.D.
Lead Pharmacologist

Yiyue Zhang, Ph.D.
Visiting Associate

Final Classification:

Analytical

NAI – [redacted] (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Fenty-Stewart/Nkah/CDER-OSIS-BEQ
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chen/Zhang
OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au

Draft: YZ 8/3/2018, 8/7/2018
Edit: ZC 8/3/2018; RCA 8/3/2018; 8/7/2018; GB 8/8/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/[redacted] (b) (4)

OSIS File#: [redacted] (b) (4)
FACTS#: [redacted] (b) (4)

[redacted] (b) (4)

Attachment 1

Studies in Support of Pending Application

Application #	Study #	Study Type	Drug Name	Dates of conduct
NDA 210598	0126	In Vivo PK	Revefenacin	(b) (4) [redacted]
	0127	In Vivo PK		
	0135	In Vivo PK		

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/s/

YIYUE ZHANG
08/09/2018

ZHOU CHEN
08/09/2018

RUBEN C AYALA
08/09/2018

GOPA BISWAS
08/09/2018
Gopa Biswas signing on behalf of Charles Bonapace.

CLINICAL INSPECTION SUMMARY

Date	June 1, 2018
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Khalid Puthawala, M.D., Medical Officer Bob Lim, M.D., Clinical Team Leader Nina Ton, Pharm. D., Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
NDA	NDA 210598
Applicant	Theravance Biopharma Ireland Limited
Drug	Revefenacin
NME	Yes
Therapeutic Classification	Long-acting muscarinic antagonist
Proposed Indication	(b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD), including (b) (4)
Consultation Request Date	January 17, 2018
Summary Goal Date	July 20, 2018
Action Goal Date	November 13, 2018
PDUFA Date	November 13, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Lynn, Lisberg, and Cruz) were selected for inspection for Protocols 0126, 0127, and 0128, respectively, for NDA 210598 revefenacin. The study data derived from these clinical sites, based on the inspections and as submitted by the sponsor, are considered acceptable in support of the requested indication.

The final classification of Drs. Lynn and Cruz sites is No Action Indicated (NAI). The preliminary classification of Dr. Lisberg's site is Voluntary Action Indicated (VAI). Although protocol deviations were noted, they appear unlikely to have significant impact on the overall efficacy and safety of the study. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

2. BACKGROUND

Revefenacin is a long-acting muscarinic antagonist developed as an inhalation solution for administration via standard jet nebulizer. The proposed indication for revefenacin is the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). (b) (4). Revefenacin is to be administered via oral inhalation using a standard jet nebulizer connected to an air compressor and is to be dosed once a day at a proposed dose of 175 mcg.

The sponsor conducted two replicate Phase 3 pivotal studies (Study 0126 and Study 0127) and a long-term safety study (Study 0128) to evaluate the efficacy and safety of revefenacin in patients with moderate to very severe COPD.

Protocols 0126 and 0127

Protocols 0126 and 0127 were two identically-designed Phase 3 studies.

Protocol Titles: A Phase 3, 12-week, Randomized, Double−Blind, Placebo−Controlled, Parallel Group Study of Nebulized TD−4208 in Subjects with Chronic Obstructive Pulmonary Disease

These were Phase 3, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group studies in subjects with moderate to very severe COPD. Subjects were randomized to receive 1 of 2 doses of revefenacin (88 mcg or 175 mcg) or matching placebo, administered QD in the morning by a standard jet nebulizer for 12 weeks.

The primary objective of studies was to characterize the efficacy of revefenacin (TD-4208) administered once daily (QD) for 12 weeks in a population of subjects with moderate to very severe chronic obstructive pulmonary disease (COPD). The secondary objectives were to characterize the safety and tolerability and to characterize the population pharmacokinetics (PK) of revefenacin administered QD for 12 weeks in a population of subjects with moderate to very severe COPD.

The primary efficacy endpoint was trough FEV1 (defined as the mean of the 23.25-hour and 23.75-hour spirometry assessments following the 84th dose) on Day 85.

The main inclusion criteria of the studies included eligible male or female subjects with a documented history of COPD, 40 years of age or older, smoking history of at least 10 pack-years, a post-ipratropium forced expiratory volume at 1 second (FEV1)/forced vital capacity (FVC) ratio <0.7 and a post-ipratropium FEV1 of <80% of predicted normal and >700 mL (moderate to very severe COPD).

Study 0126 randomized 619 subjects and enrolled the first patient on July 28, 2015 and the last patient completed the last visit on August 24, 2016.

Study 0127 randomized 610 subjects and enrolled the first patient on September 8, 2015 and the last patient completed the last visit on August 15, 2016.

Protocol 0128

Protocol Title: A Phase 3, 52-week, Randomized, Active−Controlled Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized TD−4208 in Subjects with Chronic Obstructive Pulmonary Disease.

This was a randomized, active-controlled, parallel-group study in subjects with moderate to very severe stable chronic obstructive pulmonary disease (COPD). Subjects were randomized to one of three treatment groups (revefenacin 88 mcg, revefenacin 175 mcg, or tiotropium 18 mcg) administered once daily in the morning for 52 weeks.

The primary objective of this study was to characterize the safety and tolerability of revefenacin administered once daily for 52 weeks in a population of patients with moderate to very severe COPD. The exploratory objectives were to evaluate the change from baseline forced expiratory volume at 1 second (FEV1) over 12 months, to evaluate concomitant use of rescue medications over 12 months, and to evaluate the effect of revefenacin on Health Outcomes assessments.

The primary safety and tolerability were evaluated by frequency and severity of adverse events, clinical laboratory measurements, physical examinations, ECGs (including Holter subset), vital signs, and vital status. For exploratory efficacy endpoints, FEV1 were measured by spirometer in the clinic at pre-dose and at 1, 3, 6, 9 and 12 months. The use of rescue medication (puffs per day) and days without any use of rescue medication were also analyzed. Health Outcomes Assessments included St. Georges Respiratory Questionnaire (SGRQ) (with a 1-month recall period), Modified Medical Research Council Dyspnea Scale (mMRC), COPD Assessment Tool (CAT), Clinical COPD Questionnaire (CCQ), Treatment Satisfaction Questionnaire, and Baseline and Transition Dyspnea Index (BDI/TDI).

The main inclusion criteria of the study included eligible male or female subjects with moderate to very severe COPD, 40 years of age or older, smoking history of at least 10 pack-years, a post-ipratropium FEV1/forced vital capacity (FVC) ratio < 0.7, and a post-ipratropium FEV1 of < 80% of predicted normal and > 700 mL.

The study randomized 1060 subjects and enrolled the first patient on September 21, 2015 and the last patient completed the last visit on May 24, 2017.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Lon D. Lynn, DO 5115 N. Armenia Avenue Tampa, FL 33603	Site 38823 Protocol 0126 Subjects: 24	February 12-16, 2018	NAI

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Edward E. Lisberg, MD 7420 Central Avenue, Suite 2020 River Forest, IL 60305	Site 38705 Protocol 0127 Subjects: 30	April 4-6, 9, 16-18, 23, 2018	*VAI
Humberto Cruz, DO 10967 Lake Underhill Road, Suite 117 Orlando, FL 32825	Site 38713 Protocol 0128 Subjects: 37	February 27-March 2, 2018	NAI

Key to Compliance Classifications
NAI (No Action Indicated) = No deviation from regulations.
VAI (Voluntary Action Indicated) = Deviation(s) from regulations.
OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.
*Pending = Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. Lon D. Lynn, D.O. (Site 38823, Protocol 0126, Tampa, FL)

The site screened 39 subjects and enrolled 24 subjects for Study Protocol 0126. Among the 24 enrolled subjects, 17 subjects completed the study and seven subjects discontinued from the study. The reasons for discontinuations were due to withdrawal by subject (Subjects (b) (6) and (b) (6) and adverse events (COPD exacerbation [Subjects (b) (6) dyspnea [Subjects (b) (6) and right hip fracture [Subject (b) (6)). The discontinuation data listing provided in the NDA were verified by review of source documents. An audit of all 24 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, case report forms, electronic files, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted. Protocol deviations noted during inspection mainly including prohibited medication taken by subjects, out of window spirometry tests, and out of window visits, which were reported to clinical study report.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Edward E. Lisberg, M.D. (Site 38705, Protocol 0127, River Forest, IL)

The site screened 44 subjects and enrolled 30 subjects for Study Protocol 0127. Among the 30 enrolled subjects, 24 subjects completed the study and six subjects discontinued from the study. The reasons for discontinuations were due to withdrawal by subject (Subjects (b) (6) (b) (6) and adverse events (COPD exacerbation for Subjects (b) (6) The discontinuation data listing provided in the NDA were verified by review of source documents. An audit of 24 of 30 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, case report forms, electronic files, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

A Form FDA 483 was issued with the observations listed below at the end of inspection:

1) An investigation was not conducted in accordance with the investigational plan. Specifically,

   - Subject (b) (6) used an antibiotic for respiratory tract infection within 6 weeks of visit 1B and should have been excluded from the study.
   - Subject (b) (6) experienced a severe exacerbation of COPD on (b) (6) but was not discontinued from the study until (b) (6)

Other observations were discussed at the close of the inspection included the following:

- Subject (b) (6) back dated the date of their signature on the Authorization to Use and Disclose Personal Health Information section of the informed consent document.
- The site failed to obtain an annual update financial disclosure form from Noemi Mendoza, CCRC, Sub-investigator.
- One whole blood sample and one PK sample for Subject (b) (6) was sent to the lab unlabeled.
- One 30 minutes Post dose PK sample was not taken for Subject (b) (6) at visit 5.
- There was no documentation, for all subjects, of date/time when PK samples were stored into the freezer or when they were removed for processing/shipping to the laboratory for analysis.

- Incomplete source data were noted
  - Subject (b) (6) relationship to drug blank on AE form
  - Subject inclusion criteria 3 and 4 blank on CRF
  - Subject visit 3 spirometry values blank in source

OSI Reviewer's comments:
The protocol deviations in Form 483 observations were reported in the NDA submission by the sponsor. These protocol deviations appear isolated and unlikely to have significant impact on the primary efficacy endpoint and safety results of the study. PK sampling procedure review was added to this inspection per DPARP clinical team request and the findings were shared with DPARP clinical review team and clinical pharmacology review team. Additional PK data inspections were requested by clinical pharmacology review team for this application and will be conducted by OSIS to verify PK data in the NDA submission.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. Data submitted by this clinical site appear acceptable in support of efficacy and safety of this application.

3. Humberto Cruz, D.O. (Site 38713, Protocol 0128, Orlando, FL)

The site screened 54 subjects and enrolled 37 subjects for Study Protocol 0128. Among the 37 enrolled subjects, 26 subjects completed the study and 11 subjects discontinued from the study. The reasons for discontinuations were due to withdrawal by subject (Subjects (b) (6) and adverse events (pulmonary embolism [Subject (b) (6) and fatal cardiac arrest [Subject (b) (6) The discontinuation data listing provided in the NDA were verified by review of source documents. An audit of 25 of 37 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents, IRB documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

cc:
Central Doc. Rm.
Review Division /Medical Team Leader/ Bob Lim
Review Division/Medical Officer/ Khalid PuthawalaReview Division /Project Manager/ Nina Ton
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan Thompson
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Min Lu
OSI/ GCP Program Analyst/Yolanda Patague

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/s/

MIN LU
06/01/2018

KASSA AYALEW
06/01/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	April 11, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 210598
Product Name and Strength:	Revefenacin Inhalation Solution, 175 mcg/3 mL
Product Type:	Single-Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Theravance Biopharma Ireland Limited
FDA Received Date:	November 13, 2017
OSE RCM #:	2017-2337
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Revefenacin Inhalation Solution for areas of vulnerability that could lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review as part of their evaluation of NDA 210598.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Theravance Biopharma Ireland Limited submitted a 505(b)(1) NDA 210598 on November 13, 2017, with the proposed indication of maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD), (b) (4)

DMEPA evaluated the proposed container labels, carton labeling, instructions for use, and prescribing information to determine whether there are any vulnerabilities that may lead to medication errors.

4 CONCLUSION AND RECOMMENDATIONS

We reviewed the proposed container labels, carton labeling, instructions for use, and prescribing information. We note that the label and labeling currently contain the placeholder 'Tradename' as the proposed proprietary name is currently under review. We make recommendations in section 4.1.

4.1 RECOMMENDATIONS FOR THERAVANCE BIOPHARMA IRELAND LIMITED

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

A. Labels and Labeling

1. We acknowledge that your proposed proprietary name is currently under review. Replace the placeholder 'Tradename' once you have an approved proprietary name and submit the updated labels and labeling for review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Revefenacin received on November 13, 2017 from Theravance Biopharma Ireland Limited.

Table 2. Relevant Product Information for Revefenacin	
Initial Approval Date	N/A
Active Ingredient	Revefenacin
Indication	Maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4)
Route of Administration	Oral Inhalation
Dosage Form	Inhalation solution
Strength	175 mcg/3 mL
Dose and Frequency	One 175 mcg vial (3 mL) once daily
How Supplied	Sterile solution in low-density polyethylene vials. Each vial is overwrapped in a foil pouch and supplied in cartons containing 30 individually pouched unit-dose vials.
Storage	Store at room temperature from 68°F to 77°F (20°C to 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C). Protect from direct sunlight and excessive heat.
Container Closure	Paperboard shelf carton, each containing 30 individual aluminum foil laminate pouched LDPE vials

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Revefenacin labels and labeling submitted by Theravance Biopharma Ireland Limited.

- Foil Pouch received on November 13, 2017
- LDPE embossed vial received on November 13, 2017
- Carton labeling received on November 13, 2017
- Professional Sample Foil Pouch received on November 13, 2017
- Professional Sample Carton Labeling received on November 13, 2017
- Instructions for Use (Image not shown) received on November 13, 2017
- Medication Guide (Image not shown) received on November 13, 2017
- Prescribing Information (Image not shown) received on November 13, 2017

G.2 Label and Labeling Images

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

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

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

/s/

LISSA C OWENS
04/11/2018

SARAH K VEE
04/11/2018

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

IND or NDA	NDA 210598
Brand Name	
Generic Name	Revefenacin (TD-4208) Inhalation Solution
Sponsor	Theravance Biopharma US Inc.
Indication	Chronic Obstructive Pulmonary Disease
Dosage Form	Inhaled nebulized dose
Drug Class	Long-acting muscarinic receptor antagonist
Therapeutic Dosing Regimen	175 mcg once-daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	700 mcg once-daily
Submission Number and Date	SDN 001; 10 Nov 2017
Review Division	DPARP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of revefenacin (TD-4208) (175 mcg and 700 mcg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between revefenacin (175 mcg and 700 mcg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The moxifloxacin profile over time is demonstrated in Figure 1. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms. The analytical results and the moxiflexicin profile adequately indicate that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 48 healthy subjects were randomized to receive revefenacin 175 mcg, revefenacin 700 mcg, placebo, and a single oral dose of moxifloxacin 400 mg. The point estimates and 90% CIs corresponding to the largest upper bounds for revefenacin (175 mcg and 700 mcg) and the largest lower bound for moxifloxacin is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Revefenacin (175 mcg and 700 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Revefenacin 175 mcg	6	0.9	(-2.0, 3.8)
Revefenacin 700 mcg	8	0.8	(-1.3, 3.0)
Moxifloxacin 400 mg*	3	15.5	(13.9, 17.1)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints was 13.4 ms.

The supratherapeutic dose of revefenacin (700 mcg) produces approximately 4.1-fold and 4.9-fold the mean C_{max} values of the mean C_{max} for the therapeutic dose (175 mcg) of revefenacin and its major metabolite (THRX-195518), respectively. The supratherapeutic dose covers revefenacin and THRX-195518 exposures in the worst-case scenario of COPD patients with severe renal impairment or moderate hepatic impairment.

2 PROPOSED LABEL

The sponsor included the following QT-related language in their current proposed label.

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, double-blind, placebo- and positive-controlled, single dose, crossover trial in 48 healthy subjects. Following a single dose of revefenacin 700 mcg (4 times the recommended dosage), no effects on prolongation of QTc interval were observed.

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose of 4 times the maximum approved recommended dose, revefenacin does not prolong the QT interval to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Revefenacin (TD-4208) is a potent long-acting muscarinic receptor antagonist under development by Theravance Biopharma US Inc for the treatment of chronic obstructive pulmonary disease (COPD). Revefenacin is being developed as an inhalation solution for administration via standard jet nebulizer at a once daily dose of 175 mcg.

3.2 MARKET APPROVAL STATUS

Revefenacin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

IC50 values for human hERG channel are 11.4 μM for revefenacin and 524 μM for its major metabolite, THRX-195518, which are >10,000-fold the C_{max} values in subjects receiving 700 mcg of TD-4208. Increased HR was observed in dogs at inhaled doses of approximately 300 mcg/kg. At the no-effect dose level for increases in HR (100 mcg/kg), the C_{max} in dogs is approximately 4-fold greater than clinical concentrations after a 700 mcg dose. No other treatment-related changes in ECG or cardiovascular parameters were observed in dogs at exposures (C_{max}) up to 13-fold the clinical concentrations after a 700 mcg dose.

3.4 PREVIOUS CLINICAL EXPERIENCE

Revefenacin inhalation solution was evaluated in 3 single-dose studies in a total of 80 healthy adults, and in 7 repeat-dose studies in a total of 1,951 patients with COPD. Once daily repeat-doses ranging from 22 mcg to 700 mcg were well tolerated with no significant systemic anti-muscarinic activity. 88 mcg and 175 mcg once daily doses were evaluated in the Phase 3 study for a treatment duration of 52 weeks.

Atrial fibrillation was the most frequently reported cardiovascular treatment emergent adverse event (TEAE) in the phase 3 studies (pooled analysis of studies 0126, 0127 and 0128), with a 0.9% (n=7), 0.4% (n=3) and 0.5% (n= 2) incidence in the 88 mcg revefenacin, 175 mcg revefenacin and placebo group, respectively. Tachycardia was observed in 0.3% (n=2), 0.1% (n=1) and 0.2% (n=1) of the patients in the 88mcg revefenacin, 175 mcg revefenacin and placebo group, respectively. There were incidences of palpitations (88 mcg revefenacin: n=2, 175 mcg revefenacin: n=1) in the both the active groups. There were 3 incidences of ventricular extrasystoles in the 175 mcg group. QT-related TEAEs observed in the phase 2 studies are summarized in Appendix 6.1. (source: Summary of Clinical Safety-NDA210598)

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 119840 on 02/02/2016. The proposed TQT study was acceptable to FDA in the protocol review.

The sponsor submitted the study report 0136 for revefenacin, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Period Crossover Thorough QT Study to Evaluate the Effect of a Single Dose of TD-4208 on Cardiac Repolarization in Healthy Subjects

4.2.2 Protocol Number

0136

4.2.3 Study Dates

05 May 2016 - 29 Aug 2016

4.2.4 Objectives

The primary objective of this study was to:

- Characterize the effect of a supratherapeutic (700 mcg) inhaled single dose of TD-4208 (hereafter referred to as revefenacin) on cardiac repolarization in healthy subjects.

The secondary objectives were to:

- Characterize the effect of a therapeutic (175 mcg) inhaled single dose of revefenacin on cardiac repolarization in healthy subjects.
- Evaluate the pharmacokinetics of revefenacin following therapeutic and supratherapeutic inhaled single doses of revefenacin in healthy subjects.
- Evaluate the safety and tolerability following therapeutic and supratherapeutic inhaled single doses of revefenacin in healthy subjects.
- Characterize the effect of therapeutic (175 mcg) and supratherapeutic (700 mcg) inhaled single doses of revefenacin on other electrocardiogram (ECG) parameters (heart rate [HR], PR, and QRS interval) in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-sequence, crossover design with four dosing occasions. Each dosing occasion was followed by a washout period of at least 14 days.

4.2.5.2 Controls

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

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded. Other treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treatment arms:

- Revefenacin 175 mcg (single dose, inhaled nebulized dose)
- Revefenacin 700 mcg (single dose, inhaled nebulized dose)
- Placebo (single dose, inhaled nebulized dose)

- Moxifloxacin 400 mg (single dose, oral tablet)

4.2.6.2 Sponsor's Justification for Doses

Revefenacin was generally well tolerated in a dose-ranging Phase 2b study that evaluated 44 mcg to 350 mcg once daily dosing for 28 days. 88 mcg was shown to be the minimally effective dose after 7 days of treatment. In a 7-day crossover study evaluating once-daily doses in the range of 22 mcg to 700 mcg, all doses were well tolerated and there was no indication of significant systemic antimuscarinic activity. In the 7-day study, all doses showed a sustained effect over 24 hours; the 700-mcg dose did not provide additional effect on lung function over the 350 mcg effect. A mechanistic study evaluating 175 mcg once daily and 44 mcg twice daily dosing regimens confirmed once-daily dosing as the appropriate dose frequency for revefenacin, with no advantage observed for the twice-daily regimen.

Reviewer's Comment: Acceptable. The supratherapeutic dose (700 mcg) has a 4.1-fold and 4.9-fold higher mean C_{max} values of revefenacin and THRX-195518, respectively, than that with the therapeutic dose (175mcg). Less than 1.6-fold accumulation in plasma was observed for both revefenacin and THRX-195518 upon once daily multiple-dose administration of inhalation solution. Metabolite: parent ratio for C_{max} and AUC ranges from 1.5 to 3.8 and 3.5 to 6, respectively, in COPD patients. In healthy adults, mean C_{max} and AUC of THRX-195518 were approximately 25-30% and 30-98% of revefenacin. The geometric mean C_{max} of revefenacin and THRX-195518 is 1.06 and 1.79-fold higher, respectively, in individuals with severe renal impairment compared to those with normal renal function. Geometric mean C_{max} of revefenacin and THRX-195518 is 1.02 and 1.49-fold higher, respectively, in moderate hepatic impairment compared to normal hepatic function. Overall, the supratherapeutic dose covers revefenacin and THRX-195518 exposures in the worst-case scenario of COPD patients with severe renal impairment or moderate hepatic impairment.
(Source: 2.5 Clinical Overview, 2.7.2 Summary of Clinical Pharmacology studies)

4.2.6.3 Instructions with Regard to Meals

Study drugs were administered following an overnight fast of at least 10 hours (water was allowed during the fast). Administration of revefenacin or the placebo proceeded until nebulization of the study drug solution was complete, which was expected to take approximately 10 minutes and was evidenced by "spluttering" of the nebulizer. No food was administered within the 4 hours after the start of nebulization or after administration of the oral moxifloxacin tablet.

Reviewer's Comment: Revefenacin is administered by inhalation route. Food is not expected to affect drug absorption.

4.2.6.4 ECG and PK Assessments

PK: Blood samples for revefenacin, THRX-195518 and moxifloxacin PK assessment were collected pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose.

ECG: On Day 1 of each study period, 25-hour continuous digital ECG monitoring was performed with replicate (minimum of 3) recordings at the following time points: -60, -

45, and -30 minutes predose, 15 and 30 minutes, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose.

Reviewer's Comment: The timing of ECG/PK sampling is acceptable as the T_{max} for revefenacin and its major metabolite (~0.25 h to 0.5h) is covered and the timing also supports evaluation of potential delayed effects on the QTc interval.

4.2.6.5 Baseline

The average of 3 pre-dose QT/QTc values was used as baseline.

4.2.7 ECG Collection

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

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 48 healthy subjects (29 females and 19 males) were enrolled in the study, 36 subjects (75%, 19 females and 17 males) completed all the study treatment periods. All 48 subjects were included in the safety, PK, and PD populations; 42 subjects were included in the PK/PD population.

The average age (SD) of the 48 subjects was 34.7 (9.7) years, ranging from 18.0 to 54.0 years. The majority of the subjects (46/48, 95.8%) were White. Thirty-nine subjects (39/48, 81.3%) were Hispanic or Latino, with the remaining 9 subjects (9/48, 18.8%) being Not Hispanic or Latino.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

For primary analysis, the sponsor used linear mixed-effect model with terms sequence, period, time, treatment, sex, pre-dose baseline QTc, and treatment-by-time interaction. Subject nested within sequence was included as a random effect term.

Inhalation of 175-mcg and 700-mcg doses of revefenacin did not have an effect on the QTc interval. The ΔQTcF was similar after dosing with 175-mcg and 700-mcg revefenacin and placebo, and the resulting ΔΔQTcF was therefore small at all time points for revefenacin. The largest mean ΔΔQTcF after inhalation with 175-mcg revefenacin was 1.0 msec (95% CI: -1.2 to 3.1 msec) observed at 8 hours after dosing, and the largest mean ΔΔQTcF after the higher inhalation dose (700 mcg) reached 1.0 msec (95% CI: -1.1 to 3.1 msec) at 1 hour after dosing, with the upper bound of the 1-sided 95% CI excluding 10 msec.

The sponsor's results for primary analysis are displayed in Table 2.

Table 2: Least Squares Mean Estimate of Placebo-Corrected Change-From-Baseline QT Interval Corrected for Heart Rate Using Fridericia's Formula (ΔΔQTcF) by Time (Primary Endpoint, Sponsor's Results)

Parameter	Time Point (h)	Statistics	Moxifloxacin 400 mg	Revefenacin 175 mcg	Revefenacin 700 mcg
ΔΔQTcF (msec)	0.25	LS Mean	0.1	0.2	–0.0
		SE	1.08	1.09	1.07
		95% CI for LS Mean	(–2; 2.2)	(–2; 2.3)	(–2.1; 2.1)
	0.50	LS Mean	2.7	0.7	0.9
		SE	1.07	1.08	1.07
		95% CI for LS Mean	(0.6; 4.8)	(–1.4; 2.8)	(–1.2; 3)
	1.00	LS Mean	10.8	–0.2	1.0
		SE	1.07	1.08	1.07
		95% CI for LS Mean	(8.7; 12.9)	(–2.3; 1.9)	(–1.1; 3.1)
	2.00	LS Mean	11.9	0.4	0.5
		SE	1.07	1.08	1.07
		95% CI for LS Mean	(9.8; 14)	(–1.7; 2.5)	(–1.6; 2.5)
	3.00	LS Mean	15.4	0.6	0.3
		SE	1.08	1.08	1.07
		95% CI for LS Mean	(13.3; 17.5)	(–1.5; 2.7)	(–1.8; 2.4)
	4.00	LS Mean	14.0	0.4	0.4
		SE	1.08	1.08	1.07
		95% CI for LS Mean	(11.9; 16.1)	(–1.8; 2.5)	(–1.7; 2.5)
	6.00	LS Mean	10.5	0.9	0.0
		SE	1.08	1.09	1.08
		95% CI for LS Mean	(8.4; 12.7)	(–1.2; 3.1)	(–2.1; 2.1)
	8.00	LS Mean	11.9	1.0	0.8
		SE	1.08	1.09	1.07
		95% CI for LS Mean	(9.8; 14)	(–1.2; 3.1)	(–1.3; 2.9)
	12.00	LS Mean	10.0	–1.2	0.0
		SE	1.07	1.08	1.07
		95% CI for LS Mean	(7.9; 12.1)	(–3.4; 0.9)	(–2.1; 2.1)
	24.00	LS Mean	5.8	–0.4	–0.1
		SE	1.08	1.08	1.07
		95% CI for LS Mean	(3.7; 7.9)	(–2.5; 1.7)	(–2.2; 2)

Abbreviations: ΔΔQTcF, placebo-corrected change-from-baseline QT interval corrected for heart rate using Fridericia's formula; CI, confidence interval; LS, least squares; msec, millisecond(s); SE, standard error

Note: 95% 2-sided confidence intervals were used.

(Source: the sponsor's clinical study report, Table 7, page 62)

Reviewer's Comments: The reviewer agrees with the sponsor's conclusions. The statistical reviewer conducted independent analysis using repeated measures mixed-effect model without term sex. Instead of 95% CIs, 90% CIs for placebo-corrected mean change from baseline in QTcF were displayed. Results from the reviewer's independent

analysis are consistent with the sponsor's. Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

The sponsor's results for assay sensitivity analysis are displayed in the above Table 2.

The QTc prolongation observed after dosing with moxifloxacin confirmed the study's assay sensitivity. Mean ΔΔQTcF was 10.8 msec, 11.9 msec, and 15.4 msec, respectively, at the 3 predefined time points (1, 2, and 3 hours after dosing) with the lower bound of the 95% CI above 5 msec (8.7 msec, 9.8 msec, and 13.3 msec, respectively).

Reviewer's Comments: The reviewer agrees with the sponsor's conclusions for assay sensitivity. Please see the reviewer's independent analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

From the sponsor's report table for categorical analysis, there were no QTcF outliers in terms of QTcF >480 ms or ΔQTcF >60 ms. Only one subject (1/43, 2.3%) in the revefenacin 175 mcg group had QTcF between 450 ms and 480 ms. No subjects had ΔQTcF >30 ms in revefenacin 175 mcg group or revefenacin 700 mcg group.

4.2.8.3 Safety Analysis

No deaths or serious adverse events (SAEs) occurred during the study. One subject (Subject (b) (6) was discontinued because of treatment emergent adverse events (TEAEs) during the study. The subject took a prohibited medication during the study and was recorded as a protocol deviation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for revefenacin are presented in Table 3. Following administration of 700 mcg revefenacin the mean C_{max} and AUC values in the thorough QT study were approximately 4.1 and 3.6-fold higher compared to the therapeutic dose. The mean T_{max} was approximately 0.25 hours.

Table 3: Plasma Pharmacokinetic Parameters of Revefenacin following Administration a Single Dose by Inhalation

PK Parameter (unit)	175 mcg revefenacin Arithmetic mean (SD)		700 mcg revefenacin Arithmetic mean (SD)	
C_{max} (ng/mL)	n= 43	0.345 (0.168)	n= 45	1.42 (0.690)
T_{max} (h)	n= 43	0.25 (0.25, 0.33)	n= 45	0.25 (0.25, 0.28)
AUC_{0-24} (ng*h/mL)	n= 40	0.284 (0.0998)	n= 44	1.02 (0.433)
AUC_{0-last} (ng*h/mL)	n= 43	0.265 (0.119)	n= 45	0.993 (0.454)

4.2.8.4.2 Exposure-Response Analysis

Linear mixed-effects modeling approach was used to explore the relationship between baseline-adjusted placebo- corrected QTc interval (ΔΔQTcF) and plasma concentrations of revefenacin. The estimated population slope of the exposure-response relationship was -0.298 msec per ng/mL (95% CI: -1.466 to 0.870) with an intercept of 0.319 msec. The slope of the relationship was not statistically significant and a concentration-dependent effect of revefenacin on QTcF was therefore not identified.

Reviewer's Analysis: Reviewer's analysis confirms the results of the sponsor (The estimated population slope of the exposure-response relationship was -0.35 msec per ng/mL (95% CI: -1.35 – 0.64) with an intercept of 0.3 msec). A plot of ΔΔQTcF vs. revefenacin concentrations is presented in **Figure 3**.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Since no large changes in heart rate were observed, i.e., mean changes ≤10 bpm (section 5.2.2), QTcF was used for primary analysis.

No assessment of the QT/RR correction methodology is necessary.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Revefenacin

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

Table 4: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = Revefenacin 175 mcg

	ΔQTcF (ms) Revefenacin 175 mcg (N=43)	**ΔQTcF (ms) Placebo (N=42)**	**ΔΔQTcF (ms) Revefenacin 175 mcg**	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.25	-0.5	-0.6	0.1	(-1.4, 1.6)
0.5	-1.3	-2.0	0.7	(-0.7, 2.0)
1	-2.2	-1.9	-0.3	(-1.8, 1.3)
2	-0.2	-0.6	0.4	(-1.2, 1.9)
3	0.4	-0.2	0.6	(-1.0, 2.2)
4	1.2	0.9	0.3	(-1.4, 2.1)

	ΔQTcF (ms) Revefenacin 175 mcg (N=43)	ΔQTcF (ms) Placebo (N=42)	ΔΔQTcF (ms) Revefenacin 175 mcg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
6	-3.1	-4.0	0.9	(-2.0, 3.8)
8	-3.9	-4.8	0.9	(-1.3, 3.1)
12	-4.9	-3.6	-1.3	(-3.6, 1.0)
24	0.8	1.2	-0.4	(-2.2, 1.3)

Table 5: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = Revefenacin 700 mcg

	ΔQTcF (ms) Revefenacin 175 mcg (N=45)	ΔQTcF (ms) Placebo (N=42)	ΔΔQTcF (ms) Revefenacin 700 mcg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.25	-0.5	-0.6	0.1	(-1.4, 1.6)
0.5	-1.0	-2.0	1.0	(-0.3, 2.3)
1	-0.8	-1.9	1.1	(-0.4, 2.7)
2	-0.1	-0.6	0.6	(-0.9, 2.1)
3	0.2	-0.2	0.4	(-1.2, 2.0)
4	1.4	0.9	0.5	(-1.2, 2.2)
6	-4.0	-4.0	-0.0	(-2.9, 2.9)
8	-3.9	-4.8	0.8	(-1.3, 3.0)
12	-3.4	-3.6	0.2	(-2.1, 2.4)
24	1.2	1.2	-0.0	(-1.7, 1.7)

The largest upper bounds of the 2-sided 90% CI for the mean differences between revefenacin 175 mcg and placebo, and between revefenacin 700 mcg and placebo were 3.8 ms and 3.0 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest unadjusted 90% lower confidence interval was 13.9 ms. By considering Bonferroni multiple endpoint

adjustment, the largest lower confidence interval was 13.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg (N=44)	**ΔQTcF (ms) Placebo (N=42)**	**ΔΔQTcF (ms) Moxifloxacin 400 mg**		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
0.25	-0.5	-0.6	0.1	(-1.4, 1.6)	(-1.9, 2.0)
0.5	0.6	-2.0	2.6	(1.3, 4.0)	(0.9, 4.4)
1	8.8	-1.9	10.7	(9.2, 12.3)	(8.7, 12.8)
2	11.2	-0.6	11.9	(10.3, 13.4)	(9.9, 13.9)
3	15.3	-0.2	15.5	(13.9, 17.1)	(13.4, 17.6)
4	14.9	0.9	14.1	(12.3, 15.8)	(11.8, 16.3)
6	6.5	-4.0	10.5	(7.6, 13.4)	(6.8, 14.2)
8	7.0	-4.8	11.8	(9.6, 14.0)	(9.0, 14.6)
12	6.4	-3.6	10.0	(7.7, 12.2)	(7.0, 12.9)
24	7.0	1.2	5.8	(4.0, 7.5)	(3.5, 8.1)

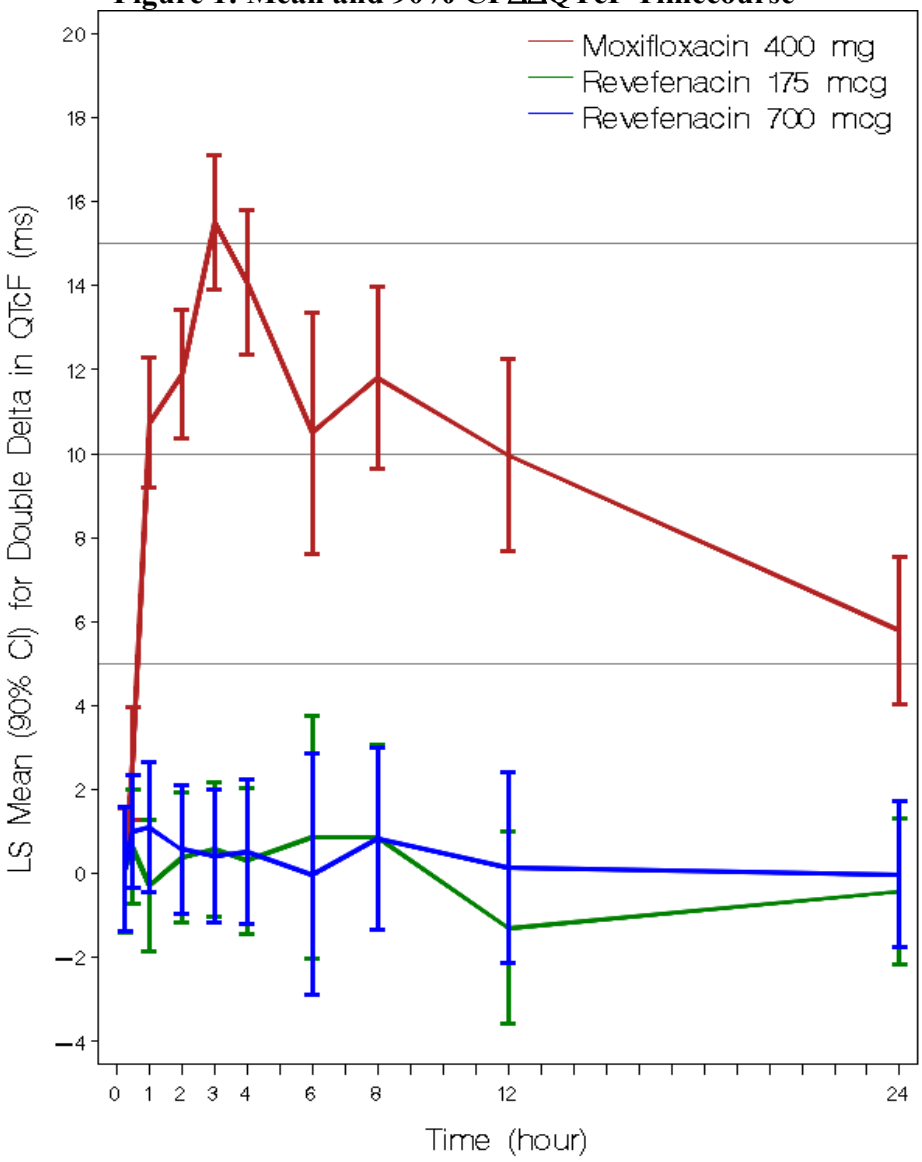
* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 3 time points around moxifloxacin C_{max}.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 1: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

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

Table 7: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline/Predose	48	522	46 (95.8%)	517 (99.0%)	2 (4.2%)	5 (1.0%)

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	42	417	41 (97.6%)	415 (99.5%)	1 (2.4%)	2 (0.5%)
Moxifloxacin 400 mg	44	437	40 (90.9%)	432 (98.9%)	4 (9.1%)	5 (1.1%)
Revefenacin 175 mcg	43	430	42 (97.7%)	422 (98.1%)	1 (2.3%)	8 (1.9%)
Revefenacin 700 mcg	45	449	45 (100%)	449 (100%)	0 (0.0%)	0 (0.0%)

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

Table 8: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	42	417	42 (100%)	417 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	44	437	42 (95.5%)	434 (99.3%)	2 (4.5%)	3 (0.7%)
Revefenacin 175 mcg	43	430	43 (100%)	430 (100%)	0 (0.0%)	0 (0.0%)
Revefenacin 700 mcg	45	449	45 (100%)	449 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper limits of 90% CI for the HR mean differences between revefenacin 175 mcg and placebo and revefenacin 700 mcg and placebo were 1.9 bpm and 1.2 bpm, respectively.

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

Table 9: Analysis Results of ΔHR and ΔΔHR

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.25	2.7	2.8	-0.2 (-1.6, 1.2)	1.7	2.8	-1.1 (-2.5, 0.3)
0.5	1.4	0.9	0.5 (-0.7, 1.7)	0.3	0.9	-0.6 (-1.8, 0.6)
1	-0.0	0.1	-0.2 (-1.3, 1.0)	-1.0	0.1	-1.1 (-2.3, -0.0)
2	-1.6	-1.1	-0.5 (-1.7, 0.7)	-2.9	-1.1	-1.8 (-3.0, -0.6)

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
3	-1.3	-0.7	-0.6 (-1.7, 0.6)	-2.3	-0.7	-1.6 (-2.7, -0.5)
4	-0.6	-0.1	-0.5 (-1.8, 0.7)	-1.3	-0.1	-1.2 (-2.5, 0.0)
6	5.6	6.6	-1.0 (-2.6, 0.6)	4.9	6.6	-1.7 (-3.3, -0.1)
8	3.6	3.3	0.3 (-1.2, 1.9)	3.1	3.3	-0.3 (-1.8, 1.2)
12	3.7	5.0	-1.3 (-2.8, 0.2)	3.2	5.0	-1.8 (-3.3, -0.3)
24	1.1	1.3	-0.2 (-1.7, 1.3)	-0.1	1.3	-1.4 (-2.9, 0.1)

Table 10: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline/Predose	48	48 (100%)	0 (0.0%)	48 (100%)	0 (0.0%)
Placebo	42	42 (100%)	0 (0.0%)	41 (97.6%)	1 (2.4%)
Moxifloxacin 400 mg	44	44 (100%)	0 (0.0%)	44 (100%)	0 (0.0%)
Revefenacin 175 mcg	43	43 (100%)	0 (0.0%)	42 (97.7%)	1 (2.3%)
Revefenacin 700 mcg	45	45 (100%)	0 (0.0%)	44 (97.8%)	1 (2.2%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the PR mean differences between revefenacin 175 mcg and placebo and revefenacin 700 mcg and placebo were 3.2 ms and 3.3 ms, respectively.

There were no subjects who experienced PR interval greater than 200 ms in revefenacin 175 mcg group or revefenacin 700 mcg group.

Table 11: Analysis Results of ΔPR and ΔΔPR

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.25	-7.8	-8.1	0.3 (-1.4, 2.0)	-7.0	-8.1	1.1 (-0.6, 2.8)

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	-4.2	-3.5	-0.7 (-2.5, 1.1)	-3.2	-3.5	0.3 (-1.5, 2.1)
1	-4.4	-3.0	-1.4 (-3.3, 0.5)	-2.7	-3.0	0.4 (-1.5, 2.2)
2	-3.6	-4.8	1.2 (-0.9, 3.2)	-3.5	-4.8	1.3 (-0.7, 3.3)
3	-4.5	-3.5	-1.0 (-2.8, 0.9)	-4.6	-3.5	-1.1 (-3.0, 0.7)
4	-5.2	-3.2	-2.0 (-3.7, -0.3)	-6.0	-3.2	-2.8 (-4.4, -1.1)
6	-6.5	-7.0	0.5 (-1.4, 2.5)	-9.3	-7.0	-2.2 (-4.2, -0.3)
8	-9.3	-9.0	-0.3 (-2.4, 1.8)	-8.6	-9.0	0.4 (-1.7, 2.5)
12	-8.9	-7.7	-1.3 (-3.3, 0.8)	-9.2	-7.7	-1.5 (-3.6, 0.5)
24	-4.1	-2.9	-1.2 (-3.2, 0.8)	-2.8	-2.9	0.1 (-1.9, 2.1)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the QRS mean differences between revefenacin 175 mcg and placebo and revefenacin 700 mcg and placebo were 0.7 ms and 0.9 ms, respectively.

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

Table 12: Analysis Results of ΔQRS and ΔΔQRS

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔQRS (ms)		ΔΔQRS (ms)	ΔQRS (ms)		ΔΔQRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.25	-0.0	-0.1	0.1 (-0.2, 0.4)	-0.2	-0.1	-0.1 (-0.4, 0.2)
0.5	0.2	0.2	-0.0 (-0.4, 0.3)	0.2	0.2	-0.0 (-0.3, 0.3)
1	0.0	-0.0	0.1 (-0.2, 0.3)	0.1	-0.0	0.2 (-0.1, 0.4)
2	-0.1	-0.2	0.1 (-0.2, 0.4)	-0.1	-0.2	0.1 (-0.2, 0.4)
3	0.1	0.0	0.1 (-0.2, 0.4)	-0.3	0.0	-0.3 (-0.5, 0.0)
4	0.2	-0.0	0.2 (-0.1, 0.6)	0.0	-0.0	0.1 (-0.3, 0.4)
6	-0.4	-0.5	0.1 (-0.5, 0.7)	-0.6	-0.5	-0.1 (-0.7, 0.5)
8	-0.7	-0.6	-0.2 (-0.6, 0.2)	-0.9	-0.6	-0.3 (-0.7, 0.1)

	Revefenacin 175 mcg (N=43)			Revefenacin 700 mcg (N=45)		
	ΔQRS (ms)		ΔΔQRS (ms)	ΔQRS (ms)		ΔΔQRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
12	-0.8	-0.7	-0.1 (-0.7, 0.4)	-0.4	-0.7	0.3 (-0.2, 0.9)
24	0.1	0.0	0.1 (-0.3, 0.4)	0.1	0.0	0.0 (-0.3, 0.4)

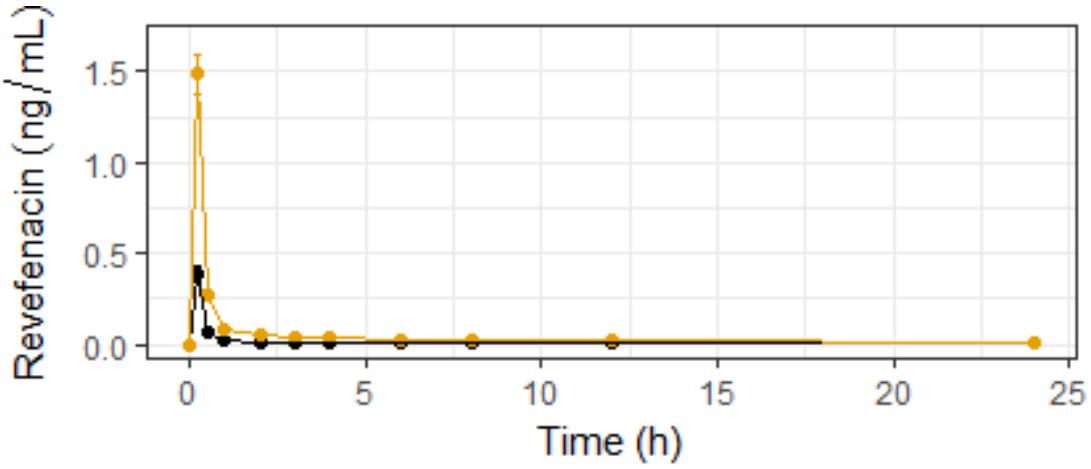
Table 13: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	48	522	40 (83.3%)	450 (86.2%)	8 (16.7%)	72 (13.8%)
Placebo	42	417	34 (81.0%)	357 (85.6%)	8 (19.0%)	60 (14.4%)
Moxifloxacin 400 mg	44	437	36 (81.8%)	378 (86.5%)	8 (18.2%)	59 (13.5%)
Revefenacin 175 mcg	43	430	37 (86.0%)	384 (89.3%)	6 (14.0%)	46 (10.7%)
Revefenacin 700 mcg	45	449	39 (86.7%)	393 (87.5%)	6 (13.3%)	56 (12.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

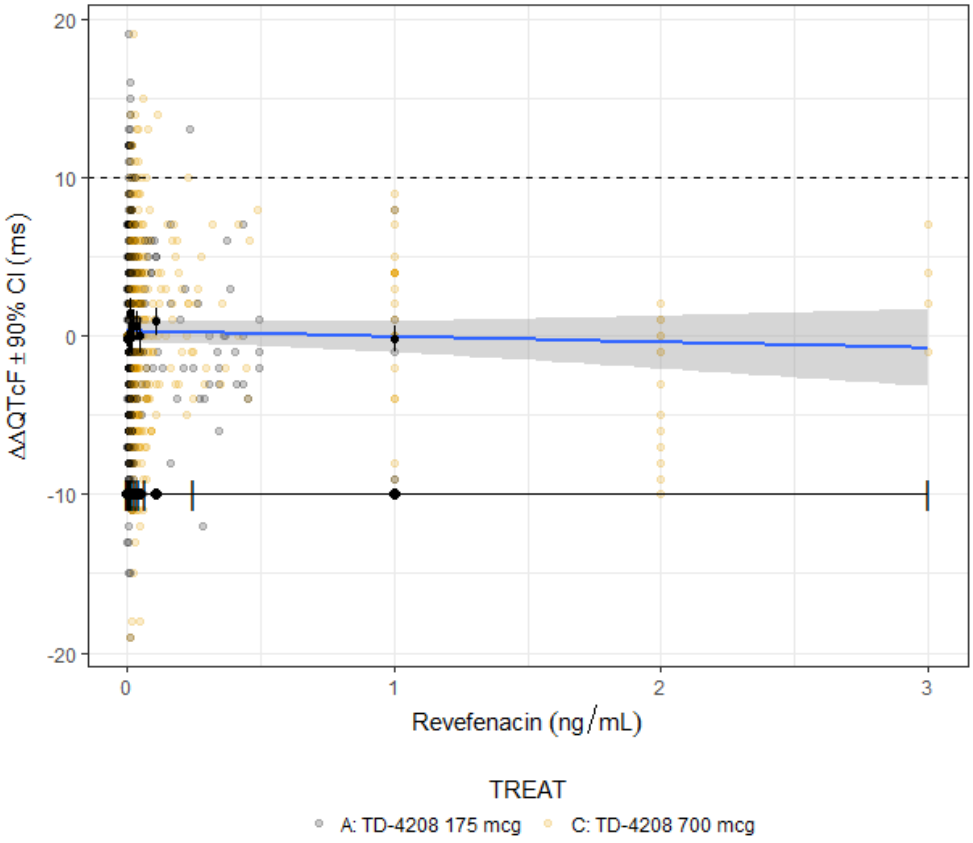
The mean revefenacin concentration-time profile is illustrated in Figure 2.

Figure 2: Mean revefenacin concentration-time profiles for 175 mcg (black line) and 700 mcg (yellow line) dose



The relationship between ΔΔQTcF and revefenacin, the predominant moiety in plasma, is shown in **Figure 3**, which did not suggest an exposure-response relationship for QTcF consistent with the sponsor's analysis.

Figure 3: ΔΔ QTcF vs. revefenacin concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

There was 1 subject in the 700 mcg dose group who experienced syncope, which was considered mild in severity and possibly/probably related to study drug.

None of the other events identified to be of clinical importance per the ICH E14 guidelines (i.e. seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There are no clinically meaningful effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

(Source: QT-IRT review – IND 119840 -02/02/2016)

Note: Hepatic and renal impairment studies were on-going at the time of protocol review of the thorough QT-study (02/02/2016). The studies were completed in April, 2016 and May, 2016, respectively.

Therapeutic dose	175 µg QD is the highest anticipated therapeutic dose	
Maximum tolerated dose	The maximum tested dose of 700 µg was the NOAEL	
Principal adverse events	Headache, dry mouth and constipation were commonly observed adverse events.	
Maximum dose tested	Single Dose	700 µg QD
	Multiple Dose	700 µg QD for 7 days
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max}: 0.537 ± 0.212 ng/mL (Mean ± SD; Study 0091) AUC_{0-t}: 0.362 ± 0.159 ng*h/mL (Mean ± SD; Study 0091)
	Multiple Dose	C_{max}: 0.577 ± 0.261 ng/mL (Mean ± SD; Study 0091) AUC_{0-t}: 0.755 ± 0.319 ng*h/mL (Mean ± SD; Study 0091)
Range of linear PK	C_{max}: 22 to 700 µg QD AUC_{0-t}: 22 to 700 µg QD	
Accumulation at steady state	TD-4208: Mean accumulation of 1.07- to 1.26-fold for C_{max} in the 22 µg to 700 µg QD dose range. Mean accumulation of 0.904- to 1.55-fold for $AUC_{(0-\tau)}$ in the 22 µg to 700 µg QD dose range. THRX-195518 (primary metabolite of TD-4208): Mean accumulation of 1.03- to 1.10-fold for C_{max} in the 22 µg to 700 µg QD dose range. Mean accumulation of 1.19 to 1.34-fold for $AUC_{(0-\tau)}$ in the 22 µg to 700 µg QD dose range.	
Metabolites	THRX-195518 is the only major metabolite quantified in the human plasma. THRX-195518 is formed by hydrolysis of the primary amide of TD-4208 to a carboxylic acid. The exposure (AUC) of THRX-195518 is ~3 to 10 fold higher than the exposure of TD-4208 following inhalation dosing. Metabolite profiling of human plasma and urine samples from clinical studies did not identify any additional metabolites of TD-4208.	
Absorption	Absolute/Relative Bioavailability	Not determined
	T_{max}	TD:4208: Median T_{max} in the range of 0.483 to 0.517 h across dose levels THRX-195518: Median T_{max} in the range of 0.467 to 0.683 h across dose levels (Study 0117; QD dosing for 28 days)
Distribution	Vd/F or Vss	Mean (%CV): 1020 (50.9) L (based on population PK analysis of Studies 0059, 0091, and 0117) Based on preliminary data following IV dosing of [^{14}C]TD-4208, the Vss is 24.8 (38.5%) L [Mean (%CV)]
	% bound	TD-4208: ~71% bound in human plasma THRX-195518: ~42% bound in human plasma

Elimination	Route	Primarily route of elimination after inhalation dosing is likely through metabolism A low fraction (<1%) of the dose is recovered unchanged in the urine following inhalation dosing. Based on preliminary metabolite profiling data following IV dosing of [^{14}C]TD-4208, approximately 11% of the dose was excreted unchanged in the urine.
	Terminal t½	TD-4208: 57.9 ± 31.5 h (Mean ± SD; Day 28; 350 µg QD dose) THRX-195518: 51.2 ± 24.8 h (Mean ± SD; Day 28; 350 µg QD dose)
	CL/F	Mean (%CV): 1056 (64.9) L/h (based on population PK analysis of Studies 0059, 0091, and 0117) Based on preliminary data following IV dosing of [^{14}C]TD-4208, the CL is 48.2 (19.0%) L/h [Mean (%CV)]
Intrinsic Factors	Age	No significant effect on C_{max} or AUC based on population PK analysis of Studies 0059, 0091, and 0117
	Sex	No significant effect on C_{max} or AUC based on population PK analysis of Studies 0059, 0091, and 0117
	Race	No significant effect on C_{max} or AUC based on population PK analysis of Studies 0059, 0091, and 0117
	Hepatic & Renal Impairment	Not investigated
Extrinsic Factors	Drug interactions	No clinical DDIs with TD-4208 or THRX-195518 as perpetrators are expected due to the low circulating concentrations of TD-4208 and THRX-195518 following inhalation dosing. As the primary route of metabolism is hydrolysis of TD-4208 to THRX-195518, increase in concentrations of TD-4208 or THRX-195518 due to drug interactions is not anticipated.
	Food Effects	The drug is administered by inhalation route. Food effects on exposure have not been investigated.
Expected High Clinical Exposure Scenario	Increase in exposure of TD-4208 due to DDIs is not expected as the major route of metabolism is hydrolysis of TD-4208 to THRX-195518. TD-4208 pharmacokinetics in subjects with hepatic impairment and renal impairment are being evaluated.	

Preclinical Cardiac Safety	Human hERG channel tail current IC_{50}: 11.4 µM for TD-4208 and 524 µM for THRX-195518
Clinical Cardiac Safety	• Five clinical studies of TD-4208 have been completed with a total of 534 subjects exposed to TD-4208. • In study AC5108696, ventricular tachycardia was observed in 1 subject at 30ug dose. • In study 0059, QT-interval prolongation observed in 1 subject at 350ug dose and 1 subject with syncope at 700ug. • In study 0091, hypotension was observed in 2 subjects at 44 ug. • In study 0116, coronary artery insufficiency (secondary to atherosclerosis) was observed in 1 subject at 175ug. • In study 0117, premature ventricular complexes (PVCs) were present in slightly higher numbers during treatment compared with baseline in all groups (including placebo). Ventricular tachycardia was noted in 2 subjects at baseline. On Day 15 of the study, ventricular tachycardia was noted in 2 (3%) subjects in the placebo group, 4 (6%) subjects in the TD-4208 44 µg group, and in 1 (2%) subject each in the TD-4208 88 and 350 µg groups

SD: standard deviation

DDI: drug-drug interaction

PK: pharmacokinetics

Study 0059: A Phase 2, Randomized, Double-Blind, Crossover Study to Examine the Pharmacodynamics, Safety and Tolerability, and Pharmacokinetics of Single Doses of TD-4208 in Subjects Diagnosed with Chronic Obstructive Pulmonary Disease

Study 0091: A Phase 2, Randomized, Double-Blind, Multiple- Dose, Five-Period, Incomplete-Block, Crossover Study to Examine the Pharmacodynamics, Safety and Tolerability, and Pharmacokinetics of Multiple Doses of TD-4208 for 7 Days in Subjects Diagnosed With Chronic Obstructive Pulmonary Disease

Study 116: A Phase 2, Randomized, Double Blind Placebo-Controlled Cross-Over Study of QD and BID Nebulized TD-4208 in COPD

Study 0117: A Phase 2B, 28-Day, Randomized, Double-Blind Placebo-Controlled Parallel Group Study of Nebulized TD-4208 in Subjects with Chronic Obstructive Pulmonary Disease

Study AC5108696: A Randomised Double-Blind, Placebo-Controlled, Crossover, Dose Escalation Study to Examine the Safety, Tolerability, Pharmacodynamics (PD) and Pharmacokinetics (PK) of Single Inhaled Doses of GSK1160724 and Tiotropium bromide.

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