CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

OTHER REVIEW(S)

Project Manager Overview

NDA 207947 Uptravi (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

Indication: Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.
PDUFA goal date: December 22, 2015
Pharmacologic Class: prostacylin receptor agonist
Type 1 NDA: New Molecular Entity
RPM: Wayne Amchin
(10-month PDUFA review clock)

Regulatory Background

As noted in the signatory authority review, Selexipag is a non-prostanoid prostacyclin agonist. A number of prostacyclin agonists are approved for pulmonary arterial hypertension (PAH), but selexipag is the only non-prostanoid agonist. Approval of selexipag is supported by a double-blind trial in which subjects with PAH WHO Group I were randomized to placebo or selexipag (titrated as tolerated) and followed for disease progression, PAH hospitalization, and death.

Uptravi (selexipag) for treatment of PAH was the subject of a Pre-IND/Pre-Phase 3 meeting with Actelion on March 26, 2009, under IND number 104504. Meeting minutes issued on April 3, 2009, and the IND was submitted on September 29, 2009.

The IND submission included a Special Protocol. FDA issued a Special Protocol- No Agreement letter on November 9, 2009. Actelion resubmitted a revised proposed Special Protocol on January 11, 2010. FDA issued a Special Protocol-Agreement letter on February 23, 2010.

Protocol amendments and additional protocols were received on the following dates:

- April 2, 2010:
  This protocol was a new protocol Protocol AC-065A303, entitled "Long-term, single-arm open-label study, to assess the safety and tolerability of ACT-293987 in patients with pulmonary arterial hypertension" Final Version 2, dated March 19,2010. The study is designed as an open label, non-comparative, multicenter study following the AC-065A302 (GRIPHON) study to assess the long-term safety and tolerability of ACT-293987 in patients with PAH. There are no efficacy endpoints in this study. During the AC-065A303 (GRIPHON OL) study, patients coming from study AC-065A302 (GRIPHON) already taking ACT-293987 will continue on the same dose. Patients who were on placebo and patients who experienced a clinical worsening of PAH (adjudicated by the CEC) during the GRIPHON study will start ACT-293987 at a low dose (200 ug bid) and will be uptitrated until their highest tolerated dose is reached. Study treatment for each patient lasts from his/her Visit 1 date until the end of the trial (i.e., until whichever

of the following occurs first: (i) the approval of ACT-293987 in this indication is obtained in the patient's country, (ii) the sponsor decides to stop study AC-065A303 (GRIPHON OL), or (iii) the patient, or the investigator decide to discontinue study drug.

- January 7, 2011:
  - • Strengthened the monitoring of the ECGs by adding 2 additional tests after study drug intake (per FDA request)
  - • Deleted precautionary wording regarding sun exposure
  - o based on the results of the Phase I study (AC-065-102: "A single-center, assessor-blind, randomized, placebo- and positive-controlled, parallel group study to evaluate the phototoxic potential, safety, tolerability, and pharmacokinetics of ACT-293987 in healthy male subjects.")
  - • Clarified statistical text concerning acceptable ranges mentioned in Section 5.4.1.6 of the protocol (per FDA request)
- January 7, 2011-amendment to Study 303.
- June 2, 2011, SPA Amendment
- August 18, 2011 SPA Amendment
- September 12, 2011 QT/IRT Study Protocol
- December 21, 2011 SPA Amendment
- June 4, 2012, New Protocol: Protocol AC-065-106 entitled "A single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group with nested cross-over, multiple-dose, up titration study of the effects of selexipag and its metabolite ACT 333679 on cardiac repolarization in healthy male and female subjects."
- September 4, 2012, amending the protocol submitted on June 4, 2012.
- October 9, 2012, amendment 2 to the protocol submitted on June 4, 2012.
- February 12, 2013, SPA Amendment.

FDA issued a Special Protocol Modification Agreement letter on February 27, 2013.

A pre-NDA submission meeting was held on August 8, 2014, and meeting minutes issued on May 2, 2014. A top-line results meeting was held on July 11, 2014 to discuss the results from the pivotal trial and to discuss any additional analysis that FDA wants included in the NDA submission. Meeting minutes issued on August 7, 2014.

Advisory Committee

It was decided early on that we would not take this NDA to an Advisory Committee. Although selexipag is a new molecular entity, its approval raised no issues that would justify an Advisory Committee meeting, and none was held. The drug is not the first in its class, and the safety profile is similar to that of other drugs approved for this indication. As noted in the signatory authority review, we might have considered convening an advisory committee meeting had we better understood the mortality findings at the beginning of our review.

Application Milestones, starting with NDA Submission:

The NDA was submitted on December 22, 2014, as an NME under the PDUFA V program, with a PDUFA goal date of December 22, 2015.

A Clinical Scoping Meeting was held on January 23, 2015, and JMP Jump start meetings were subsequently held to do a preliminary assessment of data submitted under the NDA.

The Filing Meeting was held on February 2, 2015. Potential Filing issues were discussed in the 74-day letter.

The application was Filed on February 20, 2015

The 74-day letter issued on March 2, 2015, noting that there were filing issues identified which could have resulted in refusal-to-file. The FDA chose not to RTF the application and instead allowed Actelion to address those as part of a subsequent amendment. The potential RTF issue included in the 74-day letter was:

1. We remind you that we informed you on February 10, 2015, that the executed batch records in Section 3.2.R of your application contain sections that have not been translated. This would normally result in a refuse-to-file action, but we have filed the application as originally scheduled because you were working to provide, as requested, complete, certified, English-translations of the drug product executed batch records including lot numbers, weights, dates, checkmarks, circled items, hand written annotations, instrument printouts, etc.) as expeditiously as possible, no later than a 2-3 week timeframe. We note that submission of this information is still pending and may delay the complete review of your application.

The 74-day letter also included PLR format issues identified by me.

The Mid-Cycle Meeting was held on May 13, 2015, and a Mid-Cycle Communication TCon was held with Actelion on May 27, 2015. Mid-cycle Communication Meeting Minutes issued on June 25, 2015. The Mid-cycle Communication included the following issues:

SIGNIFICANT ISSUES

PRODUCT QUALITY

The product quality review team has concerns (b) (4) and possibly result in medication errors. This is of particular concern in the early treatment phase, when patients may have more than one dose on hand as their dosage is being titrated. (b) (4)

CLINICAL PHARMACOLOGY

Clinical Pharmacology discussed two topics at the meeting - (i) use with concomitant CYP2C8 inhibitors, and (ii) use in patients with moderate and severe hepatic impairment. (b) (4) The Division (b) (4) wants to further optimize the instructions for use in these sections.

(i) Use with CYP2C8 inhibitors: As the extent of increase in exposure to selexipag and the active metabolite when dosed concomitantly with a strong CYP2C8 inhibitor is not known, the review team stated that it may lead to the inclusion of a Post- Marketing Requirement (PMR) for a drug interaction study in the action letter. Until then, selexipag should probably be labeled as 'not recommended for use' with strong CYP2C8 inhibitors. The applicant acknowledged the concern and indicated that they would consider performing a single-dose drug interaction study in healthy volunteers.

(ii) Use in moderate and severe hepatic impaired patients: The review team stated that appropriate instructions for use may be provided to these subgroups based on principles of exposure matching to healthy subjects. Based on an initial assessment, the review team proposed that a once-a-day dosing might seem appropriate in moderate and severe hepatic impaired patients. The applicant volunteered to perform modeling and simulation exercise in support of an optimal dosing regimen for these patients.

CLINICAL

Clinical review noted the following issues:

1. The Division of Cardiovascular and Renal Products is consulting the Division of Transplant and Ophthalmology Products regarding the eye findings.
2. Labeling: No final decisions have been made, but the review team is considering re- wording some of the draft labeling, particularly the results of the 6MWD and mortality (b) (4).

Mid-Cycle Communication

INFORMATION REQUESTS

PRODUCT QUALITY

FDA requested that Actelion submit photostability studies conducted under ICH guidance Q.1.B. (b) (4) Actelion agreed to provide the samples and the photostability studies within two weeks as part of revised module three documents.

CLINICAL PHARMACOLOGY

The review team requested that Actelion provide a modeling and simulation report in support of a dosing regimen for moderate and severe hepatic impaired groups based on exposure matching to healthy volunteers.

CLINICAL

The review team requested that Actelion provide justification for the proposed labeling of selexipag vs. placebo on 6MWD and mortality endpoints.

A separate Information Request was sent to Actelion by the Office of Pharmaceutical

Quality shortly after the Mid-Cycle Communication was issued.

All the issues identified in the Mid-Cycle Communication were addressed. A separate Information Request was sent to Actelion by the Office of Pharmaceutical Quality shortly after the Mid-Cycle Communication was issued. All those issues were addressed as well.

The Late-Cycle Meeting was held with Actelion on September 8, 2015, and Late-Cycle Meeting Minutes issued on October 7, 2015. Only labeling issues were discussed at the Late-Cycle Meeting.

The Wrap-up meeting was held on November 2, 2015.

Clinical Site Inspections were requested and completed in advance of approval.

Very late in the review cycle, the EMA contacted FDA about concerns they had with a mortality imbalance on Selexipag versus placebo. This led to some additional discussion and a Division Director Review Addendum, dated December 21, 2015, but it did not alter the review team's view that the NDA should be approved.

Other drugs in the same pharmacologic class considered for labeling purposes:

1. Epoprostanol
2. Ventavis (Iloprost)
3. Orenitram (treprostinil)

Selexipag has Orphan Designation, and Actelion requested 7 years Orphan Exclusivity. The application is exempt from PREA requirements.

Labeling Discussions with Actelion:

- The first labeling comments were provided to Actelion in the 74-day letter on March 2, 2015.

- DMEPA completed a labeling review on March 13, 2015. The review recommended revisions to the Carton Labeling. These changes were sent to Actelion and they agreed to them. Revised Carton Labeling was submitted on March 27, 2015 and deemed acceptable by DMEPA, as noted in their review dated April 3, 2015.

- Specific labeling issues were discussed during the Mid-Cycle Communication, but marked up labeling was not provided.

- Detailed marked-up labeling comments were provided to Actelion as part of the Late-Cycle Meeting Package, and labeling was the only item on the Late-Cycle Meeting Agenda. Actelion was encouraged at that meeting to submit revised labeling that addressed FDA's comments. FDA also noted that the next labeling comments from FDA would not be provided until all application reviews are done, including CDTL, DCRP Division Director, and ODE I Director (signatory authority) reviews.

- Following the Late-Cycle Meeting, Actelion submitted revised proposed labeling that addressed some of the suggestions FDA proposed. However, Actelion also reinserted some language that FDA had removed.

- On December 18, FDA provided near final labeling comments to Actelion. There were a couple rounds of back and forth labeling negotiations between Actelion and FDA on December 21, 2015 before the Prescribing Information labeling was agreed to. FDA provided comments on the PPI only once, and Actelion accepted those changes.

NDA Reviews and Memos-please see the Action Package Checklist for a list of items included in the Action Package.

ODE I Director

Ellis Unger: December 21, 2015

Dr. Unger's review supported approval of the NDA.

Dr. Unger will sign the approval letter.

Division Director Review

Norman Stockbridge: November 25, 2015

Dr. Stockbridge recommended approval.

DD Review Addendum: December 21, 2015, co-signed by Clinical and Statistical reviewers. The review addressed the mortality concerns raised by EMA very late in the review cycle.

CDTL Review

Shari Targum

November 19, 2015

Dr. Targum recommended approval.

Clinical Review

Maryann Gordon, M.D. and Christine Garnett, Pharm.D.

September 2, 2015

Dr. Gordon and Dr. Garnett recommended approval.

Clinical Pharmacology

Sudharshan Hariharan, Luning Zhuang, Jeffry Florian, primary reviewers, and Raj Madabushi, secondary Reviewer

November 6, 2015

Clinical Pharmacology recommended approval, with the following recommendations for the labeling:

- Once-a-day regimen in patients with moderate hepatic impairment
- Avoid use in severe hepatic impairment
- Avoid use in patients with concomitant use of strong CYP2C8 inhibitor

Biometrics Review

Steve Bai Primary Reviewer, Jim Hung Secondary Reviewer

July 29, 2015

This review concluded that the pivotal trial was adequately designed as a Morbidity/Mortality (MM) event-driven clinical outcome trial with strict statistical specifications, the primary objective of the study was met, and a clinically highly relevant treatment-effect was shown in PAH.

QT-IRT Review

March 25, 2015

Reviewers: Moh jee Ng, Qianyu Dang, Kevin Krudys, Michael Li

This review determined that no significant QTc prolongation effect of selexipag (800 µg and 1600 µg twice daily (b.i.d.)) was detected in this TQT study

Ophthalmology Consult Review

Wiley Chambers, MD. DTOP Division Director

July 27, 2015

This review concluded that It does not appear that there are sufficient ocular concerns to preclude approval of this product.

Dr. Stockbridge's DCRP review stated that reversible effects on retinal vessels prompted additional clinical work-up and a consultative review by Dr. Chambers; but that there does not appear to be any cause for concern clinically.

REMS Review

Donella Fitzgerald and Leah Hart, Primary Reviewers. Kim Lehrfeld secondary reviewer, co-signed by Reema Mehta, Acting Division Director

September 29, 2015

This review concludes that risk mitigation measures beyond labeling, are not warranted for Uptravi (selexipag). Based on the currently available data, the benefit-risk profile for Uptravi is acceptable for the treatment of PAH and DRISK does not recommend a REMS as necessary to ensure the benefits of Uptravi outweigh the risks at this time.

Product Quality Review

Wendy Wilson, Application Team Lead, Office of Pharmaceutical Quality,

August 25, 2015

OPQ recommended approval.

Nonclinical Reviews

Paul Brown, OND Associate Director for Pharmacology and Toxicology

December 18, 2015

This review supported approval from a pharmacology/toxicology perspective.

Jim Willard, Primary Reviewer, Al De Felice, Secondary Reviewer

December 11, 2015.

This review stated that although Uptravi is a non-eicosanoid prostacyclin agonist, it is expected to have toxicity, especially GI, similar to that of other prostacyclin

agonists though head to-head comparisons were not made in the animal toxicity studies. Oral bioavailability, and twice a day dosing, should promote compliance. Uptravi is approvable from a non-clinical pharmacology-toxicology perspective.

Executive Carcinogenicity Committee
December 3, 2015
The Exec CAC concluded that there were no drug-related neoplasms in the mouse and rat.

Carcinogenicity Statistical Review for Exec CAC discussion
Steve Thompson,
November 20, 2015

DMEPA Proprietary Name Review

Tingting Gao's March 13, 2015 review deemed the proposed name acceptable.

Labeling Reviews

OPDP/Patient Labeling PPI Joint Review on September 4, 2015
DMEPA CCL Review, March 13, 2015 and April 3, 2015
OPDP CCL and PI reviews September 2, 2015

Action Items:
Approve the NDA

Overview by Wayne Amchin
December 21, 2015

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

/s/

WAYNE S AMCHIN
12/22/2015

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 3, 2015
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Puja Shah, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	UPTRAVI (selexipag)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 207947
Applicant:	Actelion Pharmaceuticals Ltd. c/o Actelion Clinical Research, Inc.

1 INTRODUCTION

On December 22, 2014, Actelion Pharmaceuticals Ltd. c/o Actelion Clinical Research, Inc. submitted for the Agency's review an original New Drug Application (NDA) 207947 for UPTRAVI (selexipag) tablets with the proposed indication for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiovascular and Renal Products (DCRP) on February 3, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for UPTRAVI (selexipag) tablets.

2 MATERIAL REVIEWED

- Draft UPTRAVI (selexipag) tablets PPI received on December 22, 2014 and received by DMPP and OPDP on February 3, 2015.
- Draft UPTRAVI (selexipag) tablets Prescribing Information (PI) received on December 22, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 28, 2015.
- Approved Orenitram (treprostinil) extended-release tablets comparator labeling dated December 20, 2013.
- Approved OPSUMIT (macitentan) tablets comparator labeling dated April 30, 2015.

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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is 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 PPI 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 PPI.

Please let us know if you have any questions.

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

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/s/

KAREN M DOWDY
09/03/2015

ZARNA PATEL on behalf of PUJA J SHAH
09/03/2015

MARCIA B WILLIAMS
09/03/2015

LASHAWN M GRIFFITHS
09/04/2015

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

CLINICAL INSPECTION SUMMARY

DATE: September 3, 2015

TO: Shari Targum, Team Leader
Maryann Gordon, Medical Officer Clinical
Wayne Amchin, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluatioin
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 207947

APPLICANT: Actelion Pharmaceuticals, Ltd.

DRUG: UPTRAVI™ (selexipag) tablet

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression (b) (4)

PROTOCOL: AC-065A302: A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension

CONSULTATION REQUEST DATE: January 21, 2015

INSPECTION SUMMARY GOAL DATE: August 24, 2015

PDUFA DATE: December 22, 2015

I. BACKGROUND:

Actelion Pharmaceuticals submits NDA 207947 for the use of selexipag (UPTRAVI) in patients with pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. (b) (4)

Pulmonary arterial hypertension is the most serious chronic disorder of the pulmonary circulation. PAH is characterized by pulmonary arterial vasoconstriction and vascular remodeling resulting in a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular failure and death. PAH is defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest (or > 30 mmHg with exercise), with a pulmonary capillary wedge pressure (PCWP) 15 mmHg and PVR > 3 Wood units (> 240 dyn·s·cm-5).

UPTRAVI is a selective IP prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. (b) (4)

The pivotal Study AC-065A302 (GRIPHON) was designed to demonstrate the efficacy of UPTRAVI in reducing the risk of morbidity and mortality when used for the long-term treatment of patients with PAH. The sponsor states that (b) (4) Study AC-064A301 was conducted in approximately 190 centers in approximately 44 countries. Approximately 1,150 patients were randomized into two groups, (placebo:active 1:1), 575 patients per group.

The primary efficacy endpoint was the time to first mortality-morbidity (MM) event confirmed by the Clinical Events Committee (CEC) up to seven days after last study drug intake defined as:

- Death (all-cause mortality)

or

- Hospitalization for worsening of PAH based on predefined criteria

or

- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy

or

- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH

or

- Disease progression (patients in modified NYHA/WHO functional class II-III at baseline) confirmed by:
  – decrease in 6MWD from Baseline (≥ 15%, confirmed by two tests on different days within 2 weeks) **and** worsening of NYHA/WHO functional class
  or
  -disease progression confirmed by decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and** need for additional PAH specific therapy.

Reasons for Site Selection: All sites chosen for inspection had high enrollment and high overall efficacy results as shown statistically by a high hazard ratio.

II. Results

Name of CI/ Site #	Protocol #, # of Subjects enrolled	Inspection Dates	Final Classification
Site #1601 Pavel Jansa Prague, Czech Republic	AC-065A302 23 subjects	May 11 – 14, 2015	NAI
Site #1402 Jimming Liu Shanghai, China	AC-065A302 32 subjects	May 4 – 8, 2015	VAI
Site #6202 Pablo Sepulveda Varela Santiago, Chile	AC-065A302 22 subjects	April 20 – 24, 2015	NAI

Actelion Pharmaceuticals, Ltd. Allschwil, Switzerland	AC-065A302 Sponsor inspection	May 18 – 22, 2015	Pending (preliminary NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Pavel Jansa
U Nemocnice 2
Prague, Czechoslovakia
212808

a. **What was inspected**: The inspection audited Protocol AC-065A302 (GRIPHON). Dr. Pavel Jansa has six IND studies in the CDER database and no prior inspections. This site was chosen to inspect because of high enrollment (23 subjects) and high treatment effect size in favor of study drug.

The site screened 25 subjects and randomized 23 subjects. A total of eight subjects completed the study.

The field investigator corroborated 100% of subject records for the primary endpoints (mortality and morbidity events [MM]). Secondary endpoints within the data listings were randomly reviewed and compared against source documentation. Protocol deviations were reviewed, as were adverse events, drug accountability records, monitoring logs, and data queries. Regulatory correspondences were reviewed.

b. **General observations/commentary:** There were no major discrepancies between data listings and source documentation with respect to the primary efficacy endpoints (mortality and morbidity events [MM]). The field investigator noted that for Subject #21241, the source documentation confirmed a MM event that was later overturned by the Clinical Events Committee (CEC) due to the new CEC rules which were included in the CEC Charter. The new rules required that the subject must have need for an additional PAH drug in order for it to be considered a MM event. Subject #21241did not require an additional PAH medication, and therefore the MM event was overturned.

In general, source documents were organized, complete, and legible. There was adequate documentation to ensure that all subjects were alive and available for the duration of their participation in the study.

Secondary endpoints within the data listings were randomly reviewed and compared against source documentation. There were no discrepancies. There

was no evidence of under-reporting of serious adverse events. Protocol deviations were reviewed and there was no evidence of systemic issues at this site. Drug accountability records were reviewed, and in general no issues were found. Monitoring logs were reviewed, and the field investigator observed that data query forms were adequately created for any issues that occurred. Monitoring appeared adequate. No Form FDA 483 was issued. The inspection was classified as NAI.

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

2. Jimming Liu
No. 507 Zhengmin Road
Shanghai - Yangpu District,
200433 China

a. **What was inspected:** Dr. Liu has two IND studies in the CDER database and no prior inspections. This site was chosen to inspect because of high enrollment (32 subjects) and high treatment effect size in favor of study drug.

The site screened 34 subjects and enrolled 32 subjects. A total of 31 subjects completed the study. The field investigator reviewed records for seventeen subjects during the inspection, for inclusion and exclusion criteria, primary efficacy endpoints and deaths, concomitant medications, reported protocol deviations and drug accountability. The data listings provided with the assignment were corroborated with the source documentation.

b. **General observations/commentary:** Only minor discrepancies were observed. There was no under-reporting of adverse events, and the primary efficacy endpoint data was verifiable.

At the close of the inspection, the field investigator issued a Form FDA 483 to Dr. Liu for failure to have three subjects sign updated Informed Consent Documents (ICDs) prior to completing study-related activities. For example, Subject 21110 signed ICD Version 3 on October 19, 2011 and was randomized in the study on October 21, 2011. On February 10, 2012, when Subject 21110 came to the site for Visit 4, Version 6.0 was available and the subject should have been re-consented using that form. The ICD Version 6.0 did not include any additional assessments or safety information that would have applied to Subject 21110.

Dr. Liu submitted a written response to the investigational observations dated May 20, 2015 in which he stated that the subjects had been informed of updated safety information by the investigator during an earlier visit before the Ethics Committee approval of the ICD. He also promised corrective action to ensure

that all subjects would be provided with updated informed consent documents in a timely fashion.

Although the above deficiencies were observed, they are unlikely to importantly impact the efficacy analysis for this NDA or impact the safety or integrity of human subjects involved in clinical trials.

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

3. Pablo Ulveda Varela
Av. Tabancura 1185, Vitacura
Santiago, Chile 7650018

a. **What was inspected:** Dr. Ulveda Varela has four IND studies in the CDER database and no prior inspections. This site was chosen to inspect because of relatively high enrollment (22 subjects) and high treatment effect size in favor of study drug.

The site screened 22 subjects and randomized 22 subjects. Ten subjects discontinued from the study and 12 subjects completed the study. Four subjects died (#20998, 20994, 20993, and 21012).

The inspection reviewed eleven of the 22 subject records, and corroborated the data listings provided by the sponsor with source documentation. Specific items audited included the inclusion and exclusion criteria, efficacy endpoints (primary and secondary), protocol deviations, adverse events, subject disposition, drug accountability, dosing, follow-up visits, and protocol deviations. The field investigator also audited the laboratory results, electrocardiograms, and progress notes.

b. **General observations/commentary:** The efficacy endpoints were verified, and no deficiencies were observed. A number of protocol deviations were included in the data listings and identified by the study monitor or study staff. . These included two subjects who did not sign the current version of the Informed Consent Document, three subjects who did not have a urine pregnancy test done at randomization, sixteen out- of- window visits (ranged between 1 day and five days outside of window), approximately five subjects with out- of- window telephone contacts (these varied between seven and thirteen days although one subject was listed as 48 days outside of window), and two subjects who had late reporting of serious adverse events. The SAE was reported two months late to the IRB. These protocol deviations were submitted to the sponsor and listed in the data listings.

The protocol deviations are unlikely to impact the results from the study. No Form FDA 483 was issued. The inspection has been classified as NAI.

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

4. Actelion Pharmaceuticals Ltd.
Gewerbestrasse 16
Allschwil, Baselland
Switzerland

a. **What was inspected:** The current inspection was conducted between May 18 and May 22, 2015 and focused on the following three foreign clinical investigator sites:

- Site #1601, Pavel Jansa (Prague, Czech Republic, 23 subjects)
- Site #1402, Jinming Liu (Shanghai, China, 32 subjects)
- Site #6202, Pablo Ulveda Varela (Santiago, Chile, 22 subjects)

The following items were covered during the inspection: review of monitoring records for the above three sites, organization and personnel of the firm including responsibilities and authorities for the running and monitoring of the GRIPHON study, selection and transfer of responsibilities to contractors, registration of the GRIPHON study with ClinicalTrials.gov including corroboration of all pertinent information at the website, selection of clinical investigators, monitoring procedures and processes, quality assurance and audits of clinical investigator sites, the Clinical Event Committee (CEC) and adjudication process for review of morbidity and mortality events, adverse event reporting, financial disclosure forms, and test article accountability records.

b. General observations/commentary: No objectionable conditions or deficiencies were observed during the inspection with respect to the overall study development, clinical investigator selection process, and vendor selection process, monitoring activities, drug shipments and drug accountability, quality assurance functions, the CEC adjudication processes, financial disclosure forms.

c. Assessment of data integrity: The study appears to have been conducted adequately and OSI recommends the data acceptable in support of the respective indication.

Note: The final EIR for Actelion Pharmaceuticals was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three foreign and a Sponsor inspection were conducted in support of NDA 207947, for audit of Protocol AC-065A302. No regulatory violations were found during the inspections of Drs. Jansa (Site #1601) and Dr.Ulveda Varela (Site #6202). These inspections were classified as NAI. Minor regulatory violations were found during the inspections of Dr. Liu (Site #1402) in Shanghai, China and a single observational Form FDA 483 was issued for failure to have three subjects sign updated Informed Consent Documents (ICD) prior to completing study-related activities. This issue is unlikely to have a significant impact on the outcome of the study. No objectionable conditions were found during the Actelion sponsor inspection in Switzerland. OSI recommends the data be considered acceptable for this study.

Note: The final EIR for the Actelion sponsor inspection were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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/s/

SHARON K GERSHON
09/03/2015

SUSAN D THOMPSON
09/03/2015

KASSA AYALEW
09/03/2015

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

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

Memorandum

Date: September 2, 2015

To: Wayne Amchin, RAC, MPA
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

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

Subject: NDA 207947
UPTRAVI® (selexipag) tablets, for oral use

As requested in DCRP's consult dated February 3, 2015, OPDP has reviewed the draft package insert (PI), patient package insert (PPI), and carton/container labeling for UPTRAVI® (selexipag) tablets, for oral use. OPDP's comments are based on the substantially complete version of the labeling titled "DCRP to Actelion – 1st iteration-PI track change Selexipag N207947 comapred to 7-1-15 Actelion version.docx" which was emailed by DCRP (Wayne Amchin) on August 27, 2015.

Package Insert (PI)

Our comments on the draft PI are included directly on the attached copy of the labeling.

Patient Package Insert (PPI)

Our review of the PPI will be conducted jointly with DMPP and filed under separate cover.

Carton/Container Labeling

OPDP has also reviewed the following proposed carton/container labels accessed via Sharepoint on September 2, 2015:

- bottle 200 mcg-140 count.pdf
- bottle 200 mcg-60 count.pdf

- bottle-1000 mcg.pdf
- bottle-1200 mcg.pdf
- bottle-1400 mcg.pdf
- bottle-1600 mcg.pdf
- bottle-400 mcg.pdf
- bottle-600 mcg.pdf
- bottle-800 mcg.pdf
- carton-1000 mcg.pdf
- carton-1200 mcg.pdf
- carton-1400 mcg.pdf
- carton-1600 mcg.pdf
- carton-200 mcg-140 count.pdf
- carton-200 mcg-60 count.pdf
- carton-400 mcg.pdf
- carton-600 mcg.pdf
- carton-800 mcg.pdf
- (b) (4)

OPDP does not have any comments on the carton/container labeling at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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

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/s/

PUJA J SHAH
09/02/2015

Medical Officer's Consultative Review of NDA 207947
Ophthalmology Consult

NDA 207-947	Consult Request Date:	5/19/2015
Consult Review	Review completed:	7/27/2015

Product Name: Uptravi
Product Class: Selexipag

Sponsor: Actelion

Requested: NDA 207947 is currently under review for the treatment of pulmonary artery hypertension. The Applicant submitted the attached report indicating that tortuosity and dilatation of retinal vessels were observed in rates in Week 104 of treatment and stated that, based on the life-span nature of the rat CARC study, it was not possible to assess whether tortuosity could be reversible after a recovery period. The report further noted that mice and dogs did not show these findings, but the concurrent appearance in rats of retinal vessel tortuosity and dilatation could indicate a causal link between the two findings. The report states that the occurrence of this finding in man is considered unlikely in light of mechanistic considerations.

In the single pivotal trial, DCRP notes an imbalance between the treatment drug (selexipag) and placebo in the ophthalmologic AE.

Retinal Disorders	Selexipag (N=575)		Placebo (N=577)	
Patients with at least 1 Adverse Event (AE)	63	11%	45	8%
Patients with at least 1 Serious Adverse Event	8		5	
Annualized rate (per 100 patients treated in 1 year)	3	<1%	0	
Patients with at least 1 AE leading to Discontinuation	2	<1%	0	
Patients with at least 1 AE leading to Dose Reduction	4	<1%	1	<1%

We ask DTOP to answer the following questions:
1. Is this imbalance clinically relevant?
2. If so, how?
3. How should the clinically relevant issues be labeled.

We have attached the applicant submitted Ophthalmology study and their proposed labeling. You can also find it in the EDR at \\CDSESUB1\evsprod\NDA207947\207947.enx
Submission date December 22, 2014, under 5.3.5.3, Reports of Analyses of Data from More than One Study.

Summary of subjects with adverse events in the Eye disorders SOC in completed Phase 1 studies with selexipag

		Number of Subjects with at least 1 AE		
AE Preferred Term	**Study(ies)**	**Selexipag**	**PBO**	**Active Control**
Optic neuritis retrobulbar	QGUY Part A (single dose) N=30 sel/10 PBO	1		
Diplopia	QGUY Part A (single dose) N=30 sel/10 PBO	1		
Dry eye	QGUY Part D N=18 sel/19 PBO		1	
Eyelid edema	AC-065-101 N=12 sel/4 PBO AC-065-106 N=91 sel/68 Moxifloxacin/PBO	 3	1	
Lacrimation increased	QGUY Part C N =19 sel/6 PBO		1	
Eye irritation	AC-065-102 N=28 sel /12 PBO/12 ciprofloxacin			1
Vision blurred	QGUY Part C N =19 sel/6 PBO AC-065-101 N=12 sel/4 PBO AC-065-102 N =28 sel /12 PBO/12ciprofloxacin	1	 1	 1
Photophobia	QGUY Part D N=18 sel/19 PBO AC-065-101 N=12 sel/4 PBO AC-065-106 N=91 sel/68 Moxifloxacin/PBO	1 1 1	 1	
Abnormal sensation in the eye	AC-065-102 N=28 sel /12 PBO/12 ciprofloxacin	4		
Blepharospasm	AC-065-106 N=91 sel/68 Moxifloxacin/PBO	1		1
Eye pain	AC-065-106 N=91 sel/68 Moxifloxacin/PBO	9		
Visual impairment	AC-065-106	3		
	N=91 sel/68 PBO			
Asthenopia	AC-065-108 N = 80 sel	1		

PBO = placebo; sel = selexipag

Treatment-emergent adverse events of special interest “eye disorders” sorted by PT incidence in the selexipag group, SAF

AE of special interest Eye disorders related AE	Selexipag N=575 n	%	Placebo N=577 n	%
Patients with at least one AE	63	11.0%	46	8.0%
Number of AEs	84		63	
Comparison of selexipag to placebo Point estimate and two-sided 95% CI for the relative risk	1.374(0.957, 1.974)			
for the hazard ratio (recurrent occurrence)*	1.330(0.869, 2.035)			
Preferred Term				
Eye Pain	9	1.6%	2	0.3%
Cataract	8	1.4%	6	1.0%
Vision Blurred	5	0.9%	5	0.9%
Dry Eye	4	0.7%	8	1.4%
Visual Acuity Reduced	4	0.7%	4	0.7%
Conjunctivitis	4	0.7%	3	0.5%
Lacrimation Increased	4	0.7%	1	0.2%
Photophobia	4	0.7%	1	0.2%
Eye Swelling	3	0.5%	2	0.3%
Glaucoma	3	0.5%	2	0.3%
Eye Irritation	2	0.3%	3	0.5%
Conjunctivitis Allergic	2	0.3%	1	0.2%
Cconjunctival hyperemia	2	0.3%	-	
Dacryostenosis Acquired	2	0.3%	-	
Eye Pruritus	1	0.2%	3	0.5%
Ocular Hyperemia	1	0.2%	3	0.5%
Eyelid Edema	1	0.2%	2	0.3%
Angle closure glaucoma	1	0.2%	1	0.2%
Conjunctival hemorrhage	1	0.2%	1	0.2%
Exophthalmos	1	0.2%	1	0.2%
Eye Discharge	1	0.2%	1	0.2%
Ocular discomfort	1	0.2%	1	0.2%
Abnormal sensation in the eye	1	0.2%	-	
Age-related macular degeneration	1	0.2%	-	
Arteriosclerotic Retinopathy	1	0.2%	-	
Choroiditis	1	0.2%	-	
Corneal erosion	1	0.2%	-	
Diplopia	1	0.2%	-	
Eye disorder	1	0.2%	-	
Eye hemorrhage	1	0.2%	-	
Eyelid bleeding	1	0.2%	-	
Eyelid Ptosis	1	0.2%	-	
Keratitis	1	0.2%	-	
Macular Degeneration	1	0.2%	-	
Macular edema	1	0.2%	-	
Maculopathy	1	0.2%	-	
Myopia	1	0.2%	-	
Periorbital edema	1	0.2%	-	
Retinal artery spasm	1	0.2%	-	
Retinal degeneration	1	0.2%	-	
Visual acuity reduced transiently	1	0.2%	-	
Visual impairment	1	0.2%	-	
Amaurosis fugax	-		2	0.3%
Astigmatism	-		1	0.2%
Blepharospasm	-		1	0.2%
Diabetic eye disease	-		1	0.2%
Iris Adhesions	-		1	0.2%
Optic Neuropathy	-		1	0.2%
Photopsia	-		1	0.2%
Presyopia	-		1	0.2%
Retinal vascular disorder	-		1	0.2%
Retinopathy	-		1	0.2%
Vitreous hemorrhage	-		1	0.2%

"Number of AEs" sums up the number of unique AE Preferred Terms by patient for each treatment group.
*Andersen-Gill model for recurrent events.
Source: Table 12-14 [D-13.361]

Phase 3 AC-065A302 GRIPHON Study

Study AC-065A302 was a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with symptomatic PAH.

The primary objective was to demonstrate the effect of selexipag on time to first morbidity and/or mortality event in PAH patients. The secondary objectives were to evaluate the effects of selexipag on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH. The safety and tolerability of selexipag in PAH patients were also evaluated.

The study treatment (selexipag or placebo) was initiated at a dose of 200 µg b.i.d orally in tablets in a blinded fashion and was up-titrated in increments of 200 µg b.i.d at weekly intervals up to a maximum dose of 1600 µg b.i.d., depending on the patient's tolerability.

The study was conducted at 181 sites in 39 countries (Asia, Australia, Europe, Latin America, and North America). The OL treatment extension study AC-065A303 is currently ongoing.

Ocular assessments

An ophthalmology sub-study was introduced during the course of the study following Protocol Amendment 3 and included fundoscopy with digital pictures at the baseline/randomization visit (or within the screening period [28 days before Visit 1]), Month 12 and EOS visit (or within 2 weeks before or after the scheduled EOS visit) or discontinuation of study drug treatment for patients enrolled at selected sites. Overall, 33 sites in 22 countries participated in the ophthalmology sub-study.

Reviewer's Comment: *The ophthalmology sub-study included only taking and reviewing digital fundus pictures. There were no measures of visual function and no ascertainment of other potential ocular abnormalities. It is recommended that any ocular evaluation include a measurement of visual function.*

Procedures for the fundus assessment

Pictures were taken by the ophthalmologist / qualified ophthalmologist technician according to common guidelines and were transferred to an external central reading center.

At baseline/randomization and at follow-up assessments, the central reader was to report the abnormal findings that were observed on the fundus images. In addition, retinal arterial tortuosity was to be quantitatively assessed in order to measure the change from baseline in this parameter at each post-baseline time point. In case of treatment-emergent abnormal findings, the central reader could advise on additional ophthalmological check-up. The central reader had no access to clinical information or study treatment assignment at the time of evaluating the images. In addition, the Ophthalmology Safety

Board reviewed the ophthalmology data and was consulted for their opinion and recommendations in case of specific findings.

A total of 1351 patients at 181 sites in 39 countries were screened in study AC-065A302; a total of 1156 were randomized in a 1:1 ratio to selexipag (N = 574) or placebo (N = 582). Of the 1156 randomized patients, 1152 patients (selexipag: 574 [100%], placebo: 578 [99.3%]) received study treatment during the AC-065A302 treatment period. The OAS included all patients who participated in the ophthalmology sub-study (selexipag: 54, placebo: 48 patients).

Overview of analysis sets

	Selexipag N=574 n	%	Placebo N=582 n	%
Full analysis set				
Patients included	574	100%	582	100%
Safety analysis set (SAF)				
Patients included	574*	100%	578	99.3%
Ophthalmologic analysis set (OAS)				
Patients included	54	9.4%	48	8.2%
Baseline funduscopy	47		44	
Baseline with at least one finding	32		24	
Post-baseline funduscopy (12 Month or End of Study)	41		36	
Post-baseline with at least one finding	24		27	
Baseline and Month 12 funduscopy	22		16	
Baseline and End of Study funduscopy	33		31	

*Patient 1601-21235 randomized to placebo received a single dose of 8 tablets of selexipag due to an error in the dispensation of the medication bottle. This patient was assigned to the selexipag group in the Safety Analysis Set, i.e., Selexipag, N = 575 and Placebo, N = 577.

Source: Table 10-3 (modified from Table 15-11) [D-13.361]

Reviewer's Comment: *The subset of patients evaluated in the OAS sub-study is too small to provide an adequate assessment: only a small number of patients had both a baseline exam and a follow-up exam, more than half of those studied had a post-baseline findings, no information on visual function was available and the majority of patients had abnormalities at baseline making it difficult to distinguish the cause of any finding.*

Baseline and post-baseline ophthalmology findings in study AC-065A302, OAS

	Selexipag N=54 n	%	Placebo N=48 n	%
Ophthalmology findings at baseline				
Number of patients with baseline assessment	47		44	
Patients with at least one Ophthalmology finding	32	68%	24	55%
Number of Ophthalmology findings	49		46	
MACULAR DEGENERATION	22	47%	18	41%
RETINAL DEPIGMENTATION	6	13%	7	16%
RETINAL PIGMENTATION	6	13%	6	14%
RETINAL VASCULAR DISORDER	4	9%	4	9%
RETINAL DEGENERATION	2	4%	1	2%
RETINAL HAEMORRHAGE	2	4%	1	2%
RETINAL ANEURYSM	2	4%	-	
CHORIORETINAL ATROPHY	1	2%	2	5%
EYE NAEVUS	1	2%	2	5%
FUNDOSCOPY ABNORMAL	1	2%	-	
MACULOPATHY	1	2%	-	
VITREOMACULAR INTERFACE ABNORMAL	1	2%	-	
MACULAR FIBROSIS	-		3	7%
RETINAL EXUDATES	-		1	2%
RETINOPATHY	-		1	2%
Ophthalmology findings post-baseline				
Number of patients with post-baseline assessment	41		36	
Patients with at least one Ophthalmology finding	24	59%	27	75%
Number of Ophthalmology findings	36		46	
MACULAR DEGENERATION	15	37%	21	58%
RETINAL PIGMENTATION	6	15%	4	11%
RETINAL DEPIGMENTATION	5	12%	5	14%
RETINAL VASCULAR DISORDER	3	7%	3	8%
CHORIORETINAL ATROPHY	1	2%	2	6%
EYE NAEVUS	1	2%	1	3%
FUNDOSCOPY ABNORMAL	1	2%	1	3%
RETINAL DEGENERATION	1	2%	1	3%
MACULOPATHY	1	2%	-	
PRE-EXISTING CONDITION IMPROVED	1	2%	-	
VITREOMACULAR INTERFACE ABNORMAL	1	2%	-	
MACULAR FIBROSIS	-		3	8%
OPTIC DISC DISORDER	-		1	3%
OPTIC NERVE CUPPING	-		1	3%
RETINAL ANEURYSM	-		1	3%
RETINAL HAEMORRHAGE	-		1	3%
RETINOPATHY	-		1	3%

Source: Table 15-238 [D-13.361]

Questions:

1. Is this imbalance clinically relevant?

Reviewer's Comment: *It cannot be determined whether the imbalance is clinically relevant. The imbalance is driven primarily by eye pain, photophobia and retinal disorders (age-related macular degeneration, arteriosclerotic retinopathy, choroiditis, macular degeneration, macular edema, maculopathy, retinal artery spasm, retinal degeneration) which are of potential concern, but without a full clinical description, it is not possible to ascertain. There are also some events listed in the placebo group which are highly unlikely to be newly acquired events, such as astigmatism, diabetic eye disease and presbyopia. The inclusion of baseline events in the placebo group serves to decrease the reported imbalance.*

2. If so, how?

Reviewer's Comment: *See response to Question 1.*

3. How should the clinically relevant issues be labeled?

Reviewer's Comment: *Eye pain should be included in the labeling. There are insufficient details and/or evaluations to reliably include other ocular events in the labeling at this time.*

Summary:

Based on the submitted clinical studies, the potential for selexipag to cause ocular abnormalities has not been adequately evaluated. The subset of patients evaluated in the ocular sub-studies was too small to provide an adequate assessment considering only a small number of patients had both a baseline exam and a follow-up exam, more than half of those studied had a post-baseline findings, no information on visual function was available and the majority of patients had abnormalities at baseline making it difficult to distinguish the cause of any finding.

It cannot be determined whether the imbalance in reported ocular adverse events is clinically relevant. The imbalance is driven primarily by eye pain, photophobia and retinal disorders which are of potential concern, but without a full description of the clinical circumstances, it is not possible to ascertain.

Recommendations:

It is recommended that potential for eye pain be included in the labeling of the drug product if it is approved. The specific mechanism by which eye pain is caused is not known. If further information on the potential effects of selexipag on the eye is needed, it is recommended that a more comprehensive ocular examination be included in future studies of the drug product. It does not appear that there are sufficient ocular concerns to preclude approval of this product. If long term (>2 years treatment) is expected, postmarketing studies including an evaluation of visual function, and examinations using fluorescein angiography and ocular coherence tomography should be considered.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
07/27/2015

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:	April 3, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 207947
Product Name and Strength:	Uptravi (selexipag) Tablets, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg
Submission Date:	March 27, 2015
Applicant/Sponsor Name:	Actelion Pharmaceuticals
OSE RCM #:	2015-257-1
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Cardiovascular and Renal Products requested that we review the revised carton labeling for Uptravi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised carton labeling is acceptable from a medication error perspective.

[1] Gao T. Label and Labeling Review for Uptravi (NDA 207947). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAR 13. 16 p. OSE RCM No.: 2015-257.

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/s/

TINGTING N GAO
04/03/2015

CHI-MING TU
04/03/2015

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

NDA	207947
Brand Name	UPTRAVI®
Generic Name	Selexipag (ACT-293987)
Sponsor	Actelion Pharmaceuticals Ltd.
Indication	Pulmonary arterial hypertension (PAH)
Dosage Form	Tablets
Drug Class	Prostacyclin Receptor Agonist
Therapeutic Dosing Regimen	800 µg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1,600 µg b.i.d.
Submission Number and Date	001 / 12/22/2014
Review Division	DCRP

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

1 SUMMARY

No significant QTc prolongation effect of selexipag (800 µg and 1600 µg twice daily (b.i.d.)) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between selexipag (800 µg b.i.d. and 1600 µg b.i.d.) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 9, indicating that assay sensitivity was established.

In this randomized, double-blinded, placebo- and positive-controlled, parallel-group with nested cross-over study, 159 subjects received selexipag 800 µg b.i.d., selexipag 1600 µg b.i.d., placebo and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Selexipag (800 µg BID and 1600 µg BID) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Selexipag 800 µg BID	0.5	1.3	(-1.2, 3.9)
Selexipag 1600 µg BID	2	-0.7	(-3.6, 2.1)
Moxifloxacin 400 mg*	3	9.7	(7.8, 11.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.1 ms.

The recommended starting dose of selexipag is 200 µg given twice daily. To achieve optimal clinical response, the dose is increased in increments of 200 µg twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced.

The highest dose in this TQT study (1600 µg) is maximum dose evaluated for efficacy and is also the maximum tolerated dose in healthy subjects. The tested dose of 1600 µg b.i.d. is unlikely to cover high exposure clinical scenario. If patients with mild or moderate hepatic impairment receive the maximum proposed dose (1600 µg), they are expected to have selexipag exposures that are 2- and 4-fold the exposures in this study. Similarly, patients receiving a strong CYP3A4 inhibitor and the maximum proposed dose are expected to have twice the selexipag concentrations than were observed in this study. Therefore, the possibility of QT prolongation in these scenarios cannot be ruled out based on the results of this study. Over the concentration range observed in this study, however, there was not a relationship between selexipag concentrations and QTcI.

2 PROPOSED LABEL

12.2 Pharmacodynamics

Cardiac electrophysiology:
At the maximum tolerated dose of 1600 mcg twice daily, selexipag does not prolong the QT interval to any clinically relevant extent.

Reviewer's Comment: The Sponsor's proposed labeling language is acceptable.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Selexipag is a selective IP prostacyclin receptor agonist being developed for the treatment of pulmonary arterial hypertension.

3.2 MARKET APPROVAL STATUS

Selexipag is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The effects of selexipag and ACT-333679 on hERG K^+ current were measured using the whole-cell patch-clamp technique in recombinant CHO-K1 cells that express the hERG K^+ channel [(b)(4)08.268, (b)(4)08.270]. Peak tail currents were measured before and 10 min after superfusion of cells with 0, 3, 1 0, and 30 µM of test compound. Selexipag had no effect on hERG current at concentrations ≤ 10 µM (83,000-fold unbound human C_{max} at a dose of 1600 µg b.i.d.) and significantly inhibited hERG current to 85.2 ± 1.8% at 30 µM. ACT-333679 had no effect on hERG current up to 30 µM (105,000-fold unbound human C_{max}). The positive control E-4031 (1 µM) evoked almost complete inhibition of peak tail current (1.4 ± 0.5%).

QT prolongation was not observed in dogs.

3.4 PREVIOUS CLINICAL EXPERIENCE

No cases of torsades have been reported in the clinical program.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 104,504. The sponsor submitted the study report AC-065-106 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group with nested cross-over, multiple-dose, up-titration study of the effects of selexipag and its metabolite ACT-333679 on cardiac repolarization in healthy male and female subjects.

4.2.2 Protocol Number

AC-065-106

4.2.3 Study Dates

First subject, first visit: 27 June 2012
Last subject, last visit: 24 November 2012

4.2.4 Objectives

The primary objective: To demonstrate that selexipag and its metabolite ACT-333679 do not have an effect on cardiac repolarization exceeding the threshold of regulatory concern, as measured by the corrected QT (QTc) interval at steady-state at 2 oral dose levels (800 and 1600 µg twice daily (b.i.d.)) in healthy male and female subjects.

Secondary objectives were:

- To evaluate the safety and tolerability of selexipag and its metabolite ACT-333679 at oral doses of up to 1600 μg b.i.d. in healthy male and female subjects.
- To evaluate the pharmacokinetics (PK) of selexipag and its metabolite ACT-333679 at steady-state after multiple-ascending oral doses of selexipag up to 1600 μg b.i.d. to healthy male and female subjects.
- To assess the time course of any QTc interval effect in relation to plasma levels of selexipag and ACT-333679 using concentration-effect modeling.

4.2.5 Study Description

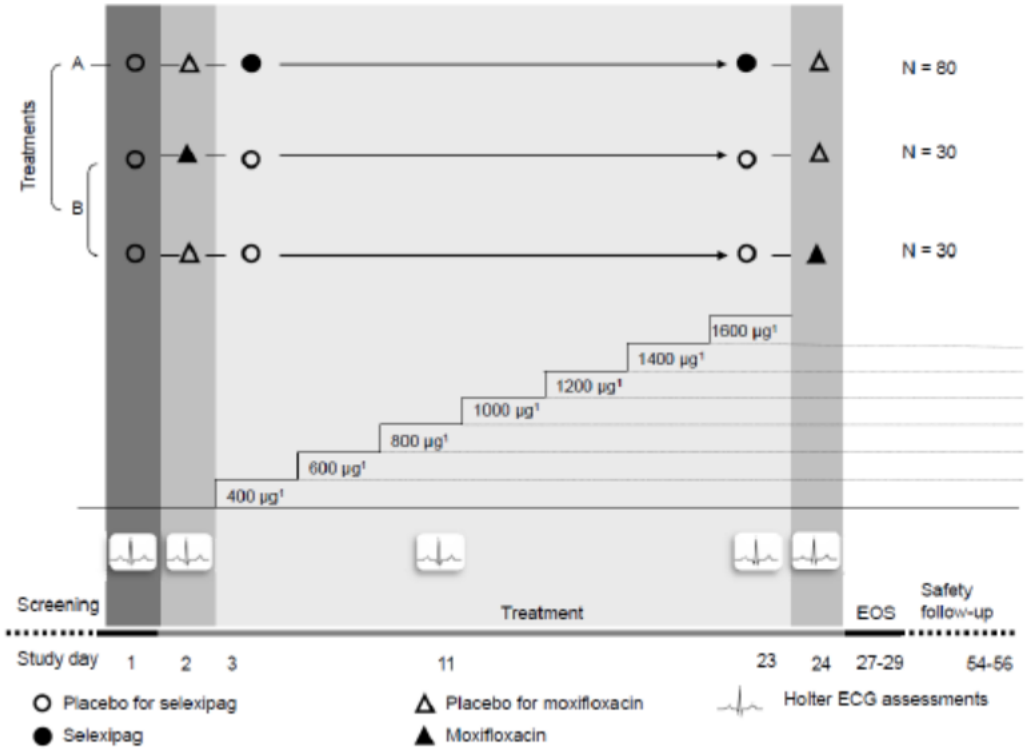
4.2.5.1 Design

This was a single-center, double-blind, randomized, placebo- and positive-controlled, parallel-group, multiple-dose, up-titration study with a nested cross-over comparison between moxifloxacin and placebo in healthy male and female subjects.

All subjects in both treatment groups received a selexipag-matching placebo tablet on Day 1.

Subjects in Treatment A (selexipag) were to receive selexipag as multiples of 200 μg tablets, after a meal in the morning and after a meal in the evening starting at 400 μg on Day 3, up-titrating in increments of 200 μg b.i.d. with 3 days at every dose level up to a dose of 1600 μg (on Day 23 only morning dose was administered). Moxifloxacin-matching placebo capsules were administered once on Days 2 and 24.

Subjects in Treatment B (placebo/moxifloxacin) were assigned to one of 2 sequences, B1 or B2. Subjects in sequence B1 received 400 mg moxifloxacin on Day 2 and moxifloxacin-matching placebo on Day 24. Subjects in sequence B2 received moxifloxacin-matching placebo on Day 2 and 400 mg moxifloxacin on Day 24. In both sequences B1 and B2, all subjects received placebo for selexipag on Days 3 to 23. An up-titration of placebo for selexipag was performed.



[1]Given twice a day with the exception of Day 23 (only morning administration).
ECG = electrocardiogram; EOS = end-of-study; N = planned number of subjects to be enrolled.

4.2.5.2 Controls

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

4.2.5.3 Blinding

This study was conducted in a double-blind fashion. The investigator and study staff (except the responsible pharmacist and his/her designee), subjects, monitors (except the monitor performing the drug accountability visits), sponsor, and CRO staff remained blinded to the treatment until closure of the database. The investigational drug and its matching placebo and the active comparative drug (moxifloxacin) and its matching placebo were indistinguishable.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomly assigned to Treatment A (selexipag) or Treatment B (placebo/moxifloxacin) in a 4:3 ratio. Subjects in Treatment B were further assigned to 1 of 2 treatment sequences in a 1:1 ratio: 400 mg moxifloxacin followed by moxifloxacin-matching placebo and moxifloxacin-matching placebo followed by moxifloxacin.

4.2.6.2 Sponsor's Justification for Doses

In this study selexipag was tested at the maximum tolerated dose level in healthy subjects (i.e., 1600 µg b.i.d.) as determined in study AC-065-101. The highest dose given in the

AC-065-101 trial was 1800 µg b.i.d. and was associated with an increase in adverse events (AEs; headache, myalgia, and nausea) that required administration of concomitant medication. At the same time, 1600 _g b.i.d. is the highest dose allowed in the current Phase 3 study (AC-065A302 / GRIPHON), based on up-titration to the individual's highest tolerated dose. The determination of a potential pharmacological effect of selexipag and its active metabolite, ACT-333679, on cardiac repolarization at the lower dose (800 µg b.i.d.) was included in order to allow characterization of any concentrationresponse relationship for QT/QTc prolongation.

Reviewer's Comment: The dose (1600 µg) is reasonable as it is the maximum tolerated dose. We note, however, that this dose does not cover the maximum expected exposures according to the dosing proposed by the Sponsor. If patients with mild or moderate hepatic impairment receive the maximum proposed dose (1600 µg), they are expected to have selexipag exposures that are 2- and 4-fold the exposures in this study. Similarly, patients receiving a strong CYP3A4 inhibitor and the maximum proposed dose are expected to have twice the selexipag concentrations than were observed in this study.

4.2.6.3 Instructions with Regard to Meals

Doses will be administered within one hour after meals.

Reviewer's Comment: Acceptable. There is a minimal food effect on the pharmacokinetics of selexipag. Also, the drug seems to be more tolerable in the fed state.

4.2.6.4 ECG and PK Assessments

Triplicate ECGs were extracted from continuous Holter recordings on Days 1, 2, 11, 23 and 24 prior to morning drug administration and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post-dose. PK blood samples were obtained at the same timepoints on Days 11 and 23 for assessment of selexipag concentrations and on Days 1, 2 and 24 for assessment of moxifloxacin concentrations.

Reviewer's Comment: The timing of ECGs is adequate to capture potential effects at the T_{max} of selexipag (~2 hours) and its metabolite (~4 hours).The sampling schedule should also be adequate to capture delayed effects as the drug is administered twice daily to steady-state prior to ECG sampling days.

4.2.6.5 Baseline

The sponsor used time-matched QTc values on Day 1 as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring used to obtain digital ECGs.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 159 subjects were randomized and entered the study; of these, 91 subjects were randomized to Treatment A (selexipag) and 68 subjects were randomized to

Treatment B (moxifloxacin/placebo). In Treatment B, 34 subjects were assigned to sequence B1 (moxifloxacin/moxifloxacin-matched placebo), and 34 subjects were assigned to sequence B2 (moxifloxacin-matched placebo/moxifloxacin).

In Treatment A, 31 of the 91 randomized subjects (34%) were female and in Treatment B, 25 of the 68 randomized subjects (37%) were female.

In total, 122 subjects (77%) completed the study in accordance with the protocol and the treatment randomization, with 56 subjects (62%) completing in Treatment A and 66 subjects (97%) completing in Treatment B. Of the female subjects, 16 (52%) completed Treatment A and 23 (92%) completed Treatment B.

Overall, 37 subjects (23%) were prematurely discontinued from the study; 35 subjects (38%, 15 females and 20 males) in Treatment A and 2 subjects (3%, both females) in Treatment B.

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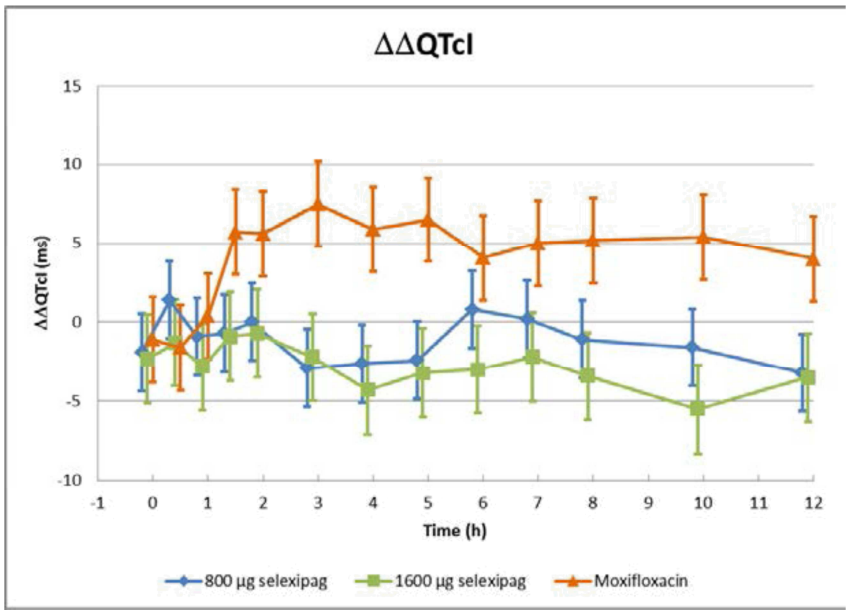
		Number of subjects (%)				
			Treatment B			
		Treatment A (selexipag)	Moxifloxacin-Placebo	Placebo-Moxifloxacin	Placebo/Moxifloxacin Overall	Overall
Entered study		91	34	34	68	159
Completed study	Yes	56 (62%)	33 (97%)	33 (97%)	66 (97%)	122 (77%)
	No	35 (38%)	1 (3%)	1 (3%)	2 (3%)	37 (23%)

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between selexipag (800 µg b.i.d. and 1600 µg b.i.d.) and placebo in QTcI. The sponsor used mixed model and the results are presented in Figure 8 and Table 2. The upper limits of the 2-sided 90% CI for selexipag (800 µg b.i.d. and 1600 µg b.i.d.) were below 10 ms.

Figure 1: Placebo-corrected change from time-matched baseline QTcI QTcl, ms) across treatment groups and timepoints



Results from the statistical modeling, assuming equal variance across treatment and timepoint Mean ± 90% CI presented. QT/QTc analysis set. QTcI = QT interval corrected using the individualized formula. 800 µg selexipag: Day 11; 1600 µg selexipag: Day 23; Moxifloxacin: Day 2 or Day 24.
Source: : Clinical Study Report GS-US-313-0117, Figure 9, Pg 78/9886

Table 2: Sponsor's Result of ΔQTcI across treatment goups and time points

			90% CI				90% CI	
	Mean	SE	Lower	Upper	Mean	SE	Lower	Upper
Time (h)		800 µg selexipag				800 µg selexipag placebo		
0	3.8	1.0	5.4	2.1	1.9	1.1	3.7	0.1
0.5	0.9	1.0	2.6	0.7	2.4	1.1	4.2	0.5
1	0.4	1.0	2.0	1.2	0.5	1.1	1.3	2.4
1.5	0.3	1.0	1.9	1.3	0.3	1.1	1.5	2.2
2	0.4	1.0	2.0	1.2	0.4	1.1	2.2	1.4
3	2.1	1.0	3.7	0.5	0.8	1.1	1.0	2.6
4	1.9	1.0	3.5	0.3	0.7	1.1	1.1	2.5
5	2.9	1.0	4.6	1.3	0.5	1.1	2.4	1.3
6	1.8	1.0	3.4	0.2	2.6	1.1	4.4	0.8
7	2.5	1.0	4.1	0.9	2.7	1.1	4.5	0.9
8	1.9	1.0	3.5	0.3	0.8	1.1	2.6	1.1
10	4.1	1.0	5.8	2.5	2.6	1.1	4.4	0.7
12	6.8	1.0	8.4	5.2	3.6	1.1	5.4	1.8
Time (h)		1600 µg selexipag				1600 µg selexipag placebo		
0	4.5	1.2	6.6	2.5	2.2	1.2	4.1	0.3
0.5	2.9	1.2	4.9	0.9	1.6	1.2	3.5	0.3
1	2.7	1.2	4.7	0.6	0.2	1.2	1.7	2.1
1.5	0.8	1.2	2.9	1.2	0.1	1.2	1.8	2.0
2	0.3	1.2	2.4	1.7	0.4	1.2	1.5	2.3
3	3.6	1.2	5.7	1.6	1.5	1.2	3.4	0.4
4	5.5	1.2	7.6	3.5	1.3	1.2	3.2	0.7
5	6.9	1.2	9.0	4.9	3.7	1.2	5.6	1.8
6	4.7	1.2	6.7	2.7	1.7	1.2	3.6	0.2
7	5.4	1.2	7.5	3.4	3.2	1.2	5.1	1.3
8	4.9	1.2	6.9	2.9	1.5	1.2	3.4	0.4
10	7.4	1.2	9.4	5.4	1.9	1.2	3.8	0.0
12	7.7	1.2	9.7	5.6	4.2	1.2	6.1	2.3
Time (h)		Moxifloxacin				Moxifloxacin placebo		
0	0.5	1.2	1.5	2.4	1.6	1.2	0.4	3.5
0.5	0.4	1.2	1.5	2.4	2.0	1.2	0.1	3.9
1	2.6	1.2	0.7	4.6	2.2	1.2	0.2	4.1
1.5	7.0	1.2	5.1	9.0	1.3	1.2	0.6	3.3
2	8.5	1.2	6.5	10.4	2.8	1.2	0.9	4.8
3	8.0	1.2	6.1	10.0	0.5	1.2	1.4	2.5
4	8.1	1.2	6.2	10.1	2.2	1.2	0.3	4.2
5	8.2	1.2	6.2	10.1	1.6	1.2	0.3	3.6
6	5.2	1.2	3.2	7.2	1.1	1.2	0.8	3.1
7	6.9	1.2	4.9	8.8	1.8	1.2	0.1	3.8
8	7.0	1.2	5.0	8.9	1.8	1.2	0.2	3.7
10	6.4	1.2	4.5	8.4	1.0	1.2	0.9	2.9
12	5.3	1.2	3.3	7.2	1.2	1.2	0.7	3.2

CI = confidence interval; QTcI = QT interval corrected using the individualized formula; SE = standard error.
For definition of the respective baselines see Section 9.8.2.

Source: *Clinical Study Report* GS-US-313-0117, *Table 9, Pg 70/9886*

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcI effect for moxifloxacin. The analysis results were presented in Figure 8. The largest unadjusted lower bound 1- sided 95% was greater than 5 ms. Thus, assay sensitivity in this thorough QTcI study was established.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.3 Categorical Analysis

There was no subject with QTcI exceeding 480 ms or change from baseline QTcI > 30 ms was in selexipag 800-ug and 1600-ug twice daily groups.

Sponsor Analyses of Categorical Analysis in QTcI

Treatment	Subject				Event			
	N	> 450 ms n (%)	> 480 ms n (%)	> 500 ms n (%)	N	> 450 ms n (%)	> 480 ms n (%)	> 500 ms n (%)
800 µg selexipag	84	1 (1%)	0	0	1090	1 (< 1%)	0	0
1600 µg selexipag	58	0	0	0	752	0	0	0
Moxifloxacin	66	3 (5%)	0	0	855	4 (< 1%)	0	0
800 µg selexipag placebo	67	0	0	0	870	0	0	0
1600 µg selexipag placebo	66	0	0	0	856	0	0	0
Moxifloxacin placebo	66	2 (3%)	0	0	856	2 (< 1%)	0	0

N = number of subjects/timepoints included in the set; n (%) = number of subjects/timepoints (percentage of respective N); QTcI = QT interval corrected using the individualized formula.
Source: Table 15.3.8B of the Cardiac Safety Report [Section 15.3]).

Sponsor Analyses of Categorical Analysis in QTcI

Treatment	Subject			Event		
	N	> 30 ms n (%)	> 60 ms n (%)	N	> 30 ms n (%)	> 60 ms n (%)
800 µg selexipag	84	0	0	1090	0	0
1600 µg selexipag	58	0	0	752	0	0
Moxifloxacin	66	4 (6%)	0	855	5 (1%)	0
800 µg selexipag placebo	67	0	0	870	0	0
1600 µg selexipag placebo	66	0	0	856	0	0
Moxifloxacin placebo	66	0	0	856	0	0

N = number of subjects/timepoints included in the set; n (%) = number of subjects/timepoints (percentage of respective N); QTcI = QT interval corrected using the individualized formula.
Source: Table 15.3.9B of the Cardiac Safety Report [Section 15.3]).

4.2.8.2.4 Additional Analyses

Selexipag was associated with a mild increase of the HR with the largest placebo-corrected change-from-baseline HR reaching 6 bpm to 7 bpm at 1.5 to 3 hours after dosing with 800 µg selexipag and 9 bpm to 10 bpm at the same timepoints after 1600 µg selexipag.

Figure 2: Sponsor's Change from time-matched baseline heart rate (LHR, bpm) on 800 µg selexipag and 800 µg selexipag placebo across timepoints

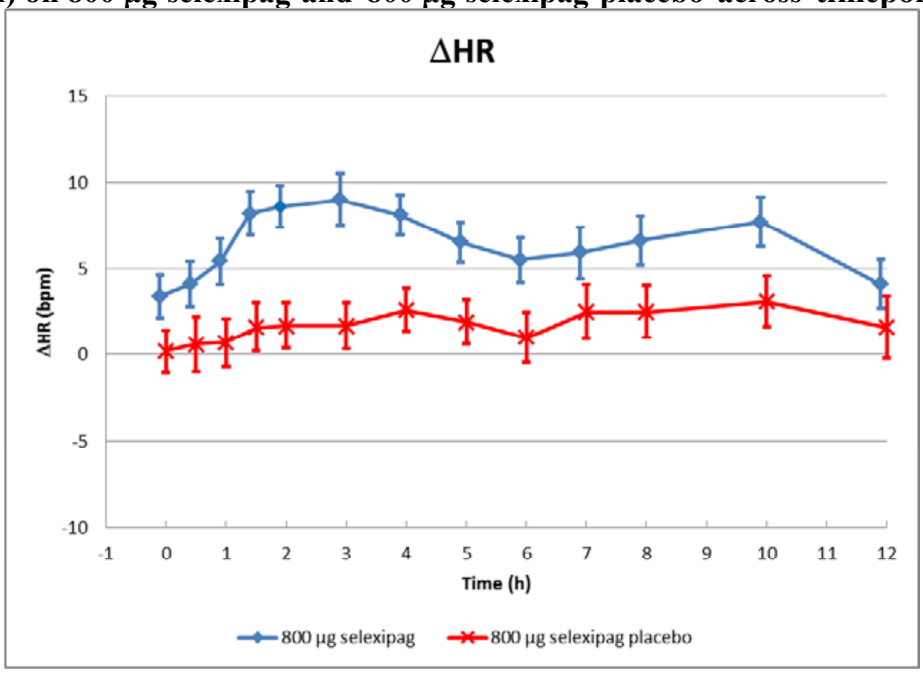
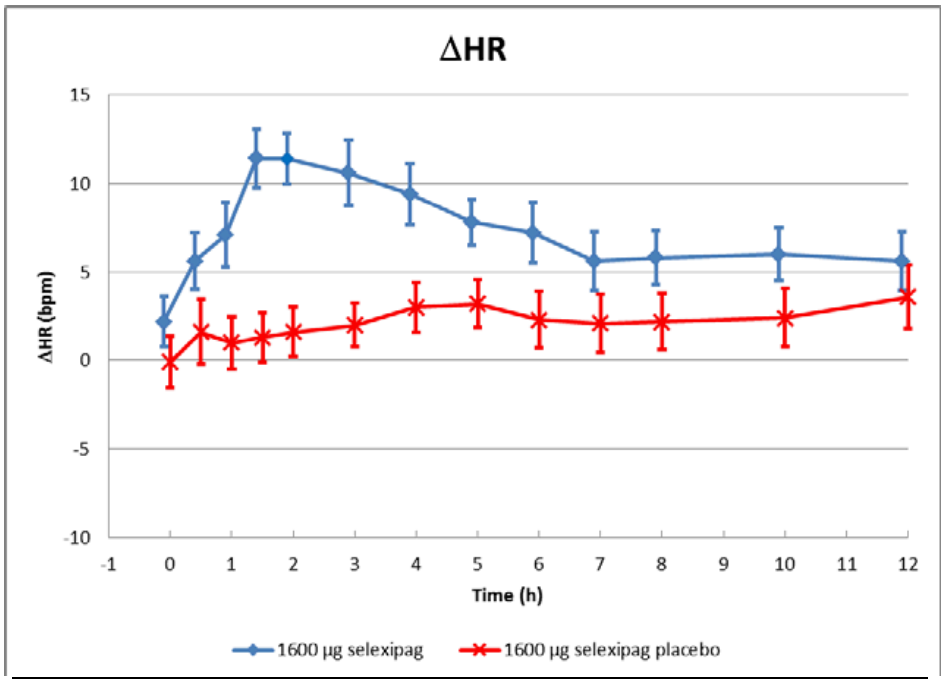


Figure 3:Change from time-matched baseline heart rate (LHR, bpm) on 1600 µg selexipag and 1600 µg selexipag placebo across timepoints



4.2.8.3 Safety Analysis

There were 823 AEs reported by 84 (92%) subjects in the selexipag treatment group versus 228 AEs reported by 48 subjects (71%) in the placebo/moxifloxacin group (Day 1–EOS).

In the selexipag treatment group (Day1–EOS), slightly more females reported at least one AE (100% females, 88% males). In the placebo/moxifloxacin treatment group (Day 1–EOS), as in the selexipag treatment group, the percentage of females reporting at least one AE was higher (88% females, 60% males).

The most frequently reported AEs following multiple dosing with selexipag (Days 3–23), which occurred at a higher incidence than following placebo/moxifloxacin, were headache, dizziness, myalgia, Temporomandibular Joint Syndrome, nausea, diarrhea, and vomiting.

In total, 26 subjects were discontinued due to AEs following multiple doses of selexipag (Days 3–23) and 2 following multiple doses of placebo/moxifloxacin (Days 3–23).

The most frequent type of AE leading to premature discontinuation from the study in the selexipag group was headache (16 subjects), followed by myalgia (8 subjects), nausea (8 subjects), and Temporomandibular Joint Syndrome (6 subjects).

There was one SAE reported by a female subject following multiple doses of selexipag (symptomatic hypotension following administration of 1200 μg selexipag). This event was severe in intensity, considered to be related to study treatment by the investigator, and resolved without sequelae on the same day. Three other female subjects discontinued from the study due to events of hypotension following multiple doses of selexipag (at 800 to 1000 μg). These events were moderate in intensity and considered to be related to study treatment by the investigator.

(24 subjects [26.4%] in the selexipag treatment group and 24 subjects [35.3%] in the placebo/moxifloxacin group). None of the treatment-emergent ECG abnormalities were considered to be clinically relevant.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3, Figure 1 and Figure 2 for selexipag, in Table 4, Figure 3 and Figure 4 for ACT-333679 and Table 5 and Figure 5 for moxifloxacin. C_{max} and AUC values in the thorough QT study are expected to be similar to the values at the maximum intended clinical dose of 1600 μg. The Sponor notes that the C_{max} for moxifloxacin (1.98 μg/mL) was lower than expected and might contribute to the smaller effect of moxifloxacin observed in this study.

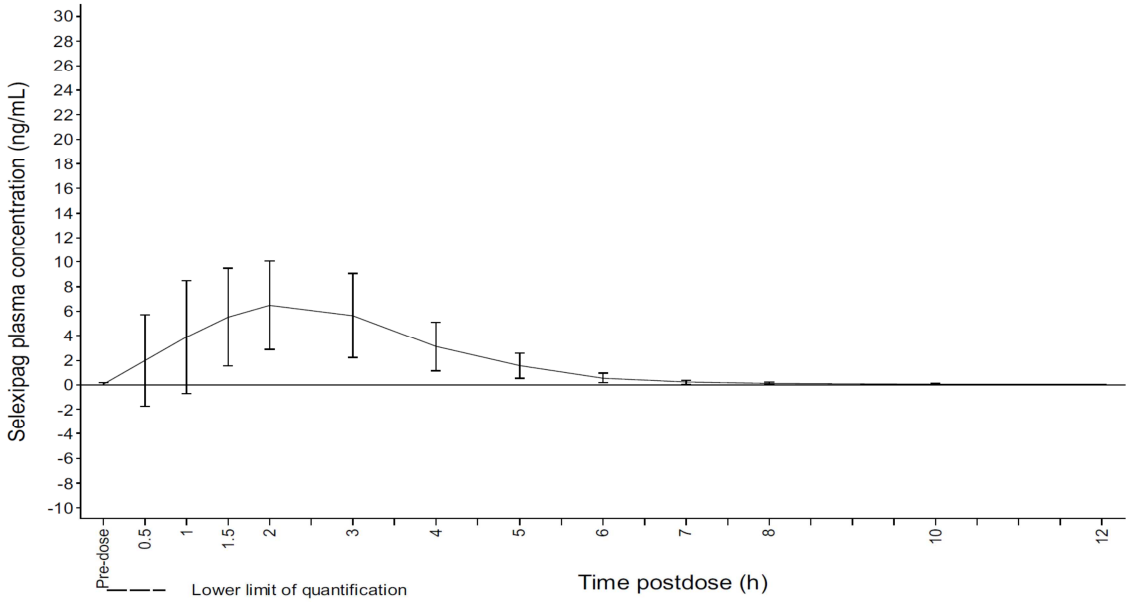
Table 3: Summary of Pharmacokinetic Statistics of Selexipag

Day	N	t_{max} (h)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)
11	84	2.00 (0.500–4.00)	8.20 (7.45, 9.03)	20.1 (18.3, 22.1)
23	58	2.00 (0.500–4.00)	18.0 (16.0, 20.2)	44.0 (39.7, 48.8)

AUC_{τ} = area under plasma concentration-time curve during one dosing interval; C_{max} = maximum measured plasma concentration; t_{max} = time to reach maximum plasma concentration.
Data are geometric means (and 95% CI) or for t_{max} the median (and range).

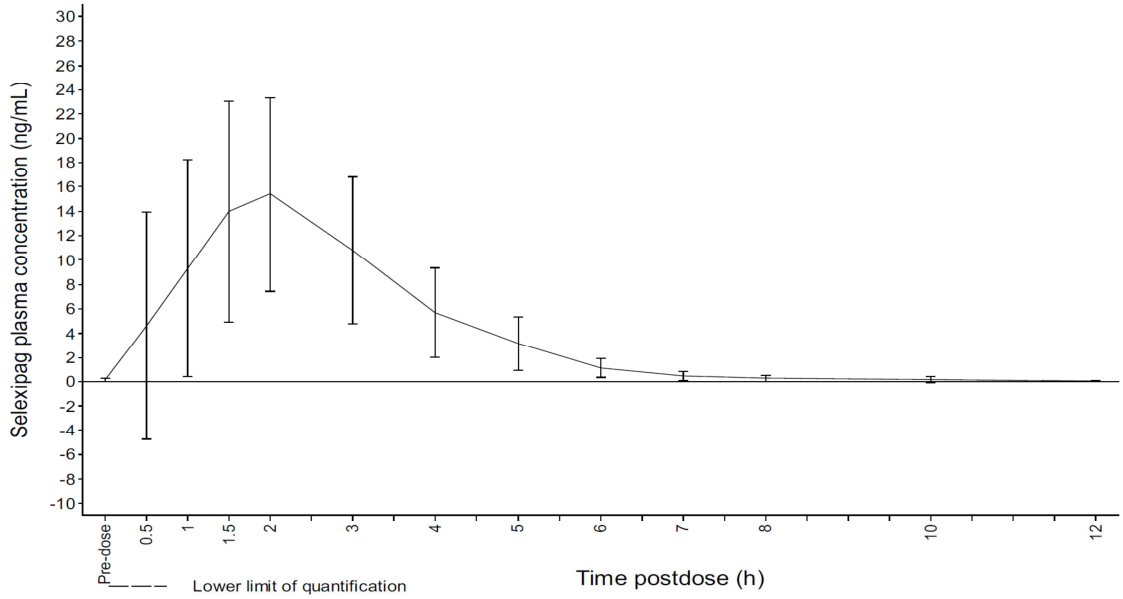
Source: Study Report, Table 22, Page 97.

Figure 1: Mean Concentration-Time Profile (±SD) of 800 µg selexipag (Day 11)



Source: Study Report, Figure 22, Page 98.

Figure 2: Mean Concentration-Time Profile (±SD) of 1600 µg selexipag (Day 23)



Source: Study Report, Figure 23, Page 98.

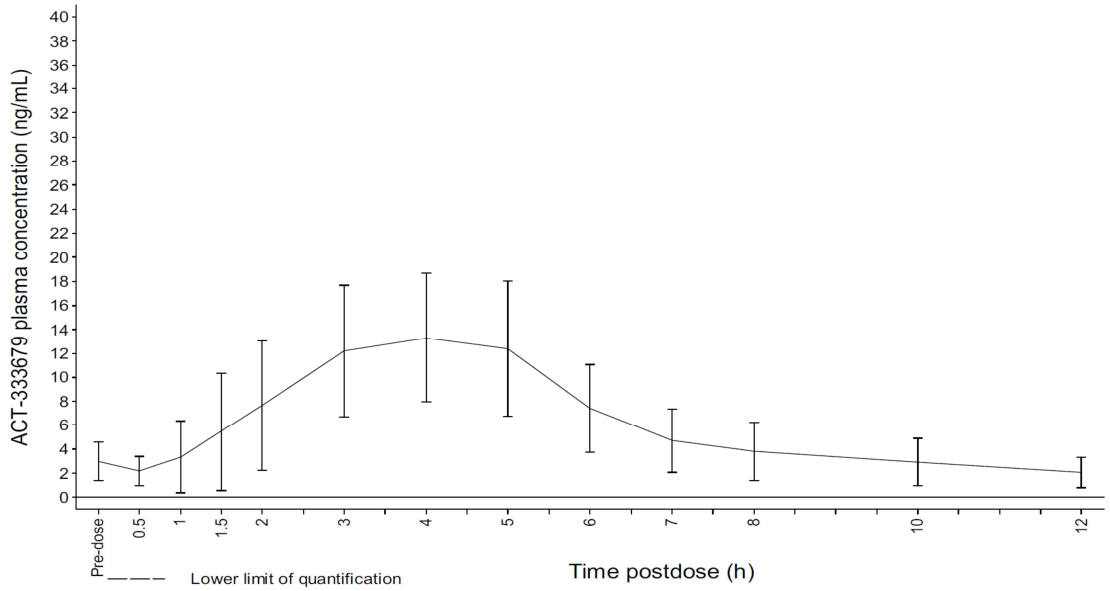
Table 4: Summary of Pharmacokinetic Statistics of ACT-333679

Day	N	t_{max} (h)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)
11	84	4.00 (1.50–6.00)	13.4 (12.3, 14.7)	69.3 (63.3, 76.0)
23	58	4.00 (2.00–5.00)	26.9 (24.3, 29.7)	138 (124, 154)

AUC_{τ} = area under plasma concentration-time curve during one dosing interval; C_{max} = maximum measured plasma concentration; t_{max} = time to reach maximum plasma concentration.
Data are geometric means (and 95% CI) or for t_{max} the median (and range).

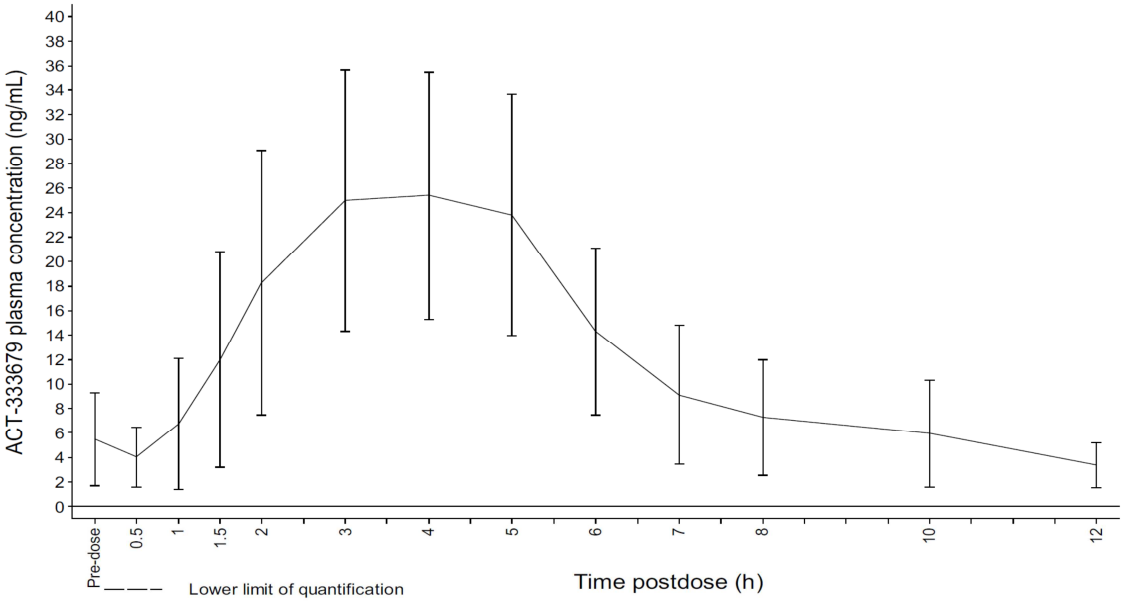
Source: Study Report, Table 23, Page 97.

Figure 3: Mean Concentration-Time Profile of ACT-333679 (±SD) following 800 µg selexipag (Day 11)



Source: Study Report, Figure 24, Page 99.

Figure 4: Mean Concentration-Time Profile of ACT-333679 (±SD) following 1600 µg selexipag (Day 23)



Source: Study Report, Figure 25, Page 99.

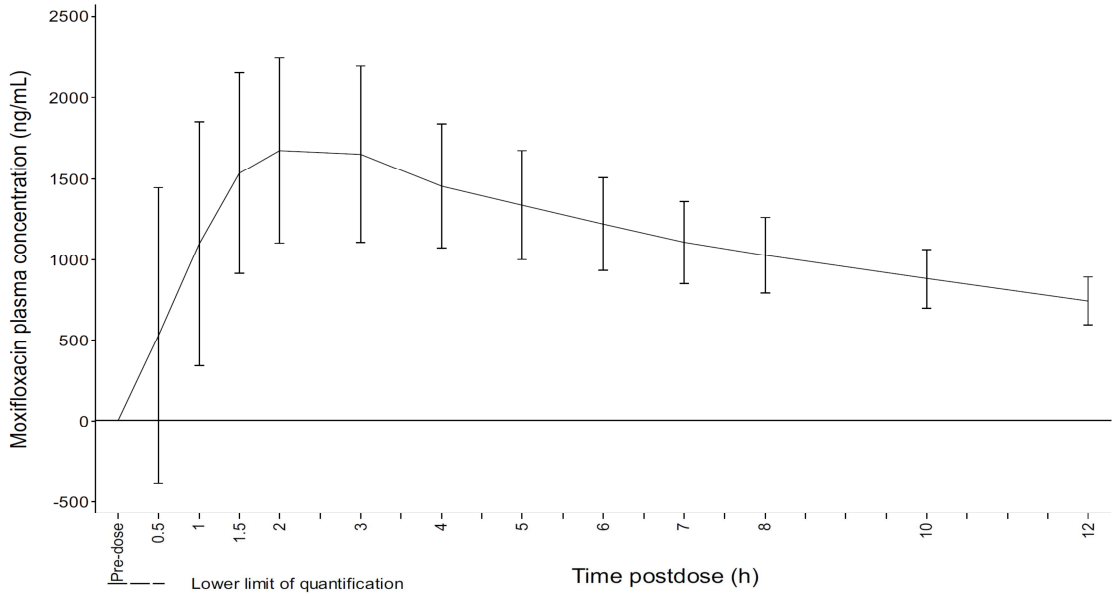
Table 5: Summary of Pharmacokinetic Statistics of Moxifloxacin

N	t_{max} (h)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)
67	2.00 (0.50–6.00)	1987 (1850, 2134)	13,340 (12,634, 14,085)

AUC_{τ} = area under plasma concentration-time curve during one dosing interval; C_{max} = maximum measured plasma concentration; t_{max} = time to reach maximum plasma concentration.
Data are geometric means (and 95% CI) or for t_{max} the median (and range).

Source: Study Report, Table 24, Page 97.

Figure 5: Mean Concentration-Time Profile of Moxifloxacin



Source: Study Report, Figure 28, Page 101.

4.2.8.4.2 Exposure-Response Analysis

The Sponosr perfomed exposure-response analyses according to QT-IRT's recommendations and did not identify a significant concentration-dependent effect of selexipag or ACT-333679 on QTcI (Figure 6 and Figure 7). A significant relationship was identified for moxifloxacin (slope = 0.005 ms per ng/mL). The projected ΔΔQTcI at the typical C_{max} following 400 mg moxifloxacin (2.9 µg/mL) is 13.1 ms.

Figure 6: ΔΔQTcI vs. Selexipag Concentrations with Mean Prediction

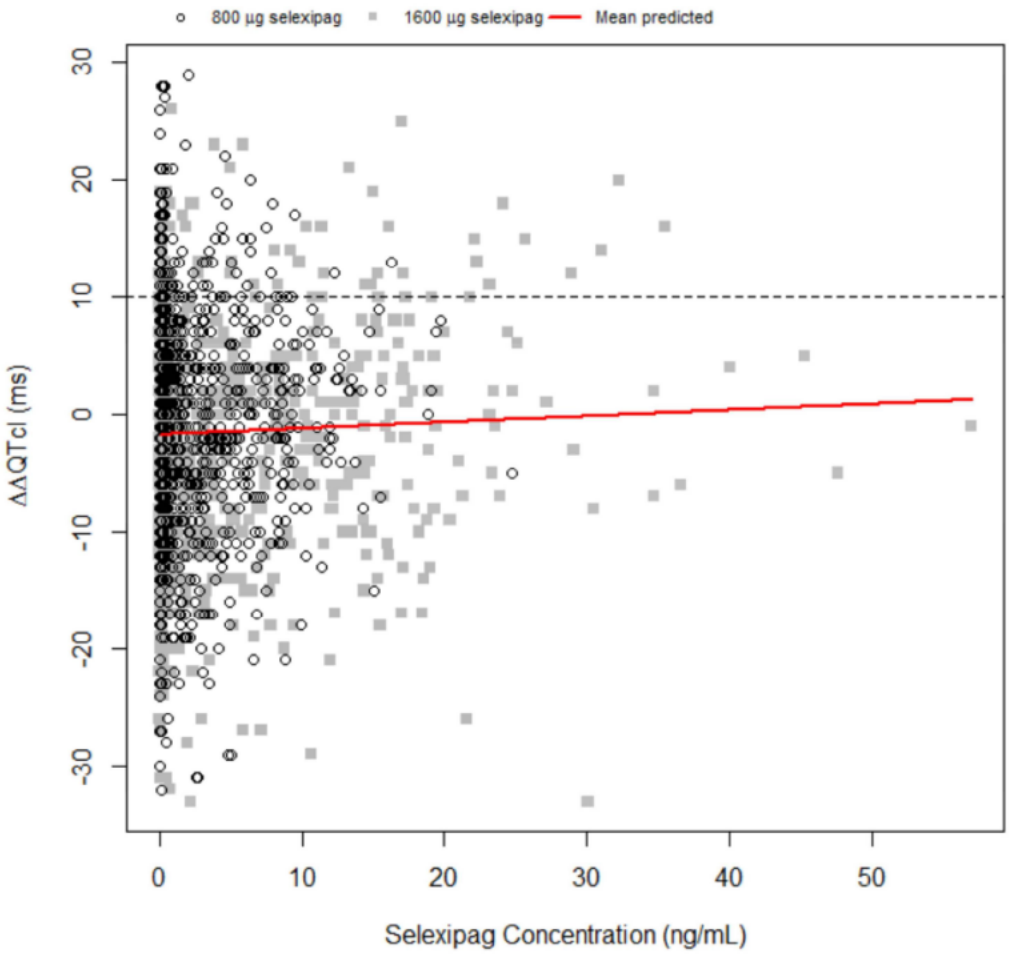
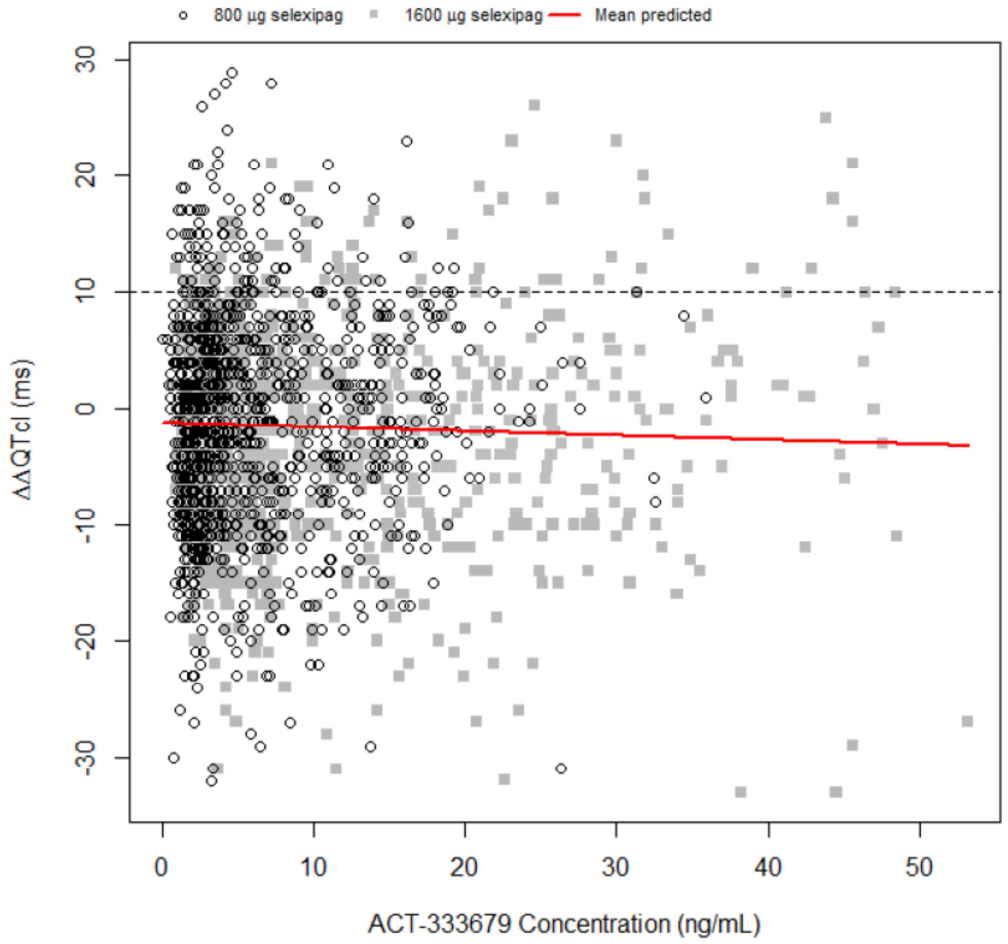


Figure 7: ΔΔQTcI vs. ACT-333679 Concentrations with Mean Prediction



Reviewer's Analysis: Plots of ΔΔQTcI vs. selexipag and ACT-333679 concentrations are presented in Figure 10 and Figure 11.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

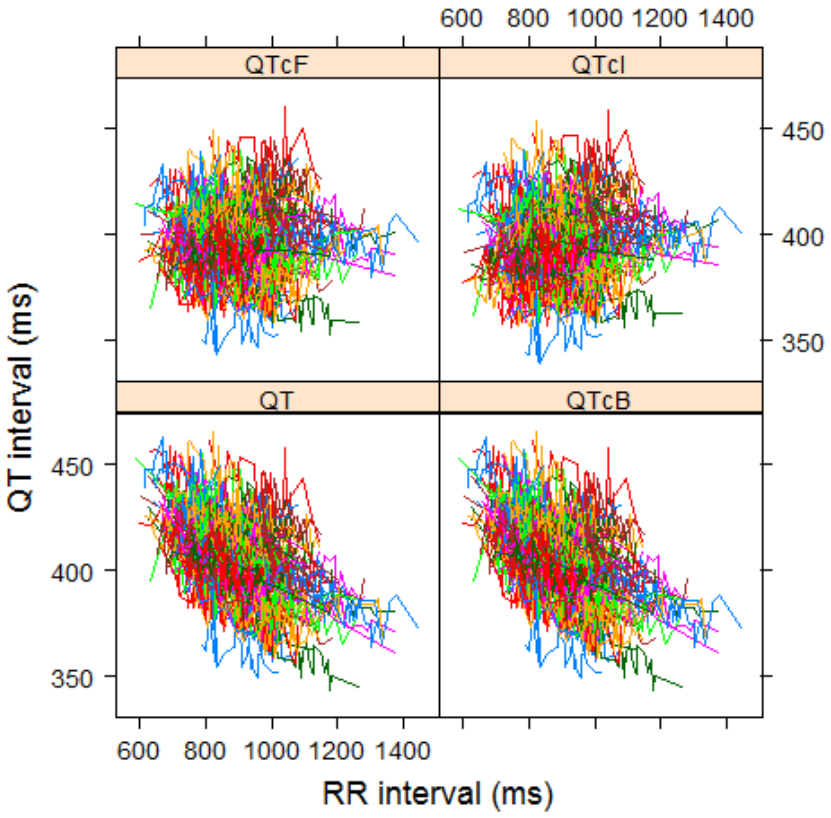
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcI is better than QTcF. This reviewer used QTcI as primary statistical analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**
Placebo for Selexipag	159	0.00108	159	0.00061
Placebo for Moxifloxacin	158	0.00096	158	0.00079
Moxifloxacin 400 mg	67	0.00180	67	0.00196
Selexipag 800ug BID	84	0.00181	84	0.00156
Selexipag 1600ug BID	58	0.00134	58	0.00096
All	159	0.00066	159	0.00045

The relationship between different correction methods and RR is presented in Figure 8.

Figure 8: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.1 STATISTICAL ASSESSMENTS

5.1.1 QTc Analysis

5.1.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7 and Table 8 for selexipag 800 ug b.i.d. and selexipag 1600 ug b.i.d., respectively. The largest upper bounds of the 2-sided 90% CI for the mean differences between selexipag 800 ug b.i.d. and placebo, and between selexipag 1600 ug b.i.d. and placebo are 3.9 ms and 2.1 ms, respectively.

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI for Selexipag 800 ug BID on Day 11

	Treatment Group				
	Placebo	SELEXIPAG 800 ug BID			
	ΔQTcI	ΔQTcI		ΔΔQTcI	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-2.3	83	-1.0	1.3	(-1.2, 3.9)
1	0.6	84	-0.4	-1.0	(-3.5, 1.5)
1.5	0.4	84	-0.3	-0.7	(-2.9, 1.5)
2	-0.3	84	-0.5	-0.1	(-2.5, 2.2)
3	0.8	84	-2.1	-2.8	(-5.3, -0.4)
4	0.7	84	-1.9	-2.7	(-5.2, -0.1)
5	-0.4	84	-3.0	-2.7	(-5.1, -0.2)
6	-2.5	84	-1.9	0.6	(-1.8, 3.1)
7	-2.5	84	-2.7	-0.2	(-2.7, 2.4)
8	-0.9	84	-1.9	-0.9	(-3.1, 1.2)
10	-2.5	84	-4.2	-1.8	(-4.1, 0.6)
12	-3.5	84	-6.9	-3.4	(-6.0, -0.7)

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for Selexipag 1600 ug BID on Day 23

	Treatment Group				
	Placebo	SELEXIPAG 1600 ug BID			
	ΔQTcI	ΔQTcI		ΔΔQTcI	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-1.6	58	-2.9	-1.3	(-4.0, 1.5)
1	0.2	58	-2.6	-2.8	(-5.4, -0.2)
1.5	0.1	58	-0.8	-0.9	(-3.7, 1.9)
2	0.4	58	-0.4	-0.7	(-3.6, 2.1)
3	-1.6	58	-3.4	-1.8	(-4.4, 0.8)
4	-1.2	58	-5.6	-4.4	(-7.3, -1.5)
5	-3.7	58	-7.0	-3.3	(-6.1, -0.6)
6	-1.6	57	-5.0	-3.4	(-6.0, -0.7)
7	-3.0	58	-5.6	-2.6	(-5.4, 0.3)
8	-1.6	58	-4.7	-3.1	(-5.7, -0.5)
10	-1.9	58	-7.5	-5.6	(-8.2, -3.0)
12	-4.1	58	-7.8	-3.7	(-6.4, -0.9)

5.1.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 7.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.1 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of ΔQTcI and ΔΔQTcI for Moxifloxacin 400 mg

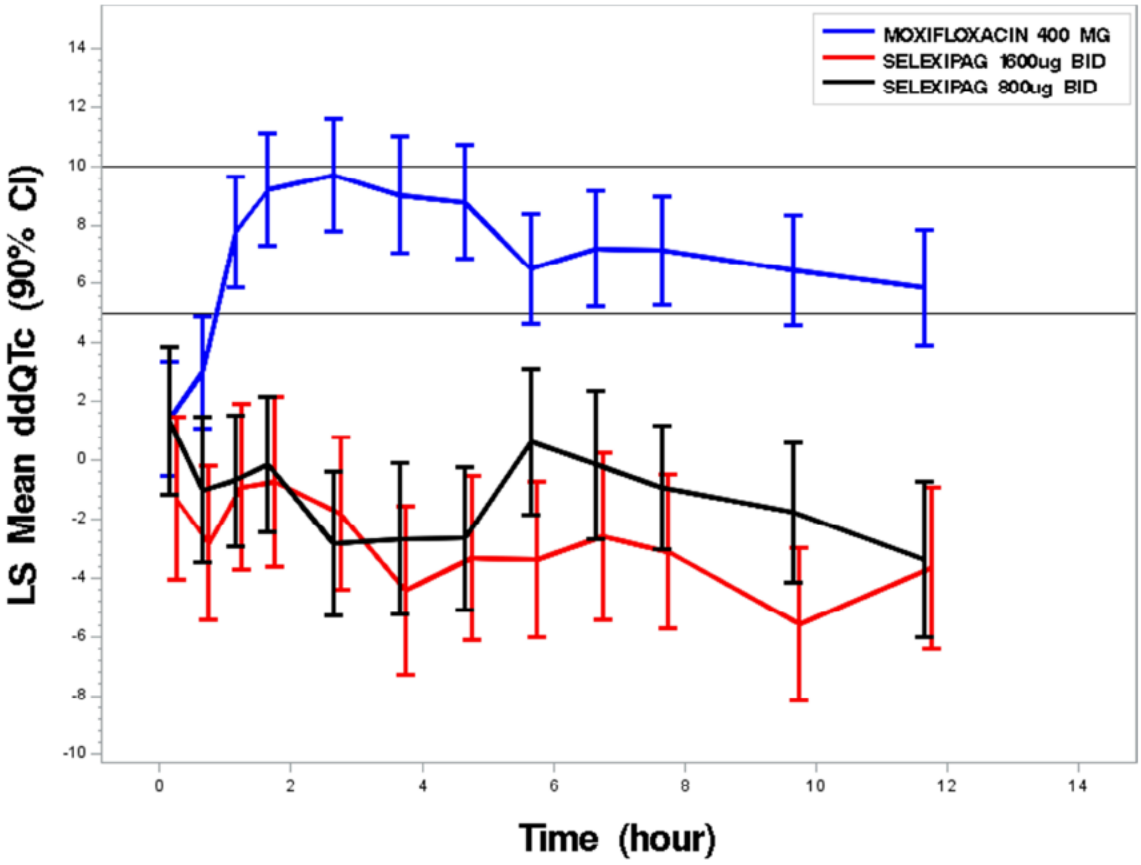
	Treatment Group					
	Placebo	MOXIFLOXACIN 400 MG				
	ΔQTcI	ΔQTcI		ΔΔQTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	*Adj. 90% CI
0.5	-2.4	67	-1.0	1.4	(-0.5, 3.3)	(-1.2, 4.0)
1	-1.8	67	1.2	3.0	(1.1, 4.9)	(0.4, 5.6)
1.5	-1.5	67	6.3	7.7	(5.9, 9.6)	(5.2, 10.3)
2	-1.5	67	7.7	9.2	(7.3, 11.1)	(6.6, 11.8)
3	-2.1	67	7.6	9.7	(7.8, 11.6)	(7.1, 12.3)
4	-2.2	67	6.8	9.0	(7.0, 11.0)	(6.3, 11.7)
5	-4.3	67	4.5	8.8	(6.8, 10.7)	(6.1, 11.4)
6	-2.9	66	3.6	6.5	(4.6, 8.4)	(4.0, 9.1)
7	-3.4	67	3.8	7.2	(5.2, 9.2)	(4.5, 9.9)
8	-3.3	67	3.8	7.1	(5.3, 9.0)	(4.6, 9.7)
10	-4.0	67	2.4	6.5	(4.6, 8.3)	(3.9, 9.0)
12	-4.9	67	1.0	5.9	(3.9, 7.8)	(3.2, 8.5)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.1.1.3 Graph of ΔΔQTcI Over Time

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

Figure 9: Mean and 90% CIΔΔQTcI Time Course



5.1.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcI is above 480 ms.

Table 10: Categorical Analysis for QTcI

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
MOXIFLOXACIN 400 MG	67	64 (95.5%)	3 (4.5%)
PLACEBO for MOXIFLOXACIN 400 MG	158	156 (98.7%)	2 (1.3%)
PLACEBO for SELEXIPAG 1600 ug BID	66	66 (100%)	0 (0.0%)
PLACEBO for SELEXIPAG 800 ug BID	67	66 (98.5%)	1 (1.5%)
SELEXIPAG 1600 ug BID	58	58 (100%)	0 (0.0%)
SELEXIPAG 800 ug BID	84	83 (98.8%)	1 (1.2%)

Table 11 lists changes from baseline QTc ≤30 ms and between 30 and 60 ms. No subject's change from baseline above 30 ms is in selexipag 800-ug or 1600-ug groups.

Table 11: Categorical Analysis of ΔQTcI

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
MOXIFLOXACIN 400 MG	67	65 (97.0%)	2 (3.0%)
PLACEBO for MOXIFLOXACIN 400 MG	158	158 (100%)	0 (0.0%)
PLACEBO for SELEXIPAG 1600 ug BID	66	66 (100%)	0 (0.0%)
PLACEBO for SELEXIPAG 800 ug BID	67	67 (100%)	0 (0.0%)
SELEXIPAG 1600 ug BID	58	58 (100%)	0 (0.0%)
SELEXIPAG 800 ug BID	84	84 (100%)	0 (0.0%)

5.1.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 12 and Table 13 for selexipag 800 ug b.i.d. and selexipag 1600 ug b.i.d., respectively. The largest upper bounds of the 2-sided 90% CI for the mean differences between selexipag 800 ug b.i.d. and placebo, and between selexipag 1600 ug b.i.d. and placebo are 9.6 bpm and 11.7 bpm, respectively. Table 14 presents the categorical analysis of HR. Two subjects who experienced HR interval greater than 100 bpm are in selexipag 800-ug twice daily group.

Table 12: Analysis Results of ΔHR and ΔΔHR for Selexipag 800 ug BID on Day 11

	Treatment Group				
	Placebo	SELEXIPAG 800ug BID			
	ΔHR	ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	0.6	83	4.2	3.7	(1.8, 5.6)
1	0.6	84	5.5	5.0	(3.1, 6.8)
1.5	1.5	84	8.2	6.7	(4.9, 8.5)
2	1.7	84	8.6	6.9	(5.2, 8.6)
3	1.6	84	9.2	7.7	(5.8, 9.6)
4	2.4	84	8.2	5.8	(4.1, 7.4)
5	1.9	84	6.4	4.6	(2.9, 6.2)
6	0.9	84	5.6	4.6	(2.9, 6.4)
7	2.6	84	5.9	3.3	(1.3, 5.3)
8	2.5	84	6.5	3.9	(2.0, 5.8)
10	3.0	84	7.7	4.6	(2.7, 6.6)
12	1.4	84	4.3	2.8	(0.8, 4.8)

Table 13: Analysis Results of ΔHR and ΔΔHR for Selexipag 1600 ug BID on Day 23

		Treatment Group			
	Placebo	SELEXIPAG 1600 ug BID			
	ΔHR	ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.8	58	5.3	3.5	(1.3, 5.8)
1	1.1	58	6.9	5.9	(3.8, 7.9)
1.5	1.5	58	11.2	9.8	(7.9, 11.7)
2	1.6	58	11.3	9.7	(7.8, 11.6)
3	1.9	58	10.8	8.9	(6.9, 10.8)
4	2.9	58	9.4	6.5	(4.5, 8.6)
5	3.3	58	7.5	4.2	(2.5, 6.0)
6	2.4	57	7.0	4.6	(2.6, 6.7)
7	2.4	58	5.3	3.0	(0.9, 5.0)
8	2.3	58	5.6	3.2	(1.2, 5.2)
10	2.3	58	6.0	3.8	(1.7, 5.8)
12	3.6	58	5.6	2.0	(-0.2, 4.1)

Table 14: Categorical Analysis for HR

Treatment Group	Total N	HR <= 100 ms	HR >100 ms
MOXIFLOXACIN 400 MG	67	66 (98.5%)	1 (1.5%)
PLACEBO for MOXIFLOXACIN 400 MG	158	158 (100%)	0 (0.0%)
PLACEBO for SELEXIPAG 1600 ug BID	66	66 (100%)	0 (0.0%)
PLACEBO for SELEXIPAG 800 ug BID	67	67 (100%)	0 (0.0%)
SELEXIPAG 1600 ug BID	58	58 (100%)	0 (0.0%)
SELEXIPAG 800 ug BID	84	82 (97.6%)	2 (2.4%)

5.1.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 15 and Table 16 for selexipag 800 ug b.i.d. and selexipag 1600 ug b.i.d., respectively. The largest upper bounds of the 2-sided 90% CI for the mean differences between selexipag 800 ug b.i.d. and placebo, and between selexipag 1600 ug b.i.d. and placebo are 0.1 ms and 1.3 ms, respectively. Table 17 presents the categorical analysis of HR. Three subjects who experienced PR interval greater than 200 ms are in selexipag 800-ug and 1600-ug twice daily groups.

Table 15: Analysis Results of ΔPR and ΔΔPR for Selexipag 800 ug BID on Day 11

		Treatment Group			
		SELEXIPAG 800ug BID			
	ΔPR	ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	3.0	83	-1.4	-4.4	(-7.4, -1.5)
1	2.1	84	-2.7	-4.8	(-7.7, -2.0)
1.5	2.1	84	-2.9	-5.0	(-7.6, -2.5)
2	2.1	84	-3.1	-5.2	(-7.6, -2.7)
3	2.9	84	-2.5	-5.3	(-8.1, -2.5)
4	3.2	84	-2.8	-6.0	(-8.9, -3.1)
5	1.6	84	-3.3	-4.9	(-7.5, -2.3)
6	2.5	84	-3.6	-6.1	(-8.9, -3.4)
7	1.0	84	-2.7	-3.7	(-6.2, -1.3)
8	0.8	84	-1.7	-2.6	(-5.2, 0.1)
10	1.6	84	-1.7	-3.3	(-5.8, -0.9)
12	1.1	84	-2.1	-3.2	(-5.7, -0.7)

Table 16: Analysis Results of ΔPR and ΔΔPR for Selexipag 1600 ug BID on Day 23

		Treatment Group			
		SELEXIPAG 1600ug BID			
	ΔPR	ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	3.6	58	2.0	-1.7	(-4.7, 1.3)
1	2.9	58	-1.7	-4.6	(-7.5, -1.6)
1.5	2.8	58	-2.8	-5.6	(-8.2, -3.0)
2	1.9	58	-3.1	-5.0	(-7.7, -2.3)
3	3.8	58	-3.0	-6.9	(-9.7, -4.0)
4	3.2	58	-3.0	-6.2	(-8.9, -3.5)
5	2.7	58	-4.0	-6.7	(-9.3, -4.1)
6	2.1	57	-3.3	-5.4	(-8.0, -2.9)
7	1.7	58	-2.8	-4.5	(-7.0, -2.0)
8	2.8	58	-2.1	-4.8	(-7.2, -2.5)
10	2.3	58	-1.2	-3.4	(-5.9, -1.0)
12	3.1	58	-1.4	-4.5	(-7.1, -1.9)

Table 17: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
MOXIFLOXACIN 400 MG	67	63 (94.0%)	4 (6.0%)
PLACEBO for MOXIFLOXACIN 400 MG	158	146 (92.4%)	12 (7.6%)
PLACEBO for SELEXIPAG 1600 ug BID	66	59 (89.4%)	7 (10.6%)
PLACEBO for SELEXIPAG 800 ug BID	67	60 (89.6%)	7 (10.4%)
SELEXIPAG 1600 ug BID	58	56 (96.6%)	2 (3.4%)
SELEXIPAG 800 ug BID	84	82 (97.6%)	2 (2.4%)

5.1.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 18 and Table 19 for selexipag 800 ug b.i.d. and selexipag 1600 ug b.i.d., respectively. The largest upper bounds of the 2-sided 90% CI for the mean differences between selexipag 800 ug b.i.d. and placebo, and between selexipag 1600 ug b.i.d. and placebo are 0.7 ms and 0.9 ms, respectively. Table 20 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms are in selexipag 800-ug and 1600-ug twice daily groups.

Table 18: Analysis Results of ΔQRS and ΔΔQRS for Selexipag 800 ug BID on Day 11

		Treatment Group			
		SELEXIPAG 800 ug BID			
	Placebo	dQTc		ddQTc	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.1	83	0.1	-1.0	(-1.9, -0.0)
1	0.6	84	0.2	-0.5	(-1.4, 0.5)
1.5	0.6	84	-0.2	-0.8	(-1.7, 0.0)
2	0.5	84	-0.3	-0.8	(-1.6, 0.1)
3	0.5	84	-0.9	-1.4	(-2.3, -0.6)
4	0.5	84	-0.4	-0.9	(-1.9, 0.0)
5	0.4	84	-0.4	-0.8	(-1.7, 0.0)
6	0.1	84	-0.5	-0.6	(-1.5, 0.4)
7	-0.1	84	-0.2	-0.2	(-1.1, 0.7)
8	0.7	84	-0.4	-1.1	(-1.9, -0.3)
10	0.2	84	-0.6	-0.8	(-1.6, -0.0)
12	-0.4	84	-1.2	-0.7	(-1.6, 0.2)

Table 19: Analysis Results of ΔQRS and ΔΔQRS for Selexipag 1600 ug BID on Day 23

		Treatment Group			
		SELEXIPAG 1600ug BID			
	Placebo	dQTc		ddQTc	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.0	58	0.5	-0.5	(-1.5, 0.6)
1	0.6	58	0.3	-0.3	(-1.4, 0.7)
1.5	0.8	58	0.1	-0.6	(-1.7, 0.4)
2	0.8	58	-0.3	-1.0	(-2.0, -0.1)
3	0.5	58	-0.3	-0.8	(-1.7, 0.2)
4	0.5	58	-0.4	-0.9	(-1.9, 0.0)
5	0.3	58	0.0	-0.3	(-1.3, 0.6)
6	0.0	57	-0.2	-0.2	(-1.2, 0.9)
7	0.2	58	0.2	-0.0	(-1.0, 0.9)
8	0.5	58	0.2	-0.2	(-1.2, 0.7)
10	-0.0	58	-0.4	-0.3	(-1.3, 0.7)
12	-0.1	58	-0.4	-0.3	(-1.4, 0.7)

Table 20: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
MOXIFLOXACIN 400 MG	67	66 (98.5%)	1 (1.5%)
PLACEBO for MOXIFLOXACIN 400 MG	158	155 (98.1%)	3 (1.9%)
PLACEBO for SELEXIPAG 1600 ug BID	66	65 (98.5%)	1 (1.5%)
PLACEBO for SELEXIPAG 800 ug BID	67	66 (98.5%)	1 (1.5%)
SELEXIPAG 1600 ug BID	58	57 (98.3%)	1 (1.7%)
SELEXIPAG 800 ug BID	84	82 (97.6%)	2 (2.4%)

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔΔQTcI and selexipag and ACT-333679 concentrations is visualized in Figure 10 and with no evident exposure-response relationship.

Figure 10: ΔΔ QTcI vs. Selexipag concentration

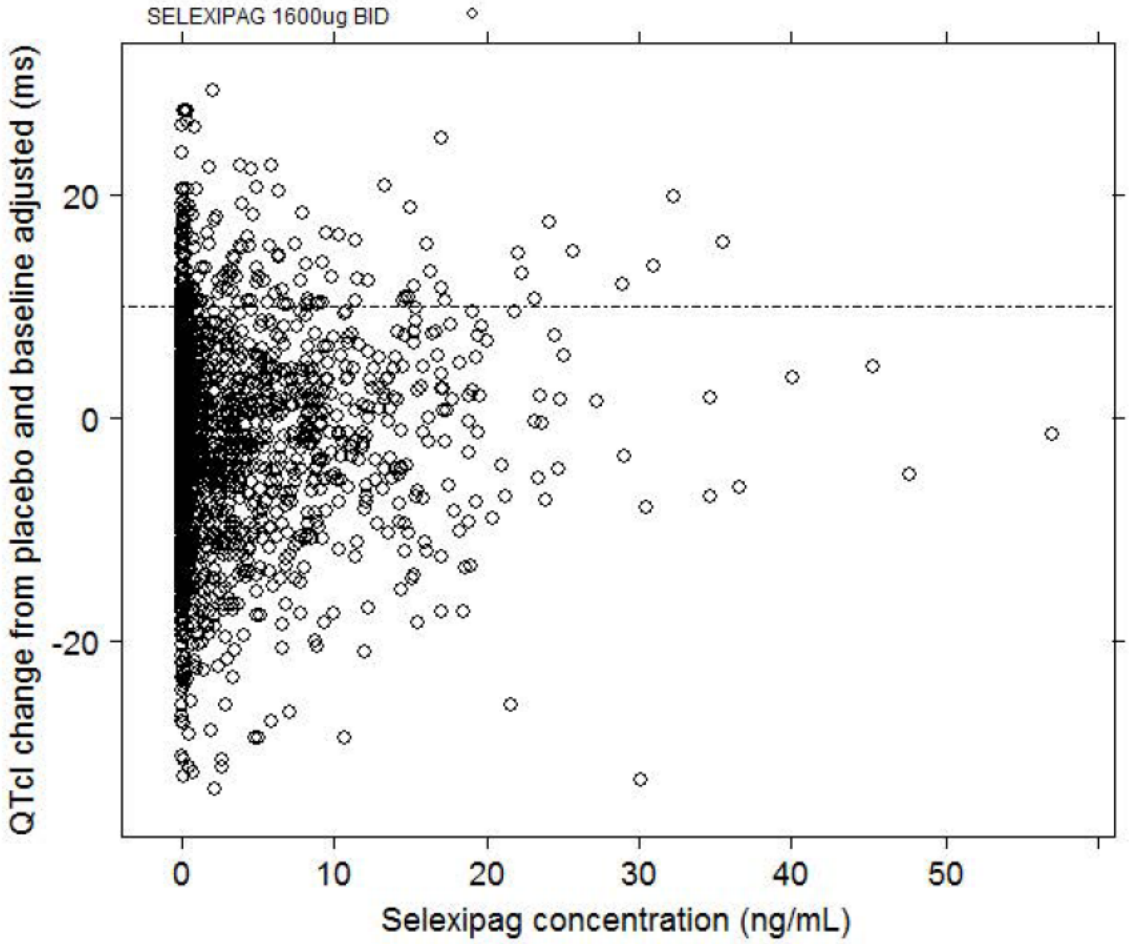
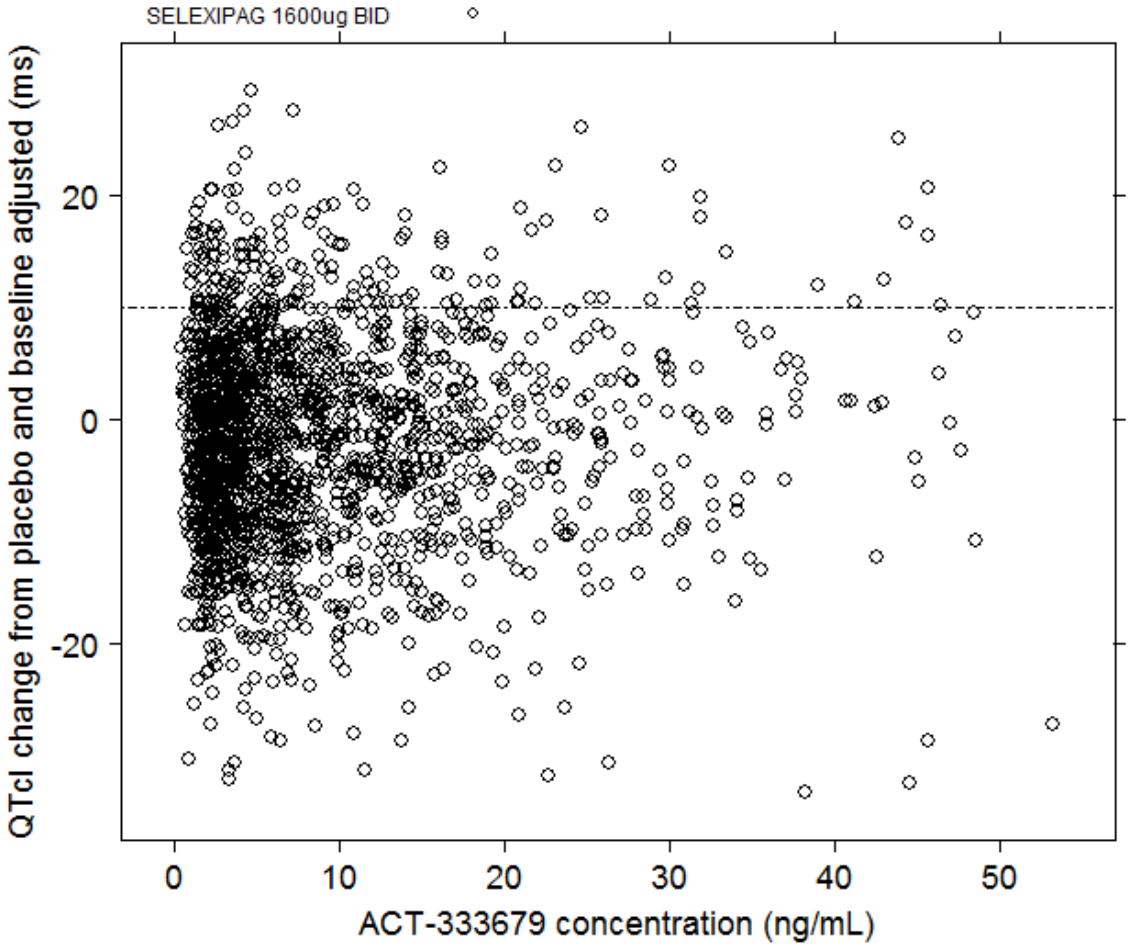


Figure 11: ΔΔ QTcI vs. ACT-333679 Concentration



5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

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

5.3.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

Selexipag did not show an effect on cardiac repolarization (the QTc interval) or conduction (PR and QRS intervals) and had a mild accelerating heart rate effect.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

A table of the highlights of clinical pharmacology was submitted with the protocol and is included in the protocol review (09/27/2011). From the Sponsor's proposed label, the following key intrinsic/extrinsic factors were identified:

1. Selexipag exposure was 2- and 4-fold higher in subjects with mild or moderate hepatic impairment, respectively, when compared to healthy subjects. Exposure to ACT-333679 was doubled in subjects with moderate impairment but unchanged in subjects with mild impairment.
2. Selexipag and ACT-333679 exposure was increased 1.4- to 1.7-fold, in patients with severe renal impairment
3. In the presence of a strong CYP3A4, OATP and P-gp inhibitor, exposure to selexipag increased 2-fold.

(b) (4)

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/s/

MOH JEE NG
03/25/2015

QIANYU DANG
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03/25/2015

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:	March 13, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 207947
Product Name and Strength:	Uptravi (selexipag) Tablets, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Actelion Pharmaceuticals
Submission Date:	December 22, 2014
OSE RCM #:	2015-257
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Actelion Pharmaceuticals submitted NDA 207947 for Uptravi (selexipag), a new molecular entity on December 22, 2014. The Division of Cardiovascular and Renal Products (DCRP) requested that we review the submitted container labels, carton labeling, and prescribing information for areas of vulnerability that could lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container labeling and find it acceptable from medication error perspective. For the carton labeling, we recommend to move the strength presentation slightly closer to the established name and away from the net quantity statement. We recommend this to minimize the risk of net quantity being confused as the strength or vice versa.

We evaluated the proposed prescribing information and believe that it can be improved to clarify important information. For example, in Section 16, How Supplied/Storage and Handling, the strengths listed on the first column should have unit of measure 'mcg' at the end of each strength number (e.g. 200 mcg, 400 mcg, etc).

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling for Uptravi may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Section 16. How Supplied/Storage and Handling, Full Prescribing Information

a. Add the unit of measure 'mcg' to the end of each strength (e.g. 200 mcg, 400 mcg, etc.) in the table under the "Strength" column for clarity.

4.2 RECOMMENDATIONS FOR ACTELION PHARMACEUTICALS

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

A. Carton labeling

1. Move the strength slight upwards to be closer to the established name and away from the net quantity statement. We recommend this to minimize the risk of net quantity being confused as the strength or vice versa.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Uptravi that Actelion Pharmaceuticals submitted on December 22, 2014.

Table 2. Relevant Product Information for Uptravi	
Initial Approval Date	N/A
Active Ingredient	Selexipag
Indication	Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.
Route of Administration	Oral
Dosage Form	Tablet
Strength	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg
Dose and Frequency	The recommended starting dose of UPTRAVI is 200 micrograms (mcg) given twice daily, (b) (4) • To achieve optimal clinical response, the dose is increased in increments of 200 mcg twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced. • The maximum dose evaluated for efficacy was 1600 mcg twice daily. • If a patient reaches a dose that cannot be tolerated the dose should be reduced to the previous dose level. • UPTRAVI may be taken with or without food. • Tablet should not be split, crushed or chewed.
How Supplied	**Bottle of 60 tablets** for 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg (all strengths). **Bottle of 140 tablets** for 200 mcg tablets
Storage	20°C to 25°C (68°F to 77°F)
Container Closure	Bottle

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,[1] along with postmarket medication error data, we reviewed the following Uptravi labels and labeling submitted by Actelion Pharmaceuticals on December 22, 2014.

- Container label
- Carton labeling
- (b) (4)

G.2 Label and Labeling Images

(b) (4)

[1] 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/

TINGTING N GAO
03/13/2015

CHI-MING TU
03/13/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 207947
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name: Uptravi
Established/Proper Name: selexipag
Dosage Form: Tablets
Strengths: 200; 400; 600; 800; 1000; 1200; 1400; and1600 mcg</td></tr>
<tr><td colspan="3">Applicant: Actelion Clinical Research Inc.
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: December 22, 2014
Date of Receipt: December 22, 2014
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: December 22, 2015</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: February 20, 2015</td><td>Date of Filing Meeting: February 2, 2015</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
X Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression; reduced hospitalization for PAH.</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>X 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	X Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review X Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 104504	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	X	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	X	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid X Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** X Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	X		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	X	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	X	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	X	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

X legible NO☐ English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain. *The drug product executed batch records in Section 3.2.R. contain sections that have not been translated from German to English. OPQ sent an IR to Actelion requesting submission of certified English translations by noon on February 19, the day before filing. Actelion responded that they were working on it but could not provide the requested information until roughly two weeks after the filing date, but offered to provide handwritten translations in advance of the official submission. DCRP pointed out to OPQ that this makes the application subject to RTF, but deferred to OPQ. OPQ decided that they were comfortable filing, given that Actelion was working on providing the certified translation as an official submission.*				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		*The 356(h) form originally submitted by Actelion did not include the drug substance testing sites* (b) (4) *(Heavy Metals Testing;* (b) (4)

				(b) (4) *(Microbiology Testing;* (b) (4) *the drug product testing site* (b) (4) *(Microbiology Testing;* (b) (4) *or the drug product packaging site* (b) (4) *OPQ sent an IR and the applicant submitted an updated 356h.*
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	See comment above.
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with	X	☐	☐	

authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	X		Orphan Designation
If the application triggers PREA, is there an agreed Initial	☐	☐	☐	

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	X	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) X Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent X Other (specify) (b) (4) for Carton			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X	☐		
Is the PI submitted in PLR format?[4]	X	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request?	☐	☐	☐	

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X	☐	☐	QT-IRT consult issued on QT-IRT final study report
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** April 8, 2014. ***If yes, distribute minutes before filing meeting***	X	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** November 9, 2009 (SPA no agreement); SPA	X	☐		

Revision submitted January 11, 2010; February 23, 2010 SPA Agreement. SPA Amendment (Protocol Amendment 4) August 18, 2011-not implemented due to FDA concerns; October 17, 2011 Advice letter. SPA tcon on October 24, 2011. SPA Amendment (Prtocol Amend #5) submitted December 21, 2011. Protocol amendment 6 submitted Feb 12, 2013) ***If yes, distribute letter and/or relevant minutes before filing meeting***				

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2015

BACKGROUND: The Selexipag (ACT-293987) development program initiated with a pre-IND meeting under IND 104504 on March 26, 2009 to discuss CMC, nonclinical, and clinical aspects of the development program for pulmonary arterial hypertension. The IND was submitted on September 29, 2009. A special protocol agreement (SPA) was requested on September 29, 2009. The SPA history is as follows: FDA responded on November 9, 2009 (SPA no agreement); a SPA Revision was submitted January 11, 2010; February 23, 2010 SPA Agreement. SPA Amendment (Protocol Amendment 4) August 18, 2011-not implemented due to FDA concerns; October 17, 2011 Advice letter. SPA tcon on October 24, 2011. SPA Amendment (Protocol Amend #5) submitted December 21, 2011. Protocol amendment 6 submitted Feb 12, 2013). This is the pivotal Griphon trial.

A QT-IRT study protocol was submitted on September 12, 2011. The QT-IRT study report was submitted under the IND on December 20, 2013. The final QT-IRT review team has been consulted on the final QT-IRT study report under the NDA.

A type C meeting was scheduled for May 1, 2013 to discuss a review of an interim analysis by the data monitoring committee (DMC). However, to maximize the ability to maintain full blinding of the sponsor during the conduct of the GRIPHON trial, the sponsor had pre-specified that the cancellation of this teleconference should be made without their knowledge if certain circumstances should occur. Indeed, based on the DMC recommendations made today, those circumstances did occur, and the meeting was cancelled.

The pre-NDA meeting was held on April 8, 2014, and a top-line results meeting was held on July 11, 2014. The NDA was submitted on December 22, 2014 as an NME application under "The Program" provisions of PDUFA V.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Wayne Amchin	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Division Director/Deputy	Norman Stockbridge/Steve Grant		Y
Office Director/Deputy	Ellis Unger		Y
Clinical	Reviewer:	Maryann Gordon	Y

	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sudharshan Hariharan Luning Zhuang (Pharmacometrics)	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	Jim Hung	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jim Willard	Y
	TL:	Al De Felice	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Akm Khairuzzaman Katherine Windsor Mariappan Chelilah Olga Simakova	Y N Y Y
	TL:	Wendy Wilson	Y
Biopharmaceutics	Reviewer	Elsbeth Chikhale	Y
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Vibhakar Shah	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Tingting Gao	Y
	TL:	Alice Tu	Y
OSE/DRISK (REMS)	Reviewer:	Somya Dunn	Y
	TL:	Kim Lehrfeld	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Thompson	Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Michael Monteleone (ADL/DCRP) Puja Shah (OPDP) Karen Dowdy (Patient Labeling) Amy Chen (OSE/DPV)		Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain: sections of CMC were not translated from German-see earlier discussion.	☐ YES X NO
• Electronic Submission comments **List comments**:	☐ Not Applicable X No comments
CLINICAL **Comments**: No issues known at Filing for 74DL, per	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

clinical filing review.	
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason: Per email from Clinical Reviewer: ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable

Comments:	X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Filing Review indicates No issues for 74DL at this time.	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Three issues were identified during the filing period. These are potentially RTF issues. OPQ issued an IR to the applicant on three of the issues (b) (4); 2: facilities missing from 356 h, and 3 translation to English. Actelion provided the required information prior to filing on two of the issues. On the third issue, translation to English, the applicant was unable to provide the certified translation prior to the filing date. OPQ recommended Filing based on the fact that the applicant was working on this and would provide the certified translation within 2-3 weeks. Two days before the filing date, the applicant also requested to add a manufacturing site under the (b) (4) program.	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 X YES

	☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Noted in OPQ filing review	X YES ☐ NO ☐ YES ☐ NO X YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	X Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: OPQ handles this now.	☐ Not Applicable X YES ☐ NO X YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES X NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES X NO See comments under CMC section regarding missing translations.
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Ellis Unger, Director, Office of Drug Evaluation I(**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 13, 2015. **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:

X	The application, on its face, appears to be suitable for filing. There were issues related to the CMC section that meet RTF criteria, but OPQ recommended filing. DCRP accepted this recommendation. Review Issues: X No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: X Standard Review ☐ Priority Review
ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

WAYNE S AMCHIN
02/19/2015