CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

CHEMISTRY REVIEW(S)

<table cellspacing=0 width="1100" > <tr><td style="text align:left;font-family:Times New Roman;font size:25px;font style:normal;font-weight:bold;color:#000080;white space:nowrap" class="TitleCell"> Facility Alerts</td></tr> <tr><td style="text align:left;font-family:Times New Roman;font size:25px;font-style:normal;font weight:bold;color:#000080;white space:nowrap" class="TitleNameCell" tabindex="0"><label></label></td></tr> <tr><td style="font-family:Microsoft Sans Serif;font-size:11px;color:#8055B7;" class="SubtitleCell"> This report displays the Alerts associated with facilities on the selected applications</td></tr> <tr><td style="text align:left;border style:none;border-bottom:solid 1px #7f7f7f;font family:Microsoft Sans Serif;font size:10px;color:#000080;" class="SubtitleCell"></td></tr></tbody> </table> <style type="text/css"> td.ResultLinksCell {} </style>
 <FONT SIZE =2><FONT COLOR="#000080"> No active OAI / POAI Alerts are present against the facilities on selected Projects</FONT></FONT>

Facility Status View for NDA 207947 Original 1

Displays information for the facilities that are associated to NDA 207947 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 12/16/2015 3:40:55 PM

Overall Manufacturing Inspection Recommendations for NDA 207947 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207947-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	ACTELION PHARMACEUTICALS LTD	Approve	Complete	8/18/2015

OPF Facility Recommendations for Facilities on NDA 207947 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 207947 -Orig1-New - User Fee Form 3674/NDA - Coversheet(1)	(b) (4)				Approve Facility	Complete	(b) (4)
NDA 207947-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					Approve Facility	Complete	
NDA 207947 -Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					Approve Facility	Complete	
NDA 207947-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					Approve Facility	Complete	
NDA 207947-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	3002995923	480007868	ACTELION PHARMACEUTICALS LIMITED	MIS NOT ELSEWHERE CLASSIFIED	Approve Facility	Complete	2/23/2015
NDA 207947 -Orig1 New - User Fee - Form 3674/NDA - Coversheet(1)	(b) (4)				Approve Facility	Complete	(b) (4)
NDA 207947-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)					Approve Facility	Complete	
NDA 207947 -Orig1 New - User Fee - Form 3674/NDA - Coversheet(1)					Approve Facility	Complete	

Data refreshed on: 12/16/15 12:15:10 AM

Recommendation: Approval

NDA 207947
Review # 01
Review Date: August 25, 2015

Drug Name/Dosage Form	Uptravi® (selexipag) Tablets
Strength	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Actelion Pharmaceuticals, Ltd.
US agent, if applicable	Actelion Clinical

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	December 22, 2014
Amendment	February 19, 2015
Amendment	March 02, 2015
Amendment	June 24, 2015
Amendment	July 16, 2015
Amendment	August 12, 2015
Amendment	August 21, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor	Branch 1/DNDAPI/ONDP
Drug Product	Mariappan Chelliah	Branch 1/DNDP1/ONDP
Process	Akm Khairuzzaman	Branch1/DPA1/OPF
Microbiology	Akm Khairuzzaman	Branch 1/DPA1/OPF
Facility	Ruth Moore	DIA/OPF
Biopharmaceutics	Om Anand	Branch 1/DBP/ONDP
Project/Business Process Manager	Maryam Kord Bacheh Changi	Branch 1/DRBPM1/OPRO
Application Technical Lead	Wendy Wilson-Lee	Branch 1/DNDP1/ONDP
Laboratory (OTR)	-	-
ORA Lead	Sharon Thoma	ORA
Environmental Assessment (EA)	James Laurenson	EA Team/IO/ONDP

Table of Contents

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

The submission did not reference any DMFs.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104504	Pulmonary Arterial Hypertension

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Complete	Stability data supports 36 months expiry for all tablet strengths in bottles (b) (4)	21-Aug-2015	Zhuang Miao
Pharmacology/Toxicology	-	-	-	-
CDRH	-	-	-	-
Clinical	-	-	-	-
Other	-	-	-	-

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend **APPROVAL** of Uptravi® (selexipag) Tablets (200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg), from a product quality perspective, when stored at USP controlled room temperature in 60-count and 140-count (200 mcg only) HDPE bottles.

OPQ Comments for the Action Letter

Based on the stability data and statistical analysis provided in the submission, and in accordance with ICH Q1E, we grant a 36 month drug product expiry for all tablet strengths stored in the 60-count HDPE bottles and a 24 month drug product expiry for the 200 mcg tablet strength stored in the 140-ct HDPE bottle.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

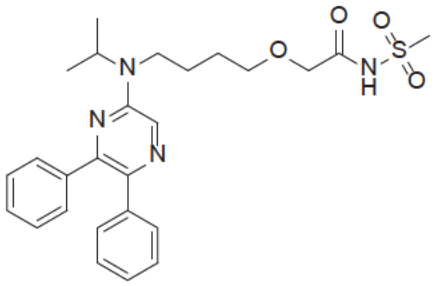
There are no post-marketing commitments or agreements at this time.

II. Summary of Quality Assessments

Selexipag is a new molecular entity indicated for the treatment of pulmonary arterial hypertension (PAH). FDA granted orphan designation April 2010 for selexipag in PAH. Selexipag is considered a narrow therapeutic index drug. Selexipag is hydrolyzed in vivo to yield the active metabolite ACT-333679, which is more potent (37-fold) than the parent compound. The content of the active metabolite is controlled in the drug product. (b) (4) the drug product is (b) (4) strengths spanning 200 mcg to 1600 mcg to allow for titration to meet individual patient needs based on tolerability. Twice daily dosing is recommended

A. Drug Substance [Selexipag] Quality Summary

Selexipag, chemically known as (2-{-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino} butoxy}-N-(methylsulfonyl)acetamide) is pale yellow, (b) (4) crystalline powder with (b) (4) (b) (4)



The drug substance is manufactured via [redacted] (b) (4)

(b) (4)

B. Drug Product [Selexipag Tablets] Quality Summary

UPTRAVI® (selexipag) is manufactured as round film coated immediate release tablets in eight different strengths: 200, 400, 600, 800, 1000, 1200, 1400 and 1600 mcg. Although the amount of the active ingredient varies between the tablet strengths, the total weight and size of the tablets remain the same. The only differences in composition between the tablets are [redacted] (b) (4)
The tablets are visually distinguished by the numbers debossed on the tablets and the colors of the film coats, which are unique for each strength. The [redacted] (b) (4) tablets are manufactured with the following excipients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The film coat of the tablets contain the following excipients: hypromellose, propylene glycol, titanium dioxide, carnauba wax, iron oxide red, iron oxide yellow and iron oxide black.

All the excipients are compendial and there are no novel excipients. [redacted] (b) (4)

owever, if there is any change in the future supply of this excipient, the newly sourced excipient should be fully evaluated before committing its use for the commercial manufacturing. [redacted] (b) (4)

Selexipag is known to exist in [redacted]. Form I, [redacted]. Although form II [redacted]. The clinical division indicated that the [redacted]. Based on the proposed commercial dissolution method, more than [redacted]% of selexipag is released from the formulation after 20 minutes, [redacted]. Even for a worst-case scenario of the [redacted] all of the drug substance is still expected to release well-before Tmax is achieved. Given the indication, [redacted] would actually provide greater clinical benefit to patients.

The non compendial analytical methods have been described in sufficient detail and they are suitable to assure the drug product meets its specification. The non compendial methods have been adequately validated by the sponsor. In addition, the non-compendial analytical methods were verified and found acceptable for quality control and regulatory purposes by the FDA's Division of Pharmaceutical Analysis, St. Louis, MO. The sponsor has provided satisfactory batch analysis data for 3 registration batches for each strength of the tablets [redacted] These batches were manufactured in the range of [redacted] kg.

Selexipag tablets are expected to be marked in two different packaging configurations. In the 'Bottle 60' configuration, 60 tablets of selexipag tablets (all strengths) will be packaged in a 50 cc HDPE container. While the sponsor has provided 24 months of long-term and intermediate term stability data for five strengths of the tablets (200, 400, 800, 1200 and 1600 mcg), they have used a [redacted] and [redacted] approach for the remaining three strengths. Based on the 24 month stability data, the proposed shelf life of 36 months may be granted for the 60-count bottles. The sponsor also propose to market the 200 mcg strength alone in an additional 'Bottle 140' configuration, where 140 tablets will be packaged in the same 50 cc HDPE container. Based on the 9 month long-term and 6-month accelerated stability data for this configuration in combination with the stability data for the 200 mcg tablets in the 'Bottle 60' configuration, a proposed shelf life of 24 months may be granted for the 'Bottle 140' configuration.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Uptravi®
Non Proprietary Name of the Drug Product	Selexipag Tablets
Non Proprietary Name of the Drug Substance	Selexipag
Proposed Indication(s) including Intended Patient Population	Pulmonary Arterial Hypertension
Duration of Treatment	[redacted] (b) (4) administration; Twice daily dosing regimen
Maximum Daily Dose	3.2 mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: An official designation has not been requested, however, the Applicant considers the drug substance as a BCS [redacted] (b) (4)
   - Drug Product: An official designation has not been requested, however, the Applicant considers the drug product as a BCS [redacted] (b) (4)

2. Biowaivers/Biostudies

   - PK studies: Bridging study for the 1 × 1600 µg and the 8 × 200 µg selexipag tablet formulation (detailed assessment in the Biopharmaceutics section).

   - Biowaiver Requests: biowaiver request for selexipag dose strengths 400, 600, 800, 1000, 1200 and 1400 µg.

   - IVIVC: Not Applicable

3. **Dissolution method: ACCEPTABLE**

   The following proposed dissolution method is acceptable:

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	50 rpm	900 mL	Phosphate Buffer, pH 6.8@37.0± 0.5° C	HPLC/UV λ=[redacted] (b) (4) nm

4. **Dissolution Acceptance Criterion: ACCEPTABLE**

The dissolution acceptance criterion of Q= (b) (4) % at 20 minutes for all strengths of Selexipag Tablets is acceptable.

5. **Bioequivalence Study AC-065-108: ACCEPTABLE**

6. **Biowaiver Request: ACCEPTABLE**

   - The Applicant's biowaiver request for selexipag dose strengths 400, 600, 800, 1000, 1200 and 1400 µg is acceptable.

E. Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable.

F. Novel Approaches

The submission did not contain any novel approaches.

G. Any Special Product Quality Labeling Recommendations

There are no special product quality labeling recommendations at this time.

H. Process/Facility Quality Summary (see Attachment A)

I. Life Cycle Knowledge Information (see Attachment B)

OVERALL OPQ RECOMMENDATION

Application Technical Lead's Assessment and Signature: We recommend **APPROVAL** of NDA 207947, from a product quality perspective. The drug substance and its synthesis are well characterized and controlled based on the in-process, release, and stability testing controls. The drug product design and formulation are robust and provide for a commercially viable product. The drug product control strategy, including dissolution testing, and the container closure ensure the quality and integrity of the drug product over the shelf life. The applicant provided adequate information to describe the manufacturing process, its control and the associated in-process tests. The manufacturing facilities identified to support commercialization were found to be in good standing.

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2015.08.25 13:24:02 -04'00'

On behalf of the OPQ review team

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

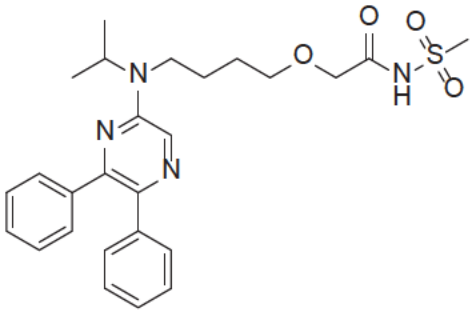
2.3.S DRUG SUBSTANCE

General Information

USAN: Selexipag
Laboratory name: ACT-293987, NS-304, MRE-304
Chemical name: 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl) acetamide

OR

2-[4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy]-N-(methylsulfonyl) acetamide
CAS number, if available: 475086-01-2



Molecular Formula: $C_{26}H_{32}N_4O_4S$ Molecular Weight 496.62
Description: Pale yellow crystalline powder
Solubility [redacted]
Melting Point: [redacted] °C
Partition Coefficient: [redacted]
Dissociation Constant: [redacted]
Hygroscopicity: Not hygroscopic
[redacted]
All clinical and commercial selexipag batches manufactured to date correspond

to the (b) (4)

(b) (4) (b) (4)

As noted above, the drug substance was (b) (4) (b) (4)

Comment #4 of Post-Mid-Cycle Information Request (14-AUG-2015):

(b) (4) *in the drug substance: We are concerned about the* (b) (4) (b) (4)

Applicant Response #4:

During development, (b) (4) (b) (4)

FDA Evaluation of Response #4: *Acceptable.* (b) (4) (b) (4)

Selexipag is considered a BCS Class (b)(4) compound, (b)(4) It has a narrow therapeutic range and undergoes enzyme-catalyzed hydrolysis to ACT-333976, which is 37-fold more potent than selexipag itself.

Reviewer's Assessment: Adequate. Selexipag is a BCS Class (b)(4) compound (b)(4) with three known (b)(4) (b)(4) The molecule and its physical properties appear to be well studied, with adequate understanding to support NDA 207947.

2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?
2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

The drug substance is manufactured via (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

[redacted]

Reviewer's Assessment: Adequate. Based on the in vitro Ames tests, 7 analyses, carryover studies, and chemical reactivity considerations, the applicant concluded that there is negligible risk associated with potentially genotoxic impurities and no PGIs are included in the DS specifications; this appears acceptable.

(b) (4)

2.3.S.4 Control of Drug Substance

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?
10. Are all the analytical procedures appropriately described and validated for their intended use?

Proposed specifications for selexipag drug substance are shown in the following table.

Drug substance specifications.

Test	Acceptance criteria	Method
Appearance	crystals or crystalline powder	Visual examination
Color	pale yellow to yellow	Visual examination

(b) (4)

In the original submission, the applicant proposed separate specifications for (b) (4) This was addressed in an information request sent on 29-MAY-2015 and shown below.

Drug Substance Comment #3 of Mid-Cycle Communication (29-MAY-2015):

We note your separate proposed drug substance specifications for (b) (4) *impurities (limited to ≤* (b) (4) *% and ≤* (b) (4) *%, respectively). Given that all*

(b) (4) impurities are observed at levels ≤ (b) (4)% in the provided batch data, adjust the drug substance specifications to contain a single general acceptance criterion of ≤ (b) (4)% (the identification threshold) to capture any (b) (4) impurity.

Applicant Response #1 (24-JUN-2015):
All impurities except the (b) (4) impurities (b) (4) will be reported as unspecified impurities with a limit of ≤ (b) (4)% each.

The sponsor proposes to (b) (4)

FDA Evaluation of Response #1: *Acceptable. (b) (4) are limited to NMT (b) (4)% (the identification threshold), according ICH Q3A.*

Identity is confirmed by (b) (4) residual solvents are controlled at (b) (4) than ICH Q3C recommended limits, and heavy metals are monitored. Control of (b) (4) identified impurities is acceptable, as discussed in 2.3.S.3 above.

(b) (4) (b) (4) controlled at NMT (b) (4)% w/w (b) (4). Specifications for particle size distribution (b) (4) were proposed based on drug product development studies that assessed the impact of particle size on various physicochemical properties of the tablets (b) (4) and bioavailability in dogs (see 3.2.P.2.2.3 of the application). Particle size results for drug substance batches used in the pivotal clinical trials and in the bioequivalence studies were also submitted (response to quality IR; 24-JUN-2015)) to justify the proposed PSD specifications. Cumulatively, the results of these studies appear to support the proposed particle size specification (b) (4) However, the data did not support the (b) (4) The applicant was asked to (b) (4) this specification in an information request sent on 14-AUG-2015 (shown below), and their subsequently proposed specification (D90 ≤ (b) (4) µm) is acceptable.

Comment #3 of Post-Mid-Cycle Information Request (14-AUG-2015):
The data you have provided in the amendment dated 24-Jun-2015 do not support the particle size specification (b) (4)

Applicant Response #3 (21-AUG-2015):
After a thorough review of the results of the (b)

FDA Evaluation of Response #3: *Acceptable.*

Analytical Procedures
All of the applicant's test methods for standard release specifications appear to be compendial, except for assay, related substances, residual solvents, PSD, and (b) (4).

Validation/Verification of Analytical Procedures
The HPLC method for assay (b) (4) was validated with respect to specificity, accuracy, precision, linearity, range, solution stability, and robustness; this is acceptable. Standard and sample solutions were stable for (b) (4) hours (b) (4).

The HPLC method for related substances (b) (4) and the (b) (4) method for residual solvents were both validated for specificity, accuracy, precision, linearity, robustness, range, and solution stability, and LOD and LOQ were established. Sufficient results were provided. Standard and sample solutions were found to be stable for (b) (4) hours at (b) (4). (b) (4)

The (b) (4) method used to (b) (4) was validated with respect to specificity, linearity, accuracy, precision, LOD, LOQ, and robustness, and sufficient results were provided.

The (b) (4) method for determining PSD was validated with respect to repeatability and robustness. Additionally, the (b) (4) identification method was validated for specificity (b) (4) and repeatability. This is acceptable.

The HPLC methods for assay and related substances and the (b) (4) method for PSD underwent FDA methods verification and were found acceptable for quality control and regulatory purposes (see Methods Validation Review, 08-JUL-2015). Note: Verification of the (b) (4) method for (b) (4) was not performed due to instrument limitations.

Batch Analysis
Batch analysis results are provided for drug substance registration (Q000000562, Q000000725, Q000000726) and commercial/validation (Q000001065, Q000001066, Q000001067) batches (b) (4) in 3.2.S.4.4. Batch results for the following additional batches were provided in 3.2.S.2.6: preclinical/clinical batches manufactured at (b) (4) (20; 21; 22; 23 – which provided aliquot "batch 24"; 25 – which provided aliquots "batch 26" and "batch 33"; and 32) and clinical (Q000000296) and pre-validation (Q000001064) batches manufactured at (b) (4) Batch analysis data for Batches Q000001065, Q000001066, and Q000001067, which were tested using the proposed drug substance specifications and methods, are shown below. (Note: The applicant has since proposed a single specification for all (b) (4) impurities, NMT (b) (4)% each.)

Parameters	Batch Q000001065	Batch Q000001066	Batch Q000001067
Appearance	crystalline powder	crystalline powder	crystalline powder
Color	pale yellow	pale yellow	pale yellow

(b) (4)

[redacted]

LOQ: limit of quantitation

The ranges for all provided batch test results are summarized as follows:
Appearance/Color: all conform to pale yellow crystalline powder

(b) (4)

[redacted]

(b) (4)

Reviewer's Assessment: Adequate. The proposed specifications are acceptable to ensure the identity, strength, and purity of the drug substance. The analytical test methods were validated appropriately and corresponding acceptance criteria were adequately justified. The batch analysis data provided support the manufacturers' ability to generate quality drug substance. Particularly after the process was transferred to and optimized at (b) (4) (the proposed commercial manufacturing site), levels of impurities were minimized affording drug substance of consistent quality. Therefore, there appears to be minimal risk of quality issues in the material sourced from (b) (4)

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

Reviewer's Assessment: Adequate. Based on the batch data summarized above, there is minimal risk associated with the applicant's proposed control strategy. The acceptability of the control strategy has been demonstrated through adequate batch data for at least (b) (4) of drug substance (b) (4) manufactured at commercial scale using the commercial process.

2.3.S.5 Reference Standards or Materials

12. Are the drug substance reference standards satisfactory?

The applicant is using in-house standards for the drug substance and all of the specified impurities (b) (4) The selexipag reference standard (b) (4) which is a portion of registration batch Q000000726 (b) (4) was characterized as discussed in 3.2.S.3. Each of the impurity reference standards was characterized using (b) (4)

Reviewer's Assessment: Adequate. Each of the reference standards was characterized using (b) (4) which supported the proposed structures. In addition to structural elucidation, the identity, purity, and strength of each standard were determined to be adequate.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

The drug substance is packed into (b) (4) The applicant stated that the (b) (4) used in the (b) (4) packaging is food grade certified, complying with (b) (4) (b) (4)

Reviewer's Assessment: Adequate. The proposed container closure system appears adequate to protect the drug substance, given that solid state selexipag is not considered hygroscopic or light-sensitive.

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

In the original submission, the applicant provided (b) months of (b) (4) data (b) (4) for the (b) (4) drug substance registration batches, along with (b) (4) months of

(b) (4) stability data for one batch (Q000000562) and (b) (4) months of (b) (4) data for each of the other two batches (Q000000725 and Q0000000726). (b) (4) months of (b) (4) and (b) (4) months of (b) (4) supportive stability data were provided for the clinical batch (Q000000296) of selexipag manufactured using the commercial process on commercial scale at (b) (4) Based on this data, the applicant was requesting a (b) (4)-month retest date. According to ICH Q1E, the maximum retest period that could be granted based on this amount of data would be (b) (4) months. The applicant was notified of this in an information request on 29-MAY-2015 as follows.

Drug Substance Comment #1 of Mid-Cycle Communication (29-MAY-2015):

We acknowledge your proposal of a (b) (4)-month retest period for selexipag drug substance. However, the (b) (4) data provided (b) (4) only support a (b) (4)-month retest period. Adjust the retest period for the drug substance accordingly.

Applicant Response #1 (24-JUN-2015):

Since the initial submission, the (b) (4) months stability data at (b) (4) for the batches Q000000725 and Q000000726 became available and are consistent with those data reported previously for the registration batch Q000000562. Overall, no significant changes in the physical, chemical and pharmaceutical characteristics were observed for three registration batches with little variability. In addition, the (b) (4) months stability data on a previous clinical batch (batch Q000000296) became available. A slight increase of (b) (4) can be observed, but the value after (b) (4) months (b) (4) remains below the limit of (b) (4) %.

Overall, the (b) (4) data and accelerated data showed little change over time and little variability. Based on these data, the proposed retest date of (b) (4) months is justified for selexipag, (b) (4) as proposed.

FDA Evaluation of Response #1: *Acceptable. The data establish a (b) (4)-month retest date.*

The stability specifications include routine testing of appearance/color, (b) (4) related substances, and assay and non-routine testing of (b) (4), particle size distribution, and microbial quality; the acceptance criteria are consistent with the release specifications. There is a slight increase in (b) (4) levels (and therefore total impurities) under both (b) (4) conditions; under (b) (4) conditions, the greatest increase in (b) (4) levels among registration batches is (b) (4) % w/w (b) (4) All data remained well within specifications.

Based on these results, the applicant proposes a (b) (4)-month retest date when the drug substance is (b) (4) This extrapolation appears acceptable as there is little variability in (b) (4) data.

(b) (4) stability testing for the (b) (4) registration batches will continue up to (b) (4) months according to an acceptable stability protocol. The applicant states that samples

from the (b) (4) commercial batches have also been put on stability following the same testing protocol as the registration batches. The applicant also committed to monitoring one batch per future campaign according to an acceptable stability plan. Note: The applicant states that the additional stability results for the registration batches and the results from the commercial batches (b) (4)

Based on the applicant's stress studies, selexipag is prone to (b) (4) The drug substance also shows degradation (b) (4)

Reviewer's Assessment: Adequate. The applicant has proposed a (b) (4)-month retest period for selexipag drug substance, based on (b) (4) months of (b) (4) data and (b) (4) months of (b) (4) data for (b) (4) registration batches. Supportive stability data out to (b) (4) months on one batch manufactured at (b) (4) using the commercial process and scale are also provided. Because there is no trending observed (b) (4) a (b) (4)-month retest period appears acceptable.

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature: I recommend approval based on the drug substance information presented in this application.

Katherine Windsor, Ph.D., 23-AUG-2015

Supervisor Comments and Concurrence: I concur.

Kasturi Srinivasachar, Ph.D., Acting Branch Chief, 25-Aug-2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

(Include a summary of how the product design relates to the proposed patient population and the clinical indication. (e.g., rationale for the dosage selections, unique design features of the proposed drug product etc.).

2.3.P.1 Description and Composition of the Drug Product

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

Selexipag is manufactured as round film-coated immediate release tablets in eight different strengths. The tablets are manufactured with the following strengths of the active ingredient: 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg. Each strength of the tablets is distinguished by the color of the film-coat as well as the number that is debossed on the tablet. The following table summarizes the composition of all the eight strengths of the tablets.

Composition of selexipag film-coated tablets

Ingredients	Quality Std.	Function	Amount of Selexipag per tablet							
			200µg	400µg	600µg	800µg	1000µg	1200µg	1400µg	1600µg
			Composition of (b) (4) Tablet							
Selexipag	--	Active ingredient	0.2 mg	0.4 mg	0.6 mg	0.8 mg	1.0 mg	1.2 mg	1.4 mg	1.6 mg
D-Mannitol	USP/NF	(b) (4)								
Corn Starch	USP/NF									
Low substituted hydroxypropylcellulose	USP/NF									
Hydroxypropylcellulose	USP/NF									
Magnesium stearate	USP/NF									
(b) (4)										
Hypromellose	USP/NF	(b) (4)								
Propylene glycol	USP/NF									
Titanium Dioxide	USP/NF									
Iron oxide red	USP/NF									
Iron oxide black	--									
Iron oxide yellow	USP/NF									
Carnauba wax	USP/NF									
Weight of coating	--									
Total weight of the film-coated tablets	--									

Reviewer's Assessment: Adequate.

Selexipag is a (b) (4) *drug substance and each selexipag tablet contains only microgram levels of the active ingredient. Patients are generally titrated starting with the lowest dose of 200 µg. The dose is slowly adjusted upwards to reach a target dose, which varies between patients. To accommodate this, the sponsor is manufacturing the drug product in eight different dose strengths. Although the amount of the active ingredient varies between the tablets, the total weight and size of the tablets remain the same. The only differences in composition between the tablets are* (b) (4) *The tablets are visually differentiated by the color of the film-coat and the numbers that are debossed on the tablets. A combination of unique debossing and unique coloring helps distinguishing the tablets of different strengths. However, from the patient perspective the color may be the single most quality attribute in distinguishing the tablets of different strengths. Therefore, the colors should be sufficient to discriminate these tablets and do not cause any confusion to the patients. This is further discussed under the formulation development section (see below).*

There are no novel ingredients – all the excipients, (b) (4) *, are compendial. The colors of the film coat are* (b) (4) *. The manufacturer has reported* (b) (4) *The description and the composition of the drug product are adequate and they meet the requirements outlined in 21 CFR 314.50(d)(1)(ii).*

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

P.2.1.1 Drug Substance

The drug product contains selexipag as the active ingredient. Selexipag is a pale yellow crystalline powder with a melting point of (b) (4) C. It has a partition coefficient (log P) of (b) (4) Selexipag has (b) (4) Selexipag exists in (b) (4) The drug product is manufacturing using selexipag (b) (4) Please refer to the drug substance review section for more details about this drug substance.

P.2.1.2 Excipients

The following table summarizes the excipients and their levels in the drug product formulation.

Composition of selexipag film-coated tablets

Ingredients	Composition	IIG Limit*
D-Mannitol	(b) (4)	
Corn Starch		
Low substituted hydroxypropylcellulose		
Hydroxypropylcellulose		
Magnesium stearate		
Hypromellose		
Propylene glycol		
Titanium dioxide		
Iron oxide red		
Iron oxide black		
Iron oxide yellow		
Carnauba wax		

*Corresponds to the amounts that are present in oral tablets.
**Listed as ferrosoferric oxide in the IIG database.

P.2.2.1 Formulation Development

As part of the formulation development, the sponsor has carried out several studies to assess the impact of the excipients on the drug product quality attributes.

(b) (4)

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(b) (4)

[redacted]

Container closure system: *The pharmaceutical development shows that* 10 Page(s) of Draft Labeling have [redacted] *Though the sponsor plans to* 10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page [redacted] *within US it will be marketed exclusively in the 50 mL HDPE bottles. Therefore, only the 50 mL HDPE container closure system is relevant for this NDA.*

Manufacturing Process Development: *Refer to the process review by Dr. Akm Khairuzzaman.*

Microbiological Attributes: *The specification as per USP <61> and USP <62> is adequate for a non-sterile solid oral dosage.*

Compatibility: *Since the drug product is formulated as tablet, interaction between the packaging components and the drug product is not expected. Therefore, it is acceptable that the sponsor did not carry-out the compatibility study.*

2.3.P.4 Control of Excipients

1.Is the quality of all excipients adequately controlled with satisfactory specifications?

Applicant's Response:

The following table lists all the excipients that are used in the drug product along with the quality standard.

Excipients quality standard

Excipient	Quality Std.
D-Mannitol	Ph. Eur. and USP/NF
Corn Starch	Ph. Eur. and USP/NF
Low substituted hydroxypropylcellulose	USP/NF
Hydroxypropylcellulose	Ph. Eur. and USP/NF
Magnesium stearate	Ph. Eur. and USP/NF
Hypromellose	Ph. Eur. and USP/NF
Propylene glycol	Ph. Eur. and USP/NF
Titanium Dioxide	Ph. Eur. and USP/NF
Iron oxide red	Ph. Eur. and USP/NF
Iron oxide black	--
Iron oxide yellow	Ph. Eur. and USP/NF
Carnauba wax	Ph. Eur. and USP/NF

All the excipients, (b) (4), are compendial (b) (4) The sponsor has provided the technical data sheet for the black iron oxide (b) (4) Black iron oxide (b) (4) The technical sheet lists assay for iron at NLT (b) (4)%. The manufacturer also has listed the specification for heavy metals and microbial limits. The sponsor states that none of the excipients are derived from (b) (4)

Reviewer's Assessment: Adequate

All the excipients, (b) (4) are compendial and their quality is controlled by the compendial specification. (b) (4) Note that the IIG data base lists iron oxide black under the unique name 'ferrosoferric oxide'. The sponsor has not described the analytical methods that are used for the analysis of the excipients. Since all the excipients are compendial grade, the associated compendial analytical methods are sufficient to assure the quality of these excipients. Therefore, this is acceptable.

Although (b) (4) has the USP/NF specification, following FDA's recommendation, the sponsor has included additional in-coming acceptance criterion for the particle size (b) (4) This was implemented to minimize the risk of (b) (4) during the formulation.

As discussed under the pharmaceutical development section, the sponsor compared the (b) (4) *Since, the sponsor commits to use exclusively* (b) (4) *this will assure that the quality of the drug product will remain the same. Therefore, this is acceptable. However, if there is any potential change in the source of this excipient in the future, we will ask that the sponsor evaluates the compatibility prior to its use.*

2.3.P.5 Control of Drug Product

2. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

Applicant's Response:

P.5.1 Specification(s)

P.5.1 CONTROL OF DRUG PRODUCT: SPECIFICATIONS

The specifications at release and end of shelf-life of selexipag film-coated tablets 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg are provided in Table 1.

Table 1 Selexipag film-coated tablets specifications

Test	Acceptance criteria	Method
Appearance	Round film-coated tablet, debossed[1] on (b) (4) on one side,	Visual
Color	(b) (4) see Table 2	Visual
(b) (4)		

Table 2 Color of selexipag film-coated tablets

200 µg	400 µg	600 µg	800 µg	1000 µg	1200 µg	1400 µg	1600 µg
light yellow	red	light violet	green	orange	dark violet	dark yellow	brown

P.5.4 Batch Analyses

Actelion has provided the batch analysis data for (b) registration batches for each of the eight configurations of the selexipag tablets (b) (4) All these batches were manufactured by (b) (4). The following table lists the batch numbers of the drug product along with the corresponding batch number of the drug substance that was used in the manufacturing.

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Reviewer's Assessment: Adequate

Stability of the registration batches: This stability study was carried out using a (b) (4) *and* (b) (4) *approach and it is acceptable as per the ICH Q1D guideline (see below for justification). Although tables for the stability data are only presented for the 200 and 1600 µg tablets in this review (see the stability data table above), this reviewer reviewed the data for all the batches for which the data is available. The drug product met the acceptance criteria throughout the stability study period (up to 24 months) for all the batches and no out of specification excursion was noted. The 200 µg strength of the tablet* (b) (4) *. Irrespective of the strength, the only impurities that are detected at* (b) (4) *% are the degradants* (b) (4) *The levels of these two degradants* (b) (4) *. However, even at the* (b) (4) *month time point, these two degradants are present at* (b) (4) *their acceptance criteria limit. The dissolution profile during the stability study will be reviewed by Dr. Om Anand.*

Shelf-life for the 'Bottle 60' configuration: The sponsor has provided the long term stability data for up to 24 months for 5 strengths of this configuration and they propose a shelf-life of 3 years based on the ICH Q1E guideline (b) (4) *The sponsor has submitted statistical analysis supporting their extrapolation of the shelf-life. The statistical analysis of the stability data was also carried out at FDA by Dr. Zhuang Miao from the Office of Biostatistics. This study used the 24 month stability data to generate the 95% one sided confidence interval for the selexipag content (i.e. assay) during its shelf life. While the sponsor estimated the shelf life by pooling the batches of different strengths, the FDA's assessment was based on the analysis of batches corresponding to each strength. As a result, the FDA's estimation of shelf life differs slightly from the sponsor's estimation. The projected shelf life for each strength that was calculated by FDA is given below:*

200 µg tablets: (b) (4) *months*

400 µg tablets: (b) (4) *months*

800 µg tablets: (b) (4) months

1200 µg tablets: (b) (4) months

1600 µg tablets: (b) (4) months

The estimated shelf life for the 1200 µg tablet from FDA's statistical evaluation is (b) (4) months, which is (b) (4) to the proposed shelf life of 36 months. The proposed shelf-life of 36 months may be granted for all the strengths of the selexipag tablets based on the following reasoning:

- *The stability evaluation can be considered as (b) (4) approach.*
- *All the strengths have the same container volume, head space and (b) (4) /tablet ratio. Therefore, the role of the CCS on the stability behavior of the tablets is expected to be the same across all strengths.*
- *The lowest and the highest strengths have ≥ (b) (4) months of projected shelf-lives respectively.*
- *The most likely reason for (b) (4)*
- *(b) (4)*
- *(b) (4)*

Therefore, in this reviewer's assessment, a shelf-life of 36 months may be granted for the 'Bottle 60' configuration irrespective of the selexipag strength.

Shelf-life for 'Bottle 140' configuration: For this configuration (200 µg tablets only), the sponsor has provided the long term stability data for up to 9 months for one batch. The stability profile of the 200 µg tablets in this configuration appears to be similar to that of the same tablet packaged as 'Bottle 60'. In addition, the head space for 'Bottle 140' is

lower than that of 'Bottle 60'. Therefore, based on the 24 month stability data for the 'Bottle 60' configuration and the 9-month stability data for the 'Bottle 140' configurations, we can expect that the shelf-life of the 'Bottle 140' configuration should be at least 2 years. This reviewer agrees with the sponsor's proposal of 2 years of shelf life for the 200 µg tablets that will be packaged in the 'Bottle 140' configuration.

(b) (4)

(b) (4)

<u>Photostability:</u> The sponsor has evaluated the photostability of all the eight strengths of the selexipag tablets. (b) (4)

(b) (4)

(b) (4)

The photostability method itself is adequate.

As discussed under the pharmaceutical development section, patients are likely to use the color of the film coat to differentiate various strengths of selexipag tablets. Therefore, the CMC review team was concerned whether there is a potential for color fading over shelf life which could potentially result in medication error. However, the result from the photostability study indicates that the color is quite stable under the photostability condition and in addition, (b) (4) *Therefore, the reviewer believes that the risk of color fading over shelf life is low and it is unlikely to cause medication error.*

In summary, the sponsor has demonstrated that selexipag tablets marketed in 'Bottle 60' and 'Bottle 140' have adequate stability and that the drug product is expected to meet the stability/regulatory specification through its proposed shelf life. Therefore, the identity, strength, quality, purity, potency and bioavailability of the drug product is expected remain with the specification limits through its proposed shelf life. Based on the available stability data, this reviewer recommends that the following shelf-lives may be granted: 'Bottle 60': 36 months and 'Bottle 140': 24 months.

R.2 Comparability Protocols

9. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Applicant's Response:

Reviewer's Assessment: There are no comparability protocols.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

This NDA is recommended for approval from the CMC drug product perspective. All the CMC issues related to the drug product have been resolved. The composition and specification for selexipag 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg are adequate. The drug substance and the excipients are adequately controlled through compendial and non-compendial specifications. The analytical methods are adequate to control the quality of the drug product through its shelf life. The container closure system and the labeling are adequate to assure the integrity of the drug product. The drug product has adequate stability to support 36 months of shelf life for the 'Bottle 60' configuration (all the 8 strengths) and 24 months of shelf life for the 'Bottle 40' configuration (200 µg strength).

Mariappan Chelliah, 24-Aug-2015

Supervisor Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, 24-AUG-2015

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Batch Formula

10. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Applicant's Response:

The proposed formulation composition provided under the 3.2.P.1 section is as follows:

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[redacted] will conduct testing for microbiology only on the drug product. The last three inspections conducted [redacted] and [redacted] were classified NAI. The facility is approvable for the responsibilities listed in the application based on profile and inspection history.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:
Following a review of the submission and inspectional documents there are no significant outstanding issues that would prevent approval of the manufacturing facilities for NDA 207947. Based on the compliance history and the adequacy of the processes, control strategies and data reviewed during the pre-approval inspections, the manufacturing facilities listed above for NDA 207947 are recommended for approval.

Ruth Moore, Ph.D.
Chemist
August 24, 2015

Supervisor Comments and Concurrence: I concur with the facility reviewer's assessment and recommendation for approval.
Zhihao Peter Qiu, Ph.D.
Branch Chief
Division of Inspectional Assessment
OPF/OPQ/CDER

ASSESSMENT OF BIOPHARMACUETICS INFORMATION

Review: The Biopharmaceutics review focuses on the evaluation and acceptability of the following:

a) The dissolution method and acceptance criteria;
b) The bioequivalence study including its design, conduct, and the results;
c) The biowaiver request.

16. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

Yes. The in-vitro dissolution test method and the acceptance criterion [Q= [redacted]% at 20 minutes] is acceptable and adequate for assuring consistent bioavailability of the drug product.

16.1 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

As per the Applicant, Selexipag is considered to be a biopharmaceutics classification system (BCS) class (b) (4) compound, (b) (4) Selexipag is (b) (4) The solubility data are presented below in Table 16.1.1 below:

Table 16.1.1 Solubility of selexipag in aqueous buffer

(b) (4)

The permeability of selexipag was investigated in vitro (b) (4) (b) (4)

16.2 What is the proposed dissolution method?

The proposed dissolution method for Selexipag Tablets is summarized in Table 16.2.1. Dissolution testing is performed at release and in the stability program. The (b) (4) conditions for quantifying Selexipag concentrations are summarized in Table 16.2.2.

Table 16.2.1: Summarized dissolution testing conditions for Applicant's proposed dissolution method for Selexipag tablets,

Parameter	Description
Dissolution apparatus	USP apparatus 2 (paddle)
Dissolution medium	Phosphate buffer pH = 6.8
Volume	900 mL
Paddle speed	50 rpm/min
Temperature	37.0± 0.5° C

(b) (4)

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testing. Please provide a revised drug product specification table and update your stability protocol accordingly.

Applicant Response [dated 8/21/2015]: The dissolution specification at release and during stability has been changed to Q= (b)(4)% at 20 minutes. The revised specification for dissolution of Q= (b)(4)% at 20 minutes will be applicable for Selexipag film-coated tablets for release and stability testing from October 2015 onwards (at the next planned manufacturing campaign and at the next stability time-points). The CTD documents 3.2.P.5.1 Specification and 3.2.P.5.6 Justification of specification have been updated accordingly. The stability protocol will also be updated accordingly.

Reviewer's Assessment of the dissolution Acceptance Criterion:
Acceptable

The Applicant accepted the recommended dissolution acceptance criterion of **Q= (b)(4)% at 20 minutes** for all strength of Selexipag Tablets for release and stability testing.

17. **Are the changes in the formulation, manufacturing process, and/or manufacturing sites during the development appropriately bridged to the commercial product?**

Yes. The applicant intends to supply selexipag commercially as film-coated tablets in eight different dose strengths (200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg).

(b) (4)

The following information is reviewed in this section:

17.1 Bioequivalence study [AC-065-108]
17.2 Biowaiver Request

17.1 **Bioequivalence study [AC-065-108]**

Background: Selexipag (ACT-293987) is an orally available, selective non-prostanoid agonist of the prostacyclin (IP) receptor. Selexipag and its active metabolite, ACT-333679, are active at the IP receptor. ACT-333679 has a 13-fold higher affinity than selexipag for the human IP receptor. It is at least 16-fold more potent than selexipag in cellular systems and is present at 3- to 4-fold higher levels than the parent drug at

steady-state in humans. ACT-333679 is the major contributor to the efficacy of selexipag in animals and man.

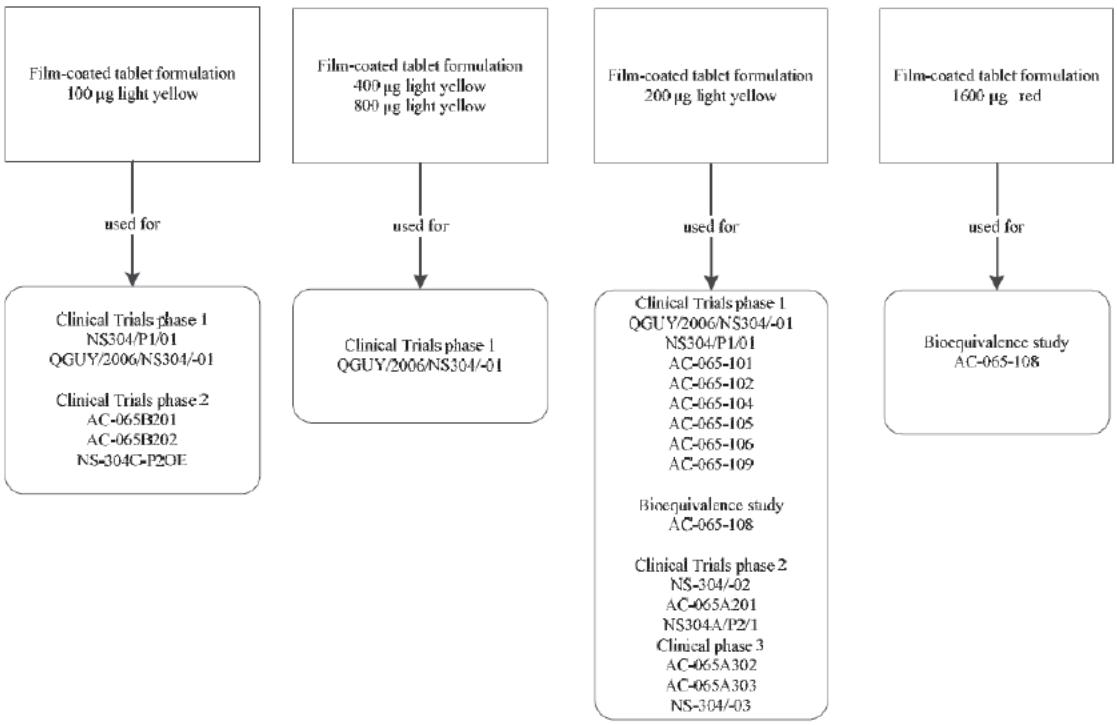
Bridging of formulations used in the two pivotal studies

Selexipag 200 µg and 1600 µg film-coated tablets were used in the bioequivalence study (AC-065-108). The applicant intends to supply selexipag commercially as film-coated tablets in eight different dose strengths (200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg). The composition remained the same during the clinical development and will be identical to the composition of the to be marketed tablets. Therefore, the 200 µg clinical and commercial dose formulations are identical.

(b) (4)

Selexipag 100 µg, 400 µg and 800 µg film-coated tablets were used in the initial clinical Phase 1 and 2 studies. In the pivotal placebo-controlled Phase 3 study (AC-065A302/GRIPHON) only the 200 µg film-coated tablet strength was administered up to a dose 1600 µg (8 tablets of 200 µg each) b.i.d., which was the highest dose allowed in this study.

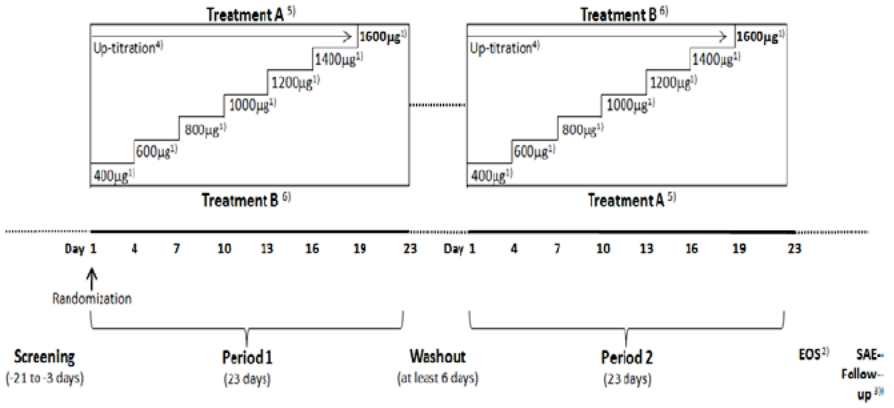
Figure 17.1.1: Dose strengths used during development



In order to bridge the clinical tested strength (200 µg) to the commercial strengths, the following information was provided:

- an *in vivo BE* study [AC-065-108] demonstrating bioequivalence between the highest strength (1600 µg) following an up-titration regimen and the lowest strength tablets (8 x 200 µg).
- comparative in vitro dissolution profiles for all strengths (200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg).
- a biowaiver request for the selexipag dose strengths: 400, 600, 800, 1000, 1200, and 1400 µg.

Review of the in vivo BE study [AC-065-108]

Study Title	A single-center, open-label, randomized, two-period, two-treatment, crossover study in healthy male subjects to demonstrate bioequivalence of 1600 µg Selexipag administered as eight tablets of 200 µg (reference drug: 8 x 200 µg) or as single tablet of 1600 µg (test drug: 1x1600 µg).
Design	Single-center, open-label, randomized, two-period, two-treatment, crossover, multiple-dose, up-titration, Phase 1, bioequivalence study in healthy male subjects under fed conditions.
Methodology	A total of 80 subjects were enrolled and treated in the study. All of these 80 subjects were included in the analysis of safety and tolerability endpoints, and 65 were included in the analysis of the PK endpoints. The drop-out rate observed in this study was approximately 20%. Randomization (1:1): treatment sequence AB or BA Up-titration scheme (200 µg strength tablet for both treatments): Day 1–3: 400 µg b.i.d. Day 4–6: 600 µg b.i.d. Day 7–9: 800 µg b.i.d. Day 10–12: 1000 µg b.i.d. Day 13–15: 1200 µg b.i.d. Day 16–18: 1400 µg b.i.d. **Figure 17.1.2 Study design**  1) Administered b.i.d. (in the morning and in the evening) with the exception of Day 23 when only the morning dose was administered. 2) End-of-study visit (3–5 days after last study drug administration). 3) Contact performed by telephone (30–32 days after last study drug administration). 4) Up-titration during Treatments A and B was performed in 200 µg steps with multiples of 200 µg film-coated tablets starting with 400 µg selexipag b.i.d.

5) Treatment A: selexipag 1600 µg administered as 8 film-coated tablets of 200 µg b.i.d. from Day 19 to the morning dose of Day 23 (reference drug).

6) Treatment B: selexipag 1600 µg administered as single film-coated tablet of 1600 µg b.i.d. from Day 19 to the morning dose of Day 23 (test drug).

Reference: **Treatment A (reference drug: strength 200 µg) only:** Day 19–22: 1600 µg (8 × 200 µg tablets) b.i.d. Day 23: 1600 µg (8 × 200 µg tablets) o.d.).

Test: **Treatment B (test drug: strength 1600 µg) only: Day 19–22: 1600 µg (1 × 1600 µg tablet) b.i.d. Day 23: 1600 µg (1 × 1600 µg tablet) o.d.)**

Washout: Between the last dose of Period 1 and the first dose of Period 2 there was a washout lasting at least 6 days.

- Blood sampling: pre-dose, 0.30, 1.0, 1.30, 2, 3, 4, 5, 5:15, 6, 7, 8, 10, 11, 12, and 14 h. Total volume of blood collected during the study: 350 mL [45 mL for laboratory tests and 305 mL for bioanalysis].

- Anticoagulant: Lithium heparin

Subjects/ Demographics

A total of 80 subjects were enrolled and treated in the study.
All of these 80 subjects were included in the analysis of safety and tolerability endpoints, and 65 were included in the analysis of the PK endpoints. The drop-out rate observed in this study was approximately 20%.
Demographic summary of the patients recruited for the study is summarized in the following table :

Variable	Statistic/ Category	Sequence AB	Sequence BA	Total
Gender	Male	40 (100.0)	40 (100.0)	80 (100.0)
Race	White	30 (75.0)	28 (70.0)	58 (72.5)
	Black or African American	8 (20.0)	10 (25.0)	18 (22.5)
	Asian	2 (5.0)	1 (2.5)	3 (3.8)
	Other		1 (2.5)	1 (1.3)
Age (years)	N	40	40	80
	Mean	32.3	29.0	30.7
	SD	12.1	10.8	11.5
	SE	1.9	1.7	1.3
	Median	27.0	24.0	25.0
	Minimum	18	18	18
	Maximum	55	54	55
Height (cm)	N	40	40	80
	Mean	182.0	180.0	181.0
	SD	8.5	8.8	8.7
	SE	1.3	1.4	1.0
	Median	181.5	179.5	181.0
	Minimum	166	164	164
	Maximum	202	201	202
Weight (kg)	N	40	40	80
	Mean	78.99	77.38	78.19
	SD	11.22	12.17	11.66
	SE	1.77	1.92	1.30
	Median	80.30	76.20	78.65
	Minimum	60.3	57.9	57.9
	Maximum	103.0	105.4	105.4

Treatment: A and B on Day 1-18: up-titration, on Day 19-23: A = 8 x 200 µg tablets, B = 1 x 1600 µg tablet
Production date: 15JUL2013 15:43 1/2

Variable	Statistic/ Category	Sequence AB	Sequence BA	Total
Body Mass Index (kg/m^2)	N	40	40	80
	Mean	23.84	23.88	23.86
	SD	2.84	3.20	3.00
	SE	0.45	0.51	0.34
	Median	23.90	23.35	23.75
	Minimum	18.9	19.1	18.9
	Maximum	30.3	30.0	30.3

Treatment: A and B on Day 1-18: up-titration, on Day 19-23: A = 8 x 200 µg tablets,
Production date: 15JUL2013 15:43

BIOANALYTICAL

Table 17.1.1: Summary of Bioanalytical Method Validation BA-12.396, used in BE study AC-065-108

	Data
Bioanalytical method validation report location	Module 5, BA-12.396, one volume, 136 pages
Analyte	ACT-293987 (selexipag) and its active metabolite ACT-333679
Internal standard (IS)	ACT-293987B (b) (4) and ACT-333679B (b) (4)
Method description	(b) (4)
Limit of quantitation	
Average recovery of drug (%)	
Average recovery of IS (%)	
Standard curve concentrations (units/mL)	
QC concentrations (units/mL)	
QC Intra batch precision (%)	
QC Intra batch accuracy range (%)	
QC Inter batch precision (%)	
QC Interday accuracy range (%)	

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Summary of the BE study Results

A total of 80 subjects were enrolled in the study and were included in the All-treated analysis set. The subjects were randomized 1:1 to the treatment sequences AB (40 subjects) or BA (40 subjects), in which Treatment A was the reference treatment and Treatment B the test treatment. Fifteen subjects prematurely discontinued the study: 10 subjects within the treatment sequence AB and 5 subjects within the treatment sequence BA. 65 subjects completed the study according to the protocol and were included in the per-protocol analysis set: 30 subjects within the treatment sequence AB and 35 subjects within the treatment sequence BA.

Table 17.1.4: The PK parameters of selexipag and ACT-333679 are summarized in the following table:

BE Study No. AC-065-108								
Treatments (dose, dosage, form, Route) [Product ID]	Subject's No., sex, age (mean, range)	Analyte	Mean parameters +/-SD (% CV)					
			C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h·ng/mL)	AUC_{∞} (h·ng/mL)	$t_{1/2}$ (h)	k_{el} (h^{-1})
Test: (Up-titration from 400 to 1400 µg b.i.d. selexipag, with increments of 200 µg b.i.d., followed by 1 × 1600 µg tablet, 4.5-days b.i.d., Film-coated tablet, oral) [ACT-293987]	65 evaluable for PK analysis, sex: male age mean (range): 30.3 (18–55 years)	selexipag	19.41 ± 8.56 (44.1)	2.84 ± 0.90 (31.8)	51.0 ± 19.89 (39.0)	51.32 ± 20.16 (39.3)	1.72 ± 0.49 (28.3)	0.43 ± 0.09 (20.9)
		ACT-333679	25.48 ± 8.66 (34.0)	4.20 ± 0.85 (20.3)	131.94 ± 48.06 (36.4)	169.51 ± 81.58 (48.1)	5.05 ± 2.73 (54.1)	0.16 ± 0.05 (33.0)
Reference: (Up-titration from 400 to 1400 µg b.i.d. selexipag with increments of 200 µg b.i.d., followed by 4.5-days 8x 200 µg tablets b.i.d., Film-coated tablet, oral) [ACT-293987]	65 evaluable for PK analysis, sex: male age mean (range): 30.3 (18–55 years)	selexipag	17.93 ± 7.64 (42.6)	2.54 ± 1.10 (42.1)	49.56 ± 19.15 (38.6)	49.78 ± 19.28 (38.7)	1.67 ± 0.28 (16.8)	0.426 ± 0.067 (15.8)
		ACT-333679	24.51 ± 7.78 (31.7)	4.14 ± 0.86 (20.9)	127.83 ±44.26 (34.6)	160.52 ± 63.06 (39.3)	5.12 ± 2.48 (48.5)	0.16 ± 0.05 (32.9)

The statistical analysis of the PK parameters is summarized in the following table:

Table 17.1.5 Statistical analysis of the PK parameters

Analyte	Drug: Selexipag (No of subjects completed = 65)	Average BE Statistical Approach Dose (multiple-dose, 1600 µg b.i.d.)					
	Parameter**	Test	N	Reference	N	Ratio*	90 % CI
Selexipag	AUC_{0-t}	46.03 (40.02 , 52.95)	65	46.26 (42.14 , 50.78)	65	0.9907	0.9238 , 1.0625
	AUC_{∞}	46.29 (40.24 , 53.25)	65	46.45 (42.31 , 51.00)	65	0.9920	0.9254 , 1.0634
	C_{max}	17.28 (14.92 - 20.01)	65	16.51 (14.92 - 18.27)	65	1.0425	0.9520 , 1.1416
ACT-333679	AUC_{0-t}	120.82 (107.11 , 136.29)	65	120.06 (109.66 , 131.45)	65	1.0039	0.9498 , 1.0612
	AUC_{∞}	149.79 130.73 , 171.63)	65	147.97 (133.40 , 164.13)	65	1.0067	0.9466 , 1.0707
	C_{max}	23.46 (20.79 , 26.48)	65	23.30 (21.50 , 25.26)	65	1.0050	0.9404 , 1.0740

** Geometric mean (95% CI)
*Ratio of geometric means
Test: up-titration phase followed by 4.5 days b.i.d. 8x 200 µg tablet
Reference: up titration phase followed by 4.5 days b.i.d. 1600 µg tablet

The mean plasma concentrations of selexipag and metabolite ACT-333679 over 12 h in healthy subjects (N = 65) for both treatments are presented in Figures 17.1.3 and 17.1.4 below:

Figure 17.1.3: Arithmetic mean (± SD) plasma concentration-time profiles of selexipag over 12 h in healthy subjects (N = 65) at steady-state (Day 23) after treatment with 1600 µg of selexipag in Treatment A (reference) and Treatment B (test), Per-protocol set (linear and semi-logarithmic scales)

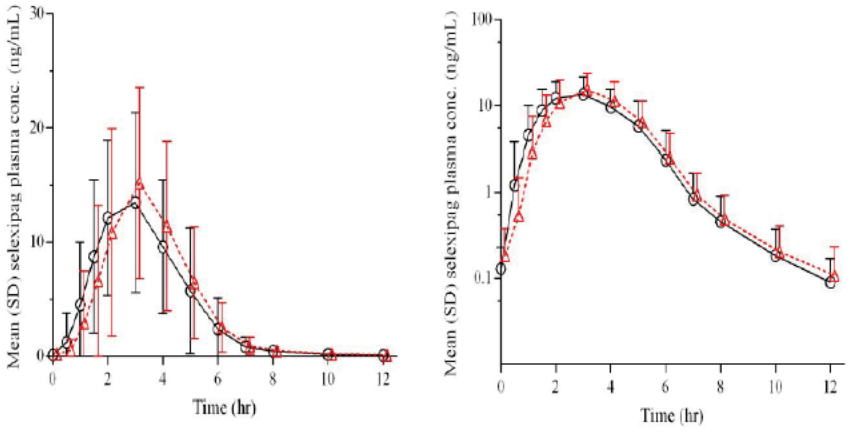
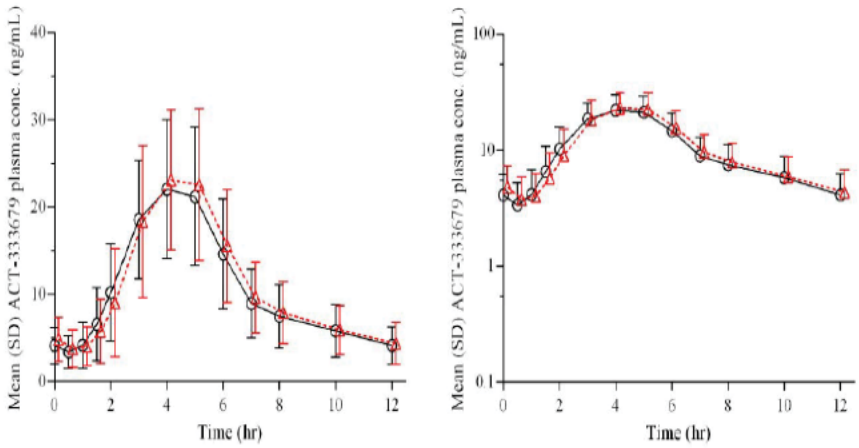


Figure 17.1.4: Arithmetic mean (± SD) plasma concentration-time profiles of the metabolite ACT-333679 over 12 h in healthy subjects (N = 65) at steady-state (Day 23) after treatment with 1600 µg of selexipag in Treatment A (reference) and Treatment B (test), Per-protocol set (linear and semi-logarithmic scales)



Treatment A (black continuous line and circles) = up-titration phase followed by 4.5 days b.i.d. 8 × 200 µg tablets, Treatment B (red dashed line and triangles) = up-titration phase followed by 4.5 days b.i.d. 1 × 1600 µg tablet.

Summary of Safety (BE study)

The safety evaluation included all subjects who received at least one dose of the study drug. No deaths or SAEs (Serious adverse event) were reported during this study. In total, 77 out of the enrolled 80 subjects reported at least one treatment-emergent AE during the study. The most frequent AEs were headache (86%), myalgia (73%), jaw pain (73%), fatigue (44%), nausea (46%), diarrhea (28%), dizziness (20%), and vomiting (18%). All AEs were of mild intensity. There was no difference in nature or overall frequency of AEs between treatments: 90% and 93% of the subjects reported at least one AE during Treatment A and Treatment B, respectively.

Reviewer's Assessment: BE Study ACCEPTABLE

Bioanalysis: The Applicant provided a detailed pre-study method validation report of the bioanalytical method for ACT-293987 (selexipag) and its active metabolite ACT-333679. The validation report investigated the **selectivity**, recovery and (b) (4) effects, carryover, calibration, intra- and inter-day accuracy and precision, linearity, and stability. The reported results met the acceptance criteria outlined in the bioanalytical method validation guidance. The pre-study method validation is satisfactory. The Applicant also provided bioanalytical report and summary of summary of standard curve and QC data for BE sample analyses. In addition, incurred sample re-analysis (ISR) was performed and (b) (4) % of the individual ISR measurements were within (b) (4) % of the mean of the initial and ISR results.

In the bioequivalence (BE) study AC-065-108, the Applicant reported that in the preparation of the calibration and quality control samples of ACT-293987 and ACT-

333679, two different approaches were used due to an error in the processing of the calibration and quality control samples. The Applicant was asked to explain why the error in the processing of the calibration and quality control samples, should not affect the analysis of the BE study samples and outcome of PK results of this study.

Therefore, the following Information request on the preparation of the calibration and quality control samples was sent to the Applicant[7] on 5/29/2015:
In bioequivalence (BE) study AC-065-108, you reported " (b) (4)

Explain why the error in the processing of the calibration and quality control samples, i.e. absence of the stabilizing agent hydrochloric acid, should not affect the analysis of the BE study samples and outcome of PK results of this study.

Applicant Response [dated 6/24/2015]:
Selexipag is metabolized (b) (4)

(b) (4)

[7] Information Request dated 5/29/2015 (DARRTS: NDA 207947: COR-NDAIR-01(Information Request): 05/29/2015: CLAYTON, TANYA D

(b) (4)

Reviewer's Assessment of Applicant's Response: The Applicant erroneously prepared calibration and QC samples using a modified analytical method which affected the selexipag and ACT-333679 plasma concentrations and therefore the Applicant adapted a correction factor. Though, this is not an ideal approach but it is deemed acceptable in this case since all the samples were prepared using the correct sample preparation method, the modified analytical method effects the outcome of the test and the reference samples in similar manner and therefore should not affect the outcome of the BE study. The Applicant's response is satisfactory and acceptable.

The bioanalysis of selexipag and ACT-333679 samples from the **BE Study is acceptable.**

Clinical and Pharmacokinetic outcome of the BE study AC-065-108:
Eighty (80) subjects were enrolled, of whom 15 prematurely discontinued the study, 65 subjects completed the study and included in PK and statistical analysis. The AE profile of selexipag was similar in both treatments. All AEs recorded were of mild intensity. No deaths or SAEs were reported during the study. Headache was the most frequently reported AE, followed by myalgia, jaw pain, fatigue, and nausea.

There were several deviations from the BE study protocol. Protocol deviation of "one or more than one dose missed" led to exclusion of 15 subjects from PK assessment. A number of minor deviations (e.g., visits out of time-window), were also recorded during the study and the Applicant provided details in the BE study report. The Applicant's handling of dropouts, adverse events, and protocol deviations, is acceptable. In the bioequivalence (BE) study, no concentrations were reported for subject # 129 plasma concentration-time profiles (Day 23) of selexipag, after treatment B, [page # 1518/2199]. The Applicant was asked to explain this in the following **Information request**[8]:
In bioequivalence (BE) study AC-065-108, for subject # 129 plasma concentration-time profiles (Day 23) of selexipag, after treatment B, no concentrations were reported [page # 1518/2199]. Explain no plasma concentration for this subject 129 after treatment B.

Applicant's Response (dated 6/24/2015): Subject 129 had very low concentrations of selexipag and ACT-333679 in treatment period B, (test treatment), after Day 21 compared to treatment period A. (reference treatment). Subject 129 completed the study, did not miss any pivotal PK assessment, and did not have any major protocol violation. He was a 54 years old, white man, with BMI 23.5 kg/m^2, and body weight

[8] Information Request dated 5/29/2015 (DARRTS: NDA 207947: COR-NDAIR-01(Information Request): 05/29/2015: CLAYTON, TANYA D

67.9 kg and had no relevant medical history and had 4 mild adverse events in period A and 3 in period. He received acetaminophen two times in treatment period A and no concomitant medication in treatment period B and study drug was administered according to the protocol in both treatment periods. From a bioanalytical point of view all PK samples for this subject were analyzed together in a single valid analysis run. The low concentrations of this subject in treatment period B could not be explained. In the absence of any clarification for these low concentrations and as a conservative approach he was included in the BE analysis.

In order to demonstrate that this subject did not affect the overall analysis of the study, the BE test was also performed after excluding Subject 129. The results show that the 90% CIs for the geometric mean ratios (test: reference treatment) for AUC_{τ} and $C_{max,ss}$ of selexipag and the metabolite, ACT-333679, lie within the acceptance interval of 80.00–125.00%.

Table 17.1.6: AC-065-108: Comparison of AUCτ and Cmax,ss, Treatment B vs Treatment A (N:64, Subject 129 excluded)

Statistic	Analyte	AUC_{τ} (h·ng/mL)	$C_{max,ss}$ (ng/mL)
Geometric mean ratio 90% CI	Selexipag	1.0094	1.0650
		0.9754 , 1.0446	0.9987 , 1.1357
	ACT-333679	1.0145	1.0183
		0.9862 , 1.0436	0.9774 , 1.0610

Treatment B (Test): up-titration phase followed by 4.5-days b.i.d. 8x 200 µg tablet
Treatment A (Reference): up-titration phase followed by 4.5-days b.i.d. 1600 µg tablet

Reviewer's Assessment of Applicant's Response: The plasma levels selexipag and ACT-333679 in subject 129 on day 23 were low. There was use of concomitant medication and a few side effects reported. There were no protocol deviations and the Applicant appropriately included the subject in the PK and the statistical analysis. However, the anomalous concentrations could not be explained. The Applicant excluded the subject # 129 from the PK and the statistical analysis and the study outcomes remains the same. This Reviewer confirmed the results and concluded that excluding the subjects does not affect the outcome of the study. The Applicant's response is satisfactory.

This Reviewer confirmed the BE results for the parent drug selexipag (ACT-293987) and its active metabolite ACT-333679 using SAS analysis and the following results were obtained:

Table 17.1.7 Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer for the parent drug Selexipag

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr * ng /ml)	45.67	46.10	0.99	92.38	106.25
AUC∞ (hr *ng /ml)	45.83	46.22	0.99	92.53	106.24
Cmax (ng /ml)	17.14	16.44	1.04	95.18	114.16

Table 17.1.8 Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer for the active metabolite ACT-333679

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr * ng /ml)	120.00	119.38	1.01	95.11	106.24
AUC∞ (hr *ng /ml)	141.58	140.02	1.01	95.08	107.53
Cmax (ng /ml)	23.31	23.20	1.00	94.04	107.40

These results are in agreement with those reported by the Applicant. The ratios of the geometric mean for selexipag and its metabolite ACT-333679 AUC_{τ} and $C_{max,ss}$, (Treatment B: Treatment A), are within the acceptance interval of 80.00–125.00%. The 12 hours plasma concentration-time profiles of selexipag and its metabolite ACT-333679, at steady-state (on Day 23), are similar between the test and the reference treatments.

Based on the provided data, it can be concluded the 1 × 1600 µg selexipag tablet and the 8 × 200 µg selexipag tablets administered following a multiple-dose up-titration scheme are bioequivalent.

17.2. BIOWAIVER:

17.2.1 Is there enough information to support the Biowaiver request for the middle strengths?

Yes, the biowaiver request for the middle strengths (400, 600, 800, 1000, 1200, and 1400 µg tablets) is supported by the provided information.

The intended commercial strengths are 200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg tablets. The clinical formulation (200 µg film-coated tablet used to dose patients up to 1600 µg bid.) was bridged with the commercial formulation using a BE study (AC-065-108-8X 200 µg vs. 1600 µg) and dissolution testing on all the dose strengths.

A biowaiver request for the selexipag tablet strengths 400, 600, 800, 1000, 1200, and 1400 µg is based on the fact that all the strengths are in the same dosage form and (b) (4) have similar dissolution data at the same dose level, bioequivalence is demonstrated between the 200 µg vs. 1600 µg strengths and dose-proportional pharmacokinetics is demonstrated over the therapeutic dose range.

Table 17.2.1 Composition of selexipag film-coated tablets (200–800 µg)

Ingredients	Selexipag film-coated tablet			
	200 µg	400 µg	600 µg	800 µg
Selexipag	0.2 mg	0.4 mg	0.6 mg	0.8 mg
D-Mannitol Corn starch Low substituted hydroxypropylcellulose Hydroxypropylcellulose Magnesium stearate	(b) (4)			
(b) (4)				
Hypromellose Propylenglycol Titanium dioxide Iron oxide red Iron oxide black Iron oxide yellow Carnauba wax	(b) (4)			
Coating weight				
Total weight of film-coated tablet				
(b) (4)				

Table 17.2.2 Composition of selexipag film-coated tablets (1000–1600 µg)

Ingredients	Selexipag film-coated tablet			
	1000 µg	1200 µg	1400 µg	1600 µg
Selexipag	1.0 mg	1.2 mg	1.4 mg	1.6 mg
D-Mannitol	(b) (4)			
Corn starch				
Low substituted hydroxypropylcellulose				
Hydroxypropylcellulose				
Magnesium stearate				
(b) (4)				
Hypromellose	(b) (4)			
Propylenglycol				
Titanium dioxide				
Iron oxide red				
Iron oxide black				
Iron oxide yellow				
Carnauba wax				
Coating weight				
Total weight of film-coated tablet				
(b) (4)				

Note that the difference between 200 µg film-coated tablets used in the bioequivalence study and commercial material is only in the color and debossing of the tablets.

Dissolution Studies:
An in vitro dissolution testing study was conducted to compare the dissolution profiles of the 400, 600, 800, 1000, 1200, 1400 µg film-coated tablets with that of the dose strength of 200 µg and 1600 µg tested in clinical studies in dissolution media (900 mL) of four different pH values: (b) (4) pH 6.8 using USP 2 apparatus (paddle).

The dissolution profile (n = 12) of a single tablet of the 200 µg dose was compared to that of a single tablet of higher strengths (e.g., 1 × 200 µg tablet vs 1 × 400 µg tablet). In addition, the dissolution profile (n = 12) of a single tablet of the 1600 µg dose was compared to that of a single tablet of lower strengths (e.g., 1 × 1600 µg tablet vs 1 × 1400 µg tablet).

Dissolution profiles and f_2 values are presented as follows:

Single tablet comparison
The dissolution profile (n = 12) of a single tablet of the 200 µg dose was compared to that of a single tablet of higher strengths (e.g., 1 × 200 µg tablet vs 1 × 400 µg tablet). The f2 values results are presented in Table 17.2.3.

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Reviewer's Assessment of the Biowaiver Request: ACCEPTABLE

The Applicant established the dose-proportionality across the therapeutic dose range (200 µg to 1600 µg for biowaiver purposes). Bioequivalence was established between 200 µg vs. 1600 µg at a dose level of 1600 µg. All the selexipag dose strengths 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg tablets have the same (b) (4) composition, (b) (4) All tablet strengths can be regarded as (b) (4) in active/inactive ingredients. The in vitro performance, using the proposed quality control method (pH 6.8), of all the tablet strengths is similar as indicated by the f_2 values and the dissolution profiles presented above.

(b) (4)

The f_2 values were above 50 at all dose strengths (Table 17.2.5 and Table 17.2.6) and dissolution pH tested, demonstrating that the differences in dissolution profile (b) (4) . Based on the information presented above, the Applicant's biowaiver request for selexipag dose strengths 400, 600, 800, 1000, 1200 and 1400 µg is justified and acceptable.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Conclusions, Recommendation and Signature:

Dissolution method: ACCEPTABLE

The following proposed dissolution method is acceptable:

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	50 rpm	900 mL	Phosphate Buffer, pH 6.8@37.0± 0.5° C	HPLC/UV λ=(b) (4) nm

Dissolution Acceptance Criterion: ACCEPTABLE

The dissolution acceptance criterion of Q= (b) (4)% at 20 minutes for all strengths of Selexipag Tablets is acceptable.

BE [AC-065-108] Study: ACCEPTABLE

Biowaiver Request: ACCEPTABLE

The Applicant's biowaiver request for selexipag dose strengths 400, 600, 800, 1000, 1200 and 1400 µg is acceptable..

Therefore, from the Biopharmaceutics perspective, NDA 207947 for selexipag film-coated tablets (200, 400, 600, 800, 1000, 1200, 1400, and 1600 µg) is recommended for APPROVAL.

8/21/15

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Anand's conclusions and recommendation.

8/21/15

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

18 Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: n/a

Reviewer's Assessment: Solid oral dosage form; See Assessment of Process section

2.3.P.6 Reference Standards or Materials

19 Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: N/A

Reviewer's Assessment: Solid oral dosage form; See Assessment of Process section

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

20 Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment: **Not applicable.**

21 If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment: **Not applicable.**

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

22 Is the applicant's claim for categorical exclusion acceptable?

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The claim was not accompanied by an adequate required statement of no extraordinary circumstances, but this was rectified through an IR.

23 Is the applicant's Environmental Assessment adequate for approval of the application?

Not applicable

Applicant's Response: None. Refer to the submission for information provided by the applicant.

Reviewer's Assessment: The categorical exclusion claim is appropriate for the anticipated amount of drug to be used, and the calculation is accurate. The expected introduction concentration (EIC) of 0.0004 ppb is almost four orders of magnitude below the 1 ppb categorical exclusion value. In light of new draft environmental assessment (EA) guidance, Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (FDA 2015), FDA conducted a literature search and examined the clinical and nonclinical data submitted with the application for any signals of estrogenic, androgenic, or thyroid activity. No signals were found. The applicant also described quantitative structure–activity relationship (QSAR) modeling (b) (4) Finally, an adequate statement of no extraordinary circumstances is present.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The claim for a categorical exclusion from an EA is acceptable.
James P. Laurenson, CDER/OPQ/ONDP EA Team, 7/22/2015

Secondary Review Comments and Concurrence:
Scott Furness, CDER/OPQ/ONDP, 8/25/2015

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

UPTRAVI® safely and effectively. See full prescribing information for UPTRAVI®.

UPTRAVI® (selexipag) tablets, for oral use
Initial U.S. Approval: XXXX

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Selexipag Established Name: Uptravi	**Adequate**
Dosage form, route of administration	Dosage: IR solid dosage form Route: Oral	**Adequate**
Controlled drug substance symbol (if applicable)	N/A	**N/A**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	The selexipag IR tablet is expected to be marketed in 8 different strengths: 200, 400, 600, 800, 1000, 1200, 1400 and 1600 mcg	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

UPTRAVI is available in the following strengths:

- 200 mcg [Light yellow tablet embossed with 2]
- 400 mcg [Red tablet embossed with 4]
- 600 mcg [Light violet tablet embossed with 6]
- 800 mcg [Green tablet embossed with 8]
- 1000 mcg [Orange tablet embossed with 10]
- 1200 mcg [Dark violet tablet embossed with 12]

- 1400 mcg [Dark yellow tablet embossed with 14]
- 1600 mcg [Brown tablet embossed with 16]

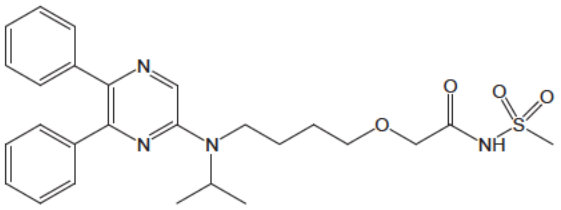
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		**Adequate**
Strengths: in metric system		**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		**Adequate**

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

UPTRAVI (selexipag) is a selective non-prostanoid IP prostacyclin receptor agonist. The chemical name of selexipag is 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-*N*-(methylsulfonyl) acetamide. It has a molecular formula of $C_{26}H_{32}N_4O_4S$ and a molecular weight of 496.62. Selexipag has the following structural formula:



Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive.

Depending on the dose strength, each round film-coated tablet contains 200, 400, 600, 800, 1000, 1200, 1400, or 1600 mcg of selexipag. The tablets include the following inactive ingredients: D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with mixtures of iron oxide red, iron oxide yellow or iron oxide black. The film-coated tablets are not light sensitive.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		**Adequate**
Dosage form and route of administration		**Adequate**
Active moiety expression of strength with equivalence statement for salt (if applicable)		**N/A**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		**Adequate**
Statement of being sterile (if applicable)		**N/A**
Pharmacological/ therapeutic class		**Adequate**
Chemical name, structural formula, molecular weight		**Adequate**
If radioactive, statement of important nuclear characteristics.		**N/A**
Other important chemical or physical properties (such as pKa, solubility, or pH)		**Adequate**

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

UPTRAVI (selexipag) film-coated, round tablets are supplied in the following configurations:

Strength	Color	Debossing on Tablets	NDC-XXX Bottle of 60	NDC-XXX Bottle of 140
200	Light yellow	2	66215-602-06	66215-602-14
400	Red	4	66215-604-06	Not Applicable
600	Light violet	6	66215-606-06	Not Applicable
800	Green	8	66215-608-06	Not Applicable
1000	Orange	10	66215-610-06	Not Applicable
1200	Dark violet	12	66215-612-06	Not Applicable
1400	Dark yellow	14	66215-614-06	Not Applicable
1600	Brown	16	66215-616-06	Not Applicable

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		**Adequate**
Available units (e.g., bottles of 100 tablets)		**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		**Adequate**
Special handling (e.g., protect from light, do not freeze)		**N/A**
Storage conditions		**Adequate**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Actelion Pharmaceuticals US, Inc. 5000 Shoreline Court, Ste. 200 South San Francisco, CA 94080, USA ACT20150630	**Adequate**

Conclusion: Adequate

2. Labels

1) Immediate Container Label

(b) (4)

[redacted]

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(b) (4)

[redacted]

Reviewer's Assessment: Adequate

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		**Adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		**Adequate**
Net contents (21 CFR 201.51(a))		**Adequate**
Lot number per 21 CFR 201.18		**Adequate**
Expiration date per 21 CFR 201.17		**Adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)		**Adequate**
Storage (not required)		**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		**Adequate**
Bar Code per 21 CFR 201.25(c)(2)**		**Adequate**
Name of manufacturer/distributor		**Adequate**
Others		**N/A**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Cartons

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		**Adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		**Adequate**
Net contents (21 CFR 201.51(a))		**Adequate**
Lot number per 21 CFR 201.18		**Adequate**
Expiration date per 21 CFR 201.17		**Adequate**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		**N/A**
Sterility Information (if applicable)		**N/A**
"Rx only" statement per 21 CFR 201.100(b)(1)		**Adequate**
Storage Conditions		**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		**Adequate**
Bar Code per 21 CFR 201.25(c)(2)**		**Adequate**
Name of manufacturer/distributor		**Adequate**
"See package insert for dosage information" (21 CFR 201.55)		**Adequate**
"Keep out of reach of children" (optional for Rx, required for OTC)		**Adequate**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		N/A

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: The proposed carton and container labels are acceptable. The PI will be negotiated with the applicant through the OND division.

Mariappan Chelliah, 24-Aug-2015

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, August 24, 2015

II. List of Deficiencies To Be Communicated

There are no deficiencies to be communicated at this time.

IV. Attachments

A. Facility

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			Medium The firm has not previously manufactured APIs for commercial use.	**Approve**
			Low risk	**Approve**
			Low risk	**Approve**
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			High (PAI required)	**Approve**
			(b) (4)	
			Low risk	**Approve**
			Low risk	**Approve**

B. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay	Formulation Container closure (b) (4) Process parameters Scale/Equipment/Site	Low (release and stability)	End product testing with (b) (4) acceptance criterion (b) (4) compared to other solid oral dosage forms	**Acceptable**	(b) (4) are considered a medium risk unit operations for this CQA (b) (4)
Solid state – (b) (4)	Formulation (b) (4) Process parameters Scale/Equipment/Site	Medium	Content of (b) (4) controlled in drug substance	**Acceptable**	The applicant is currently exploring modifications to the current (b) (4) method to improve (b) (4) (b) (4) are considered medium risk unit operations for this CQA since the current analytical method cannot quantify the amount of different (b) (4) present
Content Uniformity	Formulation (b) (4) Process parameters Scale/Equipment/Site	High	End product testing	**Acceptable**	Due to the (b) (4) all changes to the manufacturing process should be evaluated for their potential impact to CU; (b) (4) is considered a high risk unit operation for this CQA; (b) (4) are considered medium risk unit operations for this CQA
Microbial limits	Formulation (b) (4) Process parameters Scale/Equipment/Site	Low	End product testing at release and on stability during development; End product testing on one batch annually as part of	**Acceptable**	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
			the stability protocol		
Dissolution	Significant changes in formulation	Medium	(b) (4) the dissolution acceptance criterion	**Acceptable**	(b) (4)
Particle Size Distribution	Formulation (b) (4) Container Closure (API) Process parameters Scale/Equipment/Site	Medium	API PSD testing at release controls D50 and D90	**Acceptable**	
Degradants	Formulation Container Closure (b) (4) Process parameters Scale/Equipment/Site	Medium	Film-coating of tablets (b) (4) End product testing for identified degradants at release and on stability	**Acceptable**	(b) (4) are considered medium risk unit operations for this COA due to (b) (4) the potential for

*Risk ranking applies to product attribute/CQA **For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO:

Katherine Windsor, DS CMC Reviewer
Mariappan Chelliah, DP CMC Reviewer
Wendy Wilson-Lee, Application Technical Lead (ONDP)
Office of New Drug Products (ONDP)
E-mail Address: mariappan.chelliah@fda.hhs.gov, katherine.windsor@fda.hhs.gov
Mariappan: (301)-796-1724
Katherine: (240)-402-9927

FROM: FDA

Division of Pharmaceutical Analysis
Laura C. Pogue, Ph.D., MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: David Keire, Ph.D., Lab Chief, Branch I
Phone: (314) 539-3850

SUBJECT: Methods Validation Report Summary

Application Number:	207947
Name of Product:	Uptravi (Selexipag) Tablets (200, 400, 600, 800, 1000, 1200, 1400, 1600 μg)
Applicant:	Actelion Pharmaceuticals, Ltd.
Applicant's Contact Person:	James B. Davis, Associate Director US Drug Regulatory Affairs
Address:	1820 Chapel Avenue West, Suite 300, Cherry Hill, NJ 08002
Telephone: (856) 773-5719	Fax: (856) 773-4247

Date Methods Validation Consult Request Form Received by DPA: 03/24/2015

Date Methods Validation Package Received by DPA: 03/24/2015

Date Samples Received by DPA: 05/08/2015

Date Analytical Completed by DPA: 07/08/2015

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-2162
FAX (314) 539-2113

Date: July 8, 2015

To: Katherine Windsor, DS CMC Reviewer
Mariappan Chelliah, DP CMC Reviewer
Wendy Wilson-Lee, Application Technical Lead (ONDP)

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Xiaofei Liu, Chemist, CDER/OPQ/OTR/DPA

Through: David Keire, Ph.D., CDER/OPQ/OTR/DPA, Lab Chief, Branch I

Subject: Method Verification of NDA 207947: Uptravi (Selexipag) Film-Coated Tablets 0.2 mg, 0.8 mg, and 1.4 mg

The following methods were verified and found acceptable for quality control and regulatory purposes:

(b) (4)

The following methods were not performed due to instrument limitations:

1) 3.2.S.4.2 Control of Drug Substance: (b) (4)

Analyst worksheets are available here: http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880aeb985

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Reporting:

(b) (4)

For (b) (4) impurities between (b) (4)% (LOQ) and (b) (4)%, the total of (b) (4) impurities are reported.

(b) (4)

6) **3.2. P.5.2 Control of Drug Product: Analytical Procedures Dissolution: To determine the dissolved amount of Selexipag in Film-Coated Tablets in (b) (4) minutes by using the Dissolution Apparatus 2 (paddle) and HPLC.**

(b) (4)

Q value for each tablet after (b) (4) minutes was greater than (b) (4)% of declared content, so the sample met the specification.

According to USP 37, Dissolution <711> Immediate –Release Dosage forms, Acceptance table 1, S_1.

Limits: Each unit is greater than Q (b) (4)% which is (b) (4)%.

Based on the results after 30 minutes, the sample met the Acceptance Criteria.

Conclusion:
Based on these results, all listed methods Selexipag (0.2 mg, 0.8 mg and 1.4 mg) are acceptable for quality control and regulatory purposes.

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

/s/

LAURA POGUE
07/08/2015

DAVID A KEIRE
07/08/2015

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207947	**Submission Type:** NDA	**Established/Proper Name:** Selexipag
Applicant: Actelion Pharmaceuticals, Ltd.	**Letter Date:** 12/22/14	**Dosage Form:** Tablet, Film-Coated
Chemical Type: 1	**Stamp Date:** 12/22/14	**Strength:** 200, 400, 600, 800, 1000, 1200, 1400, 1600 micrograms

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	No filing issues
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?	X		Comments will be sent to the applicant in an information request prior to the 74-day letter

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☒	☐	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
18.	Combination Product _____	☐	☒	
19.	Other_____	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	Pre-NDA agreements on (b) (4) / (b) (4) of drug product stability; Pre-NDA agreement on requesting biowaivers for the 400 mcg, 600 mcg, 800 mcg, 1000 mcg, and 1200 mcg strength tablets; No agreement on designation of starting materials pre-IND or pre-NDA
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	(b) (4)
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☒	☐	Ames test (b) (4) analysis using two programs, fate of impurities data provided
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Categorical exclusion claimed

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	Drug substance testing sites missing from 356(h): (b) (4) [redacted] Drug product packaging site missing from 356(h): (b) (4) [redacted]
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	No DMFs referenced
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient	☒	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☒	☐	☐	BE study (AC-065-108) **Primary objective** • To demonstrate bioequivalence in the rate (maximum plasma concentration at steady-state [Cmax,ss]) and extent (area under plasma concentration-time curve during a dose interval [AUCτ]) of absorption between 1600 µg selexipag test drug (administered orally as film-coated tablet of 1600 µg twice daily [b.i.d.]) and 1600 µg selexipag reference drug (administered orally as 8 film-coated tablets of 200 µg b.i.d.) at steady-state, in healthy male subjects, following a multiple-dose up-titration scheme. **Secondary objectives** • To investigate 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 subjects.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
					• PK data are provided in JMP format. An inspection is not needed for BE study (AC-065-108).
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☒	☐	☐	The clinical Phase 3 pivotal study used only the 200 µg tablet. This formulation is the same as that of the to be marketed 200 µg tablets. However, all other strengths proposed for marketing were not used in the clinical Phase 3 pivotal study.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	A biowaiver request for the middle strengths (400, 600, 800, 1000, 1200, and 1400mg) is requested based on the FDA 2003 Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration,". No CFR section was cited.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☒	☐	☐	Significant portions of each executed batch record are in a foreign language; No translated versions were included in the submission
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.:	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

Information Requests (Product Quality):

1. Confirm that the to-be-marketed product will be available only the HDPE packaging configuration. Section 3.2.P.2.4.2 indicates that selexipag film-coated tablets can be packaged in HDPE bottles [redacted (b) (4)]. However, Section. 3.2.P.7 of the submission only includes information supporting the use of the HDPE configuration. [redacted (b) (4)]
2. Update the 356(h) form to include all testing and packaging sites for the drug substance and drug product. The current 356(h) form does not include the drug substance testing sites [redacted (b) (4)] or the drug product packaging site [redacted (b) (4)]
3. Provide 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.). The executed batch records in Section 3.2.R contain sections that have not been translated.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Initial Risk Assessment: Selexipag is classified as a High Risk Drug based on the narrow therapeutic range and high potency which increase the risk of causing significant patient harm if dosed in error

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMECA RPN	Comment
Assay	• Formulation • Container closure • (b) (4) • Process parameters • Scale/equipment/site	1	4	Release = 1	4	(b) (4) tablets are ligh-sensitive (b) (4) (b) (4)
				Stability = 3	12	
Solid state – (b) (4)	• Formulation • (b) (4) • Process parameters • Scale/equipment/site	3	4	4	48	(b) (4) (b) (4) No control for (b) (4) in final drug product; The need for control of (b) (4) at release and on stability should be evaluated; Specificity of proposed identification methods for desired (b) (4) should be evaluated; Impact of drug product manufacturing process on (b) (4) (b) (4) should be evaluated.
Content uniformity	• Formulation • (b) (4) • Process parameters • Scale/equipment/site	4	5	4	80	(b) (4) however we consider this CQA high risk
Microbial limits	• Formulation • (b) (4) • Process parameters • Scale/equipment/site	1	2	3	6	Controls for total aerobic microbial count, total combined yeast and molds, and E. coli included in release specification in accordance with compendial standards.
Dissolution	• Formulation • (b) (4) • Process parameters • Scale/equipment/site	4	4	4	64	
Particle size distribution	• Formulation • Container closure • (b) (4) • Process parameters • Scale/equipment/site	3	4	3	36	Controlled in final drug substance but only the Dv50 and Dv90 are specified; Impact of changes in particle size distribution with respect to content uniformity and dissolution should be evaluated; (b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Product Property/Impact of Change/CQAs	Factors Affecting CQA	O	S	D	FMECA RPN	Comment
Degradants	• Formulation • Container closure • (b) (4) • Process parameters • Scale/equipment/site	4	4	2	32	The active metabolite ACT-3336797 (b) (4) (b) (4)

RPN < 25 is considered low risk; RPN 25 – 60 is considered moderate risk; RPN > 60 is considered high risk

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2015.02.06 15:42:04 -05'00'

/s/ On behalf of the NDA 207947 OPQ review team