CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

James B. Davis
Associate Director, US Drug Regulatory Affairs

25 November 2015

NEW PATENT INFORMATION

Norman Stockbridge, MD, Ph.D., Director Center for
Drug Evaluation and Research
Food and Drug Administration
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 207947, Sequence Number 0029
UPTRAVI (selexipag)
Indication: Pulmonary arterial hypertension (PAH)

Dear Dr. Stockbridge:

Reference is made to the initial New Drug Application (NDA) for UPTRAVI (selexipag) 207947, submitted on December 22, 2014 (SN 0000) for the indication of pulmonary arterial hypertension.

On November 3, 2015, Actelion was issued a US Patent (9,173,881) by the US Patent and Trademark Office for use of selexipag (IP receptor agonist) in combination with the endothelin receptor antagonist, macitentan.

Pursuant to 21 CFR 314.53(d)(1): "If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under 314.60."

At this time, Actelion is submitting Form FDA 3542a for the above-referenced US Patent to the NDA. Based on 12 CFR 314.60(b)(3), Actelion does not considers this submission a major amendment and thus should not extend the initial review cycle.

All electronic files included in this submission are less than 5 MB. All files were checked and verified to be free of viruses, prior to being transmitted using Symantec Endpoint Protection Edition, program version 12.1.5337.5000 with a virus definition date of Sunday, November 22, 2015 revision 2.

If you have any comments or questions or require additional information about this submission, please contact me by phone at 856-773-5719 or by email at james.davis @actelion.com.

Sincerely,

{See appended electronic signature page}

James B. Davis
Associate Director, US Drug Regulatory Affairs

Actelion Clinical Research, Inc.
1820 Chapel Avenue West | Suite 300 | Cherry Hill, NJ 08002 | USA | phone +1 856 773 5719 |
fax +1 856 773 4247 | mobile +1 685 3995 | james.davis @actelion.com | www.actelion.com

ACTELION

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd HH:mm)
James Davis	DRA Approval	2015-11-23 18:00 GMT+010

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

NDA NUMBER
207947

NAME OF APPLICANT/NDA HOLDER
Actelion Pharmaceuticals Ltd

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
UPTRAVI®

ACTIVE INGREDIENT(S)	STRENGTH(S)
selexipag	0.2mg, 0.4mg, 0.6mg, 0.8mg, 1.0mg, 1.2mg, 1.4mg, 1.6mg

DOSAGE FORM
tablet, oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
9,173,881	November 3, 2015	August 12, 2029

d. Name of Patent Owner	Address *(of Patent Owner)*	
Actelion Pharmaceuticals Ltd	Gewerbestrasse 16	
	City/State: Allschwil	
	ZIP Code: 4123	FAX Number *(if available)*: 0041 61 565 66 91
	Telephone Number: 0041 61 565 65 65	E-Mail Address *(if available)*: joerg.velker@actelion.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	Actelion Clinical Research, 1820 Chapel Ave West, Suite 300	
	City/State: Cherry Hill, New Jersey	
	ZIP Code: 08002	FAX Number *(if available)*: (856) 773 - 4247
	Telephone Number: (856) 773 - 5719	E-Mail Address *(if available)*: james.davis@actelion.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Publishing Services (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 1, 3-19	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* "indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH, (b) (4) (b) (4)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Jörg Velker	Nov. 20, 2015

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dr. Joerg Velker, Associate Director, Senior Patent Counsel	
Address Actelion Pharmaceuticals Ltd, Gewerbestrasse 16	City/State Allschwil
ZIP Code 4123	Telephone Number 0041 61 565 64 67
FAX Number *(if available)* 0041 61 565 66 91	E-Mail Address *(if available)* joerg.velker@actelion.com

This section applies only to requirements of the Paperwork Reduction Act of 1995

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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See OMB Statement on Page 3.

NDA NUMBER
207947

NAME OF APPLICANT/NDA HOLDER
Actelion Pharmaceuticals Ltd

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TRADE NAME (OR PROPOSED TRADE NAME)
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ACTIVE INGREDIENT(S)	STRENGTH(S)
selexipag	0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg

DOSAGE FORM
tablet, oral

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
7,205,302	April 17, 2007	April 4, 2023

d. Name of Patent Owner	Address *(of Patent Owner)*	
Nippon Shinyaku Co., Ltd	14, Kisshoin Nishinosho Monguchicho, Minami-ku, Kyoto-shi	
	City/State 601-8550 Kyoto	
	ZIP Code Japan	FAX Number *(if available)* +81 75 314 3269
	Telephone Number +81 75 321 9086	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
James B. Davis Associate Director, Drug Regulatory Affairs	Actelion Clinical Research, 1820 Chapel Ave West, Suite 300	
	City/State Cherry Hill / New Jersey	
	ZIP Code 08002	FAX Number *(if available)* (856) 773-4247
	Telephone Number (856)-773-5719	E-Mail Address *(if available)* james.davis@actelion.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 15	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* "indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression."		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Jörg Velker	19. 11. 2014

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dr. Jörg Velker, Associate Director, Senior Patent Counsel	
Address Actelion Pharmaceuticals Ltd. Gewerbestrasse 16	City/State 4123 Allschwil
ZIP Code Switzerland	Telephone Number +41 61 565 64 67
FAX Number *(if available)* +41 61 565 66 91	E-Mail Address *(if available)* joerg.velker@actelion.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Identify the precise words of the approvel labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
8,791,122	July 29, 2014	August 1, 2030

d. Name of Patent Owner	Address *(of Patent Owner)*	
Nippon Shinyaku Co., Ltd	14, Kisshoin Nishinosho Monguchicho, Minami-ku, Kyoto-shi	
	City/State 601-8550 Kyoto	
	ZIP Code Japan	FAX Number *(if available)* +81 75 314 3269
	Telephone Number +81 75 321 9086	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
James B. Davis Associate Director, Drug Regulatory Affairs	Actelion Clinical Research, 1820 Chapel Ave West, Suite 300	
	City/State Cherry Hill / New Jersey	
	ZIP Code 08002	FAX Number *(if available)* (856) 773-4247
	Telephone Number (856)-773-5719	E-Mail Address *(if available)* james.davis@actelion.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
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3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Jörg Velker	19. 11. 2014

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dr. Jörg Velker, Associate Director, Senior Patent Counsel	
Address Actelion Pharmaceuticals Ltd. Gewerbestrasse 16	City/State 4123 Allschwil
ZIP Code Switzerland	Telephone Number +41 61 565 64 67
FAX Number *(if available)* +41 61 565 66 91	E-Mail Address *(if available)* joerg.velker@actelion.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Identify the precise words of the approvel labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 207947 SUPPL # HFD #

Trade Name Uptravi

Generic Name Selexipag

Applicant Name Actelion

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES X NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Orphan Drug exclusivity for a period of 7 years.

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Wayne Amchin, RAC
Title: Senior Consumer Safety Officer
Date: September 2, 2015

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

WAYNE S AMCHIN
09/03/2015

NORMAN L STOCKBRIDGE
09/03/2015

ACTELION

01 December 2014

DEBARMENT CERTIFICATION STATEMENT

Actelion Pharmaceuticals Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

F. Duffy-Warren

Frances Duffy-Warren, PhD
Vice President, US Drug Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207947 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Uptravi Established/Proper Name: Selexipag Dosage Form: Tablets		Applicant: Actelion Pharmaceuticals Ltd. Agent for Applicant (if applicable):
RPM: Wayne Amchin		Division: DCRP

NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 12-22-15	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 3864181

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

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None **X** FDA Press Release (standard on NMEs, per OEXA/OMA ☐ FDA Talk Paper ☐ CDER Q&As X Other SnapShot
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	X No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**X** Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date December 21, 2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	X Included December 18, 2015
• Original applicant-proposed labeling	X Included December 22, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide X Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	X Included December 18, 2015
• Original applicant-proposed labeling	X Included December 22, 2014
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	X Included March 27, 2015
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	February 25, 2015 February 19, 2015
❖ Labeling reviews *(indicate dates of reviews)*	RPM: X None 3-2-15 (labeling format issues included in 74-day letter); 12-21-15) DMEPA: ☐ None 4-3-15; 3-13-2015 DRisk: 9-29-15 DMPP/PLT: ☐ None 9-4-15 OPDP: ☐ None 8-31-2015 SEALD: X None CSS: X None Product Quality ☐ None 8-25-15 Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	2-9-15 X Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	

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

• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation	
❖ Breakthrough Therapy Designation	X N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	December 14, 2014; December 11, 2015; May 29, 2015, May 12, 2015, March 26, 2015; February 27, 2013; February 23, 2010
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	X N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg April 8, 2014
• EOP2 meeting *(indicate date of mtg)*	X No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A May 27, 2015
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A September 9, 2015
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	July 11, 2014 (top-line results)
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None December 21, 2015
Division Director Summary Review *(indicate date for each review)*	☐ None November 25, 2015; December 21, 2015 (addendum)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None November 19, 2015
PMR/PMC Development Templates *(indicate total number)*	X None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	X No separate review
• Clinical review(s) *(indicate date for each review)*	September 2, 2015; February 6, 2015
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See September 2, 2015 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None September 29, 2015
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested September 3, 2015
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	X No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	X No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None August 21, 2015 (stability data); July 29, 2015; February 2, 2015
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None November 6, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	X None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review December 18, 2015
• Supervisory Review(s) *(indicate date for each review)*	X No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None December 11, 2015; February 18, 2015; June 28, 2010 (IND)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc November 20, 2015
❖ ECAC/CAC report/memo of meeting	☐ None December 3, 2015 Included in P/T review, page 69
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	X None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	X None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	X None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None August 25, 2015; July 8, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None Ophthamology Consult Review July 27, 2015; QT-IRT Consult Review, March 25, 2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See August 25, 2015 Chemistry Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
X Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	**X** Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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/s/

WAYNE S AMCHIN
12/22/2015

Amchin, Wayne

From: Amchin, Wayne
Sent: Monday, December 14, 2015 8:19 AM
To: James Davis
Cc: Brian Schlag
Subject: Re: NDA 207947 Uptravi (selexipag) New Information Request

Hi James. Please add the following to Actelion's response:

at the time of death in 303 :

Dose of selexipag at that time of death (mcg per day)
Cumulative dose of selexipag (expressed in mg and mg/day) at the time of death (or censoring)

Thanks

Wayne

Sent from my BlackBerry 10 smartphone.

From: Amchin, Wayne
Sent: Monday, December 14, 2015 7:10 AM
To: James Davis
Subject: Re: NDA 207947 Uptravi (selexipag) New Information Request

Hi James. Just checking in as to when you think we might receive Actelion's response. I just need a rough timeframe, like by 9am today, sometime later in the day, not today. Thanks.

Wayne

Sent from my BlackBerry 10 smartphone.

From: James Davis
Sent: Friday, December 11, 2015 7:01 PM
To: Amchin, Wayne
Subject: Re: NDA 207947 Uptravi (selexipag) New Information Request

Wayne I did receive your email.

Thanks,
JBD

James B. Davis
Associate Director DRA Global Project Leader

Actelion Pharmaceuticals Ltd. • Gewerbestrasse 16 • CH-4123 Allschwil • Switzerland

Phone: 856-773-5719 • Fax: 856-773-4247 •Mobile: 856-685-3995 • VOIP: 82 5719
james.davis@actelion.com • www.actelion.com
Address for visitors: 1820 Chapel Avenue West • Suite 300 • Cherry Hill • NJ • 08002

On Fri, Dec 11, 2015 at 6:20 PM, Amchin, Wayne <Wayne.Amchin@fda.hhs.gov> wrote:
Hi James. Please confirm receipt so I know not to forward to Brian or one of the other Actelion contacts I work with.

Thanks.

Wayne

Sent from my BlackBerry 10 smartphone.

From: Amchin, Wayne
Sent: Friday, December 11, 2015 5:55 PM
To: james.davis@actelion.com
Subject: NDA 207947 Uptravi (selexipag) New Information Request

Hi James. This replaces the Information Request I just sent you.

Actelion's NDA is under review and we have the following new information request Given the PDUFA date on this application, time is of the essence. Please provide Actelion's response as soon as possible (ASAP). You may provide Actelion's response by email, followed in close proximity by official submission to your NDA. When you provide the email response, please let me know when the official submission will be submitted:

1. Please provide a flow chart of the disposition of subjects during the time GRIPHON (302) was conducted.

The first level is the number of subjects randomized to each treatment group.

The second level is the number in each treatment group who had an adjudicated MM event or did not have an MM event (in Study 302).

The third level is the disposition of the patients:

For patients WITH adjudicated MM events, please provide the numbers who: 1) completed study 302 and then enrolled in study 303, 2) continued in study 302 on assigned treatment, 3) continued in 302, but were not taking their assigned treatment, 4) completed 302 without further follow-up, 5) stayed in 302 while being enrolled in 303 (if that was possible).

For patients WITHOUT adjudicated MM events, please provide the corresponding numbers, as above.

Please indicate how many subjects dropped out before observation of an MM event in each level, and the number who died in each level.

To support this analysis, please provide a datafile (SAS transport) that includes one line per subject enrolled in GRIPHON.

The fields should include:

- **Subject number**
- **Initial treatment actually received (selexipag/placebo)**
- **Date of first treatment**
- **Whether patient received selexipag at any time during the time period 302 was conducted, including being administered selexipag**

  in 303 during that time (y/n)
- **Date(s) selexipag begun**
- **Date(s) selexipag stopped (if drug doses were missed for 7 days or less, please consider treatment continuous)**
- **Date(s) placebo or no treatment begun**
- **Date(s) placebo or no treatment stopped**
- **For each component of the composite endpoint, please provide:**

  Date of event (or date of censoring)

  Days (from start of treatment) to event or censoring

  Censoring variable (1/0)

Dose of selexipag at that time (mcg per day)

Cumulative dose of selexipag (expressed in mg and mg/day) at the time of event (or censoring)

- **Date of enrollment in 303 (also study day from beginning of 302)**
- **Date of death (also day of death from initial treatment)**

*****Please provide a corresponding dataset considering studies 302 and 303 as a continuous experience.**

2. **Please provide the reference for the Rank-Preserving Structural Accelerated Failure Time (RPSFT) model cited in Appendix 3A/3B or point us to reference in the NDA.**

Wayne Amchin, RAC, MPA, M International Affairs

Senior Consumer Safety Officer

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Office of New Drugs

CDER

phone: 301-796-0421

email: wayne.amchin@fda.hhs.gov

(b) (6)

*note that FDA does not accept .zip or .exe files either by email or over the gateway.

For technical submission questions, please contact cder esub at esub@fda.hhs.gov

Address for desk and courtesy copies:
Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4164
Silver Spring, MD 20993

Address for official submissions to your administrative file:
Division of Cardiovascular and Renal Products

FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

The information of this email and in any file transmitted with it is strictly confidential and may be legally privileged.
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Any views expressed in this message are those of the individual sender, except where the message states otherwise and the sender is authorized to state them to be the views of the sender's company.

Executive CAC
Date of Meeting: December 1, 2015

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
John Leighton, Ph.D., DHOT, Alternate Member
Albert De Felice, Ph.D., DCRP, Pharm Tox Supervisor
James Willard, Ph.D., DCRP, Presenting Reviewer

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

NDA # 207947
Drug Name: Uptravi (selexipag)
Sponsor: Actelion Pharmaceuticals, ltd.

Background:
Selexipag is a non-prostanoid prostacyclin agonist for the treatment of pulmonary arterial hypertension. In the genotoxicity assays in bacteria, eukaryotic cell cultures and *in vivo,* selexipag was found to be negative. The sponsor did not obtain dose concurrence from the Executive CAC.

Mouse Carcinogenicity Study
B6C3F1/Crlj SPF mice (55/sex/group) were administered 0, 125, 250 or 500 mg/kg/day of selexipag in 0.5% methylcellulose via oral gavage daily for 104 weeks. Dosages were selected to achieve an AUC exposure up to, or more than, 25x the human exposure. Significant mortality occurred in the female 500 mg/kg/day group beginning around week 72 due to severe gastric erosion, with 24 of 55 animals dying from this adverse effect. This group was prematurely sacrificed at week 100 of 104 weeks. AUC values were similar between high dose males and females, while Cmax values were much higher in the females for selexipag, the parent compound (24,900 ng/mL for the males versus 43,900 ng/mL for the females on day 1). This difference may help account for the severe gastric erosion in the high dose female group, while sparing the high dose male group. No other treatment related mortality was seen in the study. After correcting for multiplicity testing, CDER statisticians found no significant dose-related excess in any tumor incidence.

Rat Carcinogenicity Study
Sprague-Dawley rats (60/sex/group) were administered 0, 10, 30, or 100 mg/kg/day of selexipag in 0.5% methylcellulose via oral gavage for 104 weeks. As in the mice, doses were selected to achieve an AUC exposure of up to, or more than, 25x the human exposure. No significant treatment related mortality occurred in the study. There was no significant dose-related increase seen in incidence of any tumor type in the selexipag treated groups at margins of exposure of approximately 170x of the human AUC for the parent compound and >300x of the human AUC

for the active metabolite at the high dosage.

Executive CAC Recommendations and Conclusions

Mouse:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms

Rat:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms.

Karen Davis Bruno, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DCRP
Albert De Felice/Team leader, DCRP
James Willard/Reviewer, DCRP
Wayne Amchin/CSO/PM, DCRP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
12/03/2015

KAREN L DAVIS BRUNO
12/03/2015

From:	Tsong, Yi
To:	Chelliah, Mariappan; Kord Bacheh Changi, Maryam; Miao, Zhuang
Cc:	Wilson, Wendy; Shen, Meiyu
Subject:	RE: reviewer request for NDA 207947
Date:	Thursday, June 18, 2015 12:51:30 PM

Hello Mari,

I am assigning this review to Zhuang Miao and let Meiyu Shen be his secondary reviewer.

Thanks,

Yi

From: Chelliah, Mariappan
Sent: Thursday, June 18, 2015 12:35 PM
To: Kord Bacheh Changi, Maryam; Tsong, Yi
Cc: Wilson, Wendy
Subject: RE: reviewer request for NDA 207947

Yi,

I am specifically looking for someone to look though the statistical evaluation of the stability data.

Thanks
Mari

From: Kord Bacheh Changi, Maryam
Sent: Thursday, June 18, 2015 12:28 PM
To: Tsong, Yi
Cc: Chelliah, Mariappan; Wilson, Wendy
Subject: reviewer request for NDA 207947

Good Afternoon,

My name is Maryam Changi I am a new RBPM for NDA 207947. I was wondering if you could assign a Statistic reviewer for this NDA.

Maryam Changi, PharmD,
RBPM, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
Phone:(240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov


OPQ
OFFICE OF
PHARMACEUTICAL QUALITY

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/s/

MARYAM K CHANGI
09/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

INFORMATION REQUEST

Actelion Pharmaceuticals, Ltd.
Attention: James B. Davis
Associate Director US Regulatory Affairs
1820 Chapel Avenue West Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 18, 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uptravi (selexipag) Tablets.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by August 21, 2015 in order to continue our evaluation of your NDA.

Drug Product:

1. (b) (4) in the drug product: We note that your modified (b) (4) method (b) (4) (b) (4) (b) (4) However, given that this method is (b) (4) We acknowledge the difficulty of developing an analytical method (b) (4)

2. You have proposed (b) (4) (b) (4)

Drug Substance:

3. [redacted] in the drug substance: [redacted]

4. The data you have provided in the amendment dated 24-Jun-2015 [redacted]

Biopharm:

5. Your proposed dissolution acceptance criterion of Q= [redacted]% at [redacted] minutes is not supported by the dissolution data submitted and therefore not acceptable. We recommend that you implement a dissolution acceptance criterion of Q= [redacted]% at 20 minutes for all strength of Selexipag Tablets. Note that the dissolution testing may require [redacted] testing. Please provide a revised drug product specification table and update your stability protocol accordingly.

6. Provide, dissolution profiles of 1 × 200 µg tablet in pHs [redacted]

7. Provide comparative dissolution profiles at various pH [redacted] 6.8) [redacted]

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

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: 2015.08.14 13:53:28 -04'00'

Wendy Wilson-Lee Ph.D.
Branch Chief, Branch 1 (Acting)
Division of New Drug Product 1
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

INFORMATION REQUEST

Actelion Clinical Research, Inc.
Attention: James B. Davis, Associate Director, US Regulatory Affairs
US Agent for Actelion Pharmaceuticals, Ltd.
1820 Chapel Avenue West Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 18 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uptravi (selexipag) Tablets.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a written response by July 13, 2015 in order to continue our evaluation of your NDA. Please also response to me via email at: Maryam.kordbachehchangi@fda.hhs.gov.

1. FDA has reviewed your claim for a categorical exclusion from an environmental assessment (EA) for selexipag. Please note that you did not provide an explicit statement that, to your knowledge, no extraordinary circumstances exist. This statement is required by 21 CFR 25.15(a) and (d), and is particularly important given the potential for thyroid and other endocrine-related effects noted in your nonclinical data, which in general are a concern for the FDA, as described in recent draft guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf

2. Provide us a copy of the data set in SAS format as well as the SAS code that were used to generate the report in section 3.2.P.8.3 of the eCTD titled ‘Statistical Evaluation of the Registration Stability Package for Selexipag Tablets.

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

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: 2015.07.06 13:56:30 -04'00'

Wendy Wilson-Lee, Ph.D.
Branch Chief 1 (Acting)
Division of New Drug Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

MID-CYCLE COMMUNICATION

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 22, 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Uptravi (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

We also refer to the teleconference between representatives of your firm and the FDA on May 27, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Wayne Amchin, Regulatory Project Manager at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 27, 2015, 2pm

Application Number: NDA 207947
Product Name: Uptravi (selexipag)
Indication: Pulmonary Arterial Hypertension
Applicant Name: Actelion Pharmaceuticals Ltd.

Meeting Chair: Ellis Unger, M.D.
Meeting Recorder: Wayne Amchin

FDA ATTENDEES

Office of Drug Evaluation I:

Ellis Unger, M.D.	Director

Division of Cardiovascular and Renal Products:

Norman Stockbridge, M.D., Ph.D.	Director
Mary Ross Southworth, Pharm.D.	Deputy Director for Safety
Michael Monteleone, MS, RAC	Associate Director for Labeling
Shari Targum, M.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Reviewer
Christine Garnett, Ph.D.	Clinical Reviewer
James M. Willard, Ph.D.	Nonclinical Reviewer
Ed Fromm	Chief, Project Management Staff
Wayne Amchin	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:

Rajanikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader
Sudharshan Hariharan, Ph.D.	Clinical Pharmacology Reviewer
Luning Zhuang, Ph.D.	Pharmacometrics Reviewer

Office of Biostatistics, Division of Biometrics I:

Steven Bai, PhD	Biostatistician

Office of Pharmaceutical Quality

Wendy Wilson-Lee, PhD	Branch Chief, Office of New Drug Products
Mariappan Chelliah, PhD	Product Quality Reviewer
Om Anand, PhD	Biopharmaceutical Reviewer

Office of Surveillance and Epidemiology
Somya Dunn — Risk Management Analyst, Division of Risk Management

EASTERN RESEARCH GROUP
Marc Goldstein

APPLICANT ATTENDEES
Guy Braunstein, M.D. — Head of Clinical Development
Martine Clozel, M.D. — Chief Scientific Officer

Clinical Science
Alberto Gimona, M.D. — Head of Clinical Science
Ralph Preiss, M.D. — Project Lead, Clinical Science
Aline Frey, Pharm.D. — Sr. Clinical Project Scientist

Biostatistics:
Marisa Bacchi, Ph.D. — Head of Biostatistics
Lilla Di Scala, Ph.D. — Project Lead, Biostatistics

Drug Safety:
Hani Mickail, M.D. — Head of Global Drug Safety
Paul Lagarenne, M.D. — Head of US Drug Safety
Tatiana Remenova, M.D. — Project Lead, Global Drug Safety

US Medical Affairs:
Gary Palmer, M.D. — Head of U.S. Medical Affairs

CMC:
Timm Trenktrog, Ph.D. — Head of Technical Operations
Alexandra Schlicker Spain, Ph.D. — Senior Technical Project Lead
Claire Heinkele — Technical Regulatory Affairs

Clinical Pharmacology:
Jasper Dingemanse, Ph.D., Pharm.D. — Head of Clinical Pharmacology
Shirin Bruderer, Ph.D. — Project Clinical Pharmacologist

Drug Regulatory Affairs:
Sonja Pumpluen, Pharm.D. — Head of Global Drug Regulatory Affairs
James Davis — US Drug Regulatory Affairs Project Leader
Brian Schlag — US Drug Regulatory Affairs Group Leader
Samar Kelly, Ph.D. — Global Regulatory Project Leader

Project Management:
Natalia Yannoulis, Ph.D. — Life Cycle Leader

Reference ID: 3783988

Strategic Development:
Per Nilsson, M.D., Ph.D. Head of Strategic Development

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

PRODUCT QUALITY

The product quality review team has concerns (b) (4) (b) (4)

CLINICAL PHARMACOLOGY

Clinical Pharmacology discussed two topics at the meeting - (i) use with concomitant CYP2C8 inhibitors, and (ii) use in patients with moderate and severe hepatic impairment. The applicant proposed version of the label recommends (b) (4) The Division does not prefer (b) (4) terminology and wants to further optimize the instructions for use in these sections.

(i) Use with CYP2C8 inhibitors: As the extent of increase in exposure to selexipag and the active metabolite when dosed concomitantly with a strong CYP2C8 inhibitor is not known, (b) (4) Until then, selexipag should probably be labeled as (b) (4) with strong CYP2C8 inhibitors. The applicant acknowledged the concern and indicated that they would consider performing a single-dose drug interaction study in healthy volunteers.

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

Reference ID: 3783988

modeling and simulation exercise in support of an optimal dosing regimen for these patients.

CLINICAL

Clinical review noted the following issues:

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

3.0 INFORMATION REQUESTS

PRODUCT QUALITY

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

CLINICAL PHARMACOLOGY

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

CLINICAL

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

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The review team and Actelion agreed that a REMS or other risk mitigation strategy is unnecessary and normal pharmacovigilance is acceptable.

5.0 ADVISORY COMMITTEE MEETING

The Division advised that there are no plans to hold an AC meeting for this application.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-cycle Meeting is scheduled for September 9, 2015 from 10:30-12pm at the FDA White Oak Campus. We anticipate providing the Late-cycle Meeting package to Actelion by August

Reference ID: 3783988

28, 2015, and providing labeling comments and any proposed PMR to Actelion by September 4, 2015.

Reference ID: 3783988

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

/s/

ELLIS F UNGER
06/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947
INFORMATION REQUEST

Actelion Pharmaceuticals, Ltd.
Attention: James Davis
Associate Director, US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 22, 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uptravi (selexipag).

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response by June 19, 2015 in order to continue our evaluation of your NDA.

LIST COMMENTS AND INFORMATION REQUESTS

Drug Substance:

1. 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.

2. Include a test for assay with an appropriate acceptance range in the specifications of the proposed starting material (b) (4) or provide justification for the lack of this test.

3. We note your separate proposed drug substance specifications for (b) (4) (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.

4. We acknowledge your commitment that any (b) (4) will be preceded by careful evaluation to ensure the quality of the intermediate or API is not adversely impacted. Clarify which manufacturing step(s) may be subject to (b) (4) operations and include adequate provisions for this (b) (4)

Drug Product:

5. (b) (4)

6. (b) (4)

7. The debossing numbers and film-coat colors visually differentiate the eight different dose strengths of the selexipag tablets. (b) (4)

(b) (4)

8. The post-approval stability commitment includes a commitment to test at (b) (4) (b) (4)

(b) (4) If not, provide justification. In addition, provide the proposed testing schedule for these annual batches.

9. The submission includes only three (3)-months of stability data for one batch of the 200µg/140 tablets per bottle configuration. However, the proposed shelf life is two (2) years. This bottle configuration has a different fill-volume and headspace compared to the rest of the proposed commercial packaging configurations. Clarify if and when you plan to provide additional stability data to support marketing of the 140-count bottle for the 200 µg tablet strength.

Process:

10. The DOE study results in Section P.2.3-Table 18(page 30) supported (b) (4) (b) (4)

11. While the developmental and clinical batches showed acceptable content uniformity per the USP test criteria, (b) (4) In the absence of (b) (4) controls such as (b) (4) Therefore, establish either an (b) (4) control or (b) (4) for tablet content uniformity (b) (4)

12. The revised (b) (4)

13. The DOE study resul (b) (4) (b) (4)

14. We consider (b) (4) form to be a critical quality attribute for a solid oral dosage form. We note the existence of different (b) (4) forms of the selexipag drug substance. The submission does not include data (b) (4)

(b) (4)

(b) (4)

Biopharmaceutics:

16. Submit SAS Transport files (.xpt) of plasma concentration-time data (Day 23) of Selexipag and metabolite ACT-333679 for the bioequivalence (BE) study # AC-065-108. The data set should also include the first and last time points used to estimate the elimination constant (K_{el}) for each subject/period as shown. Submit the data in the following format:

(b) (4)

17. Submit SAS Transport files (.xpt) of the pharmacokinetic parameters (Day 23) of Selexipag and metabolite ACT-333679 for the bioequivalence (BE) study # AC-065-108 for the BE study #109HV112. The data should include AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, and $T_{1/2}$ as shown. Submit the data in the following format:

(b) (4)

18. In addition, for BE study AC-065-108 provide the information requested in the following summary tables:

Table 1: Summary of Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 2: Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses

Bioequivalence Study No. AC-065-108							
Parameter	**Standard Curve Samples**						
Concentration (ng, mcg/mL)							
Inter day Precision (%CV)							
Inter day Accuracy (%Actual)							
Linearity	(Range of R^2 values)						
Linearity Range (ng, mcg/mL)							
Sensitivity/LOQ (ng, mcg/mL)							
Parameter	**Quality Control Samples**						
Concentration (ng, mcg/mL)							
Inter day Precision (%CV)							
Inter day Accuracy (%Actual)							

Table 3: Summary of Pharmacokinetic Parameters

Bioequivalence Study No. AC-065-108										
Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subject's Number, Gender, Age (mean & range)	Mean Parameters +/-SD (%CV)						Study Report Location
				Cmax (units/ml)	Tmax (hr)	AUC0-t (units)	AUC∞ (units)	T½ (hr)	Kel (hr-1)	
		Test								
		Reference								

Table 4: Statistical Summary of Comparative Pharmacokinetic Data for Bioequivalence Study No. AC-065-108

Average Bioequivalence Statistical Approach						
Drug (No of subjects completed =)			Dose (# x mg)			
Parameter	Test*	N	Reference*	N	Ratio**	90% C.I.^
AUC0-t						
AUC∞						
Cmax						

19. In bioequivalence (BE) study AC-065-108, you reported (b) (4) [redacted] (b) (4)

20. 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.

21. In section P.2.2.3 physicochemical and biologicals properties, you stated that (b) (4) . However, the report of this investigation could not be located. Submit supporting dissolution data (b) (4)

22. The proposed particle size acceptance criteria (b) (4) are not supported by the data. The supportive PK data you submitted in a study conducted using dogs (B-09-034) is variable and limited (n=6). Please provide the particle size of the batches of the drug products used in human clinical trials and justify your proposed acceptance criteria in particular (b) (4) µm for D90.

23. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution and develop a discriminating dissolution method with regard to these CMAs and CPPs. (b) (4)

24. To demonstrate the discriminating ability of the selected dissolution method. (b) (4) (b) (4)

Please respond by June 19, 2015.

If you have any questions, call Maryam Kord Bacheh Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

Wendy I. Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

WENDY I WILSON-LEE
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

METHODS VALIDATION MATERIALS RECEIVED

Actelion Pharmaceuticals, Ltd.
Attention: James B. Davis
Associate Director US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill NJ 08002
FAX: 856-773-4247

Dear James B. Davis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Uptravi (Selexipag) Tablets (200, 400, 600, 800, 1000, 1200, 1400, 1600 µg) and to our March 25, 2015 letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 8th, 2015 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP Coordinator (alternate)
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
05/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

REQUEST FOR METHODS VALIDATION MATERIALS

Actelion Pharmaceuticals, Ltd.
Attention: James B. Davis
Associate Director US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill NJ 08002

Dear James B. Davis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Uptravi (Selexipag) Tablets (200, 400, 600, 800, 1000, 1200, 1400, 1600 μg).

We will be performing methods validation studies on Uptravi (Selexipag) Tablets (200, 400, 600, 800, 1000, 1200, 1400, 1600 μg), as described in NDA 207947.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

3.2.S.4.2	(b) (4)
3.2.S.4.2	
3.2.S.4.2	
3.2.P.5.2	
3.2.P.5.2	
3.2.P.5.2	

Samples and Reference Standards

2 (b) (4) mg of selexipag drug substance
2 (b) (4) mg of selexipag drug reference standard
2 (b) (4) tablets of each dosage (200, 400, 600, 800, 1000, 1200, 1400, 1600 μg) of Uptravi drug product (samples)
1 (b) (4) mg of related substance reference standards: (b) (4) (b) (4)

Equipment

1 (b) (4)
1
1

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (laura.pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator (alternate)
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
03/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

INFORMATION REQUEST

Actelion Pharmaceuticals, Ltd.
c/o Actelion Clinical Research, Inc.
Attention: Mr. James B. Davis, US Agent; Assoc. Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for UPTRAVI (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg. We refer to your December 22, 2014, submission.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

(b) (4)

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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: 2015.03.06 09:24:47 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 22, 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Uptravi (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

We also refer to your amendments dated January 7, February 2, 13, 17, 18, and 19, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is December 22, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 4, 2015.

In addition, the planned date for our internal mid-cycle review meeting is May 13, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

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

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. A Horizontal Line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI). Your proposed package insert is missing this horizontal line.
2. All headings in HIGHLIGHTS (HL) must presented in the center of a horizontal line that extends over the width of the column. The horizontal line for the **WARNINGS AND PRECAUTIONS** heading does not extend the full width of the column.
3. Since you have proposed a patient package insert, Section 17 of your package insert should state : **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.** You did not include the statement referring to the FDA-approved patient labeling.
4. In the TOC, all section headings must be **bolded**. None of your section headings have been **bolded.**
5. The SECTION and Subsection headings in the TOC must match those in the FPI.

   a. In the **WARNINGS AND PRECAUTIONS** section, you include numbers for subsections 1-5 as blank subsections (not subsection headings) before listing subsections 5.1 and 5.2 that match those in the TOC.

6. You have attempted to comply with the Pregnancy Lactation Labeling Rule (PLLR), which will be implemented before the action date on your pending NDA. However, you labeled 8.3 as Lactation, which does not comply with the current subsection title or the correct subsection under the PLLR. Please change 8.3 Lactation to 8.2 Lactation in both the TOC and the FPI.
7. The preferred presentation for cross-references in the FPI is the **SECTION** heading (not subsection heading) followed by the numerical subsection cross-reference identifier.
   a. In subsection 2.1 in the FPI, you cross-reference using the subsection heading Pharmacokinetics instead of the section header **CLINICAL PHARMACOLOGY**.
8. In the **ADVERSE REACTIONS** section of the FPI, subsection 6.1 Clinical Trial Experience, the word "conducted" is missing from the first sentence between "are" and "under"
9. We also note that you have numerically designated (b) (4) in the FPI, (b) (4) (b) (4) are not typically used in FDA-approved package inserts. Please remove (b) (4) At this stage in our review, you may retain the associated subheadings.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 27, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
03/02/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207947

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Actelion Pharmaceuticals, Ltd.
c/o Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

ATTENTION: James B. Davis
Associate Director, U.S. Drug Regulatory Affairs

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated and received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Selexipag Tablets, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg and 1600 mcg.

We also refer to your correspondence, dated and received January 7, 2015, requesting review of your proposed proprietary name, Uptravi.

We have completed our review of the proposed proprietary name, Uptravi and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your January 7, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Wayne Amchin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
02/25/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

INFORMATION REQUEST

Actelion Pharmaceuticals, Ltd.
c/o Actelion Clinical Research, Inc.
Attention: Mr. James B. Davis, US Agent; Assoc. Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for UPTRAVI (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg. We refer to your December 22, 2014, submission.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Confirm that the to-be-marketed product will be available only in the HDPE packaging configuration. Section 3.2.P.2.4.2 indicates that selexipag film-coated tablets can be packaged in HDPE bottles (b) (4) However, Section. 3.2. P.7 of the submission only includes information supporting the use of the HDPE configuration. (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 (b) (4) the drug product testing site (b) (4) or the drug product packaging site (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.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

/s/

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: 2015.02.10 09:10:46 -05'00'

From:	James Davis
To:	Flowers, Louis
Cc:	Jenkins, Darrell; Makela, Cristina
Subject:	Re: NDA 207947: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME
Date:	Wednesday, January 07, 2015 3:49:10 PM

Captain Flowers,

I would like to notify you that Actelion has made a formal request for a Proprietary Name Review to the NDA 207947 (Seq 0001). The submission was electronic and was submitted through the gateway today.

If you have any questions or comments, please don't hesitate to contact me.

Regards,
JBD

James B. Davis
Associate Director DRA Global Project Leader

Actelion Pharmaceuticals Ltd. • Gewerbestrasse 16 • CH-4123 Allschwil • Switzerland

Phone: 856-773-5719 • Fax: 856-773-4247 •Mobile: 856-685-3995 • VOIP: 82 5719
james.davis@actelion.com • www.actelion.com
Address for visitors: 1820 Chapel Avenue West • Suite 300 • Cherry Hill • NJ • 08002

On Fri, Jan 2, 2015 at 2:33 PM, Flowers, Louis <Louis.Flowers@fda.hhs.gov> wrote:

> Dear Mr. Davis:
>
> I have been notified by the Division of Cardiovascular and Renal Products in the Office of New Drugs that you have submitted on December 22, 2014, for NDA 207947, an initial New Drug Application (NDA) for UPTRAVI (selexipag). In your submission dated December 22, 2014, you requested the continuation of the review of the proprietary name UPTRAVI. However, you did not submit a formal request for a Proprietary Name Review. Please click on the link below to read the guidance that describes the information that FDA uses to evaluate proposed proprietary names. The review clock for the performance review goals begins when the Agency receives a complete submission. For the Agency to conduct a complete review of a proposed proprietary name, we need you to submit a formal request for a Proprietary Name Review.
>
> http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf
>
> For the proposed proprietary name review, include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold, capital letters on the first page of the submission. Include all labels and labeling for the product in this submission or reference in the cover letter the submission that contains the labels and labeling the Agency should utilize when reviewing your proposed proprietary name.
>
> If you have any questions or comments, please do not hesitate to contact me, Darrell Jenkins and Cristina Makela.
>
> Thanks,
>
> Louis R. Flowers III, PharmD, MS, CPH
>
> Captain - USPHS

Team Leader, Project Management Staff

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Food and Drug Administration

BLDG 22, Room 4476

10903 New Hampshire Avenue

Silver Spring, MD 20993

Phone: 301-796-3158

Email: louis.flowers@fda.hhs.gov

The information of this email and in any file transmitted with it is strictly confidential and may be legally privileged.
It is intended solely for the addressee. If you are not the intended recipient, any copying, distribution or any other use of this email is prohibited and may be unlawful. In such case, you should please notify the sender immediately and destroy this email.
The content of this email is not legally binding unless confirmed by letter.
Any views expressed in this message are those of the individual sender, except where the message states otherwise and the sender is authorized to state them to be the views of the sender's company.

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/s/

LOUIS R FLOWERS
01/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

NDA ACKNOWLEDGMENT

Actelion Pharmaceuticals, Ltd.
c/o Actelion Clinical Research, Inc.
Attention: Mr. James B. Davis, US Agent
Assoc. Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

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

Name of Product: UPTRAVI (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

Date of Application: December 22, 2014

Date of Receipt: December 22, 2014

Our Reference Number: NDA 207947

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

If you have any questions, please contact:

Mr. Wayne Amchin
Sr. Regulatory Health Project Manager
(301) 796-0421

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

EDWARD J FROMM
01/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Frances Duffy-Warren, PhD	VP, US Drug Regulatory Affairs
FIRM/ORGANIZATION: Actelion Pharmaceuticals, Ltd.	
SIGNATURE: F. Duffy-Warren	DATE *(mm/dd/yyyy)*: 12/3/14

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

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ACTELION

24 November 2014

FIELD COPY CERTIFICATION

A field copy has not been provided since NDA 207947 has been submitted as an eCTD. The District Office will be able to access the NDA directly from the FDA's Electronic Document Room.

I hereby certify that Module 3 (Quality Module - Chemistry Manufacturing and Controls) of the applicant Actelion Pharmaceuticals Ltd. New Drug Application NDA 207947 has been submitted electronically for access by the District Office.

Frances Duffy-Warren, PhD
Vice President, US Drug Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104504

MEETING MINUTES

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Selexipag (ACT-293987).

We also refer to the meeting between representatives of your firm and the FDA on July 11, 2014. The purpose of the meeting was to present your top-line results from your pivotal trial and discuss additional analyses we want included in your NDA submission.

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

If you have any questions, call Wayne Amchin, Regulatory Project Manager at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: July 11, 2014, 11:30am-1pm
Meeting Location: FDA White Oak Campus

Application Number: 104504
Product Name: Selexipag
Indication: Treatment of Pulmonary Arterial Hypertension
Sponsor/Applicant Name: Actelion Pharmaceuticals Ltd.

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Wayne Amchin

FDA ATTENDEES

Office of Drug Evaluation I:

Ellis Unger, M.D.	Director
Bob Temple, M.D.	Deputy Director

Division of Cardiovascular and Renal Products:

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Mary Ross Southworth, Pharm.D.	Deputy Director for Safety
Shari Targum, M.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Reviewer
Tzu-Yun McDowell, Ph.D.	Clinical Reviewer
B. Nhi Beasley, Pharm.D.	Clinical Reviewer
Albert Defelice, Ph.D.	Nonclinical Team Leader
James M. Willard, Ph.D.	Nonclinical Reviewer
Russell Fortney	Regulatory Project Manager
Wayne Amchin	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:

Sudharshan Hariharan, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics I:

Jim Hung, PhD	Director
Steven Bai, PhD	Biostatistician

Office of New Drug Quality Assessment

Kasturi Srinivasachar, PhD	Team Leader, Product Quality
Charles Jewell, PhD	Product Quality Reviewer
Angelica Dorantes, PhD	Team Leader, Biopharmaceutics
Elsbeth Chikhale, PhD	Biopharmaceutical Reviewer

SPONSOR ATTENDEES

Marisa Bacchi, PhD VP - Head of Biostatistics
James B. Davis, BSc. US Project Leader, Drug Regulatory Affairs
Frances Duffy-Warren, PhD VP-Head US, Drug Regulatory Affairs
Aline Frey, PharmD Director, Senior Clinical Project Scientist
Alberto Gimona, MD Head of Clinical Science
Peter Jakobs, Dipl-Math Director, Project Statistician
Priska Kaufmann, PhD Project Clinical Pharmacologist
Samar Kelly, PhD, MBA, PMP Director Senior Global DRA Project Leader
Rajiv Patni, MD VP-Medical Affairs
Ralph Preiss, MD Clinical Science Program Head
Tatiana Remenova, MD Senior Drug Safety Physician
Douglas Smith, BSc. Director, Medical Writing Group Leader
Soichiro Sasaki Nippon Shinyaku Co-Development Observer

1.0 BACKGROUND

Selexipag (ACT-293987) is a prostacyclin receptor agonist. A pre-IND/pre-Phase 3 meeting was held on March 26, 2009, to discuss the clinical, nonclinical, and CMC aspects of the development program. The IND was submitted on September 29, 2009. A special protocol agreement was issued on February 23, 2010. A waiver of the Institutional Review Board (IRB) requirements under 21 CFR Part 56 for the use of selexipag in a foreign investigational study or all foreign investigational studies conducted under this IND was granted on February 16, 2011. A special protocol modification agreement letter was issued on February 27, 2013. A pre-NDA meeting was held on April 8, 2014.

At the time, FDA informed Actelion that we wanted them to hold a separate meeting with us to present the top-line results from their pivotal trial, GRIPHON, and that we would identify additional analyses we want submitted as part of the NDA submission during the presentation of the top-line results. FDA noted that the top-line results meeting was not intended to address sponsor questions, and no meeting package was expected other than the slide deck of the top-line results they would present at the meeting. If Actelion had questions to discuss with the agency, they should request another meeting to address those questions through the normal meeting process.

DISCUSSION: During the top-line results meeting, FDA identified the following additional analyses that Actelion should include in its NDA submission:

1. Actelion noted the apparent lack of effect in the Asian population and will conduct additional analyses to explore this further. FDA asked for data in Japanese subjects and

for information on how selexipag is metabolized. FDA suggested evaluation of tolerability in the Chinese patients as the largest cohort of Asian patients.

2. In addition to on-treatment analyses, FDA requested an intention to treat (ITT) analysis up to the end of the study, i.e., not just through the end of treatment (EOT), because there appeared to be more deaths during the period from the end of treatment to study closure than during treatment.
3. The safety evaluation should also be done up to study closure, in addition to on-treatment analyses.
4. FDA requested analyses that address the effect of experiencing a morbid event on the subsequent risk for death.
5. FDA requested analysis to characterize all-cause death up to end of treatment plus 7 days and 30 days.
6. FDA requested specific safety analyses by dose, given that the dose was titrated up and down in the trial. See post-meeting note.
7. FDA requested analyses of all-cause hospitalizations compared to hospitalizations reported or adjudicated as primary efficacy endpoints.
8. FDA requested analyses of deaths according to geographic region and other demographic/baseline disease characteristics.
9. FDA requested analyses of up and down-titration of study drug, including the reason for dose change.
10. FDA requested data on deaths according to individual maintenance dose.
11. For the analysis of the primary endpoint by individual maintenance dose, FDA requested inclusion of all treatment groups on one Kaplan-Meier plot.
12. For patients with a reported event of disease progression, FDA requested the number of patients and reason for missing second 6MWT (confirmatory 6MWT), adjudication outcome, or functional class at time of assessment

3.0 ISSUES REQUIRING FURTHER DISCUSSION

1. FDA proposed to work with Actelion to achieve the most informative groupings of preferred terms for the reporting of safety data to overcome well-known fragmentation of MedDRA terms.
2. FDA agreed to the following Actelion proposal:
   – to exclude/censor events with an onset date up to 16 Aug 2011 only for the main analysis of the primary endpoint.
   – to include events with onset date up to 16 Aug 2011 in all sensitivity and subgroup analyses of the primary endpoint as well as in all secondary and exploratory time-to-event endpoints.

4.0 POST-MEETING NOTE

It is difficult to assess adverse events by dose, given that that the selexipag dose was titrated up and down. One could compute an average dose for each patient through time, categorize all patients into 2 or 3 dose levels, and then compute adverse event frequencies by patient, categorized by average dose. But this method would fail to account for the fact that doses are titrated, and a patient's average dose through time might not reflect the dose at the time the adverse event occurred. For example, a patient might be up-titrated to a dose of 1600 mcg bid

and experience a serious adverse event. At that point, the dose would be reduced. Let us assume for the sake of this example that the once the dose was reduced, it was never raised again, i.e., let us assume that that this patient never tolerated higher doses. Thus, the patient would have received, on average, a low dose, although the serious adverse event occurred only at the highest dose. The analysis should show that it was the high dose that led to the adverse reaction.

For the safety analyses, we suggest that, in addition to the usual analyses, you analyze the adverse events by unit of time, such as subject-week, to account for the changing dose. To do this analysis, you would determine the prevailing dose (e.g., 0, 200, 400, 600, 800, 1000, 1200, 1400, or 1600 mcg b.i.d) for each subject during each week they are in the study. Once this is completed, link each adverse event to its matching subject-week. The goal is to report the rate of each adverse event as number of events per total weeks of exposure at a particular dose. In essence, instead of using patients as the denominator for the adverse event analyses, you will use patient-weeks (time) at each specific dose.

Below is a simplified example of such a calculation. The table depicts 4 subjects who are followed for 7 weeks. Together, these subjects contribute a total of 28 subject-weeks of data, of which 8 weeks were at a dose of 1000 mcg b.i.d (highlighted in yellow). If two headaches were reported, both in Subject 1 (on 8/5/2014 and 8/12/2014 - weeks indicated in red font), then there were 2 headaches reported per 8 total weeks of exposure at a dose of 1000 mcg b.i.d., or 0.25 headaches per subject-week. By completing similar calculations for each adverse event for each dose, it is possible to consider the relation of all adverse events (and serious adverse events) to dose.

Week	subject 1	subject 2	subject 3	subject 4
6/29/2014	1000	600	0	600
7/6/2014	1200	600	0	800
7/13/2014	1200	600	0	800
7/20/2014	1000	600	0	1000
7/27/2014	1000	400	0	800
8/3/2014	1000	400	0	1000
8/10/2014	1000	400	0	1000

5.0 ATTACHMENTS AND HANDOUTS

The slide deck provided for the meeting, in lieu of a meeting package, is attached.

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/s/

NORMAN L STOCKBRIDGE
08/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104504

MEETING MINUTES

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Selexipag (ACT-293987).

We also refer to the meeting between representatives of your firm and the FDA on April 8, 2014. The purpose of the meeting was to obtain FDA input and guidance on the acceptability and sufficiency of the overall data package for the NDA submission and review of selexipag for the treatment of pulmonary arterial hypertension.

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

If you have any questions, call Wayne Amchin, Regulatory Project Manager at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 8, 2014, 10-11:30am
Meeting Location:	FDA White Oak Campus Building 22, Room 1421 10903 New Hampshire Avenue Silver Spring, MD 20903
Application Number:	IND 104504
Product Name:	Selexipag (ACT-293987)
Indication:	Treatment of pulmonary arterial hypertension
Sponsor/Applicant Name:	Actelion Pharmaceuticals Ltd.
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Wayne Amchin

FDA ATTENDEES

Division of Cardiovascular and Renal Products:

Norman Stockbridge, M.D., Ph.D.	Director
Mary Ross Southworth, Pharm.D.	Deputy Director for Safety
Martin Rose, M.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Reviewer
Tzu-Yun McDowell, Ph.D.	Clinical Reviewer
Nhi Beasley, Pharm.D.	Clinical Reviewer
James M. Willard, Ph.D.	Nonclinical Reviewer
Ed Fromm, R.Ph.	Chief, Project Management Staff
Russell Fortney	Regulatory Project Manager
Wayne Amchin	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:

Sudharshan Hariharan, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics I:

Steven Bai, Ph.D.	Biostatistician
John Lawrence, Ph.D.	Biostatistician

Office of New Drug Quality Assessment

Charles Jewell, Ph.D.	Product Quality Reviewer

Elsbeth Chikhale, Ph.D.	Biopharmaceutical Reviewer

Office of Compliance, Division of Good Manufacturing Practice Assessment

Vibhakar Shah, Ph.D.	Senior Policy Advisor

Office of Surveillance and Epidemiology

Susan Lu, R.Ph.	Pharmacovigilance Team Leader
Oanh Dang, PharmD, BCPS	Safety Evaluator, Division of Pharmacovigilance I
Jean Olumba, M.D., Pharm.D.	Safety Evaluator
Somya Dunn, M.D.	Risk Management Analyst
Kimberly Lehrfeld, Pharm.D.	Risk Management Team Leader
Karen Bengtson,	OSE Regulatory Project Manager

Office of Bioinformatics

Valerie Gooding	Regulatory Information Specialist

EASTERN RESEARCH GROUP ATTENDEES
So Hyun Kim, Independent Assessor, Eastern Research Group

SPONSOR ATTENDEES

Ralph Preiss, M.D,	Clinical Science Program Head, Actelion
Aline Frey, Pharm.D.	Director, Senior Clinical Project Scientist, Actelion
Carmela Gnerre, Ph.D.	Associate Director, Preclinical Pharmacokinetics and Metabolism, Actelion
Frances Duffy-Warren, Ph.D.	VP-Head US, Drug Regulatory Affairs, Actelion
Samar Kelly, Ph.D., M.B.A., P.M.P.	Global Project Leader, Drug Regulatory Affairs, Actelion
James Davis, B.Sc.	US Project Leader, Drug Regulatory Affairs, Actelion
Alexandra Schlicker Spain, Ph.D.	Senior Technical Project Leader, Actelion
Claire Heinkélé, Pharm.D.	Director, Technical Regulatory Affairs, Actelion
Marisa Bacchi, Ph.D.	VP – Head of Biostatistics, Actelion
Peter Jakobs, Dipl-Math	Director, Biostatistics, Actelion
Tatiana Remenova, M.D.	Senior Drug Safety Physician, Actelion
Shirin Bruderer, Ph.D.	Project Clinical Pharmacologist, Actelion
Douglas Smith, B.Sc.	Director, Medical Writing, Actelion
Soichiro Sasaki	Nippon Shinyaku Co-Development Observer

1.0 BACKGROUND

The sponsor requested the meeting to obtain FDA input and guidance on the acceptability and sufficiency of the overall data package for the NDA submission and review of selexipag for the treatment of PAH.

Reference ID: 3499909

Selexipag (ACT-293987) is a prostacyclin receptor agonist. A pre-IND/pre-Phase 3 meeting was held on March 26, 2009, to discuss the clinical, nonclinical, and CMC aspects of the development program. The IND was submitted on September 29, 2009. A special protocol agreement was issued on February 23, 2010. A waiver of the Institutional Review Board (IRB) requirements under 21 CFR Part 56 for the use of selexipag in a foreign investigational study or all foreign investigational studies conducted under this IND was granted on February 16, 2011. A special protocol modification agreement letter was issued on February 27, 2013.

Meeting Preliminary Comments were provided to the sponsor on April 2, 2014. On April 7, Actelion indicated that they wanted to discuss FDA's responses to questions 3-7 and 9, as well as FDA's additional requests 1, 6, 8, 14, and 15 at the meeting. Actelion also provided two slides for discussion at the meeting (see attached).

2.0 DISCUSSION

2.1. Product Quality: Stability Testing

Question 1: Actelion will use a bracketing/matrixing design for stability testing, which is in accordance with ICH guidelines to qualify the proposed shelf life for three (3) intermediate selexipag dose strengths (600, 1000, 1400 μg) based on the full stability testing for selexipag at five (5) dose strengths including the lowest and highest strengths (i.e., 200, 400, 800, 1200, and 1600 μg). Does the Agency agree to grant a single shelf-life for all eight (8) dose strengths?

FDA Response to Question 1: Since all tablets are the same size and weight, (b) (4) (b) (4) and provided all tablet-bottle configurations are appropriately accounted for in the stability data strategy, it may be possible for the Agency to assign the same expiration dating period for all strength/ count/bottle configurations depending on the data submitted to the NDA. The assignment of the expiration dating period will be made by the Agency based on analysis of all stability data provided in the NDA. Intermediate strengths that are appropriately bracketed can be assigned expiration dating based on the overall stability assessment. At the time of the NDA submission, ascertain that headspace/tablet volume ratio and bottle/closure type differences are appropriately accounted for in any bracketing/matrixing strategies, if these parameters apply to your marketing proposal.

Discussion: *This question was not discussed.*

Question 2: Actelion proposes to use a bracketing/matrixing design for stability testing of the (b) (4) commercial batches for all dose strengths. Does the Agency agree with Actelion's proposed design?

FDA Response to Question 2: Yes, the Agency agrees with your proposed design of the stability studies for the (b) (4) commercial batches for all dose strengths.

Reference ID: 3499909

Discussion: *This question was not discussed.*

2.2. Nonclinical/Drug-Drug Interaction

Question 3: Actelion proposes to include the results of the evaluation of the substrate properties of selexipag and its active metabolite ACT-333679 on the transporters OATP1B1/1B3, P-gp/MDR1, BCRP and MATE1 (ACT-333679 only), but not to investigate the substrate properties of either compound on kidney transporters such as OCT2, OAT1/3 and MATE2 for the NDA. Does the Agency agree?

FDA Response to Question 3: Yes, the Agency agrees that since selexipag and its active metabolite are excreted primarily through the bile that testing of kidney transporters may be waived at this time. However, we recommend you to test the potential for selexipag and its active metabolite ACT-333679 to be a substrate and/or an inhibitor of hepatic transporters including MRP-2 and BSEP.

Discussion: *Actelion clarified that based on the ADME study, only the active metabolite (ACT-333679) was detected in feces, but not selexipag. Hence, Actelion mentioned that they will test substrate potential for only the active metabolite towards MRP-2 and BSEP. However, both selexipag and the active metabolite will be tested for the inhibitory potential against the hepatic and renal transporters listed in the 'Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations'. FDA was in agreement with this proposal.*

2.3. Biopharm/Bioequivalence

Question 4: In accordance with the FDA 2003 Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration," Actelion has completed a series of dissolution testing and an in vivo bioequivalence (BE) study to support a biowaiver for selexipag dose strengths: 400, 600, 800, 1000, 1200, and 1400 µg. Actelion is of the opinion that the results provide sufficient evidence for a biowaiver. Does the Agency agree that a biowaiver can be granted?

FDA Response to Question 4: Your approach toward requesting a waiver of the CFR requirement to provide BA/BE data for the 400, 600, 800, 1000, 1200, and 1400 µg tablet strengths of your product appears appropriate. (b) (4)

(b) (4)

Reference ID: 3499909

We have the following advice comments regarding the additional information that should be included in your NDA.

1. ***Dissolution Method:*** Provide the dissolution method development report supporting the selection of the proposed test. The dissolution report should include the following information, obtained using the final drug product formulation:

   a. Solubility data for the drug substance covering the pH range;

   b. A detailed description of the dissolution method proposed for your product and the developmental parameters (*i.e., selection of the equipment/ apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select/identify the proposed dissolution method as the most appropriate. The testing conditions used for each test should be clearly specified;

   c. The complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and

   d. Testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

   Acceptance Criterion: We recommend that you collect complete dissolution profile data (b) (4) from the bio-batches and primary (registration) stability batches of your drug product throughout the stability program and provide the raw dissolution profile data (individual and mean) in an excel file. These profile data should be used for the setting of the dissolution acceptance criterion of your product.

   For the setting of the drug dissolution acceptance criteria, the following points should be considered:

   - The dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or (b) (4)
   - The specification-time point should be set when Q = (b) (4)% of dissolution occurs.

2. ***Bioequivalence Data:*** In your NDA, we request that you also submit the following PK data from the BE Study in SAS Transport format in two separate files as described below:

   (b) (4)

3. ***Bioanalytical Method(s):*** we request that you also provide a summary table for the bioanalytical method validation (used for BE study) in the format provided below:

Reference ID: 3499909

Matrix		
Sample Volume Required Storage Conditions Extraction Procedure		
Concentration Range		
HPLC Procedure		
Detection		
Regression Type		
Coefficient of Determination		
Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

Discussion: *Actelion referenced the two handouts provided in advance of the meeting, and they asked if the information shown in the first slide was what FDA had in mind. They further inquired if the approach outlined in the second slide was an acceptable alternative.*

FDA confirmed that the first slide accurately reflected its standard approach, and that the approach described on the second slide was not an acceptable alternative.

2.4. Clinical/Statistical

Question 5: Statistical Analysis Plan for Clinical Study Report of Pivotal

Reference ID: 3499909

Study AC-065A302/GRIPHON: Actelion considers the proposed statistical analysis plan (SAP) for the pivotal study AC-065A302/GRIPHON (conducted under a SPA) and from the ongoing AC-065A303/GRIPHON-OL extension study as adequate to support the evaluation of efficacy and safety in the NDA for selexipag. Does the Agency agree?

FDA Response to Question 5: GRIPHON SAP version 3.0 proposed a multiple imputation method to fill the missing values for the key secondary efficacy endpoint, absolute change from baseline in 6MWD at trough at Week 26. The agency has the following concerns with the imputation method proposed:

- For the patients deceased or physically incapable of walking due to illness, no imputation method is more reasonable than a value of 0 for 6MWD at Week 26.
- For the patients who missed 6MWD at Week 26, a more conservative imputation method should be used to penalize such unlikely occurrences.
- Your proposed multiple imputations rely on too many assumptions including a Bayesian posterior predictive distribution and those assumptions often cannot be justified. Hence, this method could allow too much flexibility on the model selections.

The similar multiple imputation method will be applied to another key secondary efficacy endpoint, absence of worsening from baseline in modified NYHA/WHO functional class at Week 26. Please refer to the above concerns.

Discussion: *Actelion asked for clarification on the first bullet in FDA's meeting preliminary comments, specifically whether we expected imputation of zero meters for those incapable of doing the 6MWD because of PAH. FDA concurred.*

Actelion asked for clarification on the second bullet in FDA's preliminary meeting response, specifically, whether FDA wanted a more conservative approach than what the sponsor had proposed in the meeting package with respect to a missing value from a missed visit. Actelion elaborated that they have situations where subjects did not have week 26 visit, even though they had visits prior to and after week 26. Actelion also had situations where subjects had a week 26 visit but did not do the 6MWD, for reasons unrelated to PAH (e.g., a broken leg).

Actelion proposed an alternative approach based on the mixed effect repeated disease model discussed in a 2009 paper of which Dr. Hung (FDA/Division of Biometrics) was a co-author. The paper recommended this approach, instead of the last-observed carried forward method, to generate the primary analysis instead of using imputation.

FDA agreed to discuss this issue (and missing functional class) internally and provide advice at a later time. Actelion requested a response by April 20th in order to finalize a solution prior to database lock in mid-May.

Actelion noted that for a small number of subjects the 6MWT was not done at trough. The Agency suggested leaving those subjects in the primary analysis and asked for a sensitivity analysis to show the effect of dropping them from the primary analysis.

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Question 6: Statistical Analysis for Integrated Summary of Effectiveness (ISE): The CSR for the single pivotal study AC-065A302/GRIPHON will provide the main body of evidence in support of selexipag's efficacy profile. Therefore, the Summary of Clinical Efficacy (SCE) (text portion of the ISE), will be mainly based on results from AC-065A302/GRIPHON CSR.

In addition, Actelion plans for the SCE:

1. to further display and explore the amount and impact of missing and censored efficacy data on the overall assessment of efficacy in study AC-065A302/GRIPHON
2. to explore the potential effect of patients who were randomized to placebo in study AC-065A302/GRIPHON and then switched to selexipag (in the extension study AC-065A303/GRIPHON OL) or to an approved treatment for PAH
3. to explore the potential effect of patients who were randomized to selexipag study AC-065A302/GRIPHON and experienced a transient decrease in selexipag dose due to the Titration Period in the extension study AC-065A303/GRIPHON OL
4. to evaluate a potential relationship between the occurrence of morbidity events and subsequent risk of death
5. to assess selexipag's efficacy in comparison to standard of care data from a completed US PAH patient registry called REVEAL

Does the Agency agree that the statistical analyses of efficacy planned in the SAP for study AC-065A302/GRIPHON as well as those described above are appropriate for inclusion in the NDA?

FDA Response to Question 6: The Division agrees with your proposals. We will also be interested in those subjects whose efficacy endpoints were disputed during a CEC meeting.

Discussion: *FDA clarified its interest in seeing cases where there was not unanimous agreement among the 3 members of the adjudication committee. The Agency agreed that is correct.*

FDA asked what triggered the CRF being sent to the committee, for example was there an event component or not. FDA also asked if there was any electronic triggering, independent of the investigator, and whether or not the committee itself could request CRFs. FDA asked if these rules were in the committee charter.

Actelion responded that the rules were in the committee charter. It was an investigator decision and there was also a quality control person submitting cases to the committee. Actelion indicated that there was no electronic triggering.

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Question 7: Integrated Summary of Safety (ISS): Does the Agency agree that the data cut-off date, proposed content, and presentation of the safety data as described in the Statistical Analysis Plan for the Summary of Clinical Safety (SCS) are adequate to allow for the review and evaluation of the safety profile of selexipag in patients with PAH?

FDA Response to Question 7: The Division agrees with your proposals. However, we request that you limit your initial submission of CRFs and narratives from the GRIPHON trial to those subjects who died, dropped out or discontinued study drug for any reason, reported a serious adverse event or reached an efficacy endpoint. We will contact you if we need additional CRFs.

Discussion: *Actelion asked for clarification whether they need to submit patient profiles from GRIPHON. FDA agreed that patient profiles do not need to be provided.*

Question 8: Does the Agency agree with the content and data cut-off date proposed for the Day 120 safety update for the NDA?

FDA Response to Question 8: The Division agrees with your proposals.

Discussion: *This question was not discussed.*

2.5. Regulatory:

Question 9: Clinical Datasets: Does the Agency agree with the proposed approach to the clinical datasets planned for submission within the application?

FDA Response to Question 9: Please explain which datasets were used for your analyses. In addition to the SDTM and ADaM datasets, please submit the CRF datasets for all of the Phase 2 and 3 trials , and your analysis datasets for the Phase 3 trial and ISS. Please also provide define.pdf files for all datasets. SAS code is usually submitted as *.SAS files. In all open label extension study datasets, please include a subject ID variable that links the subject to the ID used in the placebo controlled trial.

Discussion: *The Sponsor confirmed that SDTM and ADaM datasets will be used for all analyses in the GRIPHON trial, ISE, and ISS. Dr. Beasley requested any datasets used for their analyses. CRF datasets should be readily available upon request. Dr. Beasley requested that the sponsor submit all analysis code used to derive the ADaM datasets from the SDTM datasets, and a table that lists and describes each analysis code. The Sponsor agreed to all requests.*

Question 10: Nonclinical Datasets: Actelion previously submitted the 24-month mouse and rat carcinogenicity study datasets with their respective final reports to the IND. The datasets were submitted as SAS Transport files (with XPT as the file extension) and included raw and

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derived data on neoplastic lesions. Actelion is not planning to re-submit these datasets for the NDA submission. Aside from the carcinogenicity studies, no datasets will be generated for any other nonclinical studies (e.g. general toxicity studies). Does the Agency agree?

FDA Response to Question 10: Yes, it is sufficient that these studies were submitted under the IND.

Discussion: *This question was not discussed.*

Question 11: Does the Agency agree with the overall eCTD content plan to support the NDA filing for selexipag in patients with PAH?

FDA Response to Question 11: From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. Please provide hyperlinks for items referenced in Module 2 and Module 5 to aid in navigation of the application. Please see additional comments below.

- Providing a Reviewer's Guide with a high level overview of what is provided in modules 1 through 5 with hyperlinks, can be helpful to reviewers. The Reviewer's Guide is usually provided as a separate document in the cover letter section, under section m1.2, with a clear and descriptive leaf title.
- For archival purposes, you should submit a pdf file of the labeling document submitted in Word. Also, when you submit Word documents, make sure the leaf title includes "word", so reviewers could quickly identify the Word version of the document.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (CRFs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf .

- Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report forms need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml.

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Discussion: *This question was not discussed.*

2.6. Bioresearch Monitoring

Question 12: (b) (4) As part of the Pre-NDA meeting preparation, Actelion was provided with a Site Selection Information Request from the OSI. The request included instructions for a pilot program that consisted of electronic submission of site level datasets to facilitate FDA inspections. Does the Agency agree that Actelion should use the same OSI Pre-NDA site selection information request as provided on 7 March 2012 for the provision of site level data to support the selexipag NDA submission?

FDA Response to Question 12: Your proposal is acceptable. Please use the more recent attached Office of Scientific Investigations (OSI) Pre-NDA request information.

Discussion: *This question was not discussed.*

2.7. Additional Requests from the Agency

1. Please submit all versions of the protocol for GRIPHON and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.

Discussion: *FDA clarified that it wanted to know when a protocol change was communicated to a study site. Actelion stated that the date that the protocol was signed was the date that sites were notified to implement the changes. Dr. Rose asked that the Sponsor state this in the NDA. The Sponsor agreed.*

2. All versions of Statistical Analysis Plan (SAP) for GRIPHON.

Discussion: *This request was not discussed.*

3. Please submit all SAS codes used to create your analyses for GRIPHON and for your ISS. If a SAS code contains a macro, please also include the macro code.

Discussion: *This request was not discussed.*

4. Please submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the NDA. The table should contain the following:

    a. title of the table or figure in NDA
    b. a hyperlink to the location of the table or figure with page number
    c. a hyperlink to the SAS code used to create the table or figure

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Discussion: *This request was not discussed.*

5. In the NDA (for example with the review aid), please submit an annotated version of these pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested.

   Discussion: *This request was not discussed.*

6. An adjudication dataset should be submitted that contains one line per event and the event type being adjudicated (i.e., hospitalization for worsening PAH, , major bleed, etc.), what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the nature of the event, each adjudicators' result (in chronological order) and date of adjudication, final adjudication result, the study number, unique subject id, treatment arm, flag that indicates subject is included in the ITT analysis, flag that indicates subject is included in the safety analysis, and date of event.

   Discussion: *Actelion asked for clarification on how to submit the adjudication datasets. Actelion asked if they can split up the datasets. Dr. Beasley stated that her preference is for one dataset for ease of review. She stated that she might want to analyze the data by adjudicator. The Sponsor noted that an adjudicator did adjudicate more than one event. They proposed to submit the data in separate datasets, but would ensure that an adjudicator would not be split between datasets.*

7. Please submit all adjudication packages exactly and completely as seen by the adjudicators, including all source documents and query results. If adjudication packages were prepared but not sent to the CEC, please submit these as well. Please bookmark the electronic adjudication packages for ease of review.

   Discussion: *This request was not discussed.*

8. Please provide a dataset(s) for time to event (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Include whether censoring was determined by a patient visit or by telephone call. This data set(s) should allow one to analyze by ITT as well as on-treatment. The events should include all adjudicated events and any important composite endpoints.

   Discussion: *Actelion asked for clarification on the issue of "important composite endpoints". Actelion proposed providing datasets for Primary Endpoint (PE) datasets and secondary composite endpoints that leave out disease worsening. Actelion indicated they had 20 composite endpoints separate from the primary analysis, and they could look at the heart component without looking at PAH (i.e., leave out disease worsening).*

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FDA asked if Actelion, in the main PE analysis, was not doing what it says in the protocol, specifically if Actelion is censoring and they lose track of any component of a composite endpoint.

Actelion noted that with the last protocol amendment, they started collecting data in the post-treatment period through study closure. Because some patients had already ended treatment by that time they attempted to contact those patients and collect the necessary data.

9. Please submit all informed consent document(s). Please describe any country- or region-specific variations.

   Discussion: *This request was not discussed.*

10. Please note that CRFs include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.

    Discussion: *This request was not discussed.*

11. Please provide sample clinical trial kits, from both arms, identical to those used during GRIPHON. Ship them to Wayne Amchin's desk address in the same packaging as will be used for shipping to investigative sites.

    Discussion: *This request was not discussed.*

12. Please submit your site monitoring plan and all amendments for GRIPHON.

    Discussion: *This request was not discussed.*

13. Submit a description of the responsibilities of each ARO or CRO used in the GRIPHON trial.

    Discussion: *This request was not discussed.*

14. Please submit your data management plan for GRIPHON, including all manual and programmatical checks. Submit SAS codes that were used to create and/or clean up your analyses datasets.

    Discussion: *The discussion of SAS code was covered in earlier discussion during the meeting.*

15. Please include a list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets, and what you did to ensure your datasets are suitable for an NDA review.

    Discussion: *Actelion indicated that they hope that all of their datasets are of high quality. They plan to describe the data cleaning process in the reviewers guide.*

    FDA indicated that this is fine. FDA does not expect all datasets to be scrutinized at the same level. However, if a reviewer finds many discrepancies between the CRFs and the

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dataset, it might decrease the level of confidence in their submission. FDA added that Actelion should run analysis in study reports on the ADaM data set.

16. Please include a dataset that indicates those subjects for whom you submitted a CRF, narratives, and/or adjudication package(s). The dataset should contain four variables with an indicator for whether each item was submitted.

    Discussion: *This request was not discussed.*

17. Please include all charters for committees involved in conducting GRIPHON (e.g., DSMB, Steering Committee, etc.)

    Discussion: *This request was not discussed.*

18. At the time of the NDA submission, please include Steering Committee and DSMB meeting minutes (including any data/slides presented to the Committee). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the selexipag clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

    Discussion: *This request was not discussed.*

19. Please submit all newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters by date.

    Discussion: *This request was not discussed.*

20. Please submit, to the IND as soon as possible, an encrypted SAS dataset of the randomization list including the randomization number, treatment arm, and stratification factors (if any) for your Phase 3 trial. Please include an unencrypted copy of a DEFINE.PDF file describing the randomization list variables. A copy of the encryption key should be included with your NDA submission of the trial results.

Discussion: *This request was not discussed.*

ADDITIONAL DISCUSSION POINTS:

FDA added that Actelion submit a dataset that contains subjects that were unblinded. The dataset should contain the unique subject ID, the date of unblinding, who requested the unblinding, the reason for unblinding, and the treatment group. FDA also asked what adverse events would lead to a decision to unblind, what serious adverse events were clinically important to unblind to manage a patient, and how many cases of unblinding there were.

Actelion responded that unexpected serious adverse events would result in unblinding and that there were 20 unblinded cases. Actelion said that if investigators needed to initiate rescue therapy with IV prostanoid it would be important to know if the patient was on active drug or placebo.

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Actelion asked if FDA anticipated an advisory committee (AC) meeting for the application. FDA responded that we typically do have an AC for new molecular entities, and we would need to justify a decision not to go to an AC. No final decision has been made, but an AC is likely.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 21, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The sponsor had no requests for late submission.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

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- Actelion indicated that submission of a Risk Evaluation and Mitigation Strategy (REMS) was not anticipated. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Discussion: *PREA was not discussed.*

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PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion: *Labeling was not discussed.*

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion: *Manufacturing facility inspections were not discussed.*

3.0 ISSUES REQUIRING FURTHER DISCUSSION

During the meeting, FDA agreed to provide an agreeable approach for handling missing data and missing functional values to Actelion by April 20, 2014. As a post-meeting discussion point, FDA issued an advice letter on April 17, 2014. The advice letter stated:

> During our April 8, 2014, pre-NDA meeting, we agreed to follow-up with you by April 20, 2014, to provide an acceptable approach for handling missing data and missing functional values in your pivotal trial.
>
> We propose that you use the following procedure to rank the missing 6MWD at trough at week 26:
>
> 1. For patients unable to walk because of death or worsening PAH at week 26, assign a walk distance of 0 m or worst rank (regardless of treatment group).
>
> 2. For other types of missing distances, assign them the second worst rank (regardless of treatment group).

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4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide an agreeable approach to handle missing values	FDA	April 20, 2014
Provide an agreeable approach to handling missing functional values	FDA	April 20, 2014

5.0 ATTACHMENTS AND HANDOUTS

The following attachments are included:

1. OSI Pre-NDA Request-this was included in the meeting preliminary comments sent to Actelion, but it was not discussed at the meeting.
2. Clinical Pharmacology Summary Aid-this was included in the meeting preliminary comments sent to Actelion, but it was not discussed at the meeting.
3. Actelion slides provided in advance of the meeting for discussing FDA's meeting preliminary comments on question 4-this was discussed as part of the discussion of question 4.

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The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

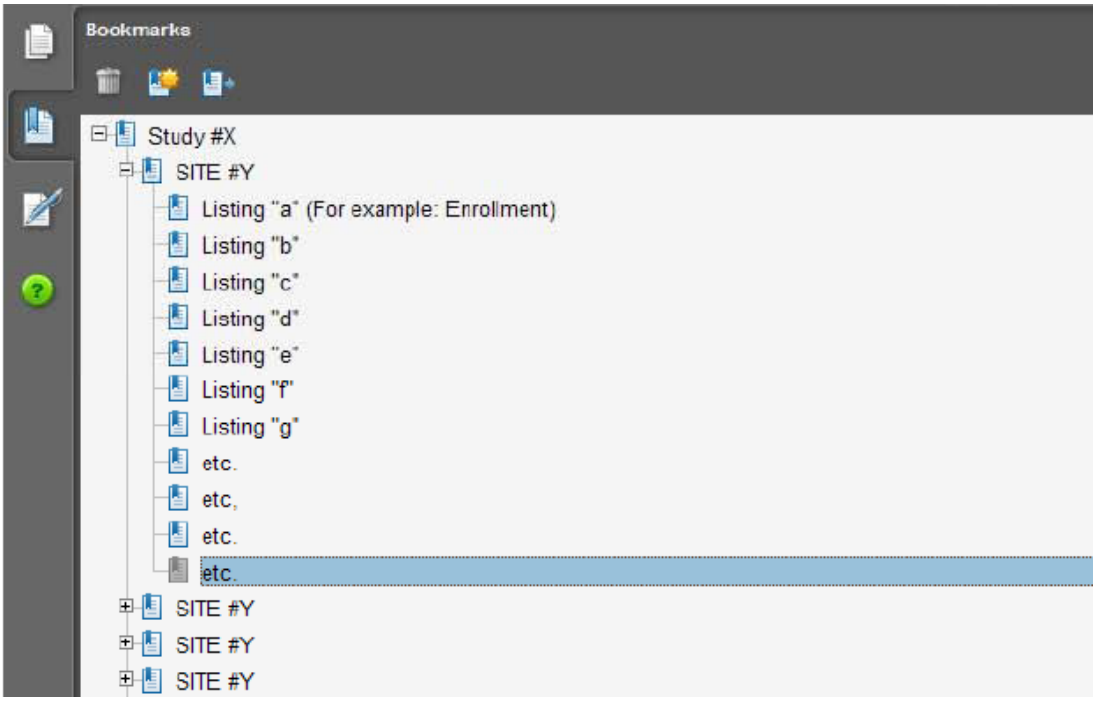
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To better communicate the expectations of the Agency and to guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a Clinical Pharmacology Summary Aid was created. The document consists of a generic questionnaire and instructions clarifying what the answers to the questions should address. The questions cover the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired backbone of the Clinical Pharmacology Summary in NDA and BLA submissions. The questions and instructions included in this aid are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics

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(Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from pivotal and other appropriate trials. Provide evidence that the exposure-response analysis supports of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If commonly known covariates are not identiiable, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for effectiveness variables if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal

status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the pivotal trials. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor,

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fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small

to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target

population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax, CL/F, CLr, V/F and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the

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sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, CL/F and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic (b) (4) impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as

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inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the

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magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the

pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH (b) (4) and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic

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regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20°$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

Applicable to therapeutic proteins only

2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.7 What is the performance of the neutralizing assay(s)?

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/s/

NORMAN L STOCKBRIDGE
05/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104504

SPECIAL PROTOCOL – AGREEMENT MODIFICATION

Actelion Pharmaceuticals, Ltd.
Attention: Lester Gibbs, Ph.D.
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Gibbs:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for selexipag (ACT-293987).

We also refer to your 11 January 2010 request, received on 11 January 2010, for a special protocol assessment of a clinical protocol and to our 23 February 2010 agreement letter. The protocol is Study AC-065A302, entitled "A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension (GRIPHON)."

We acknowledge your submission dated 12 February 2013, received on 12 February 2013, amending the above protocol, which was under a special protocol agreement.

In summary, your amendment makes the following modifications:

1. A post-treatment observation period was added.
2. The study's primary objective and title were reworded: "Clinical Worsening Event" was replaced by "Morbidity and Mortality (MM) event."
3. A clarification was made regarding the pre-defined criteria for hospitalization for PAH worsening and chronic oxygen therapy.
4. Modifications to the statistical analysis section were made.
5. Two additional Critical Event Committee (CEC) responsibilities were added.

We have completed our review and, based on the information submitted, agree to these modifications. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as "**Special Protocol Assessment Amendment**". This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see "Guidance for Industry: Special Protocol Assessment").

As stated on page 9 in the "Guidance for Industry: Special Protocol Assessment," a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations

for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

If you have any questions or concerns, please contact Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

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02/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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IND 104,504

SPECIAL PROTOCOL - AGREEMENT

Actelion, Ltd.
Attention: Patricia Palumbo, BSN, JD
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Ms. Palumbo:

Please refer to your Investigational New Drug Application (IND) submitted on September 29, 2009, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACT-293987.

We also refer to your September 29, 2009, requests for two special protocol assessments of clinical protocols both entitled "A multicenter, double-blind, placebo-controlled Phase 3 study to demonstrate the efficacy and safety of ACT-293987 in patients with pulmonary arterial hypertension", and our responses dated November 9, 2009.

We have completed our review of your revised special protocol assessment and response to FDA SPA comments dated January 11, 2010, and based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see *Guidance for Industry; Special Protocol Assessment*).

We also have the following response to the one new question posed in your cover letter:

1. Does FDA agree that the Phase 3 Study GRIPHON (AC-065A302) will support the NDA submission and proposed indication of delay in time to clinical worsening and improved exercise capacity in PAH patients?

   FDA Response: **Yes, but with the caveats noted in our responses below.**

Below, you will find your original questions dated September 29, 2009, FDA's responses dated November 9, 2009, your responses dated January 11, 2010, and our responses/comments if any. We note that agreement was previously reached for questions 2 and 8 so those questions are not included below.

Actelion Question 1

1. Actelion expects that the two studies (AC-065A301) and (AC-065A302) support an NDA submission and the proposed indication

- if the null hypothesis of no difference from placebo for 6MWT is rejected simultaneously in both studies AC-065A301 and AC-065A302 **or**
- if the null hypothesis of no difference from placebo for time to event is rejected for the pool of the two studies.

Does the FDA agree?

FDA response to Question 1

While establishing an effect on 6MWT or time to clinical worsening can support an NDA submission and serve as a basis for approval for pulmonary arterial hypertension, we have concerns with these endpoints as defined or measured in the proposed studies. Changes in 6MWT should not be included as part of the definition of clinical worsening. Effects on 6MWT will be established via your other proposed coprimary endpoint; moreover, not all patients who discontinue from the study may undergo this assessment. With regard to ascertaining effects on 6MWT, testing should be restricted to the period corresponding to ACT-293987's trough. Finally, it should be noted that the absence of dose-response data for your drug in the PAH population could adversely impact any decision regarding drug approval. If your phase 3 trials establish an effect on time to clinical worsening, you may be able to obtain approval without dose-response data; however if your development program only establishes an effect on 6MWT, such data could be critical.

Actelion response

Actelion has redesigned the Phase 3 program into a single Phase 3 pivotal study (GRIPHON), rather than two separate Phase 3 studies. In addition, Actelion has revised the protocol design so that the primary objective will be to demonstrate the effect of ACT-293987 on time to first clinical worsening in patients with PAH.

As a secondary objective, the Phase 3 study will evaluate the effect of ACT-293987 on exercise capacity expressed as change from Baseline to Week 16 in 6MWD at trough, which will be the first secondary endpoint of the study. Actelion has also clarified the wording in the protocol for the 6MWT so that the test is performed at trough.

Actelion's response to Question 5 also concerns endpoints (see below).

FDA response: **Your proposal to conduct a single study with a primary endpoint of clinical worsening and an overall type I error rate set to 0.01 is acceptable.**

Actelion Question 3

3. The strategy for a valid confirmatory analysis of the secondary endpoints requires that they will be analyzed on the pool of the studies AC-065A301 and AC-065A302, at the 0.05 two-sided level, in the sequence provided in Sections 3.8.1.2 and 5.5.2 of the protocol and only if the program's primary objective is met and significance is obtained for all the endpoints preceding in the given sequence. As this hierarchical procedure preserves the type-I error, any significant result obtained from this procedure will be treated as confirmatory for the relevant endpoint. Does the FDA agree with the analysis strategy for the secondary endpoints?

FDA response to Question 3

Some consideration needs to given to the purpose of the secondary endpoints. Some do not seem valuable. For example, having won on an end point, allocating alpha to test the same end point at another time does not seem useful. Where there is an end point of use to support a claim, that may (symptoms) or may not (mortality) require either replication or a low p-value.

Actelion response

Actelion has revised the protocol design to demonstrate the effect of ACT-293987 on time to clinical worsening in a single pivotal Phase 3 trial (see also the response to Question 1). The newly designed single study will evaluate the effect of ACT-293987 on exercise capacity as a secondary objective, and the change from Baseline to Week 16 in 6MWD at trough will be the first secondary endpoint of the study.

FDA response: We believe that 6MWD should be tested at the 0.01 level since you are seeking a secondary claim of improved exercise capacity based on a single study. We also reiterate our previous response to this question.

Actelion Question 5

5. The Sponsor has delineated the definition of a clinical worsening event as:

- Death (all-cause mortality), **or**
- Hospitalization for worsening of PAH, **or**
- Worsening of PAH resulting in lung transplantation or balloon atrial septostomy, **or**
- Worsening of PAH resulting in initiation of parenteral prostanoid therapy or chronic oxygen therapy, **or**
- Disease progression (patients in NYHA/WHO functional class II-III at baseline) confirmed by:
  - o decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and**
  - o worsening of NYHA/WHO functional class, **or**
- Disease progression (patients in NYHA/WHO functional class III-IV at baseline) confirmed by:
  - o decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and**
  - o need for additional PAH specific therapy.

Clinical worsening will be adjudicated by an independent Critical Event Committee (CEC).

Does the FDA agree with the proposed delineation of the definition of a clinical worsening

event (see Section 3.8.1 of the protocol)?

FDA response to Question 5

No, we do not agree (see FDA Response to Question 1).

Actelion response

Actelion has revised the definition of a clinical worsening event in the protocol as follows:

In this study (AC-065A302) the primary endpoint will be the time to first clinical worsening up to 7 days after last study drug intake defined as:

- Death (all-cause mortality)
  or
- Hospitalization for worsening of PAH based on predefined criteria
  or
- Worsening of PAH resulting in the need of lung transplantation or balloon atrial septostomy
  or
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy for worsening of PAH
  or
- Disease progression (patients in NYHA/WHO functional class II-III at baseline) confirmed by :
  - decrease in 6MWD from Baseline (≥ 15%, confirmed by 2 tests on different days within 2 weeks) **and**
  - worsening of NYHA/WHO functional class

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

Clinical worsening will be adjudicated in a blinded fashion by an independent Critical Event Committee (CEC).

Actelion considers it appropriate to include the criterion of ≥ 15% decrease in 6MWD from Baseline (confirmed by two tests on different days within 2 weeks) for confirming the disease progression component of the clinical worsening definition. As described above, change in 6MWD at Week 16 will no longer be a co-primary endpoint. The proposed definition of a clinical worsening event is consistent with the recently-published international guidelines for the design of pivotal clinical trials in PAH [McLaughlin 2009][1]. Moreover, in order to ensure consistency and accuracy, every clinical worsening event will be submitted to an independent Critical Event Committee, which will adjudicate the event while remaining blinded to treatment allocation.

FDA response: **We recognize that changes in 6MWD will no longer be assessed as a coprimary endpoint and acknowledge that requiring that a study subject manifest other signs/symptoms of disease progression in concert with changes in 6MWD likely strengthens the clinical import of this component of your composite. While your definition of clinical worsening is acceptable, efficacy findings may be difficult to interpret if they hinge on how the missing data for this component of clinical worsening are addressed or imputed.**

[1] [McLaughlin 2009] McLaughlin M, Badesch D, Delcroix M, et al. End Points and Clinical Trial Design in Pulmonary Arterial Hypertension. J Am Coll Cardiol 2009; 54 (1 Suppl): S97-107.

Actelion responses to additional FDA comments

FDA Clinical pharmacology comment 1

1. The results of your Phase 2a study (study NS-304) do not show a clear and continuous dose-response relationship either for PVR or six minute walk distance. It is understood that the study was not powered to explore dose-response. However, there is no information supporting the doses and the dosing regimen you intend to implement in the proposed Phase 3 studies. We recommend that you perform a dose-ranging study prior to the phase 3 trials that will inform your starting dose and dose increments for titration.

Actelion response

A clear dose-response relationship could not be observed in the Phase 2a study for the efficacy endpoints PVR and exercise capacity. It will be difficult to establish such a relationship within a dose-ranging study because it is a generally-accepted strategy to up-titrate prostacyclin receptor agonists individually to the highest tolerated dose. Individual differences in susceptibility towards prostacyclin receptor agonists make it difficult to investigate the dose-response relationship in a classical dose-finding study.

A starting dose of 200 µg b.i.d. was chosen, to be uptitrated on a weekly basis in increments of 200 µg b.i.d. These starting doses and increments were investigated in Phase 1 studies and in the Phase 2a study, and showed good safety and tolerability profiles. For a drug that cannot be administered in fixed dosing regimens to PAH patients, Actelion believes that this is a reasonable approach.

FDA response: We continue to recommend further dose exploration so that important information regarding optimal dosing may be learned from your development program.

FDA Clinical comment 2

2. To avoid regression to the mean, a baseline assessment of 6-minute walk should be made and subjects should not be further excluded based on the results of this test.

Actelion response

Protocol Inclusion criterion 5 has been revised and now reads as follows:

"6-minute walk distance (6MWD) between 50 and 450 m (inclusive) at Screening (within 2 weeks prior to the Baseline Visit and on a different day than this visit). This distance must be confirmed by a second 6-six minute walk test (6MWT) at the Baseline Visit. The value of the second 6MWD should be within ± 10% of the first assessment at Screening."

Therefore, the absolute value of the second 6MWD will be used as the baseline value.

FDA response: This approach does not avoid regression to the mean. The initial and confirmatory tests used to determine subject eligibility should both be conducted during the screening period. A baseline assessment should be made after these tests and should not be used to exclude study subjects.

FDA Clinical comment 3

3. A Thorough QT study should be conducted.

Actelion response

Actelion will conduct a Thorough QT study prior to NDA filing.

FDA response: **During past discussions you reported that ECGs from the early clinical development studies were centrally read and that no signal for QT interval prolongation was detected. As previously discussed, the Division would like to review these data prior to making a final decision as to whether conducting a thorough QT study in parallel with the phase 3 study will be acceptable. Please clarify if these data have been submitted; if not, please submit the relevant data.**

FDA Clinical comment 5

5. The consent form should be submitted for review and should inform study subjects of the animal findings regarding platelet aggregation inhibition/platelet counts, ossification, bone marrow fibrosis, phototoxicity, and GI effects including nausea, vomiting, diarrhea, and intussusception.

Actelion response

The consent form has been revised in accordance with FDA's comments, and is provided as Appendix 3 to this document for FDA review.

FDA response: **In addition to the text pertaining to phototoxicity and GI effects such as nausea, vomiting and diarrhea, the consent form contains the following text describing the animal findings of platelet aggregation inhibition/platelet counts, ossification, bone marrow fibrosis, and intussusception:**

> **"In a study in dogs using very high doses of ACT-293987 (much higher than what will be provided to you), cases of intussusceptions were observed (which means that sections of the bowel slid into other sections much like pieces of a telescope) and changes in the bone structure leading to a hardening of the bone were also observed. Animal studies in rats and dogs also showed an inhibition of platelet aggregation (which is needed for blood coagulation). To date none of these adverse events have been observed in humans taking ACT-293987."**

It is critical that the consent form adequately inform study subjects of potential risks. The language used to describe the preclinical findings should be understandable to the subject and the text should clearly describe the potential clinical implications of these findings (e.g., potential increased risk of bleeding, potential increased risk of a blockage of the bowel possibly requiring medical intervention, etcetera).

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, please contact Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-104504	ORIG-1	ACTELION CLINICAL RESEARCH INC	ACT-293987 (Prostacyclin Receptor Agonist)

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

/s/

NORMAN L STOCKBRIDGE
02/23/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
MAY 7 2010
By

APR 3 0 2010

Acetelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300
Cherry Hill, New Jersey 08002

Attention: Patricia H. Palumbo, BSN, JD
Director, Drug Regulatory Affairs Project Manager

Re: Designation Request # 10-3048

Dear Ms. Palumbo:

Reference is made to your request for orphan-drug designation dated March 5, 2010, of 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-*N*-(methylsulfonyl) acetamide (company name: ACT-293987) for "treatment of pulmonary arterial hypertension (PAH)." Please also refer to our letter dated March 10, 2010.

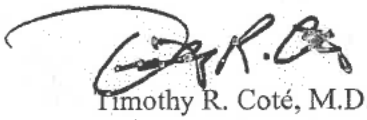
Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-*N*-(methylsulfonyl) acetamide (company name: ACT-293987) is granted for *treatment of pulmonary arterial hypertension (PAH)*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., at (301) 796-8675. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,



Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

LATE-CYCLE MEETING MINUTES

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Uptravi (Selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 9, 2015.

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

If you have any questions, call Wayne Amchin, RAC, Regulatory Project Manager at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Shari Targum, M.D.
Clinical Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 9, 2015, 10am
Meeting Location: FDA White Oak Campus, Building 22

Application Number: 207947
Product Name: Uptravi (Selexipag)
Applicant Name: Actelion Pharmaceuticals Ltd.

Meeting Chair: Shari Targum
Meeting Recorder: Wayne Amchin

FDA ATTENDEES

Office of Drug Evaluation I:

Ellis Unger, M.D.	Director

Division of Cardiovascular and Renal Products:

Norman Stockbridge, M.D., Ph.D.	Director
Mary Ross Southworth, Pharm.D.	Deputy Director for Safety
Michael Monteleone, MS, RAC	Associate Director for Labeling
Shari Targum, M.D.	Clinical Team Leader
Christine Garnett, Ph.D.	Clinical Reviewer
Al DeFelice, Ph.D.	Nonclinical Team Leader
James M. Willard, Ph.D.	Nonclinical Reviewer
Ed Fromm, R.Ph. RAC	Chief, Project Management Staff
Wayne Amchin, RAC	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:

Rajanikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader
Luning Zhuang, Ph.D.	Pharmacometrics Reviewer

Office of Biostatistics, Division of Biometrics I:

Steven Bai, PhD	Biostatistician

Office of Pharmaceutical Quality

Wendy Wilson-Lee, PhD	Branch Chief, Office of New Drug Products

Office of Surveillance and Epidemiology
Leah Hart PharmD, Risk Management Analyst, Division of Risk Management
Donella Fitzgerald PharmD, Risk Management Analyst, Division of Risk Management
Kimberly Lehrfeld, PharmD, Team Leader, Division of Risk Management
Susan Lu, RPh, Team Leader, Division of Pharmacovigilance (DPV I)
Margie Goulding PhD, Lead Epidemiologist, Division of Epidemiology II

Darrell Lyons BSN, Safety Regulatory Project Manager, OSE/Project Management Staff
Tri Bui Nguyen PhD, Safety Regulatory Project Manager, OSE/ Project Management Staff
Thao Tran, PharmD, BCPS, Safety Evaluator, Division of Pharmacovigilance I
Efe Eworuke PhD, Epidemiologist, Division of Epidemiology II
Tingting Gao PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis

Office of Scientific Investigations
Captain Sharon Gershon, Pharm.D. Clinical Inspections Analyst

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein

APPLICANT ATTENDEES
See Attachment

1.0 BACKGROUND

NDA 207947 was submitted on December 22, 2014 for Uptravi (Selexipag).

Proposed indication(s): Treatment of Pulmonary Arterial Hypertension

PDUFA goal date: December 22, 2015

FDA issued a Background Package in preparation for this meeting on August 28, 2015.

2.0 DISCUSSION

LCM AGENDA

1. INTRODUCTORY COMMENTS

Discussion:
The review team noted that, although this was the late-cycle meeting with only labeling issues to discuss, it was still early in the review process. The Cross-Discipline Team Leader (CDTL), Division Director, and Signatory Authority still needed to write their reviews, and additional, more detailed, labeling comments would not be provided, other than the high level discussion at this meeting, until the CDTL, Division Director, and Signatory Authority reviews have been completed. Actelion expressed their hope for an early action date, given that only labeling issues remained.

2. MAJOR LABELING ISSUES

Discussion:
In response to FDA comments in the Late-Cycle Meeting Package (August 28, 2015), Actelion provided revised labeling on September 5, 2015, with tracked changes.. Please see Actelion's September 5, 2015 proposal attached to these meeting minutes.

1. EVENTS PRIOR to August 16, 2011: Actelion noted FDA's request for the labeling to reflect exclusion of events prior to the August 16, 2011, protocol amendment. Actelion noted that the full dataset, including these events, has been accepted by major regulatory authorities around the world and they would want consistent labeling in all regions. Actelion further noted that it was their impression from the top-line results meeting that FDA agreed to include these censored events, at least in the sensitivity analysis, and Actelion believes including these data would make it more robust. Actelion noted that the protocol amendment in question was the result of a change in the hazard ratio which resulted in DCRP requesting that Actelion censor the events before the August 16, 2011 amendment.

   FDA responded that the pre-specified analysis, i.e., the primary analysis data set, does not include the events prior to August 16, 2011, and these data represent different primary endpoints than those represented by the primary analysis data set. FDA agreed that the amendment was in response to FDA's request due to the Hazard Ratio change. It was necessary to exclude the 45 events that already occurred before this change. The review team agreed that there was not a meaningful effect on the hazard ratio with and without the events prior to August 16, 2011, and the Agency will to consider this discussion as we get closer to providing final labeling comments. Actelion does not need to provide additional information.

[redacted] (b) (4)

   FDA responded that when describing WHO group I, [redacted] (b) (4)

   FDA noted that [redacted] (b) (4)

3. DOSAGE AND ADMINISTRATION: Actelion stated that their dosing concept for this product and in the clinical trial was to dose to the highest tolerated dose, and if tolerability issues arise, to reduce to the previous dose [redacted] (b) (4)

   FDA stated that all would agree that if a particular dose cannot be tolerated that the patient should take something less, but the additional sentence proposed by Actelion did not convey adequate information. FDA gave the example of drugs intended to treat seizures, where it was important to take the highest dose to see a treatment response. However, FDA noted that the Kaplan-Meier curves do not show a distinction among 3 selexipag doses.

Actelion agreed to consider rewording to make it clear to avoid the impression that (b) (4)

FDA and Actelion agreed to consider the best approach for discussing dosage and titration and to reflect this approach in section 2 DOSAGE AND ADMINISTRATION and section 14 CLINICAL STUDIES of the Prescribing Information. FDA recommended that Actelion include a distribution of patients in the clinical trial that achieved each dose as their tolerable dose to give providers a clear idea where most patients ended up, including the proportion of patients that experienced adverse events and were subsequently down-titrated. FDA noted that this information would not be unique to this product labeling. FDA further noted that there was a disconnect between the dosing regimen and the text preceding Figure 3, where it seemed that 60 percent of patients achieved only the lowest dose of 200 mcg as their tolerable dose.

4. SECTION 12.3 PHARMACOKINETICS: DRUG INTERACTION STUDIES: FDA requested deletion of the following sentence, as such negative findings are generally not included in the label: (b) (4)

FDA questioned the utility of the information, (b) (4) Actelion agreed to delete it.

5. SECTION 12.3 PHARMACOKINETICS: ELIMINATION: Actelion requested to retain terminal half-life, whereas FDA had requested replacing this with effective half-life. Actelion thinks terminal half-life provides relevant information to clinicians about removal of drug in plasma after treatment discontinuation. Their position on effective half-life is that it does not provide additional clinically relevant information to physicians because it is used in conjunction with dosing interval to predict the accumulation index of drug in plasma at steady-state. That information, in Actelion's view, is already included in the PI through information about dosing regimen and accumulation of parent compound and active metabolite at steady-state.

FDA responded that the effective half-life is useful information in addressing how to handle missed doses and terminal half-life provides misleading information for that purpose. FDA agreed to consider Actelion's rationale.

6. Clinical Studies: Survival Data: Actelion noted that they added an additional line "Death to End of Study to Table 2. They want to include survival data to provide information on whether or not there is a survival benefit or not and avoid false positive and false negative.

   FDA questioned why half of the deaths are not included in "death at any time." Actelion explained that death at any time is based on end of treatment. However, Actelion continued following patients after treatment until they closed the study, and that is why the death to end of study numbers are different than deaths at any time. FDA added that a more common study design is that people without terminal events continue on the study drug and it makes sense to look at those events. Counting events a year after treatment stopped is not relevant.

3. REVIEW PLANS

FDA plans to complete the CDTL, Division Director, and Signatory Authority reviews and then send Actelion what FDA hopes will be final labeling comments, recognizing that there may be an additional iteration of labeling negotiations with Actelion.

4. WRAP-UP AND ACTION ITEMS

Actelion expressed their desire for an early action date, given that there were only labeling issues to discuss. FDA responded that it was too early for us to be able to commit to an action date until all the reviews were done.

(b) (4)

FDA responded that they could (b) (4)

(b) (4)

Actelion will submit amended proposed labeling as soon as possible to address the action items identified for them in these meeting minutes.

ACTELION ATTENDEES FOR LATE CYCLE MEETING

Actelion attendees that will be at the F2F Meeting in person:

Guy Braunstein, M.D. Head of Clinical Development

Clinical Science
Alberto Gimona, M.D., Head of Clinical Science
Ralph Preiss, M.D., Project Lead, Clinical Science

Biostatistics:
Marisa Bacchi, Ph.D, Head of Biostatistics
Lilla Di Scala, Ph.D., Project Lead, Biostatistics

US Regulatory Affairs, Advertising and Promotion:
Joyce Acbay, Senior Director

Clinical Pharmacology
Shirin Bruderer, Ph.D., Project Clinical Pharmacologist

Drug Regulatory Affairs
James Davis, US Drug Regulatory Affairs Project Leader
Brian Schlag, US Drug Regulatory Affairs Group Leader

Nippon Shinyaku Co-Development Observer
Soichiro Sasaki

Actelion attendees that will joining the Meeting by teleconference:

Clinical Science
Aline Frey, Pharm.D., Sr. Clinical Project Scientist

Clinical Pharmacology
Jasper Dingemanse, Ph.D., Pharm.D., Head of Clinical Pharmacology

Drug Regulatory Affairs
Sonja Pumpluen, Pharm.D., Head of Global Drug Regulatory Affairs
Frances Duffy-Warren, Ph.D., VP-Head US, Drug Regulatory Affairs
Samar Kelly, Ph.D., Global Regulatory Project Leader

Project Management
Natalia Yannoulis, Ph.D., Life Cycle Leader

Strategic Development
Per Nilsson, M.D., Ph.D., Head of Strategic Development

Bill Fairey, President of Actelion Pharmaceutical US

Martine Clozel, M.D. , Chief Scientific Officer

Gary Palmer, M.D., Senior Vice President, Medical Affairs

Kevin Christal, Senior Director, US Pharmaceuticals

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

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

/s/

SHARI L TARGUM
10/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207947

LATE CYCLE MEETING
BACKGROUND PACKAGE

Actelion Pharmaceuticals Ltd.
Attention: James B. Davis
Associate Director, DRA Global Project Leader
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Davis:

Please refer to your New Drug Application (NDA) dated December 22, 2014, received December 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Uptravi (selexipag) Tablets, 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 9, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Wayne Amchin, RAC, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
CDER

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 9, 2015, 10am-12pm
Meeting Location: FDA White Oak Campus, Building 22

Application Number: NDA 207947
Product Name: Uptravi (selexipag)
Indication: Pulmonary Arterial Hypertension
Sponsor/Applicant Name: Actelion

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

Reference ID: 3812506

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 10 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Major labeling issues – 60 minutes

See labeling comments provided in advance of the Late-Cycle Meeting and attached to this document.

3. Review Plans – 10 minutes

   FDA plans to work with Actelion to reach final agreement on labeling.

4. Wrap-up and Action Items – 10 minutes

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

Reference ID: 3812506

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

/s/

NORMAN L STOCKBRIDGE
08/28/2015