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RESEARCH**

APPLICATION NUMBER:
204410Orig1s000

OTHER REVIEW(S)

RHPM NDA Overview
October 18, 2013

Opsumit (macitentan) Tablets

NDA 204410

Applicant: Actelion Pharmaceuticals, LTD.

Classification: 1 (NME)

Review Classification: Standard (12 month review)

Proposed Indication: treatment of pulmonary arterial hypertension (PAH , WHO Group I)

Date of Application: October 19, 2012

Receipt Date: October 19, 2012

User Fee Goal Date: October 19, 2013

REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

- Cross Discipline Team Leader
 - Mary Ross Southworth, Pharm.D.
- Medical Reviewer
 - Maryann Gordon, M.D.
- Pharmacology and Toxicology
 - William T. Link, Ph.D.
- Regulatory Health Project Manager
 - Edward Fromm, R.Ph., RAC

Office of New Drug Quality Assessment (ONDQA), Branch 1

- Thomas Wong, Ph.D.

Office of Clinical Pharmacology

- Sreedharan Sabarinath, PhD,

Office of Biostatistics, Division of Biometrics I

- Jialu Zhang, Ph.D.

Office of Surveillance and Epidemiology

- Kim Defronzo, Pharm.D., (DMEPA)
- Sharon Mills, RN, BSN, (Medication Guide)
- Jason Bunting, Pharm.D., (Risk Evaluation and Mitigation Strategy - REMS)

Office of Medical Policy, Office of Prescription Drug Promotion

- Zarna Patel, Pharm.D.

Office of Compliance, Division of Scientific Investigations (DSI)

- Sharon Gershon, Pharm.D.

BACKGROUND

Macitentan, a new orally active, dual endothelin receptor antagonist is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

The development program to support macitentan for PAH is based on a single, pivotal trial: Protocol AC-055-302, entitled “SERAPHIN: Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase 3 study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension.” Approximately 742 patients were randomized in a 1:1:1 ratio (macitentan 3 mg QD, macitentan 10 mg QD, placebo QD). The study included a screening phase (up to 28 days), followed by a treatment period from randomization to the End of Treatment (EOT) visit.

The primary endpoint was the time from start of treatment to the first mortality or morbidity event, defined as death, atrial septotomy, lung transplant, initiation of intravenous or subcutaneous prostanoids or other worsening PAH.

User Fee

The user fee for this application was exempt because of its orphan designation.

Pediatrics

The Office of Orphan Products, on September 03, 2009 granted orphan designation for the PAH indication.

Advisory Committee

Opsumit (macitentan) tablets was not referred to an FDA advisory committee because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical study designs are similar to that of previously approved products in the class, and the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

Trade name

Opsumit (macitentan) was deemed conditionally acceptable for use on January 02, 2013 and fully acceptable on August 7, 2013. The review Division did not have any concerns with the proposed name.

REGULATORY TIMELINE

- SPA Agreement Letter, December 1, 2007
- IND submitted June 3, 2008
- Pre-NDA Meeting: March 15, 2012
- NDA submitted: October 19, 2012
- Filing Meeting: November 16, 2012
- 74-day Letter issued: December 12, 2012

- Executive Carcinogenicity Assessment Committee (CAC) Meeting: April 2, 2013
- Mid-Cycle T-Con: March 21, 2013
- Late Cycle Meeting: July 17, 2013
- PDUFA Date: October 19, 2013
- Approval Date: October 18, 2013

REVIEWS

Office Memorandum (dated October 18, 2013)

Dr. Temple recommends approval of macitentan.

Divisional Memorandum (dated October 15, 2013)

Dr. Stockbridge recommends approval of macitentan.

Cross-Discipline Team Leader (CDTL) Review (dated September 19, 2013)

Dr. Southworth recommends approval of macitentan to reduce the risk of PAH-related death and hospitalization from PAH. She also recommends the following:

- Macitentan should be approved with a REMS with elements to assure safe use (ETASU) similar to that for ambrisentan to manage the risk of teratogenicity.
- The sponsor should be required to develop and implement a prospective registry to better characterize the hepatic safety profile of macitentan in the post-marketing setting.
- The sponsor should be required to perform enhanced pharmacovigilance to identify, follow-up, and report liver cases of interest in a timely fashion.
- The sponsor should be encouraged to develop a lower dose tablet for use in patients who require concomitant CYP 3A inhibitor therapy (i.e., ritonavir for HIV).

Medical Reviews (dated June 21 and July 25, 2013)

Dr. Gordon recommends approval of the 10 mg tablet for once daily use in patients with PAH, WHO Group 1. She noted neither a survival benefit nor a mortality risk with doses 10 mg once daily or less. Other benefits noted included improvements in 6MWD, WHO functional class, health-related Quality of Life (QoL), and fewer days of hospitalizations.

Dr. Gordon noted in her July 25, 2013 review addendum that she found, at best, only a weak link between possible liver injury and the use of macitentan. However, she said there is still need for vigilance because

- a.) the majority of macitentan doses studied has been 10 mg or less so the safety of higher doses is unknown, and
- b.) the total number of patients who have taken the drug is small.

- **Financial Disclosure** (pgs. 10,11 of Dr. Gordon's June 21, 2013 review)

There were sixteen investigators with financial interests to disclose for the major efficacy study AC-055-302 in section 1.3.4 of the sponsor's NDA.

She notes that the remaining investigators were without financial interests and are listed in FORM FDA 3454. Dr. Gordon also mentions that there is no indication that financial compensations compromised the integrity of the data used in support of this NDA.

Biostatistics Review (dated June 18, 2013)

Dr. Zhang noted the single phase III trial showed highly significant results in the primary endpoint. However, the primary endpoint was driven by a single component "other worsening of PAH" with no

effect shown for mortality. Overall, she felt the results in SERAPHIN trial seem to support the efficacy of macitentan 10 mg.

Clinical Pharmacology Review (dated June 29, 2013)

The Clinical Pharmacology team of Drs. Sabarinath, Marathe, Zhao, Yang, and Madabushi recommend approval for macitentan for PAH. They had the following recommendations:

- Macitentan should not be co-administered with strong CYP3A inducers
- Co-administration of macitentan with strong CYP3A4 inhibitors (such as ketoconazole or ritonavir) should be avoided

Pharmacology and Toxicology Review (dated August 26, 2013)

Dr. Link recommends approval from a pharmacology/toxicology perspective.

The Division met with the Executive Carcinogenicity Assessment Committee (CAC) on April 02, 2013 and their recommendations were as follows (minutes dated April 03, 2013):

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Office of New Drug Quality Assessment (ONDOA), Branch 1 Review (three reviews dated May 24, June 18, and August 21, 2013)

- **Tertiary Review CMC Review** (dated August 21, 2013)
Dr. Sood noted in his summary review that the macitentan application is approvable from a CMC perspective once the facilities inspections are found acceptable.
- **Drug Substance and Product Review** (dated May 24, 2013)
Dr. Wong notes that his final recommendation regarding approval is pending as the Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections. Available 12 months stability data supports 24-month expiration dating period for the tablets when packaged in the proposed commercial packages.
- **Biopharmaceutics Review** (dated June 18, 2013)
Dr. Duan recommends approval from a Biopharmaceutics perspective. He had the following additional comments:
 1. The proposed dissolution method with USP 2 (paddle) at 75 rpm in pH=6.8 buffer with 0.1% of Cetrimonium bromide (CTAB) is supported by adequate justifications and data and it is acceptable.
 2. The Applicant accepted the FDA's recommendation and implemented the dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes. The drug product specification table was revised and the relevant parts of the NDA have been updated.
 3. The proposed drug substance specification for particle size is justified by a physiologically based model. This Reviewer confirmed the results provided by

the Applicant regarding the effect of particle size distribution on the in vivo performance.

- **Facilities Inspections**
 - ACCEPTABLE recommendation on October 9, 2013.
- **Environmental Assessment**
 - Categorical exclusion granted (see Dr. Wong's review)

CONSULTS

Dr. Senior's Hepatology Review (dated September 9, 2013)

Dr. Senior remains concerned about the potential for liver injury with macitentan and proposes an Active Registry to monitor for liver adverse effects post-marketing.

Office of Scientific Investigations (OSI) Review (dated June 3, 2013)

Dr. Gershon noted that four clinical investigator sites (three foreign, one domestic) and the Sponsor were inspected in support of NDA 204410. No regulatory violations were found during the inspections at two clinical investigator sites (Dr. Bhagatuval KS Sastry, India and Dr. Murali Chakinala, U.S.), and no Form FDA-483 was issued. The inspection of Dr. Xiaofeng Zeng (China) and Dr. Tomas Pulido Zamudio (Mexico City) were classified as VAI, and a one observation, Form FDA-483 was issued for failure to follow the investigational plan with respect to enrollment of several subjects who did not meet inclusion and exclusion criteria.

Dr. Gershon noted that although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable based on available information.

Office of Surveillance and Epidemiology Review - REMS (dated October 8 and 17, 2013)

Dr. Bunting notes that the proposed REMS for Opsumit (macitentan) contains the appropriate REMS components. These include a Medication Guide and three ETASU—prescriber certification, pharmacy certification and documentation of safe use.

Overall DRISK recommends a REMS for Opsumit for the risk of teratogenicity.

Office of Prescription Drug Promotion (dated September 11, 2013)

Dr. Patel finalized her review and included a number of labeling comments in her review.

CONCLUSION

An approval letter was issued for this application and signed by the Deputy Office Director, Robert Temple, M.D., on October 18, 2013. The approval letter was appended with the agreed-upon labeling text, finalized REMS and Medication Guide.

Edward J. Fromm, R.Ph., RAC
Regulatory Health Project Manager

dr-ef-10/18/13

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/s/

EDWARD J FROMM
10/21/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204410
Product Name: Opsumit (macitentan)

PMR/PMC Description: Hepatic Safety Registry of macitentan users treated for pulmonary hypertension (PAH)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2014</u>
	Interim Report #1 (#study sites and patients enrolled)	<u>June 2014</u>
	Interim Report #2 (results)	<u>December 2014</u>
	Interim Report #3 (#study sites and patients enrolled)	<u>June 2015</u>
	Interim Report #4 (results)	<u>December 2015</u>
	Interim Report #5 (# study sites and patients enrolled)	<u>June 2016</u>
	Interim Report #6 (results)	<u>December 2016</u>
	Interim Report #7 (# study sites and patients enrolled)	<u>June 2017</u>
	Interim Report #8 (results)	<u>December 2017</u>
	Interim Report #9 (# study sites and patients enrolled)	<u>June 2018</u>
	Final study Report	<u>December 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Hepatotoxicity is associated with other members of this drug class (endothelin receptor blockers, bosentan and sitaxsentan). A signal for hepatotoxicity was not identified during the development program for macitentan, but exposure is limited. There were some cases that met the laboratory criteria for Hy's Law, but in most of these cases the rise in liver enzymes could be attributed to another cause (right heart failure). The goal of the observational registry is to better characterize the hepatic safety profile once macitentan is marketed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See #1

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Registry to evaluate rates of liver injury in PAH patients treated with macitentan

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
Registry to evaluate rates of liver adverse events in patients taking macitentan

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 204410
Product Name: Opsumit (macitentan)

PMR/PMC Description: Enhanced Pharmacovigilance Plan

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2014</u>
	Interim Report #1	<u>June 2014</u>
	Interim Report #2	<u>December 2014</u>
	Interim Report #3	<u>June 2015</u>
	Interim Report #4	<u>December 2015</u>
	Interim Report #5	<u>June 2016</u>
	Interim Report #6	<u>December 2016</u>
	Interim Report #7	<u>June 2017</u>
	Interim Report #8	<u>December 2017</u>
	Interim Report #9	<u>June 2018</u>
	Final Study Report	<u>December 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Hepatotoxicity is associated with other members of this drug class (endothelin receptor blockers, bosentan and sitaxsentan). A signal for hepatotoxicity was not identified during the development program for macitentan, but exposure is limited. There were some cases that met the laboratory criteria for Hy's Law, but in most of these cases the rise in liver enzymes could be attributed to another cause (right heart failure). The goal of the enhanced pharmacovigilance plan is to better characterize the hepatic safety profile once macitentan is marketed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

See answer to #1.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Enhanced pharmacovigilance with specialized follow up and periodic summary reporting of hepatic adverse events of interest.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Periodic reporting on cases of serious liver injury (Enhanced Pharmacovigilance Plan)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Enhanced pharmacovigilance plan

5. Is the PMR/PMC clear, feasible, and appropriate?

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PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

Lori A WACHTER
10/17/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Maternal Health Team Review Addendum

Date: October 17, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Cardiovascular and Renal Products (DCRP)

Applicant: Actelion Pharmaceuticals Ltd. (Actelion)

NDA/Drug: NDA 204410/Opsumit (macitentan)

Proposed Indication: Treatment of patients with pulmonary arterial hypertension (PAH)

Subject: Addendum to June 25, 2013 PMHS-MHT Review of Macitentan proposed labeling and REMS program to document final PMHS labeling recommendations and final labeling language.

Materials Reviewed: Proposed macitentan product labeling submitted October 14, 2013

INTRODUCTION

Actelion Pharmaceuticals Ltd. (Actelion) submitted a New Drug Application (NDA) for Opsumit (macitentan) Tablets on October 19, 2012. Macitentan is a New Molecular Entity (NME) with a proposed indication for treatment of patients with pulmonary arterial hypertension (PAH).

Per the sponsor, macitentan is a dual endothelin receptor antagonist (ERA) that prevents binding of endothelin-1 (ET-1) to its receptors, ET_A and ET_B. In PAH, ET-1 effects are up-regulated and thought to cause vasoconstriction, vascular smooth muscle and endothelial proliferation. Endothelin receptor antagonists block the binding of ET-1 to receptors, decreasing PAH symptoms¹. There are two other ERAs currently marketed and approved for treatment of PAH, Tracleer (bosentan) and Letairis (ambrisentan).

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DCRP on May 15, 2013 to assist the division in evaluating product labeling and REMS documents. Labeling comments and recommendations were provided in a PMHS-MHT review dated June 25, 2013. PMHS-MHT provided further labeling recommendations during subsequent labeling meetings, which were included in revised labeling sent to the sponsor on October 11, 2013. The applicant submitted revised labeling on October 14, 2013. PMHS-MHT reviewed the revised labeling and PMHS-MHT labeling recommendations remained unchanged. This review addendum provides updated PMHS-MHT Macitentan labeling recommendations since the June 25, 2013 review.

BACKGROUND

The PMHS-MHT provided the following labeling recommendations in the review dated June 25, 2013:



¹ Actelion. Nonclinical Overview Macitentan Endothelin Receptor Antagonist For Treatment of Pulmonary Arterial Hypertension, October 1, 2012.

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/s/

TAMMIE B BRENT HOWARD
10/17/2013

JEANINE A BEST
10/17/2013

LYNNE P YAO
10/19/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Study Proposal

Date: September 12, 2013

Reviewer(s): Jie Jenni Li, PhD, Epidemiologist
Division of Epidemiology II (DEPI-II)

Team Leader Margie R. Goulding, PhD,
Team Leader, DEPI-II

Division Director Judy A. Staffa, PhD, RPh
Director, DEPI-II

Subject Post Marketing Requirement (PMR), a hepatotoxicity-related
information registry of macitentan users treated for pulmonary
arterial hypertension

Drug Name(s): Macitentan (Opsumit) NDA 204410

Applicant/sponsor: Actelion

1 INTRODUCTION

Macitentan (Opsumit) is an orally active endothelin receptor antagonist (ERA) that is now under FDA review (NDA-204410) for the treatment of pulmonary arterial hypertension (PAH). Serious hepatotoxicity has been associated with two other ERAs, bosentan (with a boxed warning and REMS in the US) and sitaxsentan (approved in Europe only and later withdrawn from the market). A small number of cases of liver enzyme elevations were seen in macitentan RCTs which raised concerns about possible hepatotoxicity with cumulative use. The sponsor concluded that the clinical data showed no definite hepatic signal associated with macitentan, because most of the potential liver toxicity cases were confounded by biliary tract obstruction, heart failure, or concomitant medications. FDA views macitentan as possibly safer than bosentan with regard to liver toxicity, but the available data are too sparse to rule out potential hepatic adverse events. Therefore, a patient registry with the reporting of all liver (enzyme abnormality or injury) events is requested by FDA as a post marketing requirement (PMR). In response, the sponsor has submitted a proposal for a patient registry to examine patient characteristics, treatment patterns, and risk of hepatotoxicity with macitentan. The purpose of this DEPI review is to comment on the patient registry proposed by the sponsor, with regard to its design, planned data collection and analyses.

2 REVIEW METHODS AND MATERIALS

The proposed patient registry, Opsumit® (macitentan) US drug registry synopsis (dated August 14, 2013), was reviewed.

3 REVIEW RESULTS

3.1 PROPOSED REGISTRY

The sponsor proposes

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JIE J LI
09/12/2013

JUDY A STAFFA
09/13/2013

MARGIE R GOULDING
09/13/2013

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 11, 2013

To: Ed Fromm
CPMS
Division of Cardiovascular and Renal Products (DCRP)

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

Subject: Opsumit (macitentan) tablets
NDA: 204410
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on December 3, 2012, for Opsumit (macitentan) tablets (Opsumit). Our comments on the PI are based on the proposed labeling emailed to us on September 9, 2013. Our comments on the carton and container labeling are based on the version submitted by the sponsor on July 11, 2013.

Carton and Container Label

OPDP has no comments on the proposed carton and container labeling at this time.

Package Insert

OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PPI, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
09/11/2013

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

PATIENT LABELING REVIEW

Date: September 9, 2013

To: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products (DCRP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): OPSUMIT (macitentan)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 204-410

Applicant: Actelion Pharmaceuticals, Ltd
c/o Actelion Clinical Research, Inc.

1 INTRODUCTION

On October 19, 2012, Actelion Pharmaceuticals, Ltd. submitted for the Agency's review an Original New Drug Application (NDA) 204-410 for OPSUMIT (macitentan) tablets. The proposed indication for OPSUMIT (macitentan) tablets is to delay clinical worsening in patients with symptomatic pulmonary arterial hypertension (PAH, WHO Group I).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiovascular and Renal Products (DCRP) on December 3, 2012 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPSUMIT (macitentan) tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DCRP under separate cover.

2 MATERIAL REVIEWED

- Draft OPSUMIT (macitentan) tablets Medication Guide (MG) received on October 19, 2012, and received by DMPP and OPDP on August 28, 2013.
- Draft OPSUMIT (macitentan) tablets Prescribing Information (PI) received on October 19, 2012, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 28, 2013.
- Approved Letairis (ambrisentan) tablets comparator labeling dated August 17, 2013

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

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

In our collaborative review of the MG we have:

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

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/09/2013

ZARNA PATEL
09/09/2013

BARBARA A FULLER
09/09/2013

LASHAWN M GRIFFITHS
09/09/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 15 August 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)

TO: Norman Stockbridge, M.D., Director, Division of CardioRenal Products (DCRP), Office of New Drugs (OND)
Stephen Grant, M.D., Deputy Director, DRCR
Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCRP
Maryann Gordon, M.D., Medical Reviewer, DRCR

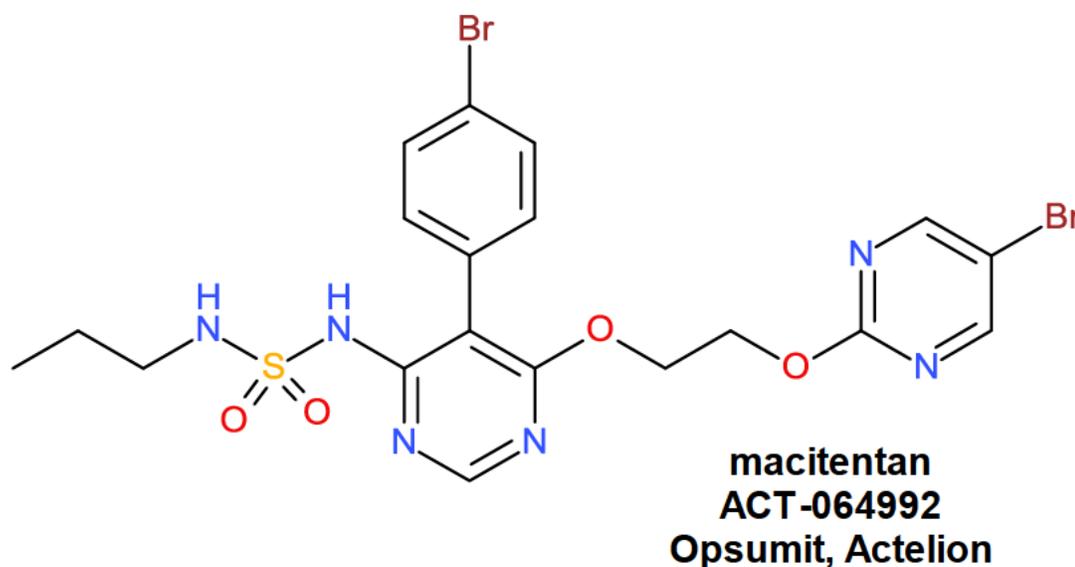
VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic safety of **macitentan** (NDA 204410), (new molecular entity) an endothelin receptor antagonist proposed for treating pulmonary arterial hypertension, submitted by Actelion Pharmaceuticals LTD on 19 October 2012, proposed trade name OPSUMIT®.

Documents reviewed:

- 1) Consultation request 14 December 2012 from Dr. Maryann Gordon via Dan Brum (Project Manager) to OSE via Ms. Cheryle Milburn (Project Manager), requesting response by 11 March 2013, OSE tracking #2012-2957;
 - 2) Sponsor's report of SERAPHIN study 302, in DARRTS 204410, document 1 (Seq.0000), 5.3.5.1: AC-055-302 Study with Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to improve clinical outcome. 1628 pages, submitted 19 October 2012.
 - 3) Hepatobiliary Safety Report, (b) (4), in DARRTS @ 5.3.5.3 Legacy Clinical Study Report, 198 pages.
 - 4) Report of mid-cycle review presentations 15 March 2013, with telecon from FDA (8 persons participating) to sponsor (22 participants); summary in DARRTS 28 March 2013
 - 5) Literature from PubMed on macitentan, bosentan, ambrisentan, sitaxsentan, and pulmonary hypertension
 - 6) Approved labeling for bosentan (TRACLEER®, Actelion; NDA 021290, approved 20 November 2001; and ambrisentan (LETAIRIS®, Gilead, NDA 022081, approved 15 June 2007)
 - 7) eDISH files prepared by Dr. Ted Guo from data submitted by sponsor for studies 302, 201, and B201: 1234 patients.
 - 8) Clinical review by Dr. Maryann Gordon dated and entered into DARRTS 21 June 2013, plus additional comments entered 25 July 2013;
 - 9) Risk Evaluation and Mitigation Strategy, in DARTTS 22 July 2013;
 - 10) Minutes of late-cycle review on 17 July, into DARRTS by E.J. Fromm 13 August 2013.
-

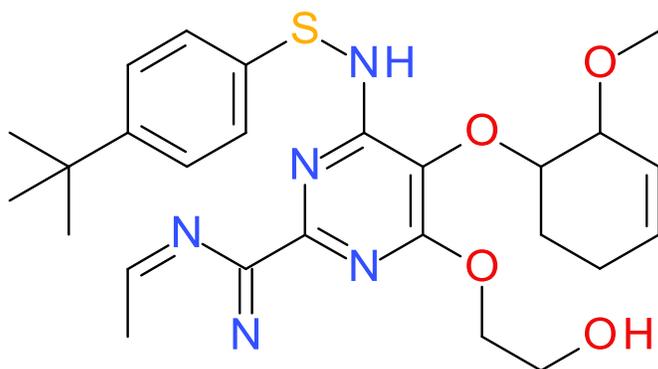
Pulmonary arterial hypertension (PAH) is one of an heterogeneous group of disorders that cause pulmonary hypertension (PH), defined by resting mean pulmonary arterial pressure of 25 mm Hg or more confirmed hemodynamically by right heart catheterization. The definition of pulmonary arterial hypertension has challenged expert groups (Galiè et al., 2009; Simonneau et al., 2009), but it is generally considered a progressive, lethal set of diseases for which treatment slows but does not stop or reverse the course. The first of the endothelin receptor blockers, bosentan, was pioneered by workers at Actelion (the same sponsor as for the current product, macitentan) and was approved in 2001 despite serious hepatotoxicity and still carries a black box warning for it in current labeling last updated 4 October 2012. In 2007, another drug of this class, ambrisentan, approved as LETAIRIS® (Gilead), does not have the same hepatotoxicity risk, but has a black box warning against fetal injury and is not to be used by pregnant women. In the interval since the latter approval, a third endothelin receptor antagonist, sitaxsentan, failed approval in the USA because of questions about efficacy, although approved as THELIN® (Encysive Phamaceuticals) by the European Union and Canada in 2006, in Australia in 2007, in 2008 by Germany, Austria Netherlands, United Kingdom, Ireland, France, Spain, Italy. Rather than carry out the additional studies requested by FDA in 2006, Encysive sold sitaxsentan to Pfizer in February 2008. That was just 16 months before the first report of serious hepatotoxicity was published in June 2009, and additional reports soon followed (Hoepfer et al., 2009; Lavelle et al., 2009; Lee et al., 2011) and strong admonitions against use of sitaxsentan (Hoepfer, 2009; Corris and Langleben, 2010; Galiè et al, 2011). Pfizer withdrew it from the market in December 2010. Pfizer withdrew also the US NDA (b)(4) for sitaxsentan in September 2012. Against this background of severe liver toxicity with the –sentans, the new candidate, macitentan, deserves close scrutiny.



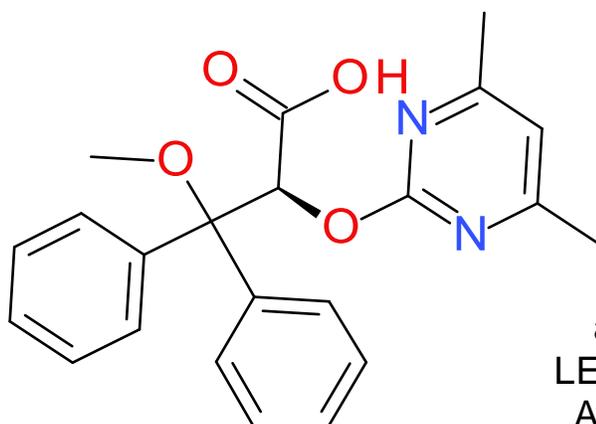
The preclinical evaluation by the Actelion chemists, toxicologists, and pharmacologists found no indication of hepatotoxicity in mice or rats from ACT-064992, and less from its circulating metabolites, ACT-132577 and ACT-373898. The introduction to the Hepatobiliary Safety Report states that macitentan contains no structure considered to be a toxicophore for liver toxicity.

Comment: That last allegation seems strange in that the bromobenzene also attached to the pyrimidine core was identified as the toxicophore of bromfenac (Williams and Park, 2003), after

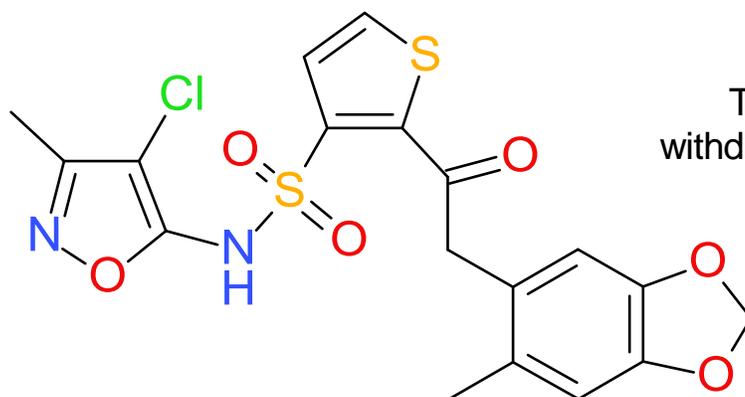
it had been withdrawn from the market in June 1998 less than a year after its approval in July 1997 because of very severe hepatotoxicity. It is still unclear whether structural differences in the four –sentans provide explanations for idiosyncratic differences in adverse hepatic effects. For comparison, the molecular structures of the other three “–sentans” are shown below:



bosentan
TRACLEER, Actelion
AP 20 Nov 2001



ambrisentan
LETAIRIS, Gilead
AP 15 Jun 2007



sitaxsentan
THELIN, Pfizer
withdrawn 10 Dec 2010

Comment: It is notable that the severe hepatotoxic potential of sixsentan was not known until after it had been approved in Europe, Canada, and Australia in 2006-8, the first reports of problem appearing in 2009 publications. It was not approved in the United States, not because hepatic toxicity was found but due to delays arising from disputes about proof of efficacy with Encysive Pharmaceuticals, the sponsoring company, and the review division. As mentioned above, Pfizer bought macitentan from Encysive in February 2008 before the hepatotoxicity of sixsentan began to become apparent as exposure to the drug increased following the approvals.

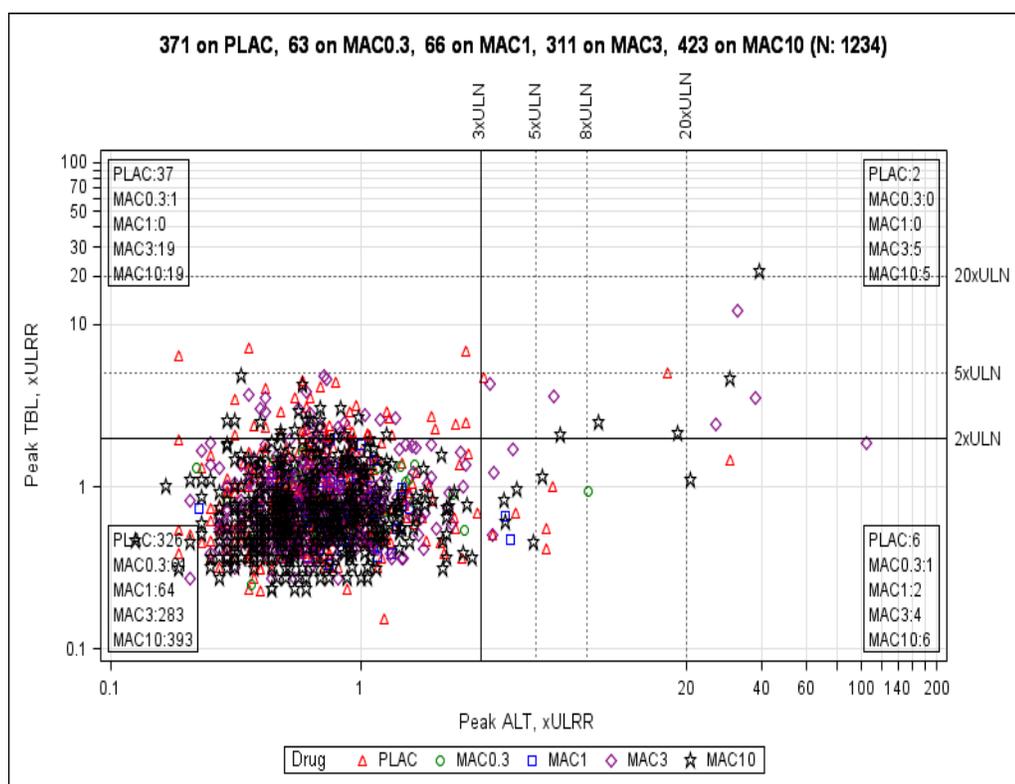
The first reported hint of trouble with sitaxsentan was published in January 2009 (McGoon et al.) by authors from Mayo Clinic; Baylor; Universities of Colorado, Michigan, Los Angeles and San Diego; plus Italy and Austria; and three coauthors from Gilead (the sponsor of ambrisentan). Transaminase elevations in patients given bosentan (32), sitaxsentan (2), or both (5) led to switch to ambrisentan, with no further evidence of liver injury. In June 2009, it was reported (Hoepfer et al.) from Hannover Germany that a 25-year-old woman with uncorrected left ventricle septum defect, Eisenmenger syndrome, and pulmonary hypertension, showed serum ALT increases after 6 months on bosentan, was switched to sitaxsentan and then showed rising ALT and AST after 4 months. She had no evidence of right heart failure, and no other cause for the liver abnormalities was found. Despite stopping sitaxsentan, the ALT elevations worsened, with increasing serum total bilirubin, and mild abdominal discomfort. She responded to a course of prednisolone. In September 2009 it was reported from Ireland (Lavalle, et al) that two patients on sitaxsentan showed what the authors called “liver failure,” but without encephalopathy or hepatorenal syndrome. Both cases were serious or severe, with visible jaundice, prolonged prothrombin time, hospitalization, and liver biopsies (abnormal but not diagnostic). This led Hoepfer to write in that same month an editorial “Liver toxicity the ‘Achilles’ heel’ of endothelin receptor antagonist therapy,” calling for increased pharmacovigilance, careful clinical monitoring of patients with or without regulatory requirements. No further case reports appeared in 2010, but Pfizer decided to withdraw sitaxsentan from the market in December 2010, just before a very strongly worded recommendation was published in February 2011 (Galiè et al.) following learning about a case of fatal liver failure in a 19-year-old Scottish woman (Lee et al.).

Comment: Clearly, the hepatotoxic potential of sitaxsentan was missed in the enthusiastic search by Encysive Pharmaceuticals for an alternative to bosentan, and they made great effort to show evidence that it was safer than bosentan (Langleben and Cacoib, 2009). Pfizer’s acquisition of sitaxsentan was ill-timed, coming just before the roof caved in for that drug. Considering this background of lessons from the past, we take a jaundiced view of what Actelion is telling us now.

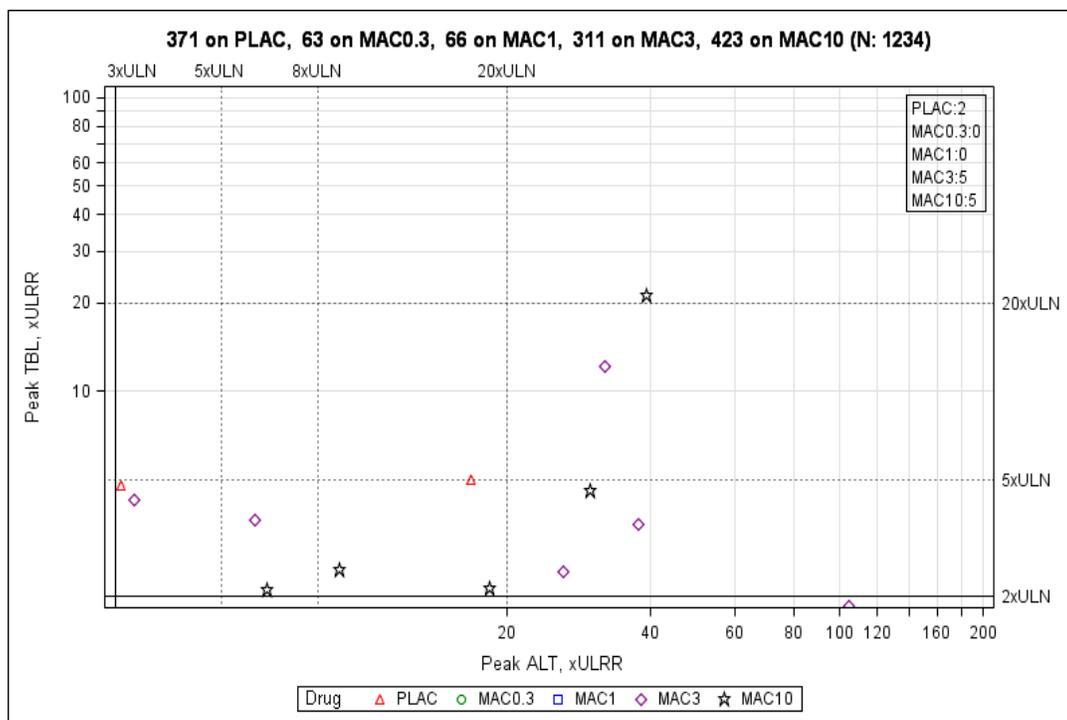
The consultation request from Dr. Gordon via Dan Brum sent 12 December 2012 asked for some comments by 11 March 2013, before the planned mid-cycle review planned for 14 March. To allow our use of eDISH, Dr. Ted Guo then asked on 12 January for clinical data to be submitted by the sponsor in suitable format, which were obtained 23 January. It was noted by Dr. Guo that they also had used their own version of eDISH in the sponsor’s Hepatobiliary Safety Report to review many of the cases, and made results available to their hepatology consultants (b) (4)) prior to submission of NDA 204410. Because of competing priorities, namely need to prepare for our annual conference on drug-induced liver injury and a pressing need to start the tolvaptan review, we were not able to submit a response before the March mid-cycle review, but a summary of the presentations made on 15 March via telecom (8 presenters

from DCRP and 22 listeners from Actelion) was provided to me by Dan Brum and also entered in DARRTS on 28 March. The clinical comments of Dr. Gordon focused on whether the 10 mg dose of macitentan was optimal, whether it had a mortality reduction effect, whether enough patients were studied in the United States. She noted that some patients had shown serum transaminase increases, especially in those receiving higher doses in Study 102. Dr Grant asked if a risk evaluation and mitigation strategy (REMS) proposal had been submitted, and Actelion said not, only one for teratogenicity. Dr. Grant also opined that 250 patients were not enough to rule out possible clinically significant rate of liver injury from 10 mg/day of macitentan. We belatedly now review what we have obtained from the sponsor to address the stated concerns. It was noted by Dr. Gordon in her presentation that of 742 patients randomized in the SERAPHIN study 302 (250 placebo, 250 macitentan 3 mg, 242 macitentan 10 mg) 55% had diagnoses of idiopathic PAH, 30% collagen vascular disease, and 8% congenital shunts. (The other 7% were not specified.) Data for eDISH analyses were provided for 1234 patients, including 314 in Study 201 and 178 in Study B201, bring the totals as follows (no data were submitted for Study 102):

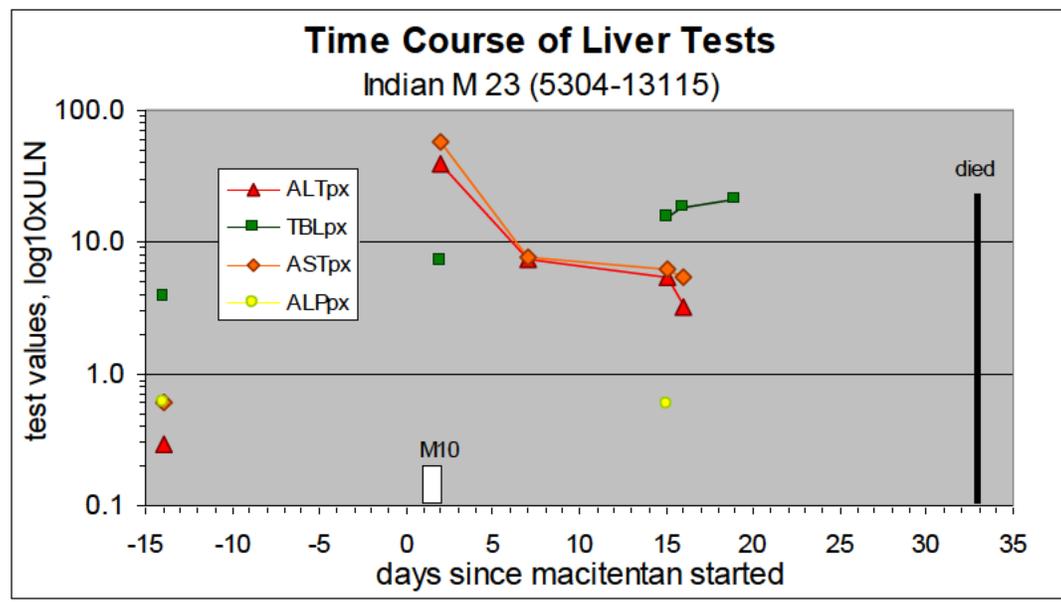
Macitentan (Opsumit®, Actelion), ACT-064992 NDA 204410, submitted 19 October 2012				
Study	AC-055-302	AC-055-201	AC-055-B201	total
dose, mg/day				
10	242	62	119	423
3	250	61		311
1		66		66
0.3		63		63
placebo	250	62	59	371
totals	742	314	178	1234



As is characteristic of eDISH plots, the great majority of patients are in the lower left quadrant of the log-log x-y plot of values for all individual patients, with the peak values for serum ALT and peak value for total bilirubin, in multiples of the upper limit of the normal (ULN) range, shown. Cut lines at 3xULN for ALT activity, and 2xULN for bilirubin concentration are conservative, and are not meant to be diagnostic. Cases of special interest and concern, requiring attention for clinical evaluation of most likely cause, are those in the right upper quadrant where liver injury as indicated by elevated ALT values may be associated with liver functional loss as indicated by serum bilirubin accumulation. Cases with very high ALT levels above 20xULN are considered by definition of the National Cancer Institute’s Common Terminology Criteria for Adverse Events as grade 4 abnormalities (*sometimes called by them as life-threatening – probably wrongly*). It can be noted at a glance that there are relatively few cases in the right upper and lower quadrants so that individual cases can be considered in more detail. This is first done by pointing to a mark representing a single patient, and clicking on it to ask the program to find all the data for ALT, AST, BLT, and ALP for that single person obtained over the entire period of their observation in the study, to plot a second graph of the time course of liver test abnormalities for that individual. The third and last step is to click on the label called Narratives to obtain the textual description of the patient’s clinical information beyond just laboratory test values, to enable medical differential diagnosis of the most likely or probable cause for the findings. To facilitate that, let us now look at an eDISH plot of the right upper quadrant only, so we can see the points better:



It is evident that there were 5 star symbols (patients on macitentan 10 mg/day), 5 diamonds (macitentan 3 mg/day), and two triangles (placebo). In eDISH, when we point to a symbol, the patient site and number, peak ALT and BLT values show so that the point can be identified. If then we click on a point, e.g., the star at ALT 40xULN and TBL 20xULN, we then get a graph of the time course for that patient (5304-13115) and see that he was an Indian male 23, very thin with a body mass index (BMI) of only 16.65, and was only on macitentan for 1 day:



By clicking then on the patient number at “Go to Narrative of Patient” [AC 055302-5304-13115](#), we bring up a block of clinical text about the patient that tells us he was an Indian male 23 with idiopathic PAH, class II who was started on macitentan on the same day he had right heart catheterization, with hypotension 8 hours later, sweating, dizziness. He recovered slowly, but was admitted to intensive care for dopamine infusion, and macitentan was stopped. He was then discharged from hospital 7 days later. The investigator assessed the cardiac shock and liver test elevations as “related to study medication” because alternative reasons could not be ruled out. The patient remained in right heart failure, was rehospitalized 32 days after the single dose of macitentan, and died in refractory heart failure the next day.

Comment: It is very unlikely that macitentan caused the sharp rise in serum aminotransferase activities immediately after a single dose of macitentan 10 mg, and very likely that cardiac shock and hypotension caused the liver injury. The data obtained at the investigative site in Hyderabad are sparse, but show that he was probably mildly jaundiced at the screening date two weeks before his first dose of macitentan on 1 September 2009, probably as a result of his chronic right heart failure. The bilirubin continued to rise despite rapidly falling aminotransferase activities when he was hospitalized for a week after the hypotensive episode, and even more when he was readmitted the day before he died of heart failure. No autopsy was done. It is of interest that although the sponsor provided the narrative to Dr. Guo, their more extensive narrative in the Hepatobiliary Safety Report (pages 59-61) is somewhat different and states that the “investigator assessed the SAEs of hypotension and RHF as not related to study treatment.”

Our use of eDISH and the concepts developed by Dr. Hyman Zimmerman and validated by over 20 years of their observation by Dr. Robert Temple have been successful since 1999 in avoiding approval by the FDA of any drug that later had to be removed from the market because of liver toxicity. It must be understood that drug-induced liver toxicity is not just a simple present/not conclusion, and that serum aminotransferase activities are not measures of liver function nor of severity unless they are accompanied or followed by increases in bilirubin or prothrombin time, which are measures of whole-organ liver functions. Therefore the individual cases that show

both ALT and TBL elevations (upper right or “NE” quadrant of eDISH initial plot) are of special interest but not yet diagnostic until the most likely or probable cause can be diagnosed. The use of their own version of eDISH was very likely the result of insistence by Dr. (b) (4) one of the three consultants, that it be used, for he has long been and enthusiastic user of it, as has Dr. (b) (4) and others ((b) (4)

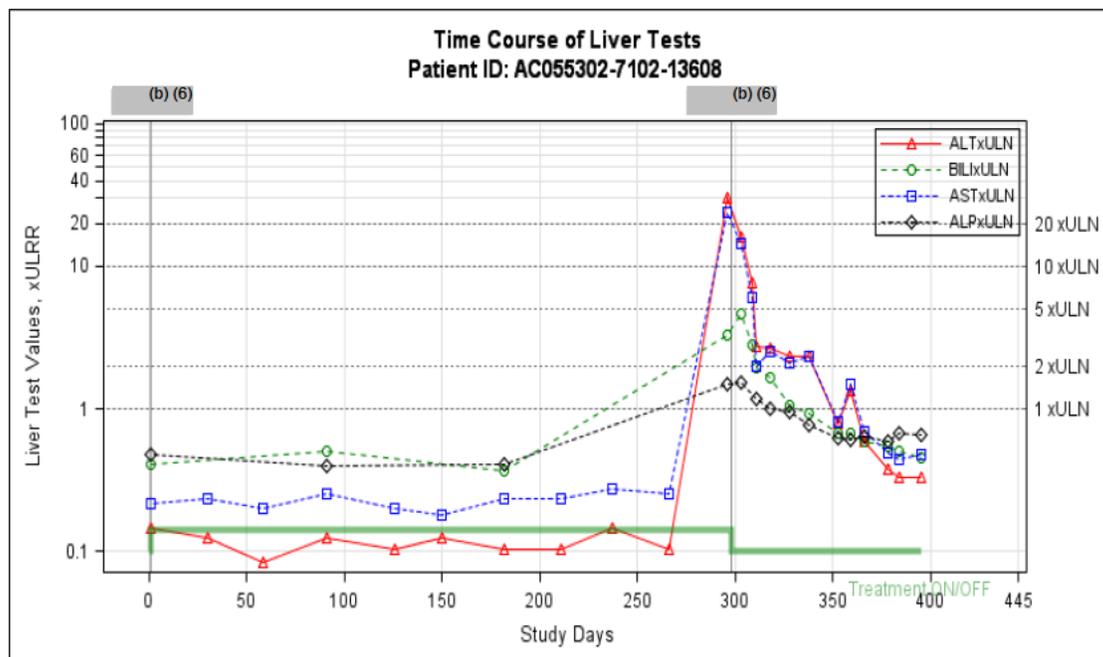
In the Hepatobiliary Safety Report (HbSR), the lead-consultant Dr (b) (4), reporting for the (b) (4) discussed two single cases briefly (pages 50-52), although the Actelion staff also reviewed them with considerably more comprehensive narratives, data listing and graphs (Patient 7102-1368 on pages 67-71, and Patient 8401-11587 on pages 94-9). He did not state how the “two patients of note” were chosen for brief discussion, but he concluded that the first was due to an undocumented biliary obstructive event, and the second possibly due to a Chinese herbal coffee consumed for two weeks before her serum transaminases rose and macitentan was stopped. To illustrate some of the difficulties in deciding what exactly was the most likely cause of the observed liver test abnormalities or other findings, we review the two cases more closely, first looking at what (b) (4) reported, then at what the Actelion staff reported, and then review what data the sponsor sent to us about the cases.

Patient 055-302-7102-13608

(b) (4) reported this 67-year-old female as one of two patients of note (page 51 of the HbSR). She was found to have marked elevations of ALT and TBIL on Day 296 after starting macitentan and the drug was stopped on Day 298, after which the liver tests returned to normal. He pointed out that the ALP rose to three-fold baseline, from 47 to 154 U/L (ULN 100 U/L) with concurrent increase in amylase to 259 U/L (ULN 100 U/L). Ultrasound examination 20 days after elevations of liver tests showed no biliary or pancreatic abnormalities, and he concluded that undocumented biliary obstruction was a possibility.

More detailed review of the case by Actelion (pages 67-71 of the HbSR) states that a Caucasian woman of 67 had PAH secondary to scleroderma, with hypertension, osteoporosis, neutropenia, thrombocytopenia, anemia, and insomnia. She was on sildenafil when she started M10 on (b) (6) (Day 1). Her serum liver tests were normal at baseline and remained so for 38 weeks, first becoming abnormal on (b) (6) (Day 296) with ALT 595 U/L (23.8xULN) and TBil 3.4 mg/dL, DBil 1.6 mg/dL, ALP 150 U/L (1.5xULN). Macitentan was stopped on Day 298, and ALT fell to 365 (14.6xULN), TBil 4.6 mg/dL, DBil 2.7 mg/dL on Day 303. All abnormalities normalized by Day 353 (b) (6) Her serum amylase was 140 U/L (1.4 xULN) at pre-treatment and until the ALT rise, peaked at 2.6xULN on Day 296, and returned to 1.6xULN when the other tests normalized. Abdominal ultrasound on Day 316 showed normal bile ducts, gallbladder, pancreas, and spleen. No mention was made of her ingesting Chinese herbal coffee, but she had been treated with lansoprazole and famotidine for reflux esophagitis from Day 252. Tests for viral hepatitis and cytomegalovirus were said to be negative. The patient reported asthenia from Days 289 to 303, prior to and during the rises in the serum liver tests. Although the TBil peaked at 4.6 mg/dL on Day 303, no overt jaundice was noted. A very nice time course graph and table of laboratory tests were provided on pages 69 and 70. The investigator, (b) (4) (b) (4), assessed the liver test abnormalities as related to study drug. The Actelion assessment (page 71) speculated about an acute biliary tract obstruction as possible.

Using eDISH and the information provided by the sponsor, we found the patient's peak values for ALT at 29.2xULN and TBL at 4.6xULN (in the right upper, NE, quadrant of the log-log plot), and her time course as shown below (very similar to that by Actelion on page 69 of the HBSR):



Comment: The data show that macitentan 10 mg/day was tolerated with repeatedly serum normal liver test results (9 sets of values) for over 9 months, when a sudden rise in activities of serum aminotransferases and bilirubin occurred, with no pain reported, just some vague asthenia for a few days before and during the period of test abnormalities. No plausible explanation other than the study drug was found, despite a moderately comprehensive work-up. It was concluded by the Israeli investigator that drug-induced liver injury was possible, and I concur that no better explanation was forthcoming. (b) (4) speculation about the Chinese herbal coffee was quite ingenuous, but not even mentioned by the sponsor. This case represents an example of how very difficult it may be to make a diagnosis of probable cause. The severity of the case was moderate, with no hospitalization, disability, or evidence of acute liver failure, which we would call level 2 severity, and weakly possible (level 2) causal likelihood of DILI.

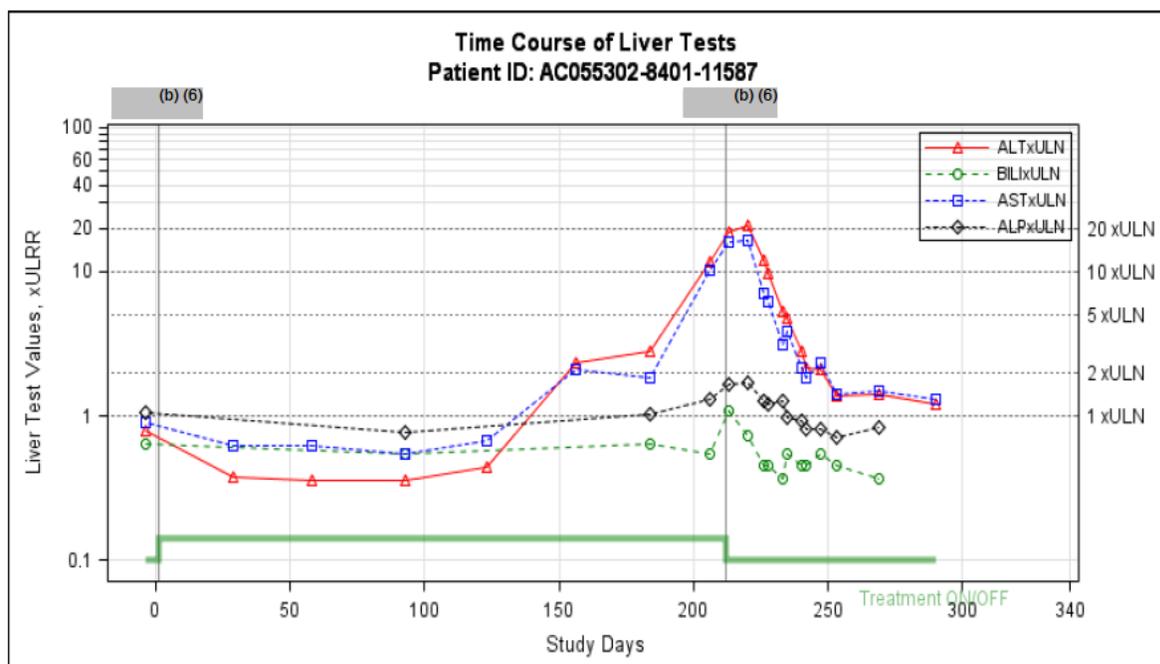
Patient 055-302-8401-11587

The other case reviewed by (b) (4) as “of note” was a 26-year-old female who showed no liver test abnormalities for over 8 months on macitentan, then on Day 206 showed ALT/AST rises to >10xULN. He commented that she had started two weeks before to use a Chinese herbal coffee product containing Ganoderma lucidum (reported as sometimes causing hepatotoxicity), which she stopped on Day 217. A much-delayed rechallenge by macitentan on Day 442 was reported as positive, but slow and weak, and subsequently resolved.

The Actelion review of this case (pages 94-9 of the HBSR) described a Hispanic woman 26 with idiopathic PAH randomized to M10 on (b) (6). She had history of hyperthyroidism,

human papilloma virus infection, cutaneous tuberculosis, upper abdominal pain, headache, and a background of previous liver test elevations. Shje worked in a veterinary office, had been treated with sitaxsentan previously, and was taking levothyroxine, omeprazole, nifedipine, ibuprofen, and acenocoumarol when macitentan was started. Slight baseline ALP elevation was noted, and she showed mild ALT and AST rises at Days 156 and 184, with mild upper abdominal pain from Day 150. She started drinking the herbal coffee containing Ganoderma lucidum (lingzhi or reishi mushroom) on Day 190 (b) (6) and two weeks later on (b) (6) (Day 206) was found to have ALT up to 357 U/L (11.9xULN), AST 255 U/L (10.2xULN), ALP 1130 U/L (1.3xULN), and the total bilirubin 0.5 mG/dL. Macitentan was stopped on Day 212 and the herbal coffee was stopped on Day 217. The investigator (b) (4), assessed the liver test rises to as related to study drug, but the herbal product was also a possible cause. Subsequently, the patient showed deterioration of her PAH,so with agreement from the Data Safety MonitoringBoard a rechallenge with macitentan10 mg was started on (b) (6) (Day 440) in hospital for daily monitoring of test results and observation for a week. No rise in ALT or AST was noted during the 7-day hospitalization, but moderate elevations of serum ALT and AST gradually rose over the next 6 weeks and macitentan was stopped on Day 486 (b) (6) despite PAH worsening with liver congestion and hepatomegaly the week before. The sponsor requested IgE assay, and it was found elevated, but its significance was unclear. The sponsor concluded that a causal relationship between macitentan and liver test abnormalities was “difficult to establish.” No rechallenge with the lingzhi mushroom herbal product was done.

Using eDISH and the information provided by the sponsor, we found the patient’s peak values for ALT at 20.8xULN and TBL at 1.1xULN (in the right lower, SE, quadrant of the log-log plot), and her time course as shown below (similar to that by Actelion on page 98 of the HBSR, except that the sponsor sent no data after Day 290, so the rechallenge was not included):



Comment: The attempt to establish by deliberate rechallenge the possible hepatotoxicity of macitentan in this patient failed. No definite conclusions could be made. This illustrates the very great difficulty in chasing down every elevation of serum transaminases unaccompanied by any true functional abnormality such as bilirubin or prothrombin increase, and is the reason that we focus more concern on reduction of true whole-organ live functions such as clearing plasma of bilirubin or synthesizing prothrombin. Serum enzyme test do not define serious hepatotoxicity but are simply indicators of the need to investigate further promptly and serially until a probable or most likely cause is found --- which is not always possible, and is often not even attempted. We would not have chosen this case for close scrutiny, and it is unclear why Dr. (b) (4) did.

Further to consider some of the other cases we found in the right upper quadrant using eDISH (see page 6), the potentially serious cases that need additional information for evaluation for severity, differential diagnosis, and adjudication for significance, let us note that there did appear to be a modest predominance of cases among patients on macitentan (5/423, 1.2% on 10 mg and 5/311, 1.6% on 3 mg) compared to placebo (2/371, 0.6%). There was no hint of a dose effect, but the patients on macitentan were a bit more likely to show the biochemical changes that stimulate a concern about whether the effects were truly drug-induced or attributable to some other cause. In PAH there is a strongly confounding negative effect of heart failure, especially right heart failure on liver function because of the dependence of the liver on oxygen supply transported to it via the circulation and impaired by inability of blood to escape centrilobular sinusoids. Shown in the table below are summary data for the 12 patients whose eDISH values placed them in the right upper or NE quadrant (see page 6):

Macitentan (Opsumit®, Actelion) – subjects for adjudication of probable cause of findings

study	site	pt #	S-A	mg/d	dose	BMI	start date	peak values, xULRR				days	probable cause
								ALT	TBL	AST	ALP		
302	5306	13115	M23	10	16.7	(b) (6)	39.3	21.1	56.5	0.6	1	hypotensive hypoxia	
302	7102	13608	F67	10	26.7	(b) (6)	29.9	4.6	23.0	1.5	296	?possible DILI/	
302	6001	11098	F17	10	16.5	(b) (6)	18.4	2.1	27.8	0.8	584	acute viral hepatitis B	
302	5401	15235	F19	10	23.5	(b) (6)	8.9	2.5	6.7	0.6	858	right heart failure	
302	4204	31155	F69	10	31.2	(b) (6)	6.2	2.1	6.1	1.3	85	respiratory failure	
302	5306	13104	M19	3	17.6	(b) (6)	32.1	12.2	40.3	2.1	473	right heart failure	
302	5306	13118	M23	3	16.1	(b) (6)	37.8	3.5	34.6	1.6	285	acute viral hepatitis E	
302	9137	12477	F70	3	33.3	(b) (6)	26.3	2.4	26.2	1.4	674	right heart failure	
201	204	1011	M71	3	24.5	(b) (6)	5.9	3.6	5.6	15.5	85	pancreatic carcinoma	
B201	9103	12093	M59	3	31.9	(b) (6)	3.3	4.3	1.3	0.9	372	? right heart failure	
302	5304	13110	M26	P	21.2	(b) (6)	3.1	4.8	2.7	1.3	995	right heart failure	
302	8203	11602	F25	P	29.3	(b) (6)	16.8	5.0	9.4	0.8	413	right heart failure	

Abbreviations: pt#, patient number; S-A, sex-age; BMI, body mass index, kg/m2; Fb, February; Mr, March; Ap, April, My, May; Jn, June; Jy, July; Sp, September; Oc, October; Nv, November; xULRR, multiples of upper limit of laboratory reference ranges; ALT, alanine aminotransferase activity; TBL, total bilirubin serum concentration; AST, aspartate aminotransferase activity; ALP, alkaline phosphatase activity; days, days since macitentan started to peak test values observed.

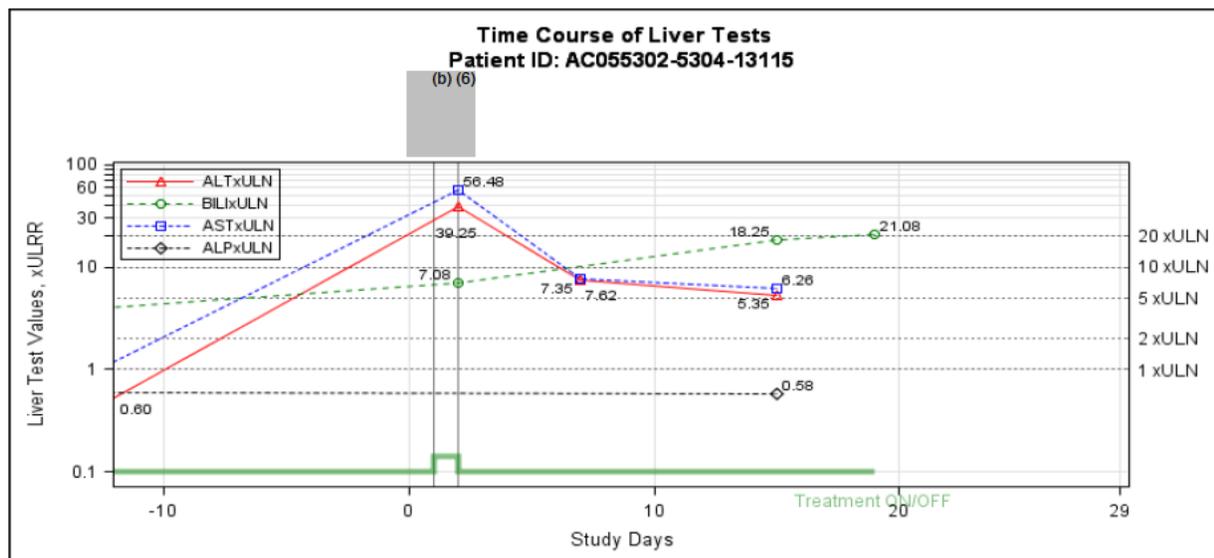
There are many notable findings in the table above, but not apparent is that only two of the patients were in the United States (12477, 12093), while four were studied in India (13115, 15235, 13104, 13118), and one each in Chile (11602), Israel (13608), Malaysia (14235), Serbia (1011), South Africa (11098), and Turkey (12093). There was only one case in which the time from starting macitentan administration to the peak of liver test abnormalities was less than 12 weeks, and that case appeared to be caused by severe

hypotensive shock following a procedure before the first single dose of 45 mg of drug was given, and seven of the cases did not appear until more than a year on macitentan. Using the time course of all liver tests (ALT, AST, ALP, TBL) over the time of treatment and follow-up, and especially the supplemental clinical information in the narratives provided, only one case (the Israeli woman 67 commented upon by Dr. (b) (4) - see pages 8-9) could even be assessed as possibly or probably caused by idiosyncratic response to macitentan, lacking convincing evidence for any alternative cause.

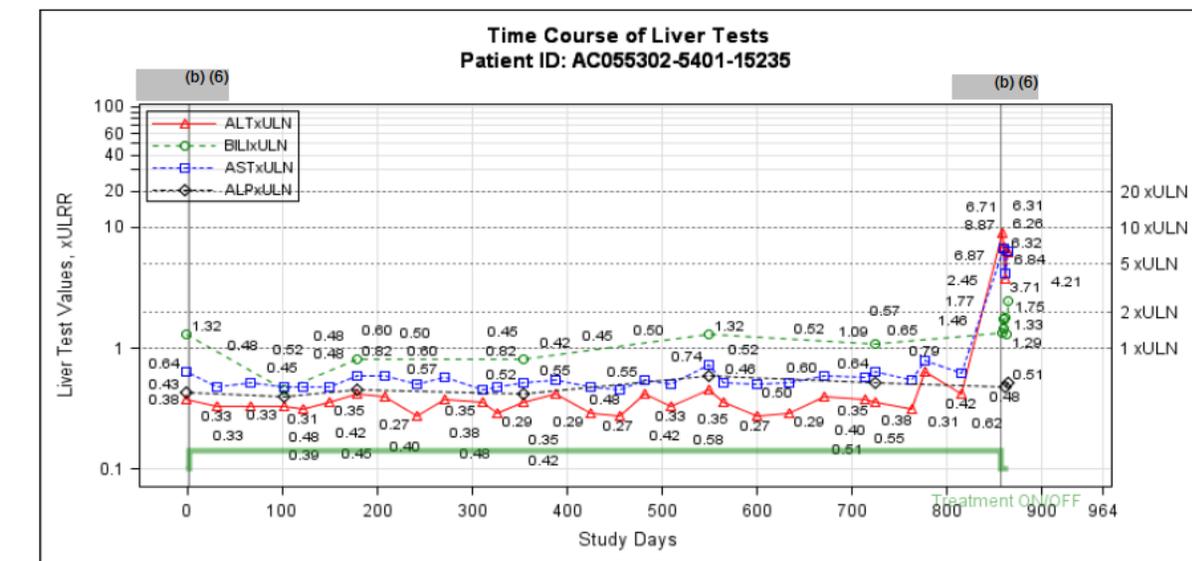
In adjudicating these cases, the first step in the eDISH program is to find them, as relatively rare cases out of many with no liver test abnormalities, or only serum ALT or TBL increases. These patients are plotted in the right upper quadrant of the first eDISH graph (see pages 5, 6) as patients of interest. Although the NE quadrant has been labeled as “Hy’s Law” quadrant, it must be emphasized that such location, based only on peak values of serum chemistries for an individual is *not diagnostic*, but only an indication to look into the case more carefully for clinical information that allows differential medical diagnosis of the most likely cause, as well as the severity of the liver injury. Severity cannot be assessed simply by how high the peak ALT elevation may be, despite confusing and incorrect grading in the Common Toxicity (now Terminology) Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), now in its fourth version since the original classification in 1982. That grading calls serum enzyme elevations >20xULN as “life-threatening,” which is certainly not true, not based on data, but just on opinions of unidentified experts or committee passed along from 1982 to 1997 to 2003 to 2009. Nobody ever died of ALT elevations, nor do such elevations even cause symptoms, and measure no function of the liver. Of much greater importance are drug-induced injuries that cause sufficiently extensive hepatocellular injury that the true functions of the whole organ may be impaired, with reduced capacity to clear circulating plasma of bilirubin, conjugate it with glucuronide, and excrete it into bile, or reduced synthesis of the finely regulated coagulation protein prothrombin, leading to elevated prothrombin time for clotting or to raised values for the international normalized ratio (INR). Thus, serum enzyme activity elevations may indicate the rate of injury to liver cells, with leakage of these normally intracellular enzymes into the plasma, but they do not measure liver function (despite their widespread appellation as “LFTs”). The only tests of liver function commonly done are serum total bilirubin concentration and INR. That understood, we seek to adjudicate each case of special interest for its severity and its most likely cause. Drug-induced liver injury (DILI) is only one of many possible causes for findings of elevated ALT and TBL, and a rather rare cause indeed, if we are concerned mainly about clinically serious liver injury that results in disabling symptoms, need for hospitalization or special treatment, is truly life-threatening, or results in death from liver failure or need for transplantation. Most of the less serious findings, of asymptomatic serum enzyme increases that are far more commonly seen as caused by drugs in certain susceptible people, resolve with no treatment, not even interruption of causative drug administration, probably by still poorly understood processes of liver cell adaptation and development of tolerance.

Assessment for severity is relatively easy for clinicians (not done at all by statisticians), but by far the most difficult task is adjudicating for the most likely cause of the findings, of which many are possible. There is no valid biomarker for diagnosing DILI; it must be done by clinical observation of the patient’s response to the drug, and carefully excluding other more common, causes, leaving DILI as a diagnosis of exclusion when no other cause can be found. We have found it useful to assess the likelihood of causality as “possible” if >25 to 50% likely, and “probable” is >50-75% likely, “very likely” if >75-95%, and as almost definite if >95% likely. For excluding other causes, 5-25% is considered “unlikely,” and <5% as “very unlikely.” Using this scheme, it may be seen that to judge a reaction as “probably” DILI means it is more likely than all other possibilities combined, and leaves only one alternative as even “possible.” An adjudication of “very likely” DILI means no alternative cause is even “possible” but there still could be several “unlikely” causes.

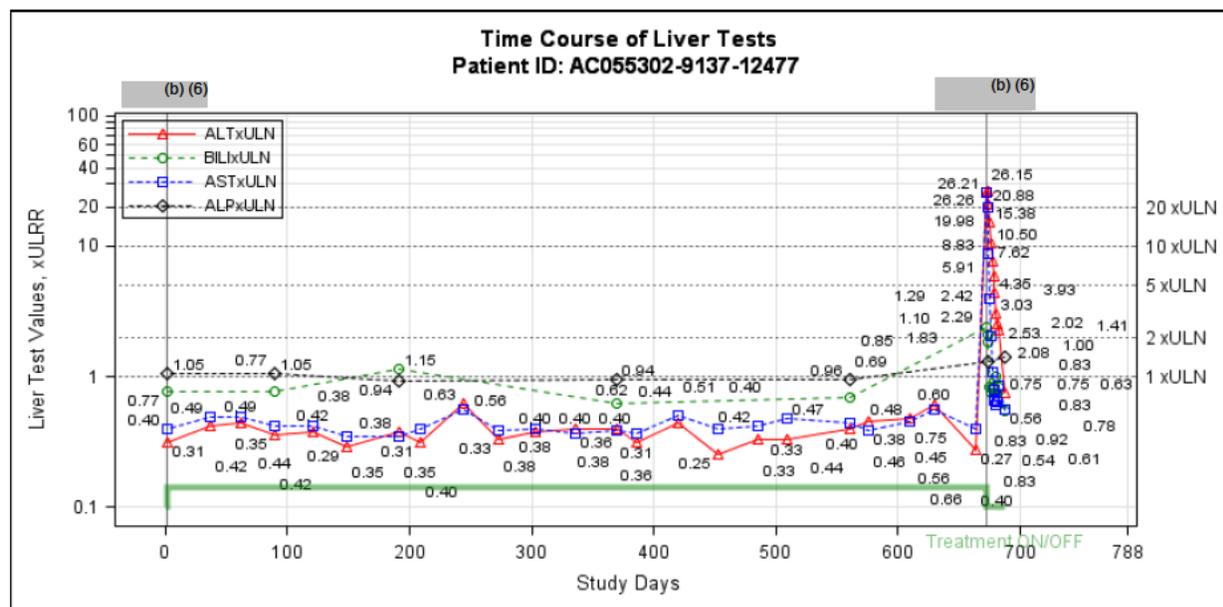
A picture may be worth many words, so let us look at the second stage of eDISH output, the time course of liver tests for a single selected individual, usual from the right upper quadrant of the first eDISH plot.



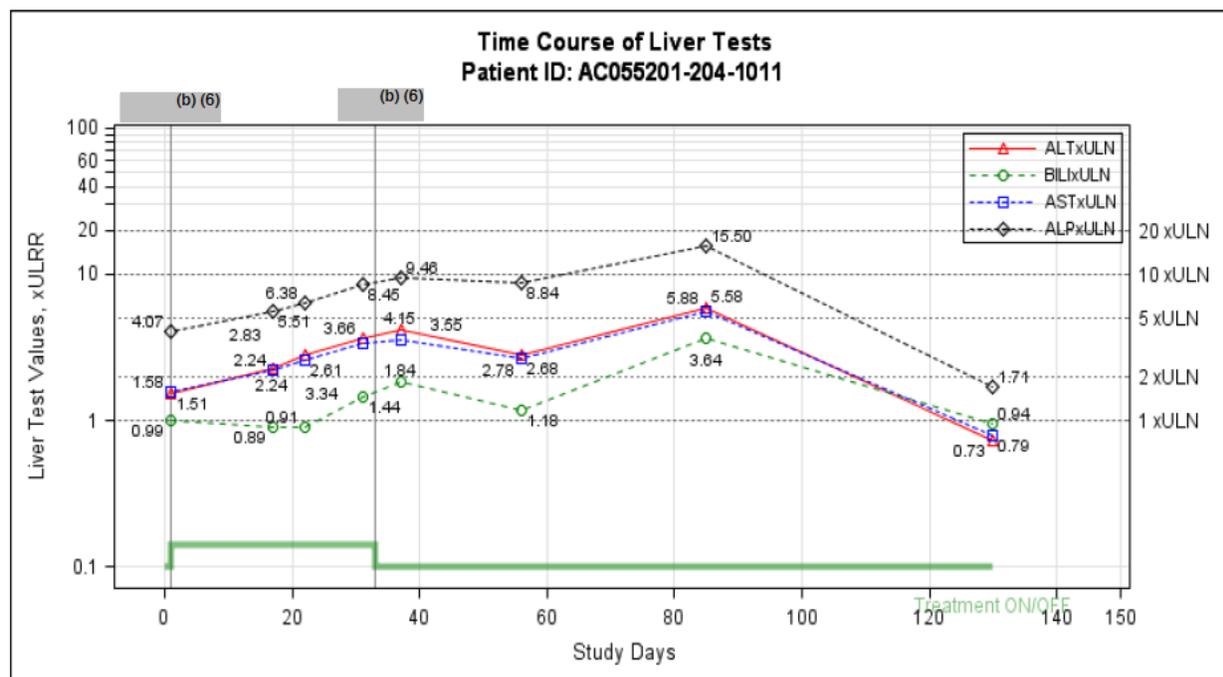
Comment: This thin (BMI 16.65) Indian male (#13115) was given 10 mg macitentan 3 hours after right heart catheterization, and within 5 hours developed hypotension, arterial hypoxemia, was treated in the intensive care unit, and gradually recovered over the next week. It could not be determined if this severe adverse reaction would have occurred had no macitentan been given but it was very unlikely a reaction solely due to macitentan.



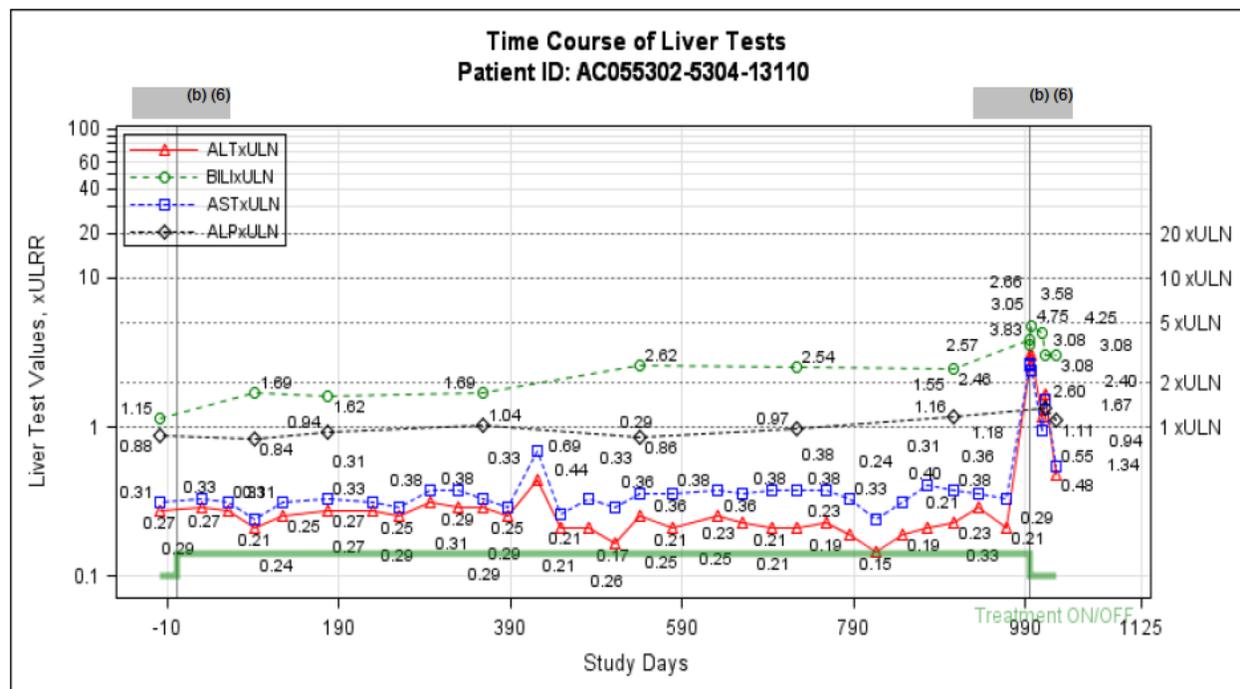
Comment: This 17-year-old black South African girl (#11098) was treated with macitentan for over 19 months, without any abnormal liver test results except for slightly elevated bilirubin (she may have had Gilbert syndrome). She developed marked abnormalities and was diagnosed as having acute viral hepatitis B.



Comment: This woman of 70 studied at Atlanta GA, showed no adverse hepatic reaction to 3 mg/day macitentan for more than 22 months, but her PAH caught up with her and she suffered acute right heart failure, with very sharp elevations of liver test results, quickly returning to the normal range as she was successfully treated for heart failure.



Comment: This Serbian man 71 (#1011) showed elevated alkaline phosphatase before treatment with 3 mg/day macitentan for 33 days Drug administration was stopped because of rising liver test values, and led to further investigations that on Day 56 disclosed pancreatic carcinoma with obstruction of the papilla of Vater. He underwent pancreatoduodenectomy at Day 95.



Comment: This 23-year-old Indian man (#13110) was treated with placebo (no macitentan) for over 33 months before going into right hear failure, with elevations in all liver rests. Prior to that he had shown modest elevations of total bilirubin, probably due to Gilbert syndrome, although the bilirubin was not fractionated. Note the similarity in time course to that of the South African girl (#11098) who was treated with 3mg/day macitentan.

These illustrations show how we use eDISH, and its power to assist in the diagnosis of severity and causality in selected individuals with abnormal liver ytest results. We have looked at all 12 of the cases in the right upper quadrant for the 1243 patients considered for the pivotal trials of macitentan for treatment of pulmonary arterial hypertension. It is conceded that that only one case (the Israeli woman #13608) may be considered probably, or strongly possibly, macitentan-induced. That is no reassurance at all that if macitentan is approved as a safer hepatotoxicity alternative to bosentan that serious liver injuries will not occur in rare individual as thousands of patients are treated, and perhaps less carefully observed for liver test abnormalities. The lessons of sitaxsentan should not be forgotten or ignored.

The recommendation for approval of macitentan, based on very modest benefits, almost ignores the hints and smoke of rare, idiosyncratic liver injury seen so far in very limited studies. That was also the case for staxsentan in 2006, when it was approved in the European Union, and only made “approvable” by DCRP in March 2006 because of deficiencies in conclusive proof of its efficacy. It took until June 2009 for the first published case of sitaxsentan-induced liver injury to be published (Hoepfer at al.), and meanwhile it was approved in Canada, Australia, and many countries in Europe in 2007-8.

(b) (4)

[Redacted text block]

(b) (4)

Approval of ambrisentan on 15 June 2007 made it impossible for Encysive to beat them to the market that had been limited by bosentan restrictions, and ambrisentan has proved in the six years since that it is considerably safer than bosentan, from an hepatotoxicity perspective. It is by no means clear that macitentan is equally so, and only the test of time and more experience with it will reveal the truth. That truth was hard and slow to come by with sitaxsentan, and there does not appear to be any compelling reason to assume macitentan safe at 10 mg/day until many more patients are treated and observed.

The history of the endothelin receptor antagonists (bosentan, ambrisentan, sitaxsentan, and now, macitentan) has been a troubled story, a rather desperate search for what in the cardiopulmonary world is close to a malignant disease for which oncologic reasoning is appropriate. Macitentan is not curative, is not a life-saver, but at best may slow progression of PAH in its progression. If it is approved, it seems that continued caution should and must be carried out, if not to avoid liver injury entirely, at least to detect it early enough so that it can be stopped before serious liver injury and dysfunction have developed. There are no known genetic markers to help us or the treating physicians to decide which patients may be a special risk, no magic biomarkers, only careful clinical observation and wise, timely actions. This is not simply a matter of automatic requirements for “monitoring,” which has been such a failure in the past, but need for true clinical observation by physicians who know what to look for, patients who understand why and are fully cooperative and even insistent that their doctors get it right.

“Pharmacovigilance is the key. Especially in orphan diseases, drugs are often approved at a stage when there is no sufficient information about long-term safety, especially regarding rare side-effects. This is justified as the authorities have to weigh the benefits of new drugs in rare, life-threatening diseases such as PAH against the potential harm caused by drug toxicity. In the case of the three ERAs, European authorities demanded the implementation of post-marketing surveillance systems to obtain further information on the safety of these drugs after approval. These systems have gathered, and continue to gather, important safety information. The post-marketing surveillance system for bosentan was closed as planned after it had been in place for 30 months collecting data from almost 5,000 patients, but the respective databases are still open for the newer ERAs, sitaxentan and ambrisentan. The final analysis of the bosentan data was reassuring as there were no cases of fatal or permanent liver toxicity, although 10 cases were reported that fulfilled the criteria for serious drug-induced liver injury [9]. For the time being, the cases reported by LAVELLE et al. [2] remind us that liver monitoring should remain an integral part of ERA therapy. Physicians are urged to report all cases of serious liver injury potentially linked to these drugs either directly to the national regulatory authorities or to any representative of the manufacturers, who are obliged to forward the reports to the authorities without delay.”

Hoeper MM. Liver toxicity: the Achilles' heel of endothelin receptor antagonist therapy? Eur Respir J. 2009 Sep;34(3):529-30. PMID 19720805

The European regulatory agencies were “burned” in approving sitaxsentan, and Pfizer was also “burned” in buying the rights to the drug from Encysive. The FDA had earlier dodged the bullet by insisting on more efficacy information that Encysive was reluctant to collect and sold the rights to Pfizer. It seems that we should learn from this experience. The question remains as to how best to do this with respect to macitentan.

After circulating the draft of this consultation in mid-June, up to the end of page 16 (above), much discussion in both DCRP and OSE has taken place; sharp differences in opinion have emerged in the past two months. During this time the clinical review has been completed (21 June), a late-cycle meeting with the sponsor was held on 17 July, and opinions have been given by the Division of Risk Assessment (DRISK) of OSE and its Division of Epidemiology II (DEPI II) in the past week or so. I shall try to summarize what I understand to be the viewpoints of others and then my own in the section to follow.

Concluding Discussion

It has become clear that:

- 1) There will be no Advisory Committee review and discussion of the use of macitentan for treatment of pulmonary arterial hypertension. (b) (5)

[Redacted text block]

- 2) The clinical reviewer recommends approval of macitentan 10 mg once daily for treatment of PAH, World Health Organizatoion Group I for its “beneficial effect in delaying the worsening of symptoms in patients with PAH probably outweighing its risks,” No recommendations were made for postmarket risk evaluation and mitigation strategies. [M. Gordon, 21 June 2013]

- 3) (b) (5)

[Redacted text block]

- 4)

[Redacted text block]

5)

- 6) I do not agree with these recommendations, for many reasons as outlined below. I do appreciate the thoughtful comments and positions expressed, but believe this course would be unnecessarily dangerous and unwise.

Reasons for dissenting opinion

- 1) Not much if anything will be learned from the above approach, and much still needs to be learned. I have not been convinced by the information obtained so far and submitted for review that we (sponsor or FDA) know exactly which patients with what form of PAH should be treated, when exactly to start treatment, how long to continue treatment, or even the best dose. Obviously PAH is a malignant disease with approximately 50 % mortality in 3 to 6 years, depending on what type of PAH is present, those with systemic sclerosis showing the greatest risk. The alternative of requiring additional clinical studies, which are time-consuming, costly, deprive any patients outside the study who might benefit from treatment, reduce patent life for the sponsor, do not appear to have any support by our several reviewers.
- 2) I do not believe that we should be overly concerned with simple mild and transient liver injuries, manifested only by elevation of serum enzyme activities without any evidence of whole liver dysfunction. What we should aim to prevent, if possible, is the progressive liver injury that becomes so extensive that the whole organ can no longer carry out its essential functions, as may be indicated by reduced capacity to clear bilirubin from the plasma, or to synthesize enough prothrombin to help clot blood and prevent bleeding. The liver is a very adaptable organ, can regrow to its original size and function even after 65% resection or necrosis of hepatocytes, and

most of those who show some initial mild injury by aminotransferase elevations adapt and become tolerant, which reduces the diagnostic value of “rechallenge.” Only a few patients, on the order of 1 per 1,000-5,000 or so are unable to adapt and therefore may progress to acute liver failure if the causative drug is given too long. It is not easy to determine exactly when that point of irreversibility may occur; there is no reliable biomarker to inform us; and only close observation of patients who are exposed can tell us. We have no way to predict in advance who they may be, and subtle genetic differences to do so are still just future hopes.

- 3) Routine monitoring, such as mandatory serum ALT measurements, have repeatedly failed as a protective solution, mainly because they are not done, or not for long. Both patients and their physicians grow weary of normal test results month-after-month, and just quit doing it. The vast majority of ALT monitoring test will always be within normal limits, in seeking rare patients who may show abnormalities at some unknown future time. Further, it has not always been made understandable to patients, or even to their prescribing physicians, why such testing is important. It is costly, inefficient, and just doesn't work.
- 4) Perhaps better than monthly testing of ALT, or whatever, may be DAILY symptom inquiry by the patients themselves, at no cost, to report promptly early symptoms of fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, dark urine, or perhaps other symptoms, then have the prescribing physician investigate to find the probable cause, and treat it if possible, or rule out other causes than the drug if possible. While this is going on, interruption of drug treatment may be advisable, with cautious resumption if another cause is found and treated successfully. This is just plain good medical practice, with the responsibility where it ought to be, on the patient and prescribing physician, rather than on pharmacists or the sponsor. It has never been proved conclusively whether elevations in serum enzyme activities or early symptom come first, but it would be interesting to find out, and very useful.
- 5) In PAH, the most likely cause of abnormal liver tests is right heart congestive failure, which can be treated quickly and reduce or eliminate drug-induced toxicity as the probable cause.
- 6) To put this together and resolve the evident impasse, let me propose a somewhat new (and surely controversial) approach, that of an **Active Registry**. This would not be just a system for recording findings but an active tool to help both physicians and patients to detect early symptoms of liver injury, confirmed by serum testing, at a time before the injuries become irreversible so that continued drug administration to the rare person who cannot tolerate it or adapt to it can be stopped, but allowing the great majority who can to enjoy the benefits of the treatment. It would also be a relatively low cost process, permit use and marketing of the drug for most patients, avoid loss of patent life and the tremendous costs of additional clinical trials, and time needed to carry them out, have them reported and reviewed. In addition, such an Active Registry would permit a great deal to be learned, could contribute also to the REVEAL registry already started, and provide very useful information on how best to treat this life-threatening disease. Admittedly, there will be many devilish details to work out, but let the debate begin.
- 7) To start, the proposal for an Active Registry, as an alternative to additional clinical trials or to doing nothing but hoping for the best, should be considered and by the

sponsor's excellent panel of hepatology consultants (Drs (b) (4) (b) (4) (b) (4) and their comments returned to FDA by mid-September if possible. It would also be of interest to have the proposal considered by those who oversee the REVEAL registry for PAH.

- 8) It is still unclear where the truth will lie: whether further experience with this fourth ETA, macitentan, will show it like ambrisentan or like sitaxsentan, even if it is safer than bosentan. Based on what we know so far, no confident prediction can be made, and only continued observation will tell us.

John R. Senior, M.D.

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/s/

JOHN R SENIOR
09/09/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Memo

Date: July 17, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Opsumit (Macitentan) Tablets, 10 mg

Application Type/Number: NDA 204410

Applicant/Sponsor: Actelion

OSE RCM #: 2012-2668-1

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1 INTRODUCTION

This review evaluates the revised container label, blister label, and carton labeling for Opsumit (Macitentan) received on July 11, 2013 (see Appendices A through D). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2012-2668 dated June 13, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling received on July 11, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2012-2668 dated June 13, 2013, to ensure all our recommendations were implemented. .

3 DISCUSSION

The Applicant incorporated all of DMEPA's recommendations except for one regarding the removal of the phrase "For Hospital Use" from the 15-count blister label. The Applicant provided the following reason for not implementing this recommendation:

The blister presentation of Opsumit (macitentan) is not child-resistant, and it is felt important to distinguish that the blister product is only available for hospital use. The wording "For Hospital Use" is felt to have additional preventative value, as it will provide instruction and act as a reminder to pharmacies to dispense the drug in a child resistant container. Actelion has followed the same principles as have been used to support hospital use of our other marketed ERA product, Tracleer, which also has a specific blister presentation that is labeled "For Hospital Use".

DMEPA made this recommendation to create additional white space on the label and enhance the readability of the other information. Upon consideration of the Applicant's rationale, DMEPA finds it acceptable to leave the "For Hospital Use" statement.

4 CONCLUSIONS AND RECOMMENDATIONS

We find the revised container label, blister label, and carton labeling acceptable. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

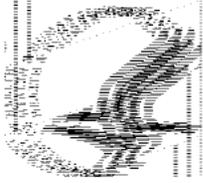
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/s/

KIMBERLY A DE FRONZO
07/17/2013

IRENE Z CHAN
07/18/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Maternal Health Team Review

Date: June 25, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Hari Cheryl Sachs, MD
Acting Associate Director, OND
Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Opsumit (macitentan) NDA 204410

Proposed Indication: Treatment of patients with pulmonary arterial hypertension (PAH)

Subject: Macitentan proposed labeling and REMS program

Applicant: Actelion Pharmaceuticals Ltd. (Actelion)

Materials Reviewed: Proposed macitentan product labeling, REMS documents and available literature regarding pregnancy and lactation

Consult Question: DCRP requested PMHS-MHT assistance in evaluating the REMS and labeling for opsumit.

INTRODUCTION

Actelion Pharmaceuticals Ltd. (Actelion) submitted a New Drug Application (NDA) for Opsumit (macitentan) Tablets on October 19, 2012. Macitentan is a New Molecular Entity (NME) with a proposed indication for treatment of patients with pulmonary arterial hypertension (PAH).

Per the sponsor, macitentan is a dual endothelin receptor antagonist (ERA) that prevents binding of endothelin-1 (ET-1) to its receptors, ET_A and ET_B. In PAH, ET-1 effects are up-regulated and thought to cause vasoconstriction, vascular smooth muscle and endothelial proliferation. Endothelin receptor antagonists block the binding of ET-1 to receptors, decreasing PAH symptoms¹. There are two other ERAs currently marketed and approved for treatment of PAH, Tracleer (bosentan) and Letairis (ambrisentan).

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DCRP on May 15, 2013 to assist the division in evaluating product labeling and REMS documents. This review includes PMHS-MHT comments and recommendations for opsumit labeling and REMS documents.

BACKGROUND

Macitentan and Pregnancy

Macitentan is an NME and there are very limited human pregnancy data available. In the proposed REMS supporting document, the applicant described seven pregnancies that occurred during the clinical development program; five pregnancies in patients treated with macitentan 3 mg (5/311, 1.6%) and two in patients receiving placebo. Of the five patients treated with macitentan, there was one spontaneous abortion (assessed as unrelated to study treatment) and one therapeutic abortion. One patient died (due to PAH worsening), before a scheduled abortion could be performed. Of the remaining two patients, one infant was delivered prematurely and died, while the other was reportedly normal. The preterm infant had no dysmorphic features at birth and prenatal screening performed at 18 weeks gestation revealed no abnormalities, however had a grade IV intracranial hemorrhage, hyaline membrane disease (complicated by sepsis) and poor skin condition. The infant died three days after birth due to persistent hypotension related to extreme prematurity. The infant's death was reported as unrelated to study treatment. There were no dysmorphic features at birth and prenatal screening performed at 18 weeks gestation revealed no anomalies. The second infant was reported born with no neonatal abnormalities, with no other outcome information reported. The patients treated with placebo (2) had therapeutic abortions².

In animal developmental reproductive studies, macitentan was teratogenic in rabbits and rats, including cardiovascular and mandibular arch fusion abnormalities at all doses tested. A No-Effect dose was not established in either species. These animal data are reported in current proposed macitentan labeling.

¹ Actelion. Nonclinical Overview Macitentan Endothelin Receptor Antagonist For Treatment of Pulmonary Arterial Hypertension, October 1, 2012.

² Opsumit (macitentan) Risk Evaluation and Mitigation Strategy Supporting Document, October 3, 2012.

Macitentan and Lactation

It is not known if macitentan is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. A search of the Micromedex, LactMed and PubMed databases revealed no human data regarding macitentan and lactation. In addition, there are no available human lactation data for other endothelin receptor antagonists regarding effects on nursing infants.

REVIEW OF SUBMITTED MATERIALS

Applicant Proposed Macitentan Labeling

The PMHS-MHT reviewed the applicant's proposed macitentan labeling, submitted October 19, 2012 and has participated in labeling/team meetings during the review period. Discussions regarding labeling and the content of REMS documents are ongoing, therefore PMHS-MHT recommendations regarding labeling and REMS documents may not reflect final recommendations, pending the outcome of discussions. A summary of current PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

Applicant Proposed Macitentan REMS Documents

The applicant submitted a proposed REMS program focused on minimizing the risk of fetal exposure in females of reproductive potential and informing/educating prescribers, pharmacists and females of reproductive potential about the risk of teratogenicity. There are two other ERA products approved for treatment of PAH that also have REMS programs for teratogenicity, Tracleer (bosentan) and Letairis (ambrisentan). The applicant noted consideration of the Tracleer REMS program and European Risk Management Plan (RMP) in development of the REMS program for macitentan and the macitentan program has similarities in design.

The proposed macitentan REMS program contains Elements to Assure Safe Use (ETASU), requiring

(b) (4)

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The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT has reviewed the proposed macitentan labeling, and labeling recommendations are provided below. Note that these recommendations may be revised while final labeling is negotiated with the sponsor.

Macitentan Proposed REMS Program

The applicant proposed a REMS program designed similarly to other currently approved ERA products, as the teratogenic risk profile for macitentan is consistent with the ERA product class (based on animal data). Discussions regarding the REMS program are ongoing. PMHS-MHT has reviewed the proposed REMS documents, and preliminary recommendations are based on review of the proposed program, and subject to amendment at a later date.

RECOMMENDATIONS

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

The REMS program for macitentan includes Elements To Assure Safe Use (ETASU). Therefore a boxed warning describing the risk, information mitigating the risk and a statement that the drug is only available through a REMS program appears in the Full Prescribing Information (FPI) and was added to labeling highlights.

(b) (4)

Nursing mothers language under “Use in Specific Populations” was revised to display preferred labeling language in a more concise format. A bullet point titled Females and Males of Reproductive Potential was added to reference information regarding contraception use in section 8.6 of the FPI.

Boxed Warning

Language describing the risk was revised to align with risk described in the FPI. A statement regarding mitigating the risk was added.

2.2 Testing Prior to Dosage in Females of Reproductive Potential

Language stating that treatment with macitentan in females of reproductive potential may only begin after a negative pregnancy test was added. Cross reference to section 8.6, Females and Males of Reproductive Potential, was added to reference information regarding pregnancy testing.

5 Warnings and Precautions

The Warnings and Precautions section was restructured to comply with requirements of the current SEALD labeling review tool for products with REMS. Sub-section 5.1 titled “Embryo-Fetal Toxicity” was added, with a brief description of the risks and reference to the REMS program, described in sub-section 5.2.

8 Use in Specific Populations

8.1 Pregnancy

The Pregnancy section was restructured to align with current labeling recommendations. (b) (4)

8.3 Nursing Mothers

The Nursing Mothers section was restructured and states that it is unknown whether macitentan is present in human milk and that it is present in the milk of lactating rats. Appropriate regulatory language was added.

8.6 Females and Males of Reproductive Potential

Information on pregnancy testing, contraception, and infertility that was located in other sections of labeling are now presented in the subsection, Females and Males of Reproductive Potential. Language was added to describe pregnancy testing and contraception requirements of the macitentan REMS program, according to current proposed REMS documents submitted by the applicant.

Reviewer Note

This section of labeling should align with requirements of the macitentan REMS program at the time of approval. (b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

17 Patient Counseling Information

The section titled [REDACTED] (b) (4) and re-titled “Embryo-Fetal Toxicity” to align with language used in Boxed Warning and Warnings and Precautions. The language was revised to comply with current REMS program requirements. (b) (4)

[REDACTED] Appropriate cross references were provided.

MHT Summary of Recommendations for Macitentan Proposed REMS Program

1. The language [REDACTED] (b) (4) should be replaced with “females of reproductive potential (FRP)” throughout all REMS documents to promote consistency across labeling and REMS products.
2. The REMS program should be targeted to the “at risk” population and should enroll all females prescribed macitentan. [REDACTED] (b) (4). A determination should be made whether the female patient is of reproductive potential or not of reproductive potential. FRPs should follow the pregnancy testing and contraception requirements as described in the proposed REMS program.
3. The definitions of females of reproductive potential, females of non-reproductive potential and menopause should be consistent with recent PMHS-MHT recommendations as agreed upon during the DSaRM AC December 2012. PMHS-MHT recommends the following:
 - **Female of Reproductive Potential (FRP) Definition:**
 - Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).
 - For the purposes of this REMS, puberty includes those girls who are at least Tanner stage 3 and have not yet had a menses (premenarchal).
 - **Females of Non-Reproductive Potential (FNRP) Definition:**
 - Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.
 - Post-Menopausal Females: Females who have passed through menopause (as defined below).
 - **Definition of Menopause:**
 - Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy.

4. Prescribers are required to monitor the status of female patients for changes in status of reproductive potential. (b) (4)
 PMHS-MHT recommends that the REMS program should require, at minimum, annual verification of reproductive status for pre-pubertal females as appropriate. Prescribers should also report any changes in reproductive status within a specified number of days of becoming aware of the change. REMS program enrollment forms should be revised to accommodate this.
5. Pre-pubertal females of non-reproductive potential and their parent/guardian should receive education regarding the risk of teratogenicity.
6. The proposed macitentan REMS program requires use of reliable contraception during treatment and for 1 month after treatment with macitentan. A list of reliable contraception is provided in both the patient and prescribers guides, and the REMS instructs patients to discuss the best method of contraception for them with their healthcare provider. PMHS-MHT concurs with the applicant's proposed instructions for contraception. The determination of the best method of contraception as advised by the patient's health care provider is appropriate, as long as the contraception is used as required in the REMS program. Of note, other approved ERA REMS programs present contraception methods in a format that describes contraception methods that may be used alone, and methods that must be used in combination.

PMHS-MHT Comments on Specific Macitentan REMS Documents:

1. Proposed Patient Enrollment and Consent Form:

- (b) (4)

2. Proposed Prescriber enrollment form:

- In signature section: Recommend including the following items as part of the list a prescriber attest to:
 - Agreement to enroll all females in the REMS program, if all females are determined the target of the REMS.
 - Agreement to determine the reproductive potential status of all female patients using the definitions provided in the prescriber guide (as recommended above).
 - Agreement to counsel all female patients regarding the risk of macitentan and the requirements of the REMS program.
 - Agreement to report any change in patient's reproductive status by.

- Agreement to counsel pre-pubertal females and their parent/guardian and report reproductive potential status annually.
- Agreement to comply with the requirements of the REMS program.

(b) (4)



Final labeling and REMS will be negotiated with the applicant and may not fully reflect changes suggested here.

Appendix A- PMHS-MHT Macitentan Labeling Recommendation Excerpts

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TAMMIE B BRENT HOWARD
06/25/2013

JEANINE A BEST
06/25/2013
Signing for Melissa Tassinari

HARI C SACHS
06/25/2013
I am signing on behalf of Lynne P. Yao, MD
Associate Director, PMHS

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: June 13, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Deputy Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Opsumit (Macitentan) Tablets, 10 mg

Application Type/Number: NDA 204410

Applicant/Sponsor: Actelion

OSE RCM #: 2012-2668

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Opsumit (Macitentan) Tablets 10 mg (NDA 204410), for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This product received Orphan drug status on September 3, 2009 under IND 077258. On October 19, 2012, the Applicant submitted a 505(b)(1) New Drug Application and a request for Proprietary Name Review for Opsumit under NDA #204410. The proposed proprietary name, Opsumit, was found acceptable under review OSE RCM #2012-2651 dated December 27, 2012.

On February 13, 2013, an information request was sent to the Applicant to confirm the net quantity statement for the blister carton (b) (4), which was inconsistent with the quantity of 15 tablets noted under the How Supplied section of the insert labeling submitted on October 19, 2012. In response to this inquiry, the Applicant submitted an amendment on February 26, 2013 confirming that the blister carton contains a total of 15 tablets. The Applicant also informed the Agency of their intent to add a safety seal to the cartons of both bottles and blisters. Accordingly, on March 29, 2013, the Applicant provided revised outer carton labeling for their 15-count blisters and 30-count bottles to depict the location of the new transparent safety seal.

On May 15, 2013, the Applicant submitted updated packaging components (including the container label for the 30-count bottle along with the outer carton labeling for the 30-count bottle and the 15-count blister packs. The reason for the revision was to align packaging design elements from a global perspective due to recent comments the Applicant received from the European Medicines Agency for the macitentan application submitted in the EU, and to maintain consistency with the FDA Guidance (Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors issued in April 2013).

1.2 PRODUCT INFORMATION

The product information below is provided in the January 24, 2013 labeling submission. Additionally, the Applicant is proposing a risk evaluation and mitigation strategy (REMS), (b) (4) to minimize the risk of fetal exposure in females of childbearing potential and to inform and educate prescribers, pharmacists and females of childbearing potential about the risk of teratogenicity.

- Active Ingredient: Macitentan
- Indication of Use: indicated for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult (b) (4) PSUMIT is effective when used as monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids

- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 10 mg
- Dose and Frequency: 10 mg once daily
- How Supplied: 15 count aluminum foil blisters in carton (NDC 66215-501-15) and 30 count tablets in white high-density polyethylene bottles in carton (NDC 66215-501-30)
- Storage: Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].
- Container and Closure Systems: Macitentan 10 mg film-coated tablets will be packaged in:
 - 50 mL high density polyethylene bottle with a heat induction sealing and a (b) (4) with 2 g silica gel desiccant
 - Polyvinyl chloride /Polyethylene/ Polyvinylidene chloride (PVC/PE/PVDC) white opaque film 250 µm/25 µm/120 µm with a push through 25 µm aluminum foil

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted January 24, 2013, including Medication Guide (no image)
- Container Label for 30-count bottle submitted on May 15, 2013 (Appendix A)
- Blister Label submitted on February 26, 2013 (Appendix B)
- Carton Labeling for 15-count hospital unit-dose blisters submitted on May 15, 2013, which was updated to confirm the placement of the safety seal (Appendix C)
- Carton Labeling for 30-count bottle submitted on May 15, 2013, which was updated to confirm the placement of the safety seal (Appendix D)
- Transparent Safety Seal submitted on March 29, 2013 which will be used on the cartons for the bottle and blister presentations (Appendix E)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our risk assessment of the packaging design as well as the associated label and labeling.

3.1 INSERT LABELING

We note that the proposed (b) (4) Full Prescribing Information (FPI) currently recommends that macitentan “tablets should not be split, crushed, or chewed”. Since this information is atypical for an immediate-release tablet formulation, DMEPA asked the Applicant for their rationale for its inclusion. The Applicant responded with the following rationale on March 29, 2013:

Recent March 2013 FDA Guidance titled “Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation”, identified concerns over doctors and insurance companies recommending that patients split their tablets to adjust a patient’s dose or as a cost-saving measure.

The macitentan 10 mg tablet is not scored nor has been evaluated for splitting. The language “tablets should not be split, crushed, or chewed” should ensure that patients receive a full recommended dose of 10 mg, and will help mitigate the possibility that a tablet is split to achieve a lower dose.

DMEPA is concerned that the inclusion of this statement may suggest that studies were conducted to assess the outcome of splitting or crushing of these tablets. Per ONDQA, no study was conducted to evaluate the effects of splitting, crushing, or chewing of the Opsumit tablets. Opsumit tablets are bi-convex, immediate-release, film-coated tablets without any special delivery system that might be jeopardized by splitting, crushing or chewing. Discussions with Clinical also confirmed that there is no expected clinical detriment to the patient in cases of inadvertent splitting, crushing, or chewing of these tablets. These tablets also lack a functional score which prevents the ability for patients to evenly split these tablets. Therefore, the usual practice is to remain silent on the issue of splitting, crushing, and chewing for immediate-release tablets in the absence of data to support its inclusion, especially for tablets without a functional score. Consequently, we find the inclusion of the warning statement “tablets should not be split, crushed, or chewed” on the label and labeling of this product to be misleading and inconsistent with other immediate-release tablets.

3.2 SAFETY SEAL

We reviewed the proposed revised safety seal and its placement on the carton labeling that was submitted on May 15, 2013. The seal is transparent except for the company logo “Actelion” which is a green color accompanied by the company artwork (see Appendix E). In this submission, the Applicant noted that any text that was potentially overlapping important information was moved away from the overlap of the safety seal. Upon examining the location of the safety seal, we find the safety seal placement to be acceptable as it does not interfere with the readability of important information.

3.3 THE 15-COUNT BLISTER PACKAGING

We note the 15-count carton labeling contains a statement that reads “if dispensed for outpatient use, dispense no more than a 7-day supply in a child resistant container”. Since this information is not commonly found on a product carton labeling, we requested the rationale for its inclusion from the Applicant and they provided the following reason:

The blister presentation of Opsumit (macitentan) is not child-resistant. Therefore, the blister presentation will only be available for hospital use. The statement on the carton refers to the hospital use of Opsumit and dispensing when the patient is discharged from the hospital. For hospital use, Actelion has followed the same principles as have been used to support hospital use of our other marketed ERA product, Tracleer, which also has a specific blister presentation for hospital use only.

Each hospital has its own standards for how much drug is normally dispensed on discharge of a patient and may be less than 7 days, therefore an upper limit has been proposed of 7 days. Upon discharge of a patient from the hospital, the hospital pharmacy will provide Opsumit in a child-resistant container for the patient to take home with them. The 7 days was proposed to allow for those patients who may have to be enrolled in the Opsumit REMS program to complete the enrollment process and start receiving product from the specialty pharmacy following discharge from a hospital. Please see Module 1.16 for details on the proposed REMS program.

As this product will be marketed under a restrictive REMS program, we find the above rationale provided by the Applicant to be reasonable.

3.4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Our review of the proposed insert labeling, container label, blister label, and carton labeling identified the following areas of vulnerability that can be improved for clarity and to increase the readability and prominence of important information on the label and labeling to promote the safe use of the product:

- Lack of dosage form following the active ingredient on the container label and carton labeling
- Inadequate prominence of the statement of strength due to location
- Net quantity placed too close to the statement of strength
- Placement of NDC number that does not meet the regulation
- Inclusion of administration instructions without supporting data
- Unnecessary statement [REDACTED] (b) (4) since this route of administration is implied for a tablet formulation
- Use of dangerous symbols in the insert labeling

We also noted the strength statement on the 15-count blister carton was not optimally expressed. The product strength on the principal display panel and other panels of the blister carton labeling should describe the milligram amount of drug per single unit (e.g., tablet, capsule) so that there is no confusion as to how much product is contained in a single unit as

compared to the total contents of the entire blister card. Therefore, we recommend the strength statement to be expressed as x mg per tablet or x mg per capsule.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved for clarity and to increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA advises the following recommendations be implemented prior to approval of this NDA.

If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Revise the storage condition statement (in Section 16) to replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement “Store at 20°C-25°C (68-77°F)...” to read “Store at 20°C to 25°C (68°F to 77°F)...”
2. Delete the statement [REDACTED] (b) (4) from the Dosage and Administration section 2.1.

4.2 COMMENTS TO THE APPLICANT

A. Container Label (30-count bottle)

1. Revise the storage condition statement to replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. Therefore, revise the statement “Store at 20°C-25°C (68-77°F)...” to read “Store at 20°C to 25°C (68°F to 77°F)...”
2. Relocate the net quantity statement away from the strength statement and minimize its prominence to avoid competing with the strength statement.
3. Add the dosage form “Tablets” immediately following the active ingredient, Macitentan, for a complete established name presentation.
4. Delete the statement [REDACTED] (b) (4) (from the side panel) to be consistent with other immediate-release tablet formulation.
5. Delete the statement [REDACTED] (b) (4) since this route of administration is implied for a tablet formulation product.
6. Minimize the prominence of the “Rx Only” statement by unbolding to avoid distraction of important information on the principal display panel.
7. Relocate the NDC number from the side panel and ensure it is located in the upper one third of the principal display panel as per CFR 207.35(3)(i).

8. Relocate the 10 mg strength designation from the top of the principal display panel to appear directly below the established name statement and increase its prominence to avoid confusion with the net quantity information.

B. Blister Label (15-count)

1. Relocate the lot and expiration date to the lower portion of the blister label. This will allow the proprietary name, established name, and strength to be presented at the top of the label and increase the prominence of this information.
2. If space permits, relocate the 10 mg strength statement to appear directly below the established name.
3. Delete the phrase “(b) (4)” to create additional white space on the label and enhance the readability of the other information.

C. Carton Labeling (30-count bottle)

1. See comments A.1 to A.6 above.
2. Minimize or remove graphic artwork on the principal display panel to avoid distraction of important information.

D. Carton Labeling (15-count blister)

1. See comments A.1 to A.5 and C.2 above.
2. Relocate the 10 mg strength designation from the middle of the principal display panel to appear directly below the established name statement.
4. Revise the strength statement to read “10 mg per tablet” to clarify that the strength noted is for each individual tablet.

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KIMBERLY A DE FRONZO
06/13/2013

IRENE Z CHAN
06/14/2013

SCOTT M DALLAS
06/14/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 3, 2013

TO: Maryann Gordon, Medical Officer
Abraham Karkowsky, Team Leader
Ed Fromm, Regulatory Project Manager
Division of Cardio-Renal Drug Products

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

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

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204410

APPLICANT: Actelion Pharmaceuticals, Ltd.

DRUG: macitentan (Opsumit[®])

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: long-term treatment of pulmonary arterial hypertension (PAH) in adult

(b) (4)

CONSULTATION REQUEST DATE: December 31, 2012

INSPECTION SUMMARY GOAL DATE: June 28, 2013 recently requested June 4, 2013

DIVISION ACTION GOAL DATE: October 18, 2013

PDUFA DATE: October 19, 2013

I. BACKGROUND:

The Sponsor Actelion Pharmaceuticals, Inc. seeks approval to market macitentan, a new orally active, dual endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension (PAH) (b) (4). PAH is a rare disorder of the pulmonary microvasculature defined as a sustained elevation in pulmonary arterial pressure greater than or equal to 25 mmHg with a mean pulmonary capillary wedge pressure of less than or equal to 15 mmHg. Recent advances in the understanding of the pathogenic factors leading to PAH have led to the development of new therapies targeting specific pathways (the prostacyclin pathway, the endothelin pathway and the nitric oxide pathway). Seven agents are currently approved for treatment of PAH in the United States and Europe, including two endothelin receptor antagonists: Tracleer® (bosentan) and Letairis® (ambrisentan).

The development program to support macitentan for PAH is based on a single, pivotal trial: Protocol AC-055-302, entitled “SERAPHIN: Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, Phase 3 study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension.” Approximately 742 patients were randomized in a 1:1:1 ratio (macitentan 3 mg QD, macitentan 10 mg QD, placebo QD). The study included a screening phase (up to 28 days), followed by a treatment period from randomization to the End of Treatment (EOT) visit. The observation period was expected to vary between 1.0 year for the last enrolled subject and up to 4.5 years for the first subject randomized. This study was event-driven, and was concluded when the target of 285 morbidity/mortality events confirmed by the Clinical Event committee (CEC) was achieved.

The primary endpoint was the time from start of treatment to the first mortality or morbidityMM event, defined as death, atrial septotomy, lung transplant, initiation of intravenous or subcutaneous prostanoids, or other worsening PAH.

II. RESULTS (by Site):

Four clinical site inspections (three foreign, one domestic) and a Sponsor inspection were conducted to support approvability for this NDA. The three foreign sites enrolled the largest number of subjects, and had a relatively high number of deaths, protocol violations, and adverse events. The U.S. site was chosen for inspection because it was a domestic site with a high enrollment compared to other U.S. sites.

Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
Bhagatuval Kutumba Srinivasa Sastry CARE Hospitals Nampally Department of Cardiology, Hyderabad Exhibition Road, Nampally Hyderabad India 500001	AC-055-302 Site #5304 19 subjects	March 18– 21, 2013	NAI
Tomas Rene Pulido-Zamudio Instituto Nacional de Cardiologia (INC) Juan Badiano No. 1, Col Seccion XVI, Delegacion Tlalpan Mexico City, MX 14080	AC-055-302 Site #8401 22 subjects	March 25-28, 2013	Preliminary VAI (EIR pending)
Xiaofeng Zeng Peking Union Medical College Hospital, Rheumatology Department No. 41 Da Mu Cang Xidan Xicheng District Beijing, China 100032	AC-055-302 Site #5105 19 subjects	March 11–15, 2013	VAI
Murali Chakinala Washington University School of Medicine Dept. of Rheumatology 660 South Euclid Ave., Campus Box 8052 St. Louis, MO 63110-1010	AC-055-302 Site 9126 4 subjects	April 25 – 29, 2013	Preliminary NAI (EIR pending)
Actelion Pharmaceuticals, Ltd. Gewerbstrasse 16 Allschwil, BL, Switzerland	AC-055-302 Sponsor	April 15-19, 2013	Preliminary NAI (EIR pending)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Bhagatuval Kutumba Srinivasa Sastry (Site #5304)

CARE Hospitals Nampally, Department of Cardiology, Hyderabad
Exhibition Road, Nampally Hyderabad India

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 21 subjects were screened, 19 subjects randomized, and 9 subjects completed the study. There were three deaths and seven subjects who discontinued treatment early.

The FDA field investigator reviewed the case history records for 19 subjects enrolled in the study. The case history records included: informed consent documents, source records, and paper case report forms. The source records contained observations, information and data on the subject's condition at the time of study entry and during their participation in the study. The FDA field investigator compared the source documents to the data listings provided with the assignment for the primary efficacy endpoints and adverse events. The FDA field investigator audited test article accountability records, monitoring visit logs, and correspondence in the regulatory file relating to monitoring visits.

- b. **General observations/commentary:**

The case history records were organized, complete and legible.

All 19 enrolled subjects met the inclusion and exclusion criteria. There was no under-reporting of adverse events, and there were no significant discrepancies between source documents and data listings. The FDA field investigator addressed several questions from the review division during the inspection:

1) **How many subjects discontinued treatment early and were the reasons documented?**

Seven subjects discontinued treatment early, and three of these subjects enrolled into the open label study. Reasons for discontinuation were documented in the subject records as follows:

5304-03: patient was hospitalized

5304-04: MM events

5304-09: PAH worsening

5304-11: road traffic accident

5304-12: worsening right heart failure

5304-13: elevated LFTs and ultimately, worsening of right heart failure

5304-14: death

5304-17: hypotension, increased renal insufficiency, worsening liver function
5304-18: heart failure symptoms/worsening of PAH

2) Was the EOT visit conducted for subjects who discontinued early?

The End of Treatment (EOT) visit was conducted on the day of or around the time of subject discontinuation, and was documented in the subject's records. Study records also documented that subjects who discontinued treatment early were contacted by telephone to their determine health status.

No FDA 483 was issued during this inspection. The following two issues were discussed at the end of the inspection: 1) There was no source documentation for three adverse events: headache for Subject 5304-01 (onset date January 29, 2012) and Subject 5304-04 (onset date September 13, 2009); pain in legs and extremity for Subject 5304-04 (onset date September 13, 2009); 2) The Pulmonary Vascular Resistance (PVR) value was not documented in the source records for all subjects prior to randomization, although the value had been calculated and documented on a worksheet tool provided by the sponsor.

- c. **Assessment of data integrity:** The above issues are unlikely to affect the integrity of the data at this site. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of this NDA

2. Tomas Rene Pulido-Zamudio

Instituto Nacional de Cardiologia (INC), Juan Badiano No. 1, Col Seccion XVI, Delegacion Tlalpan, Mexico City, MX 14080

Note: The final establishment inspection report (EIR) has not been received from the FDA field office at the time this CIS was written. The observations noted are based on a preliminary EIR and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 24 subjects were screened, 22 subjects randomized, and seven subjects completed the study. Four subjects died during the study at this site.

The FDA field investigator compared the data listings sent with the assignment to the data maintained at the site with respect to discontinued subjects, adverse events, deaths, hospitalizations due to PAH, mortality, morbidity events, walking distances, Borg Scale for Rating of Perceived Exertion, WHO functional dyspnea index, WHO functional class, concomitant medications, protocol violations, and various laboratory parameters. The field investigator also reviewed test article accountability records, monitoring logs, and

monitoring reports.

- b. **General observations/commentary:** The FDA field investigator observed that Dr. Pulido properly delegated authority for the conduct of various aspects of the study so that he retained control and knowledge of the study throughout its duration. There were no reported discrepancies with respect to the data corroborations above. A one observational Form FDA 483 was issued for an investigation not conducted according to the investigational plan with respect to inclusion and exclusion criteria. Specifically, two subjects were enrolled who did not meet the inclusion and exclusion criteria. Subject 11354 was randomized and began treatment on October 27, 2008, although the subject did not meet inclusion criteria 4b in that a pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) was not evaluated prior to randomization. The field investigator observed that Dr. Pulido completed a protocol exemption form for this subject on October 21, 2008 stating that he was unable to perform the PCWP during the right heart catheterization (RHC), but wished to include the subject into the study. The sponsor granted the exemption. In his response letter dated April 15, 2013, Dr. Pulido reiterated that the PCWP could not be performed on this subject during the RHC procedure due to the high level of risk involved.

Subject 112852 began treatment on March 10, 2009, although the subject met exclusion criteria 8 in that she was diagnosed with moderate diffuse hepatocellular dysfunction and signs of hepatic congestion (Child-Pugh B). The inspection found that Dr. Pulido had requested an exemption from the sponsor on February 19, 2009, and that this exemption was granted. Both protocol violations were submitted to the Bioethics Committee on July 15, 2009.

The FDA field investigator addressed the following questions from the review division during the inspection:

- 1) For subjects who had worsening PAH events that occurred between two scheduled visits without hospitalization, please find out how the 6-Minute Walk Distance (6-MWD) test was scheduled and conducted between the scheduled visits.**

Subjects were seen at the site once a month for the protocol-mandated monthly laboratory tests. During these visits, the subjects were asked about their health status, any symptoms of worsening, or any AEs. According to Dr. Pulido, if any sign of worsening was detected, a 6-MWD test was performed. Subjects were also told to contact the investigators in case they felt any worse, and, if considered necessary, they were requested to come to the site to perform the 6-MWD and any other assessments deemed necessary.

2) Please explain the process for a subject who deteriorated between scheduled visits. Was the 6MWD test performed after any new therapies were begun?

It appeared that subjects who deteriorated did not start new therapies. Instead, they were rolled over to the open-label extension study after confirmation of the worsening event.

3) Oral phosphodiesterate inhibitors (e.g. sildenafil, vardenafil, tadalafil, etc.) were allowed during the study if present for at least 3 months before randomization at a stable dose. As per protocol, the dose of PDE-5 should remain unchanged during the study. For any subjects, did the site increase the dose of PDE-5 at any time during the trial? Please pay attention particularly to dose changes at the time of clinical worsening.

Subject 11850 was increased from 25mg to 50mg (PDE inhibitor unspecified) three times a day on (b) (6). The subject was hospitalized as indicated by the physicians attending a hospitalization, due to a SAE of clinical worsening of PAH, which did not appear to meet the protocol worsening event criteria. Per Dr. Pulido, assessments for worsening events were done before increasing the dose.

4) How many subjects discontinued treatment early and were the reasons documented? Please select several subjects who discontinued and describe their reasons. Were end of treatment (EOT) visits conducted at the time of discontinuation, as required by the protocol? At the end of study (EOS) were subjects who discontinued early contacted for vital status, as required by the protocol?

Fifteen subjects did not complete the study treatment. All subjects alive at the time of the EOS were contacted for vital status except Subject 11854 who withdrew consent. For subjects who discontinued treatment after a worsening event and did not undergo a formal EOT visit, most EOT assessments were performed at the time of the worsening event. Specific cases are given below.

11351: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation.

11352: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation.

11353: Discontinued treatment after a worsening event, EOT visit performed.

11585: Discontinued treatment after a worsening event, EOT visit performed.

11586: Died.

11587: Discontinued treatment due to LFTs increase, EOT visit performed.

11588: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation.

11589: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation, died before EOS.

11851: Died.

11853: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation.

11855: Died.

11854: Withdrew consent, therefore not contacted at EOS, EOT labs performed, patient did not agree to a complete visit.

14723: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation, died before EOS.

14736: Discontinued treatment after a worsening event, EOT visit performed.

15468: Discontinued treatment after a worsening event, no EOT visit at the time of treatment discontinuation.

- c. **Assessment of data integrity:** Although 2 of 22 subjects did not meet inclusion and exclusion criteria and were randomized, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the NDA.

3. Xiaofeng Zeng

Peking Union Medical College Hospital, Rheumatology Department
No. 41 Da Mu Cang Xidan, Xicheng District
Beijing, China 100032

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 21 subjects were screened, 19 subjects randomized, and 10 subjects completed the study. For the nine subjects who did not complete the study, seven subjects experienced a MM event, and two subjects died.

The FDA field investigator conducted a review and data audit of the case history records for 19 subjects enrolled in the study. The case history records included: informed consent documents, source records, and paper case report forms. The source records contained observations, information, and data on the subject's condition at the time of study entry and during their participation in the study. The FDA field investigator compared the source documents to the data listings provided with the assignment for the primary efficacy endpoints and adverse events. The FDA field investigator audited test article accountability records, monitoring visit logs, and correspondence in the regulatory file relating to monitoring visits.

- b. **General observations/commentary:** Case history records were organized and complete. A total of 16 of 19 subjects met the inclusion and exclusion criteria. For the three subjects who did not meet the inclusion and exclusion criteria, hemodynamic measurements of PCWP or LVEDP were not obtained within one year prior to randomization, as per the protocol. There was no under-reporting of adverse events, and there were no significant discrepancies between source documents and data listings. Concerning test article accountability records, the FDA field investigator noted

that seven subjects were administered the test article the day following the randomization visit. The protocol (Section 3.3.3) required that the first intake of study drug would take place at the randomization visit after completion of all assessments. This latter finding is unlikely to affect the integrity of the data at this site.

A one-observational Form FDA-483 was issued at the end of the inspection for an investigation not conducted in accordance with the investigational plan. Specifically, three subjects (5105-01, 5105-03, and 5105-06) had right heart catheterization (RHC) procedures performed prior to randomization, but no Pulmonary Capillary Wedge Pressure (PCWP) was obtained during the procedure due to reportedly high pulmonary artery pressure for these subjects. These subjects were enrolled although they did not meet the inclusion criteria #4b, which required a diagnosis of PAH confirmed by PCWP or LVEDP measurement ≤ 15 mmHg performed within one year of randomization. The sponsor and the Ethics Committee were notified by letter for each subject, and documentation was collected during the inspection concerning the site's inability to obtain the PCWP for all three subjects.

In his March 29, 2013 response letter to the Form FDA 483 observation, Dr. Zeng states that the cardiologist who conducted the RHC tried to obtain the PCWP under the guidance of X-ray but did not succeed, and felt it unethical to repeat this invasive procedure a second time. Further, Dr. Zeng indicated that the site is not equipped to obtain Left ventricular end diastolic pressure (LVEDP) as an alternative measurement to PCWP. Dr. Maryann Gordon, Medical Officer, was notified of this observation and responded by email on April 2, 2013 that she finds Dr. Zeng's response acceptable.

The following questions from the review division were included in the field assignment. Responses to these questions by the FDA field investigator are provided below.

1. How was the 6MWD administered if subjects were hospitalized during visits?

Although more subjects were hospitalized, the FDA field investigator provided examples for only two subjects who were hospitalized and for which the 6MWD was not administered. For the following two examples, 6MWD was not administered because the subjects were too ill to perform the test. It is not known if the 6MWD was administered for other subjects who were hospitalized.

- a. Subject 5105-01 had worsening PAH during a scheduled visit. This subject was sent to the emergency room and treated with IV furosemide and sildenafil. The subject did not complete a 6-MWT because it would not have been appropriate to do so.*
- b. Subject 5105-15 was hospitalized at a hospital other than PUMC Hospital, where the study took place. The site contacted the physician at the hospital to have a 6MWT done, but the physician thought performing a 6MWT would put the subject at risk.*

2. Explain the process for a subject who deteriorated between scheduled visits – was the 6MWT test performed after new therapies were begun?

If a subject deteriorated between visits, or if the subject was treated with a new therapy, a 6MWT would be performed unless the subject's condition prevented them from doing so.

3. For any subjects, did the site increase the dose of phosphodiesterase inhibitors during the trial, especially during the time of clinical worsening?

No oral phosphodiesterase inhibitors (i.e., sildenafil, vardenafil, tadalafil) were increased for any subjects during the study. Some subjects were taken off sildenafil because their families could not afford this drug.

4. How many subjects discontinued early from the study? Was the reason documented?

Seven subjects discontinued early from the study due to a MM event and were subsequently enrolled into the open label study. According to an e-mail from the FDA investigator, she noted that the reasons for a subject's discontinuation were documented in the study records, but the FDA investigator did not record them in the inspection summary.

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

4. Murali Chakinala

Washington University
School of Medicine
Dept. of Rheumatology
660 South Euclid Ave., Campus Box 8052
St. Louis, MO 63110-1010

Note: The EIR was not available at the time this CIS was written. The summary below is based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, five subjects were screened, four subjects enrolled, and four subjects completed the study. The FDA field investigator reviewed study records for all four subjects enrolled.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events, and the primary efficacy variable was verifiable. The study data was organized, and the field investigator did not note any deviations from the protocol, nor any issues concerning inadequate records or recordkeeping. No FDA 483 was issued.

In response to questions from the review division, the following responses were provided by the FDA field investigator:

- there were no worsening PAH events,
- no new PAH therapies were administered,
- there was no increase in use of phosphodiesterase inhibitors,
- no subjects discontinued early from the study.

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

5. Actelion Pharmaceuticals Ltd

Gewerbestrasse 16
CH-4123 Allschwil, Switzerland

Note: The EIR was not available at the time this CIS was written. The summary below is based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.810 for sponsors, contract research organizations, and monitors. The inspection focused on four (of 179 clinical investigator sites) involved with SERAPHIN:

- Site #5304: Dr. Bhagatuval Kutumba Srinivasa Sastry, Hyderabad, India (19 subjects)
- Site #8401: Dr. Tomas Rene Pulido-Zamudio, Mexico City, Mexico (22 subjects)
- Site #5105: Dr. Xiaofeng Zeng, Beijing, China (19 subjects)
- Site #9126: Dr. Murali Chakinala, St. Louis, MO, USA (4 subjects)

The sponsor inspection covered the following areas:

- organization and personnel
- registration with ClinicalTrials.gov
- selection and monitoring of clinical investigators
- selection of monitors, monitoring procedures and activities
- quality assurance
- adverse event reporting
- data collection and handling
- record retention
- financial disclosure
- test article integrity and accountability
- specific questions included with the assignment

- b. **General observations/commentary:** The FDA field investigator found no deficiencies concerning monitoring activities, adverse event reporting, and

comparison of data listings to case report forms for selected subjects. Regarding quality assurance (QA), he found that the firm performed audits of clinical investigators both at random (including factors such as the number of subjects or adverse events) and on a for-cause basis. There were 15 subjects whose dose of PDE-5 was increased during the study. Although exact information was not given, a likely reason for an increase in the PDE-5 medication was because of worsening PAH symptoms, a component of this primary efficacy endpoint. There were three subjects whose dose was changed but it is unknown whether these changes were increases or decreases. These were reported as protocol violations.

The FDA field investigator found no examples of inadequate monitoring. The monitoring included 100% source document verification, which would note if a subject discontinued from the study. Early discontinuation by subjects was documented in all of the case report forms (CRFs) that he reviewed. At the end of the study subjects who discontinued early were contacted for vital status by the investigator in all cases that the field investigator reviewed.

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

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites (three foreign, one domestic) and the Sponsor were inspected in support of NDA 204410. No regulatory violations were found during the inspections at two clinical investigator sites (Dr. Bhagatuval KS Sastry, India and Dr. Murali Chakinala, U.S.), and no Form FDA- 483 was issued. The inspection of Dr. Xiaofeng Zeng (China) and Dr. Tomas Pulido Zamudio (Mexico City) were classified as VAI, and a one observation, Form FDA-483 was issued for failure to follow the investigational plan with respect to enrollment of several subjects who did not meet inclusion and exclusion criteria.

Although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable based on available information.

Note: The EIRs for Site #8401 (Pulido, Mexico City), Site #9126 (Chakinala, U.S.) and the Sponsor (Actelion, Switzerland) were not available at the time this CIS was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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

CONCURRENCE:

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/s/

SHARON K GERSHON
06/03/2013

SUSAN D THOMPSON
06/03/2013

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

NDA	204410
Brand Name	Opsumit
Generic Name	Macitentan (ACT-064992)
Sponsor	Actelion Pharmaceuticals Ltd
Indication	Pulmonary Arterial Hypertension
Dosage Form	Tablets
Drug Class	Endothelin Receptor Antagonists
Therapeutic Dosing Regimen	10 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	30 mg
Submission Number and Date	SDN 001/19 Oct 2012
Review Division	DCRP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of macitentan (doses of 10 mg and 30 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between macitentan and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.

In this randomized, double-blind, randomized, placebo controlled, four-way crossover study, 64 healthy subjects received macitentan 10 mg, macitentan 30 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Macitentan (10 mg and 30 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Macitentan 10 mg	3	5.3	(2.6, 8.0)
Macitentan 30 mg	1	5.4	(2.6, 8.1)
Moxifloxacin 400 mg*	1	12.9	(10.1, 15.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.1 ms

The suprathreshold dose (30 mg macitentan) produces mean C_{\max} values of 3.1-fold that of the mean C_{\max} for the therapeutic dose (10 mg macitentan). These concentrations are above those for the predicted worst case scenario (drug interaction with ketoconazole) and show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of macitentan with ketoconazole can elevate macitentan's mean C_{\max} as much as 2.0-fold that of the C_{\max} of the 10-mg dose. In hepatically impaired patients, the PK of macitentan and ACT-132577 are not affected.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

Cardiac Electrophysiology

In a randomized, placebo-controlled four-way crossover study with a positive control in healthy subjects, repeated doses of 10 mg and 30 mg macitentan had no significant effect on the QTc interval.

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT recommended labeling language is provided below. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

At a dose 3 times the maximum recommended dose, macitentan does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Macitentan is an orally active, nonpeptide, potent dual endothelin (ET) ETA and ETB receptor antagonist selected for clinical development.

3.2 MARKET APPROVAL STATUS

Macitentan is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From QT-IRT review (Feb 16 2011)

Reviewer's comments: Macitentan slightly inhibited hERG currents at concentrations ≥ 50 -fold the C_{max} human exposure after a single 600-mg dose. Macitentan's metabolite, ACT-132577, has lower affinity than the parent compound, its IC_{50} for hERG current is ≥ 100 -fold the expected C_{max} human exposure.

3.4 PREVIOUS CLINICAL EXPERIENCE

From Summary of Clinical Safety (eCTD 2.7.4)

This integrated safety analysis comprises placebo-controlled data for a total of 863 patients who received macitentan treatment and 370 patients who received placebo in Phase 2 and 3 randomized, double-blind, placebo-controlled studies for a period of up to 188 weeks. This represents a total of 1120 patient-years exposure to macitentan treatment and 484 patient-years exposure to placebo treatment. In the pulmonary arterial hypertension (PAH) indication, 492 patients were exposed to macitentan treatment and 249 were exposed to placebo treatment during the double-blind study period. Of the patients who received double-blind macitentan treatment in the PAH indication, 367 continued into an open-label extension study to receive macitentan 10 mg once daily (o.d.) treatment, along with 183 patients who switched from placebo treatment to macitentan 10 mg o.d. Overall 1046 patients have been exposed to macitentan in the double-blind studies and in the ongoing open-label PAH study (up to 26 April 2012), representing a total of 1482 patient years exposure.

The double-blind, placebo-controlled macitentan safety population comprised patients aged from 12 to 84 years, and included 13 adolescents (12–17 years), 668 adults (18–64 years) and 182 elderly adults (≥ 65 years).

Fatal AEs, SAEs and AEs leading to discontinuation of treatment were predominantly related to events associated with the underlying disease, and were reported less frequently on macitentan than on placebo, particularly at the 10 mg dose.

Reviewer's comments: An integrated analysis conducted in locally read ECGs did not show clinically relevant differences in the macitentan groups compared to the placebo group. There are no $QTcF > 500$ ms reported, no seizures or ventricular arrhythmias were reported. Most of the ECG findings are linked to underlying disease. There are sudden cardiac death,

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 77,258. The sponsor submitted the study report AC-005-114 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A double-blind, randomized, placebo controlled, four-way crossover Phase 1 study including an open-label positive control (moxifloxacin) to assess the effect of repeated daily doses of 10 mg and 30 mg macitentan on the QT/QTc interval of the ECG in healthy male and female subjects

4.2.2 Protocol Number

AC-005-114

4.2.3 Study Dates

Initiation Date: 16 August 2011

Completion Date: 30 november 2011

4.2.4 Objectives

Primary objective: To demonstrate that macitentan does not have an effect on cardiac repolarization exceeding the threshold of regulatory concern, as measured by the corrected QT (QTc) interval after repeated administration of daily oral doses of 10 and 30 mg to healthy male and female subjects.

Secondary objectives:

- To evaluate the safety and tolerability of macitentan and its metabolite ACT-132577 after repeated administration of daily oral doses of 10 and 30 mg to healthy male and female subjects.
- To evaluate the pharmacokinetics (PK) of macitentan and its metabolite ACT-132577 after repeated administration of daily oral doses of 10 and 30 mg to healthy male and female subjects.
- To assess the time course of QTc interval effect in relation to plasma levels of macitentan and its metabolite ACT-132577 using concentration-effect modeling.

4.2.5 Study Description

4.2.5.1 Design

This was a prospective, single-center, double-blind (except for the use of moxifloxacin), randomized, placebo-controlled, four-way crossover Phase 1 study in healthy male and female subjects.

The clinical study consisted of 3 parts:

- An ambulatory screening period from Day -21 to -10 before the first administration of any study treatment (Day 1)
- An experimental part consisting of four treatment periods (each from Day -1 to Day 9, with randomized study treatment administered from Day 1 to Day 8, with at least 10 days wash-out between the last administration of study treatment in the previous treatment period and the first administration of study treatment in the following period)

- A safety follow-up (telephone call) 30 ± 1 days after the last administration of study treatment during the last treatment period.

Subjects were randomized to one of 8 treatment sequences, with all subjects to receive all four study treatments in sequential treatment periods. The total duration of the clinical study for each subject was about 114 days.

4.2.5.2 Controls

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

4.2.5.3 Blinding

Moxifloxacin was administered as an open-label manner.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

During each treatment period, subjects received 1 of 4 treatments:

Treatment A: Moxifloxacin (positive control). Subjects received 3 placebo tablets once daily on Days 1–7. On Day 8, subjects received 1 moxifloxacin 400 mg tablet and 2 macitentan-matching placebo tablets.

Treatment B: Macitentan 10 mg. Subjects received 1 macitentan 10 mg tablet and 2 placebo tablets once daily on Days 1–8.

Treatment C: Macitentan 30 mg. Subjects received 3 macitentan 10 mg tablets once daily on Days 1–8.

Treatment D: Placebo. Subjects received 3 placebo tablets on Days 1–8.

4.2.6.2 Sponsor's Justification for Doses

The sponsor proposes to use a therapeutic dose of 10 mg macitentan and a suprathreshold dose of 30 mg based on the following considerations:

- The currently foreseen therapeutic dose will be 10 mg macitentan at maximum. In the current Phase 3 study (SERAPHIN - Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) in the indication of pulmonary arterial hypertension (PAH), dose levels of 3 and 10 mg once daily are tested. The therapeutic dose(s) will be determined at the end of this study.
- Multiple doses above 30 mg daily are likely to be associated with an unfavorable risk profile for healthy subjects. Like other endothelin receptor antagonists (ERA), macitentan may cause liver enzyme elevations in some subjects. In the multiple ascending-dose study in healthy subjects ([Study AC-055-102](#)), dose levels of 1, 3, 10, and 30 mg macitentan once daily were administered for 10 days. Review of the summary statistics revealed a trend for increased mean levels of the liver aminotransferases, aspartate aminotransferase (AST) and alanine transaminase (ALT), compared to baseline in the groups treated with 10 and 30 mg macitentan. One subject in the 30 mg dose group presented with increases in AST and ALT of approximately 2 and 3 \times upper limit of normal (ULN),

- respectively. In patient studies with macitentan in Phase 2 and 3, several cases of elevations in ALT and/or AST $> 3 \times$ ULN have been reported.
- There are no drug-drug interactions expected to increase exposure to greater than 2-fold. Macitentan is a substrate of cytochrome P450 (CYP) 3A4. Further, CYP3A4 is the major contributor to formation of the active metabolite ACT-132577. In the presence of ketoconazole, an approximately 2-fold increase in exposure in terms of AUC_{0-∞}. (Study AC-055-107) of macitentan was observed, whereas the effect on ACT-132577 exposure was negligible. Concomitant treatment with cyclosporine did not have any clinically relevant effect on the exposure to macitentan or ACT-132577.
 - The pharmacokinetics (PK) of macitentan and ACT-132577 are dose-proportional and are not influenced by food, sex, age, or race. In hepatically impaired patients, the PK of macitentan and ACT-132577 are not affected. In severe renal function impairment (SRFI) patients, the PK of macitentan is not affected to a clinically relevant extent, whereas the exposure to ACT-132577 increased up to 1.6-fold.

Based on the above, the 30 mg macitentan dose will evaluate the pharmacological effect on cardiac repolarization, as detected by QT/QTc prolongation, at substantial multiples of the anticipated maximum therapeutic dose of 10 mg macitentan.

Reviewer's Comment: The sponsor's rationale for the selected therapeutic dose and supratherapeutic dose appears to be reasonable.

4.2.6.3 Instructions with Regard to Meals

Doses will be administered with food. Meals are to be consumed and doses taken at the same time on each occasion.

Reviewer's Comment: The sponsor indicated no apparent food effect. Therefore, macitentan can be given with or without food.

4.2.6.4 ECG and PK Assessments

Schedule of assessment is presented in Appendix 6.2. On Day 8, macitentan and metabolite PK samples were collected at 3, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after macitentan administration; and 12-lead Holter ECG data were assessed at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after macitentan administration. PK sample and 12-lead Holter ECG data were also collected on Day 1 for baseline assessment. Pre-dose PK samples were collected daily from Day 2 to Day 8 to ensure macitentan was taken every day.

Reviewer's Comment: The sponsor's timing schedule for PK and ECG assessment appears to be reasonable. Geometric mean T_{max} is 8.5 hours for both macitentan and the metabolite after macitentan oral administration.

4.2.6.5 Baseline

The sponsor used pre-dose on Day 1 as baseline.

4.2.7 ECG Collection

Electrocardiogram data were obtained from continuous 12-lead Holter ECG recordings. Devices, procedures, and ECG evaluation were managed by the central ECG laboratory, (b) (4) ECG data were interpreted by a board-certified cardiologist at

the central ECG laboratory. The cardiologist assessed 1 ECG at each time point, selected randomly from the triplicate recordings at each time point. All ECGs from any single subject were assessed by the same cardiologist.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

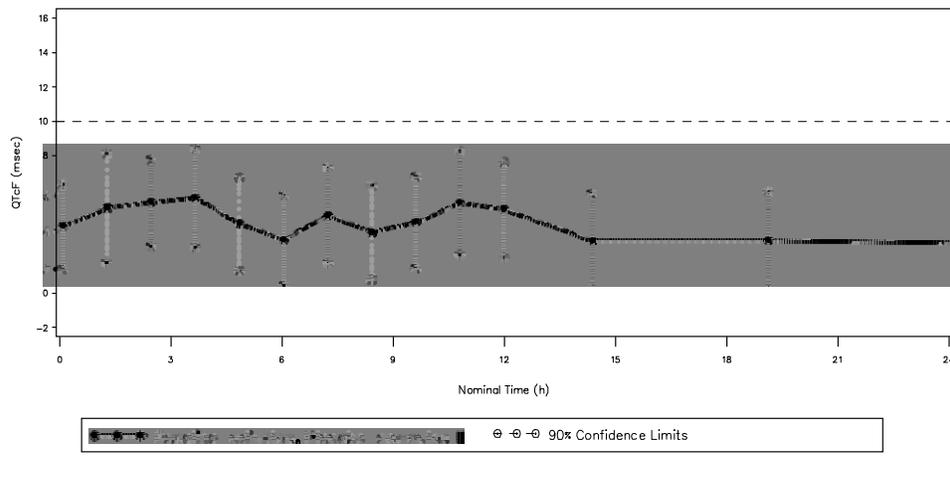
A total of 64 subjects (26 males and 38 females) were enrolled. All 64 subjects received at least 1 dose of study treatment, and 63 subjects completed the clinical study per protocol. Only Subject 160 withdrew consent, for personal reasons, after completing Treatment Period 2.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between macitentan (10 mg and 30 mg) and placebo in QTcF. The sponsor used mixed model and the results are presented in Figure 1 and Figure 2. The upper limits of the 2-sided 90% CI for macitentan (10 mg and 30 mg) were below 10 ms.

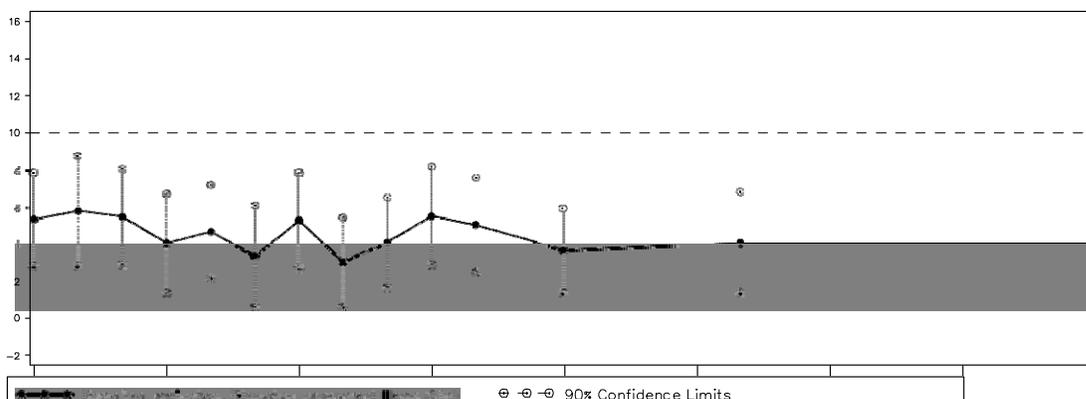
Figure 1: Sponsor Results $\Delta \Delta$ QTcF and 90% CI for Macitentan 10 mg



Section 11.1.1.1, Figure 5, Pg 76/6978

Figure 2: Sponsor Results $\Delta \Delta$ QTcF and 90% CI for Macitentan 30 mg

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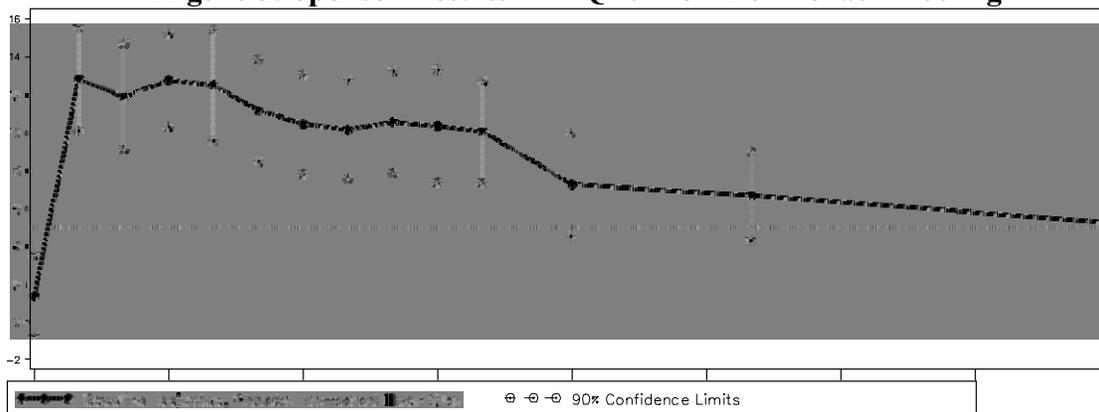
Source: Clinical Study Report No., Section 11.1.1.1, Figure 6, Pg 77/6978

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

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the Δ QTcF effect for moxifloxacin. The analysis results was presented in Figure 3. The lower limit of the two-sided 97.5% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Figure 3: Sponsor Results Δ Δ QTcF for Moxifloxacin 400 mg



Source: Clinical Study Report No., Section 11.1.1.1, Figure 7, Pg 78/6978

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

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.8.3 Safety Analysis

During each treatment period, the most frequent treatment-emergent AE was headache, which was more frequent on macitentan 30 mg (27 subjects, 42.2%) and 10 mg (14 subjects, 22.2%) than on moxifloxacin (7 subjects, 11.1%) or placebo (7 subjects,

10.9%). The incidence of headache with macitentan appeared to be dose related. Other treatment-emergent AEs with a relatively high incidence were nasopharyngitis, fatigue, nausea, and dizziness. Nasopharyngitis was more frequently reported after treatment with macitentan 10 mg (8 subjects, 12.7%) and 30 mg (6 subjects, 9.4%) than placebo (4 subjects, 6.3%) and moxifloxacin (4 subjects, 6.3%). Nausea was mostly reported after treatment with moxifloxacin (5 subjects, 7.9%) but also reported after treatment with 30 mg macitentan (2 subjects, 3.1%) and placebo (1 subject, 1.6 %). No nausea was reported after treatment with macitentan 10 mg. Fatigue and dizziness were reported with similar frequency across treatments.

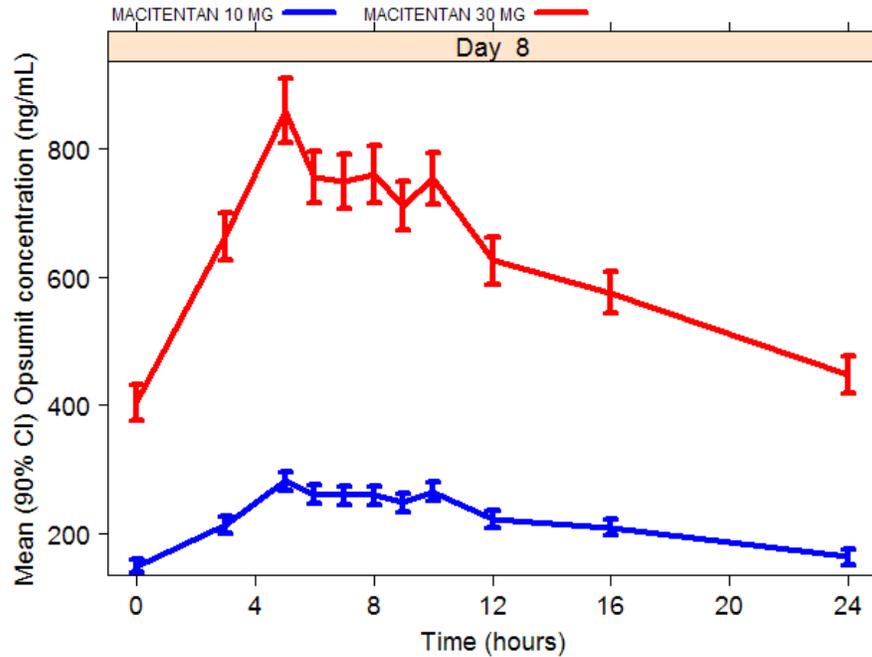
Treatment-emergent AEs considered to be related to the study drug were reported for 21 (33.3%) subjects with moxifloxacin, for 15 (23.8%) subjects with 10 mg macitentan, for 29 (45.3%) subjects with 30 mg macitentan, and for 14 (21.9%) subjects taking placebo. No deaths, other SAEs, or other significant AEs occurred during this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

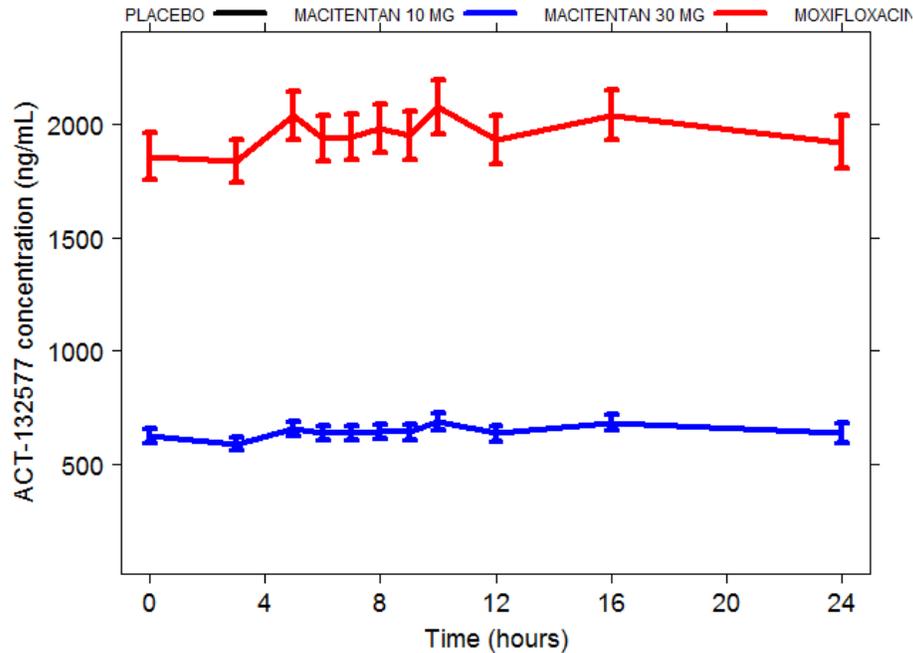
Mean concentration-time profiles of macitentan and ACT-132577 at the two dose levels are shown in Figure 4 and Figure 5. Geometric mean PK parameters are shown in Table 2. The geometric mean values of $AUC_{0-\tau}$ and C_{max} of macitentan for the suprathereapeutic dose of 30 mg were both about 3 times of that for the therapeutic dose of 10 mg, demonstrating dose-proportional pharmacokinetics. The geometric mean values of $AUC_{0-\tau}$ and C_{max} of ACT-132577 (the macitentan metabolite) for the suprathereapeutic dose of 30 mg were both about 3 times of that for the therapeutic dose of 10 mg, demonstrating dose-proportional pharmacokinetics of the metabolite.

Figure 4: Plasma Macitentan Concentration versus Time Profile on Day 8.



Source: FDA reviewer's QT analysis

Figure 5: Plasma ACT-132577 (macitentan metabolite) Concentration versus Time Profile on Day 8.



Source: FDA reviewer's QT analysis

Table 2: Pharmacokinetic Parameters of Macitentan and ACT-132577

Analyte	Treatment	N	C _{max} (ng/mL)	t _{max} (h)	AUC _t (h*ng/mL)
Macitentan	B	62	292.0 (273.3 , 312.0)	6.0 (0 - 12)	4958.12 (4605.33 , 5337.93)
	C	62	845.0 (792.0 , 901.6)	5.0 (3 - 12)	14240.95 (13369.26 , 15169.47)
ACT-132577	B	62	715.5 (673.5 , 760.0)	10.0 (0 - 24)	15140.75 (14289.68 , 16042.51)
	C	62	2119.9 (1991.1 , 2257.1)	10.0 (0 - 24)	45619.16 (42881.72 , 48531.35)

Treatment B: 10mg Macitentan C: 30mg Macitentan

Data are geometric means (and 95% CI) and for t_{max} the median (and range).

Source: Sponsor's Study Report for Protocol AC-055-114, Page 111.

4.2.8.4.2 Exposure-Response Analysis

The linear mixed pharmacokinetic/pharmacodynamics model shows that there was no statistically significant relationship between macitentan plasma concentration and QTcF. The estimate (SE) of the effect of the macitentan plasma concentration (ng/mL) on the difference between macitentan and placebo in change from baseline in QTcF (ms) was -0.000422 (0.002582) ms and not statistically significant (p = 0.871).

There was no statistically significant relationship between ACT-132577 (macitentan metabolite) plasma concentration and QTcF. The estimate (SE) of the effect of the macitentan plasma concentration (ng/mL) on the difference between macitentan and placebo in change from baseline in QTcF (ms) was -0.000238 (0.001033) ms and not statistically significant (p = 0.818).

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ versus macitentan concentration is presented in Figure 8. A plot of $\Delta\Delta QTcF$ versus ACT-132577 concentration is presented in Figure 9.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

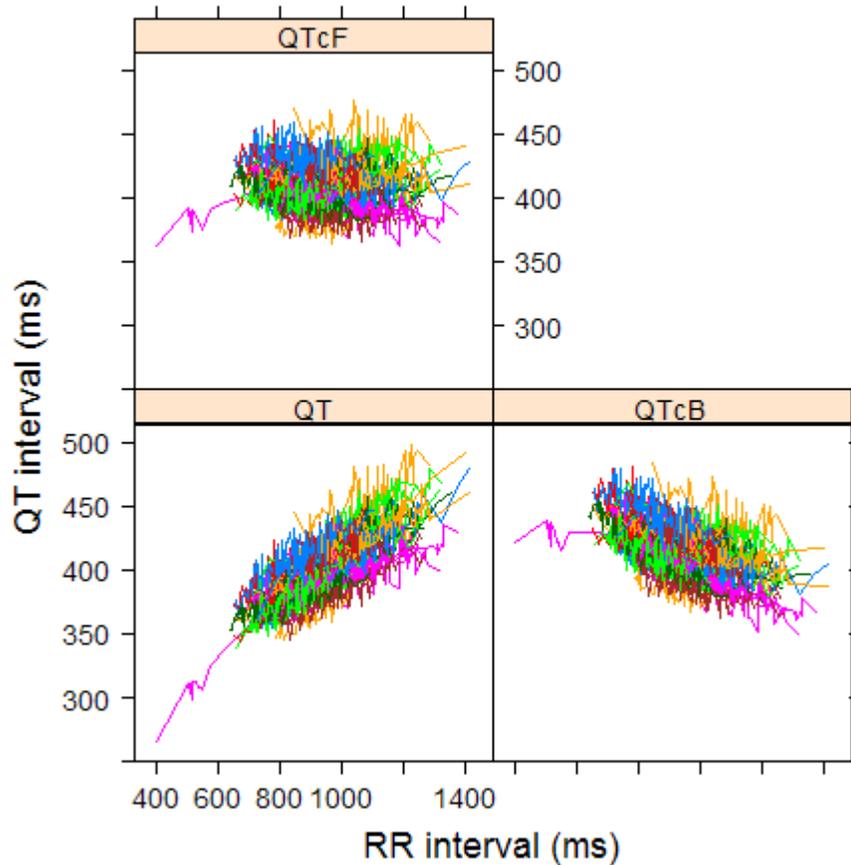
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcF is better than QTcB. To be consistent with the sponsor's analyses, we choose to present QTcF results.

Table 3: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
MACITENTAN 10 MG	63	0.0058	63	0.0015
MACITENTAN 30 MG	64	0.0051	64	0.0018
MOXIFLOXACIN 400 MG	63	0.0066	63	0.0013
PLACEBO	64	0.0047	64	0.0012
All	64	0.0052	64	0.0009

The QT-RR interval relationship is presented in Figure 6 together with the Bazett's (QTcB) and Fridericia (QTcF).

Figure 6: QT, QTcB, QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean differences between macitentan 10 mg and placebo, and between macitentan 30 mg and placebo are 8.0 ms and 4.1 ms, respectively.

Table 4: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Macitentan 10 mg, Macitentan 30 mg and Moxifloxacin 400 mg

	Placebo	MACITENTAN 10 MG				MACITENTAN 30 MG				MOXIFLOXACIN 400 MG				
	Δ QTcF	Δ QTcF		Δ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	*Adj. 90% CI
1	-6.9	62	-1.9	5.0	(2.2, 7.8)	64	-1.5	5.4	(2.6, 8.1)	63	6.0	12.9	(10.1, 15.6)	(9.1, 16.7)
2	-6.6	62	-1.5	5.1	(2.3, 7.9)	64	-1.8	4.9	(2.1, 7.6)	63	5.0	11.6	(8.9, 14.4)	(7.9, 15.4)
3	-9.9	62	-4.6	5.3	(2.6, 8.0)	64	-6.4	3.5	(0.9, 6.2)	63	2.8	12.7	(10.1, 15.4)	(9.1, 16.4)
4	-12.1	62	-7.8	4.3	(1.6, 7.0)	64	-7.8	4.3	(1.6, 6.9)	63	0.3	12.4	(9.7, 15.1)	(8.8, 16.1)
5	-10.8	62	-7.6	3.2	(0.6, 5.8)	64	-8.3	2.5	(-0.0, 5.1)	63	0.3	11.1	(8.5, 13.7)	(7.6, 14.6)
6	-13.2	62	-9.2	4.0	(1.6, 6.4)	64	-8.7	4.5	(2.1, 6.8)	63	-2.9	10.3	(7.9, 12.7)	(7.1, 13.5)
7	-11.6	62	-7.9	3.7	(1.3, 6.2)	64	-8.9	2.7	(0.3, 5.1)	63	-1.6	10.1	(7.7, 12.5)	(6.8, 13.3)
8	-11.9	62	-7.4	4.5	(2.0, 7.0)	64	-8.4	3.5	(1.0, 6.0)	63	-1.3	10.5	(8.1, 13.0)	(7.2, 13.9)
9	-13.5	62	-8.4	5.1	(2.5, 7.7)	64	-8.5	5.0	(2.5, 7.5)	63	-3.3	10.2	(7.7, 12.7)	(6.7, 13.7)
10	-11.5	62	-7.2	4.4	(1.8, 7.0)	64	-6.8	4.7	(2.2, 7.3)	63	-1.6	9.9	(7.3, 12.5)	(6.4, 13.4)
12	-9.0	62	-6.1	3.0	(0.3, 5.6)	64	-5.8	3.3	(0.7, 5.9)	63	-2.1	7.0	(4.4, 9.6)	(3.4, 10.5)
16	-2.8	62	0.9	3.7	(0.9, 6.6)	64	1.2	4.0	(1.2, 6.7)	64	4.3	7.1	(4.3, 9.9)	(3.3, 10.9)
24	-7.4	60	-4.7	2.7	(0.3, 5.1)	64	-4.0	3.4	(1.0, 5.7)	62	-2.0	5.3	(3.0, 7.7)	(2.1, 8.5)

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

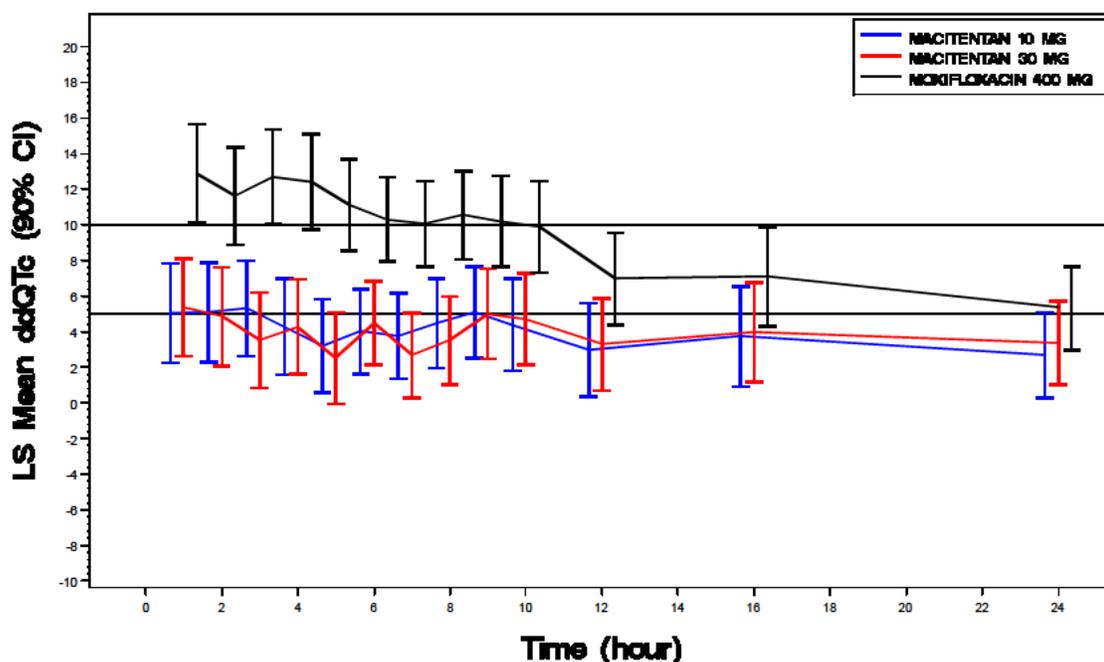
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 4. The largest unadjusted 90% lower confidence interval is 10.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.1 ms, which indicates that an at least 5-ms QTcF effect of moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcF over Time

Figure 7 displays the time profile of $\Delta\Delta$ QTcF for different treatment groups and moxifloxacin 400 mg.

Figure 7: Mean and 90% CI $\Delta\Delta$ QTcF Time Course for Macitentan 10 mg, Macitentan 30 mg and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms and between 450 ms and 480 m. No subject's QTcF was above 480 ms. No subject's change from baseline was above 60 ms.

Table 5: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
MACITENTAN 10 MG	62	60 (96.8%)	2 (3.2%)
MACITENTAN 30 MG	64	61 (95.3%)	3 (4.7%)
MOXIFLOXACIN 400 MG	63	59 (93.7%)	4 (6.3%)
PLACEBO	64	63 (98.4%)	1 (1.6%)

Table 6: Categorical Analysis for Δ QTcF

Treatment Group	Total N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms
MACITENTAN 10 MG	61	60 (98.4%)	1 (1.6%)
MACITENTAN 30 MG	64	64 (100%)	0 (0.0%)
MOXIFLOXACIN 400 MG	63	62 (98.4%)	1 (1.6%)
PLACEBO	64	64 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between macitentan 10 mg and placebo, and between macitentan 30 mg and placebo are 6.9 bpm and 9.0 bpm, respectively. Table 8 presents the categorical analysis of HR. One subject who experienced HR interval greater than 100 bpm was in macitentan 10-mg group.

Table 7: Analysis Results of Δ HR and $\Delta\Delta$ HR for Macitentan 10 mg, Macitentan 30 mg, and Moxifloxacin 400 mg

Time (h)	PLACEBO	MACITENTAN 10 MG				MACITENTAN 30 MG				MOXIFLOXACIN 400 MG			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.1	62	4.5	4.7	(2.4, 6.9)	64	6.1	6.3	(4.1, 8.5)	63	2.9	3.0	(0.8, 5.3)
2	9.7	62	13.0	3.3	(1.3, 5.3)	64	14.9	5.2	(3.2, 7.2)	63	8.3	-1.4	(-3.5, 0.6)
3	7.4	62	10.8	3.4	(1.4, 5.4)	64	12.0	4.6	(2.6, 6.6)	63	7.3	-0.1	(-2.1, 1.9)
4	4.2	62	9.3	5.1	(3.1, 7.2)	64	11.1	6.9	(4.9, 8.9)	63	6.0	1.9	(-0.2, 3.9)
5	3.2	62	6.8	3.7	(1.7, 5.7)	64	9.7	6.5	(4.5, 8.5)	63	4.7	1.5	(-0.4, 3.5)
6	7.1	62	10.6	3.5	(1.6, 5.5)	64	13.4	6.3	(4.4, 8.2)	63	8.2	1.1	(-0.8, 3.1)
7	5.2	62	8.8	3.5	(1.6, 5.5)	64	11.3	6.0	(4.1, 7.9)	63	6.4	1.1	(-0.8, 3.1)
8	2.5	62	6.4	3.9	(2.1, 5.8)	64	9.2	6.7	(4.9, 8.5)	63	3.6	1.1	(-0.7, 2.9)
9	1.9	62	6.6	4.8	(2.8, 6.7)	64	9.2	7.3	(5.4, 9.2)	63	3.1	1.3	(-0.7, 3.2)
10	1.5	62	5.4	3.8	(2.0, 5.7)	64	7.9	6.4	(4.5, 8.2)	63	2.5	1.0	(-0.8, 2.9)
12	6.7	62	10.6	3.8	(1.9, 5.8)	64	13.1	6.4	(4.4, 8.3)	63	8.1	1.4	(-0.6, 3.3)
16	0.1	62	4.2	4.2	(2.2, 6.2)	64	7.1	7.0	(5.1, 9.0)	64	0.7	0.7	(-1.3, 2.7)
24	3.6	60	6.6	3.0	(1.1, 4.8)	64	8.8	5.2	(3.4, 7.0)	62	3.7	0.1	(-1.7, 1.9)

Table 8: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR \geq 100 bpm
MACITENTAN 10 MG	62	61 (98.4%)	1 (1.6%)
MACITENTAN 30 MG	64	64 (100%)	0 (0.0%)
MOXIFLOXACIN 400 MG	63	63 (100%)	0 (0.0%)
PLACEBO	64	64 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean differences between macitentan 10 mg and placebo, and between macitentan 30 mg and placebo are 3.9 ms and 0.6 ms, respectively. Table 10 presents the categorical analysis of PR. Ten subjects who experienced PR interval greater than 200 ms were in both macitentan 10-mg and 30-mg groups.

Table 9: Analysis Results of Δ PR and $\Delta\Delta$ PR for Macitentan 10 mg, Macitentan 30 mg, and Moxifloxacin 400 mg

Time (h)	PLACEBO	MACITENTAN 10 MG				MACITENTAN 30 MG				MOXIFLOXACIN 400 MG			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-1.9	62	-4.3	-2.4	(-5.4, 0.7)	64	-4.5	-2.6	(-5.6, 0.3)	63	-2.2	-0.3	(-3.3, 2.7)
2	-5.7	62	-6.4	-0.7	(-3.4, 2.0)	64	-9.5	-3.8	(-6.5, -1.1)	63	-7.7	-1.9	(-4.7, 0.8)
3	-5.9	62	-6.8	-0.9	(-3.6, 1.7)	64	-9.0	-3.1	(-5.8, -0.5)	63	-8.1	-2.3	(-4.9, 0.4)
4	-6.2	62	-7.9	-1.7	(-4.6, 1.1)	64	-9.0	-2.8	(-5.6, 0.1)	63	-7.5	-1.3	(-4.1, 1.5)
5	-4.2	62	-7.6	-3.4	(-6.2, -0.6)	64	-9.1	-4.9	(-7.7, -2.1)	63	-7.2	-3.0	(-5.8, -0.2)
6	-8.7	62	-7.3	1.3	(-1.2, 3.9)	64	-10.6	-1.9	(-4.5, 0.6)	63	-8.7	-0.0	(-2.5, 2.5)
7	-5.9	62	-6.9	-1.0	(-4.0, 1.9)	64	-9.9	-3.9	(-6.9, -1.0)	63	-7.9	-2.0	(-4.9, 1.0)
8	-5.7	62	-6.9	-1.2	(-4.1, 1.6)	64	-8.9	-3.2	(-6.0, -0.4)	63	-6.6	-0.9	(-3.8, 1.9)
9	-5.3	62	-6.2	-0.9	(-3.7, 1.8)	64	-7.8	-2.5	(-5.3, 0.2)	63	-5.3	0.0	(-2.7, 2.7)
10	-3.4	62	-5.7	-2.4	(-5.4, 0.7)	64	-6.6	-3.2	(-6.2, -0.2)	63	-3.8	-0.4	(-3.5, 2.6)
12	-4.3	62	-5.8	-1.6	(-4.3, 1.2)	64	-8.8	-4.5	(-7.3, -1.8)	63	-5.6	-1.3	(-4.1, 1.4)
16	0.4	62	-0.5	-0.8	(-4.0, 2.3)	64	-3.9	-4.2	(-7.3, -1.2)	64	-0.0	-0.4	(-3.5, 2.7)
24	-3.0	60	-3.9	-0.9	(-3.7, 2.0)	64	-6.1	-3.1	(-5.8, -0.3)	62	-2.1	0.9	(-1.9, 3.7)

Table 10: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
MACITENTAN 10 MG	62	52 (83.9%)	10 (16.1%)
MACITENTAN 30 MG	64	56 (87.5%)	8 (12.5%)
MOXIFLOXACIN 400 MG	63	54 (85.7%)	9 (14.3%)
PLACEBO	64	53 (82.8%)	11 (17.2%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between macitentan 10 mg and placebo, and between macitentan 30 mg are 1.6 ms and 0.1 ms, respectively. Table 12 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms were in both macitentan 10-mg and 30-mg groups.

Table 11: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Macitentan 10 mg, Macitentan 30 mg, and Moxifloxacin 400 mg

	Placebo	GEn 1200 mg				GEn 6000 mg				Moxifloxacin 400 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.1	62	-0.5	-0.4	(-1.5, 0.7)	64	-1.8	-1.7	(-2.8, -0.7)	63	-0.5	-0.5	(-1.5, 0.6)
2	0.7	62	0.9	0.2	(-0.9, 1.2)	64	-0.7	-1.5	(-2.5, -0.4)	63	0.3	-0.4	(-1.5, 0.7)
3	-0.4	62	0.1	0.5	(-0.5, 1.6)	64	-1.3	-0.9	(-1.9, 0.1)	63	-0.6	-0.1	(-1.2, 0.9)
4	-0.0	62	-0.8	-0.8	(-1.8, 0.2)	64	-2.0	-2.0	(-3.0, -1.0)	63	-1.2	-1.1	(-2.2, -0.1)
5	-0.6	62	-0.9	-0.3	(-1.3, 0.7)	64	-2.1	-1.5	(-2.5, -0.5)	63	-1.6	-1.0	(-2.0, 0.1)
6	-0.4	62	-0.7	-0.3	(-1.4, 0.8)	64	-1.7	-1.3	(-2.4, -0.2)	63	-1.5	-1.1	(-2.1, 0.0)
7	-0.6	62	-1.1	-0.5	(-1.6, 0.5)	64	-2.4	-1.8	(-2.8, -0.7)	63	-2.1	-1.5	(-2.5, -0.4)
8	-0.7	62	-1.2	-0.4	(-1.4, 0.5)	64	-2.1	-1.4	(-2.4, -0.4)	63	-1.2	-0.5	(-1.5, 0.5)
9	0.1	62	-1.0	-1.1	(-2.2, -0.0)	64	-1.5	-1.6	(-2.7, -0.5)	63	-0.9	-1.0	(-2.1, 0.1)
10	-0.4	62	-0.8	-0.3	(-1.4, 0.8)	64	-1.6	-1.2	(-2.3, -0.1)	63	-1.7	-1.3	(-2.3, -0.2)
12	0.8	62	0.1	-0.7	(-1.8, 0.4)	64	-0.4	-1.1	(-2.2, -0.0)	63	-0.5	-1.3	(-2.3, -0.2)
16	1.1	62	0.8	-0.3	(-1.3, 0.7)	64	-0.8	-1.9	(-2.9, -0.8)	64	-0.2	-1.3	(-2.3, -0.2)
24	-0.1	60	-0.3	-0.2	(-1.3, 0.9)	64	-1.3	-1.3	(-2.3, -0.2)	62	-0.5	-0.5	(-1.5, 0.6)

Table 12: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS \geq 110 ms
MACITENTAN 10 MG	62	61 (98.4%)	1 (1.6%)
MACITENTAN 30 MG	64	62 (96.9%)	2 (3.1%)
MOXIFLOXACIN 400 MG	63	61 (96.8%)	2 (3.2%)
PLACEBO	64	62 (96.9%)	2 (3.1%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and macitentan concentrations is visualized in Figure 8 with no evident exposure-response relationship. The relationship between $\Delta\Delta$ QTcF and ACT-132577 (macitentan metabolite) concentrations is visualized in Figure 9 with no evident exposure-response relationship.

Figure 8: $\Delta \Delta$ QTcF versus Macitentan Plasma Concentration

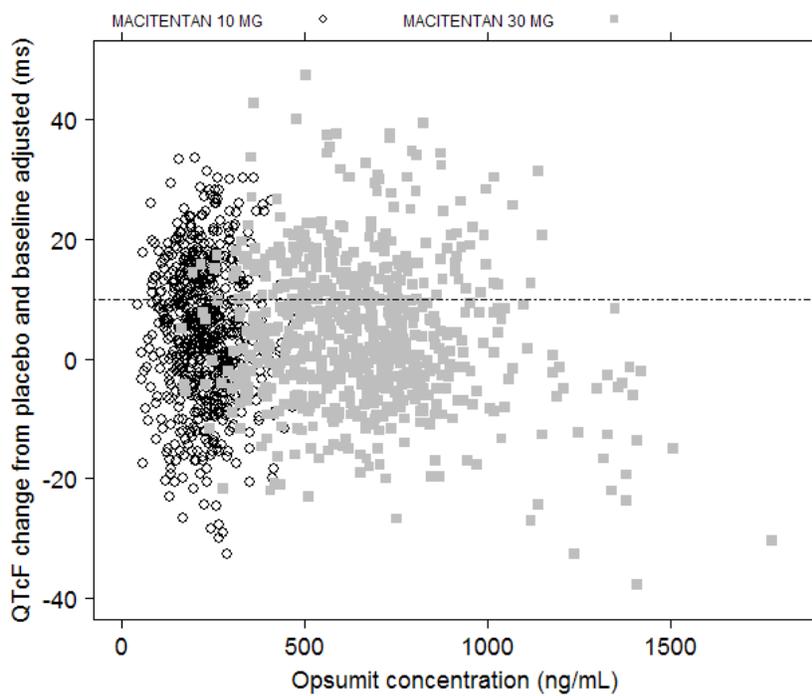
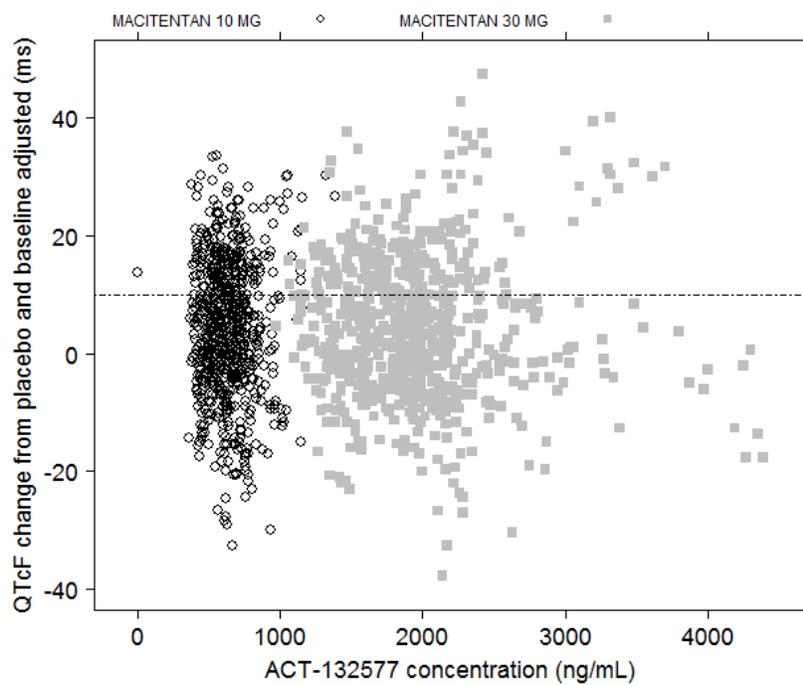


Figure 9: $\Delta \Delta$ QTcF versus ACT-132577 Plasma Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 98% of the ECGs were annotated in the primary lead II, with less than 0.26% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Ten subjects had a PR > 200 ms and two a QRS > 110 ms at baseline, and values remained similar at postbaseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The highest dose of macitentan (ACT-064992) being tested in Phase 3 studies is 10 mg once daily. The other dose tested is 3 mg once daily. The therapeutic dose(s) will be determined at the end of the ongoing event-driven Phase 3 study (AC-055-302 - SERAPHIN - Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clINical outcome).
Maximum tolerated dose	<p>In the single-ascending dose study AC-055-101, doses of up to 600 mg macitentan were studied. Subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others) than subjects receiving placebo. A dose of 300 mg was considered the maximum tolerated dose (MTD).</p> <p>In the multiple-ascending dose study AC-055-102, dose levels of 1, 3, 10, and 30 mg macitentan once daily for 10 days were studied. Based on the observations in liver enzyme elevations, 30 mg macitentan once daily was defined as the MTD (see below).</p>
Principal adverse events	<p>Macitentan was well tolerated in Phase 1 studies.</p> <p>The most frequently reported AE in the Phase 1 program was headache. Other AEs reported in the two placebo-controlled Phase 1 studies included back pain and fatigue. Except for one case of appendicitis, all AEs reported during Phase 1 were of mild to moderate intensity. No clear dose relationship could be discerned for any AE. However, in the single-ascending dose study, compared to subjects receiving placebo, subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others).</p> <p>Treatment with macitentan up to 600 mg as a single dose and 30 mg as multiple doses for 10 days (highest doses tested) was not associated with clinically relevant changes in systolic or diastolic blood pressures, heart rate, or ECG intervals and morphology.</p> <p>Three cases of asymptomatic increases in liver function tests greater than $3 \times$ ULN</p>

	<p>were observed in healthy subjects participating in the Phase 1 program. One case occurred after administration of multiple doses of 30 mg macitentan, and one case occurred in a study where a single dose of macitentan was given concomitantly with 400 mg ketoconazole. The third case occurred in a subject who had been treated during one study period with macitentan and sildenafil, followed by a second study period where he was treated with macitentan alone. However, none of the increases in liver function tests were associated with any other AEs, nor was any change in alkaline phosphatase or bilirubin noted. Also, in the studies AC-055-101 and AC-055-102, no changes in serum bile salt concentration were detected for any subject. All cases of liver transaminase increases resolved without sequelae within 14 days of observation.</p> <p>Two subjects with mild hepatic impairment also presented with an asymptomatic increase in liver function tests greater than $3 \times \text{ULN}$ at screening. In one subject, liver function tests increased by 1.8 times. This increase occurred 10 days after administration of a single dose of 10 mg macitentan. After 14 days, liver function tests were still greater than $5.4 \times \text{ULN}$. In the second case, liver function tests greater than $3 \times \text{ULN}$ present at screening were maintained throughout the study independently of the single administration of 10 mg macitentan.</p> <p>In the Phase 2 study in subjects with mild to moderate essential hypertension, macitentan was well tolerated compared to placebo with regard to the incidence of AEs. There were no AEs related to orthostatic hypotension or fluid retention, and no clinically relevant changes in heart rate were observed. Elevations in ALT and/or AST $> 3 \times \text{ULN}$ were observed in five subjects treated with macitentan, leading to unblinding and premature discontinuation of the study. Transaminase elevations resolved within 3 weeks after onset and study drug discontinuation. In most cases there were plausible reasons other than drug relationship for these observations.</p> <p>In the ongoing Phase 3 studies in PAH, and the ongoing Phase 2 study in IPF,</p>
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	<p>several cases of increased ALT and/or AST $> 3 \times \text{ULN}$ have been observed to date.</p> <p>These data suggest that, like other ERAs, macitentan may cause liver enzyme elevation in some patients.</p>									
Maximum dose tested	Single dose	In the single-ascending dose study AC-055-101, subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others) than subjects receiving placebo. A single dose of 300 mg was considered the MTD.								
	Multiple dose	In the multiple-ascending dose study AC-055-102, dose levels of 1, 3, 10, and 30 mg macitentan once daily for 10 days were studied. Based on the observations in liver enzyme elevations, 30 mg macitentan once daily was defined as the MTD (see below).								
Exposures achieved at maximum tested dose	Single dose	<p>Exposure measured for macitentan (Table 1) and its metabolite ACT-132577 (Table 2) following administration of 600 mg (study AC-055-101, n = 5).</p> <p>Table 1: Plasma PK parameters of macitentan following administration of a single dose of 600 mg of macitentan</p> <table border="1" data-bbox="857 1619 1321 1803"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>2967 (2233, 3943)</td> </tr> <tr> <td>AUC_{0-t} (ng·h/mL)</td> <td>96530 (70006, 133102)</td> </tr> <tr> <td>AUC_{0-∞} (ng·h/mL)</td> <td>127104 (82657, 195450)</td> </tr> </tbody> </table>	Parameter	Geometric mean (95% CI)	C _{max} (ng/mL)	2967 (2233, 3943)	AUC _{0-t} (ng·h/mL)	96530 (70006, 133102)	AUC _{0-∞} (ng·h/mL)	127104 (82657, 195450)
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AUC _{0-∞} (ng·h/mL)	127104 (82657, 195450)									

		<p>Table 2: Plasma PK parameters of ACT-132577 following administration of a single dose of 600 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>3688 (2591, 5249)</td> </tr> <tr> <td>AUC_{0-t} (ng.h/mL)</td> <td>104968 (73339, 150238)</td> </tr> <tr> <td>AUC_{0-∞} (ng.h/mL)</td> <td>342084 (213414, 548331)</td> </tr> </tbody> </table>	Parameter	Geometric mean (95% CI)	C _{max} (ng/mL)	3688 (2591, 5249)	AUC _{0-t} (ng.h/mL)	104968 (73339, 150238)	AUC _{0-∞} (ng.h/mL)	342084 (213414, 548331)				
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AUC _{0-∞} (ng.h/mL)	342084 (213414, 548331)													
	Multiple dose	<p>Exposure measured for macitentan (Table 1) and its metabolite ACT-132577 (Table 2) following administration of 30 mg (Day 10, study AC-055-102, n = 6).</p> <p>Table 1: Plasma PK parameters of macitentan following administration of multiple doses of 30 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>790 (662, 943)</td> </tr> <tr> <td>AUC_{0-t} (ng.h/mL)</td> <td>13000 (10665, 15845)</td> </tr> </tbody> </table> <p>Table 2: Plasma PK parameters of ACT-132577 following administration of multiple doses of 30 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (ng/mL)</td> <td>1927 (1361, 2730)</td> </tr> <tr> <td>AUC_{0-t} (ng.h/mL)</td> <td>40181 (28302, 57047)</td> </tr> </tbody> </table>	Parameter	Geometric mean (95% CI)	C _{max} (ng/mL)	790 (662, 943)	AUC _{0-t} (ng.h/mL)	13000 (10665, 15845)	Parameter	Geometric mean (95% CI)	C _{max} (ng/mL)	1927 (1361, 2730)	AUC _{0-t} (ng.h/mL)	40181 (28302, 57047)
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C _{max} (ng/mL)	1927 (1361, 2730)													
AUC _{0-t} (ng.h/mL)	40181 (28302, 57047)													
Range of linear pharmacokinetics (PK)	From 1 to 30 mg once daily oral administration													

<p>Accumulation at steady state</p>	<p>As predicted based on the terminal half-lives after single doses, the accumulation of macitentan after multiple doses (AC-055-102) was minimal (approximately 1.5-fold, Table 3) whereas that of ACT-132577 was substantial (about 8.5-fold, Table 4).</p> <p>Table 3: Accumulation index of macitentan</p> <table border="1"> <thead> <tr> <th>Dose</th> <th>Accumulation Index</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>1 mg</td> <td>1.4</td> <td>1.3, 1.6</td> </tr> <tr> <td>3 mg</td> <td>1.7</td> <td>1.4, 2.2</td> </tr> <tr> <td>10 mg</td> <td>1.5</td> <td>1.4, 1.7</td> </tr> <tr> <td>30 mg</td> <td>1.7</td> <td>1.4, 2.2</td> </tr> </tbody> </table> <p>Table 4: Accumulation index of ACT-132577</p> <table border="1"> <thead> <tr> <th>Dose</th> <th>Accumulation Index</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>1 mg</td> <td>7.1</td> <td>5.9, 8.6</td> </tr> <tr> <td>3 mg</td> <td>9.9</td> <td>7.5, 13.0</td> </tr> <tr> <td>10 mg</td> <td>7.1</td> <td>6.4, 7.8</td> </tr> <tr> <td>30 mg</td> <td>9.7</td> <td>6.3, 15.0</td> </tr> </tbody> </table>	Dose	Accumulation Index	95% CI	1 mg	1.4	1.3, 1.6	3 mg	1.7	1.4, 2.2	10 mg	1.5	1.4, 1.7	30 mg	1.7	1.4, 2.2	Dose	Accumulation Index	95% CI	1 mg	7.1	5.9, 8.6	3 mg	9.9	7.5, 13.0	10 mg	7.1	6.4, 7.8	30 mg	9.7	6.3, 15.0
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<p>Metabolites</p>	<p>Macitentan undergoes two major metabolic reactions: 1) oxidative depropylation to form ACT-132577 and 2) oxidative cleavage (oxidation of the ether side chain) to form the carboxyl acid derivative, ACT-373898 (Figure 1 from AC-055-104).</p>																														

	<p>In contrast to macitentan and ACT-132577, the metabolite ACT-373898 is not pharmacologically active on endothelin receptors. ACT-373898 has a similar pharmacokinetic profile to macitentan.</p> <p>Figure 1: Proposed metabolic pathways of macitentan in humans</p> <p>P: Plasma U: Urine, F: Faeces</p> <p>*: the position of ¹⁴C in the radiolabeled drug. §: most likely a hydroxyl metabolite. From the present data no specific allocation of the oxygen position was made.</p> <p>Results from the multiple-dose study AC-055-102 indicated that ACT-132577 and ACT-373898 were present at approximately 324% and 14% of macitentan exposure and 74% and 3% of total drug exposure, respectively. The effect of the metabolite ACT-132577 on K⁺ currents through hERG channels expressed in</p>
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	<p>HEK293 cells was also investigated using the patch clamp technique. At concentrations up to 10 μM, ACT-132577 had no effect on repolarizing currents through hERG K⁺ channels. At higher concentrations, ACT-132577 blocked both inward and outward currents slightly (IC₅₀ ~ 71 μM).</p> <p>Study AC-055-104 showed that urine represented a more important elimination route for macitentan and its metabolites than feces. On average, 49.7% (\pm 3.9%) of drug material was eliminated in urine compared to 23.9 % (\pm 4.8%) in feces.</p> <p>In urine, four entities were identified, with the hydrolysis product of ACT-373898 (M 323 u) as the most abundant one. In feces, five entities were identified, among which ACT-080803, the hydrolysis product of macitentan and ACT-132577, was the most abundant. The cytochrome P450 isoenzyme(s) responsible for the conversion of macitentan into its active circulating metabolite ACT-132577 have been identified. Using recombinant enzymes, CYP3A4 and CYP2C19 were both shown to catalyze this step. In quantitative terms, CYP3A4 is the major contributor to macitentan metabolism while the role of CYP2C19 is negligible.</p>					
Absorption	t _{max}	<p>T_{max} measured for macitentan (Table 5) and its metabolite ACT-132577 (Table 6) following multiple administration of 30 mg macitentan (Day 10, study AC-055-102, n = 6).</p> <p>Table 5: t_{max} of macitentan following administration of multiple doses of 30 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>t_{max} (h)</td> <td>8.5 (5, 9)</td> </tr> </tbody> </table>	Parameter	Geometric mean (95% CI)	t _{max} (h)	8.5 (5, 9)
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		<p>Table 6: t_{max} of ACT-132577 following administration of multiple doses of 30 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>t_{max} (h)</td> <td>8.5 (8, 10)</td> </tr> </tbody> </table>	Parameter	Geometric mean (95% CI)	t _{max} (h)	8.5 (8, 10)
Parameter	Geometric mean (95% CI)					
t _{max} (h)	8.5 (8, 10)					
	% bound	>99% bound to plasma proteins <i>in vitro</i>				
Distribution	Route	<p>The clinical study AC-055-104 showed that urine represented a more important elimination route for macitentan and its metabolites than feces.</p> <ul style="list-style-type: none"> On average 49.7% (\pm 3.9%) of drug material was eliminated in urine compared to 23.9 % (\pm 4.8%) in feces. Macitentan and ACT-132577 represented 16.9% and 14.0% of radioactivity excreted in the feces, respectively. ACT-373898 accounted for 3.6% of radioactivity excreted in the feces. <p>ACT-373898 accounted for 22.9% of radioactivity excreted in the urine. Neither macitentan nor ACT-132577 were present in urine.</p>				

Elimination	Terminal $t_{1/2}$	<p>$T_{1/2}$: PK results obtained following 30 mg tablet macitentan administration (study AC-055-102, Day 10, n = 6, Table 7):</p> <p>Table 7: $t_{1/2}$ of macitentan and ACT-132577 following administration of multiple doses of 30 mg of macitentan</p> <table border="1"> <thead> <tr> <th>Analyte</th> <th>Geometric mean (95% CI)</th> </tr> </thead> <tbody> <tr> <td>macitentan</td> <td>14.3h (12.8h - 16.1h)</td> </tr> <tr> <td>ACT-132577</td> <td>47.0h (42.1h - 52.5h)</td> </tr> </tbody> </table>	Analyte	Geometric mean (95% CI)	macitentan	14.3h (12.8h - 16.1h)	ACT-132577	47.0h (42.1h - 52.5h)
	Analyte	Geometric mean (95% CI)						
	macitentan	14.3h (12.8h - 16.1h)						
ACT-132577	47.0h (42.1h - 52.5h)							
Sex and age	<p>In study AC-055-109 evaluating the relative PK properties of macitentan in Japanese versus Caucasian healthy subjects after a single dose of 10 mg macitentan, minor differences in the pharmacokinetics were detected between genders in each ethnic group. These findings were considered to be not clinically relevant.</p> <p>In addition, exploratory analysis of the plasma concentration data measured at trough (C_{trough}) in the Phase 2 study AC-055-201 indicated no clinically relevant effects of sex and age on the pharmacokinetics of macitentan and ACT-132577.</p>							
Race	Results of study AC-055-109 indicated that the pharmacokinetics of macitentan and ACT-132577 were similar in Caucasian and Japanese subjects.							
Intrinsic factors	Hepatic & renal impairment	<p>I. Hepatic impairment (AC-055-110; preliminary) Following single-dose administration of 10 mg macitentan, the AUC and C_{max} of macitentan, ACT-132577, and ACT-373898 were comparable to healthy subjects (AC-055-110). The drug was generally well tolerated and no dose adaptation is required for patients with liver function impairment.</p> <p>II. Renal impairment (AC-055-112; preliminary results) Relative PK parameters were evaluated in healthy subjects versus subjects with severe renal function impairment (SRFI) after administration of a single dose of 10 mg macitentan. Minor differences between C_{max}, AUC₀₋₁, AUC_{0-∞}, and $t_{1/2}$ of macitentan were observed in age-, sex-, weight-, and height-matched subjects.</p> <p>C_{max} and $t_{1/2}$ of ACT-132577 were 1.39- and 1.32- fold larger in SRFI subjects than in healthy subjects, resulting in increases in AUC₀₋₁ and AUC_{0-∞} of 1.54- and 1.58-fold, respectively.</p> <p>These differences were not considered clinically relevant and no dose adjustment was recommended.</p>						
	Drug interactions	<p>I. Interaction with ketoconazole In the presence of ketoconazole, C_{max}, t_{max}, and $t_{1/2}$ of macitentan increased, resulting in an approximately 2-fold increase in exposure in terms of AUC_{0-∞} (study AC-055-107). This increase in AUC_{0-∞} was well below (approximately 8-fold) the AUC_{0-∞} of the well-</p>						

		<p>tolerated dose (300 mg macitentan) observed in the single-ascending dose study. ACT-132577 exposure was not influenced by ketoconazole treatment. Exposure to ACT-132577 in terms of $AUC_{0-\infty}$ was reduced by 26% by ketoconazole treatment, which was not considered to be clinically relevant. The magnitude of the interaction is not considered to be clinically relevant, and macitentan may therefore be administered concomitantly with CYP3A4 inhibitors.</p> <p>II. Interaction with sildenafil</p> <p>AC-055-106: sildenafil and macitentan DDI. Both drugs were administered separately and in combination until steady-state conditions had been attained.</p> <p>The PK profile of macitentan was not affected by sildenafil. The maximum plasma concentrations of ACT-132577 slightly decreased in the presence of sildenafil. No effect of sildenafil on the t_{max} of macitentan or its metabolite could be detected.</p> <p>In the presence of macitentan, the plasma concentrations of sildenafil were slightly higher than during monotherapy with sildenafil, resulting in increased C_{max} and AUC_1 values. The observed modest increases in C_{max} and AUC_1 are not considered to be clinically relevant.</p> <p>III. Interaction with warfarin</p> <p>In AC-055-105, the effect of multiple-dose treatment with macitentan on the pharmacokinetics and</p>
		<p>pharmacodynamics of a single dose of 25 mg warfarin were investigated following multiple dosing with 10 mg macitentan.</p> <p>PK and pharmacodynamic (PD) parameters for S-warfarin, R-warfarin, INR, and Factor VII were comparable between administration of macitentan plus warfarin and warfarin alone. The PK of R- and S-warfarin were not affected by macitentan.</p> <p>IV. Interaction with cyclosporine</p> <p>The effect of multiple-dose treatment with cyclosporine (Neoral®) on the PK of multiple-dose macitentan and its metabolites was evaluated in study AC-055-111.</p> <p>Geometric means of AUC_1 for macitentan and its metabolite, ACT-373898, were 10% and 7% higher during treatment with macitentan + cyclosporine compared to macitentan treatment alone. Geometric mean AUC_1 for the metabolite ACT-132577 was 3% lower in the presence of cyclosporine compared to macitentan treatment alone. Overall, co-administration of cyclosporine did not change the exposure to macitentan and its metabolites to a clinically relevant extent.</p> <p>V. Interaction with rifampin</p> <p>In a second part of the same study AC-055-111, the effects of multiple-dose treatment with rifampin (Rifadin®) on the PK of multiple-dose macitentan and its metabolites were evaluated.</p>

		Geometric means of AUC _{0-∞} in the presence of rifampin decreased by 79% and 64% for macitentan and ACT-373898, respectively, compared to macitentan treatment alone. For ACT-132577, no relevant difference in AUC _{0-∞} in the presence and absence of rifampin was observed. Overall, rifampin co-administration decreased the exposure to macitentan, whereas the exposure to the active metabolite, ACT-132577 was not affected to a clinically relevant extent.
	Food effects	Results from study AC-055-103 showed that macitentan can be taken irrespective of food intake.
Expected high clinical exposure scenario	<p>Macitentan is a substrate of CYP3A4. Further, CYP3A4 is the major contributor to formation of the active metabolite ACT-132577. Concomitant treatment of cyclosporine did not have any clinically relevant effect on the exposure to macitentan ACT-132577. In the presence of ketoconazole, an approximately 2-fold increase in exposure in terms of AUC_{0-∞} (study AC-055-107) was observed, whereas effect on ACT-132577 exposure was negligible.</p> <p>The PK of macitentan and ACT-132577 are dose-proportional and are not influenced by food, sex, age, and race. In hepatic impaired patients, the PK of macitentan and ACT-132577 are not affected. In SRFI patients, the PK of macitentan are not affected, whereas the exposure to ACT-132577 increased up to 1.6-fold. The magnitude of the increase in exposure to ACT-132577 in SRFI subjects was not considered clinically relevant.</p> <p>Based on current knowledge, the magnitude of increase in exposure in a worst case scenario is unlikely to be higher than levels achieved with a supratherapeutic dose of 30 mg.</p>	

6.2 SCHEDULE OF ASSESSMENT

An overview of the schedule of assessments is provided in

Table 13 with detailed presentation of the evens during Days 8 and 9 provided in

Appears this way on original

Table 14.

Appears this way on original

Table 14: Detailed schedule of assessment on Day 8 and Day 9

Days	Relative time (h:min) referring to dosing time on Day 8	Event	Clinical laboratory (AST, ALT, GGT, bilirubin)	Blood sampling (macitentan, ACT-132577, moxifloxacin)	12-lead Holter ECG (triplicates)	12-lead safety ECG	Vital signs (SBP, DBP, HR)
8	-00:45	Start Holter recording					
	-00:30		X ⁽¹⁾	X ⁽¹⁾	X ⁽¹⁾	X ⁽¹⁾	X ⁽¹⁾
	00:00	Treatment administration					
	01:00	Light breakfast		X	X		
	02:00			X ⁽²⁾	X		
	03:00			X ^(2,3)	X		
	04:00			X ⁽²⁾	X		
	05:00	Light lunch		X ⁽³⁾	X		
	06:00			X ⁽³⁾	X		
	07:00			X ⁽³⁾	X		
	08:00	Snack		X ⁽³⁾	X	X	X
	09:00			X ⁽³⁾	X		
	10:00	Dinner		X ⁽³⁾	X		
	12:00			X ⁽³⁾	X		
	16:00			X ⁽³⁾	X		
9	24:00			X ⁽³⁾	X		
	24:15	End Holter recording					

⁽¹⁾ Pre-dose.

⁽²⁾ Evaluation of assay sensitivity.

⁽³⁾ Evaluation of the primary endpoint.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBP = diastolic blood pressure, ECG = electrocardiogram, GGT = gamma glutamyltransferase, SBP = systolic blood pressure.

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

/s/

MOH JEE NG
03/04/2013

QIANYU DANG
03/04/2013

HONGSHAN LI
03/04/2013

KEVIN M KRUDYS
03/04/2013

MONICA L FISZMAN
03/05/2013

NORMAN L STOCKBRIDGE
03/05/2013

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information (SRPI)

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *It is worth noting that bosentan and ambrisentan have boxed warnings in labeling.*

Boxed Warning

N/A

12. All text must be **bolded**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: *Please revise as follows: "OPSUMIT is an endothelin receptor antagonist indicated for..."*

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information (SRPI)

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information (SRPI)

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

DANIEL BRUM
12/01/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 204410 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Opsumit Established/Proper Name: macitentan Dosage Form: tablets Strengths: 10 mg		
Applicant: Actelion Pharmaceuticals, Ltd. Agent for Applicant (if applicable):		
Date of Application: October 19, 2012 Date of Receipt: October 19, 2012 Date clock started after UN:		
PDUFA Goal Date: October 19, 2013		Action Goal Date (if different): October 18, 2013
Filing Date: December 18, 2012		Date of Filing Meeting: November 16, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): pulmonary arterial hypertension (PAH)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 77258 (PAH), (b) (5)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		Note: Although not requested, the product has orphan designation with expected orphan exclusivity if approved = 7 years
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

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

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		X		
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	eCTD
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>		X		
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			DMEPA conditionally accepted the name OPSUMIT (FDA correspondence dated 7 August 2012). Actelion requested the continuation of the review of the proprietary name "OPSUMIT".
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI)	<input type="checkbox"/> Patient Package Insert (PPI)	<input type="checkbox"/> Instructions for Use (IFU)	<input checked="" type="checkbox"/> Medication Guide (MedGuide)	<input checked="" type="checkbox"/> Carton labels	<input checked="" type="checkbox"/> Immediate container labels	<input type="checkbox"/> Diluent	<input type="checkbox"/> Other (specify)
	YES	NO	NA	Comment				
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X							
Is the PI submitted in PLR format? ⁴	X							
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X					
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X							
MedGuide, PPI, IFU (plus PI) consulted to patient labeling team? (send WORD version if available)	X							
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X							
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable							
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label	<input type="checkbox"/> Immediate container label	<input type="checkbox"/> Blister card	<input type="checkbox"/> Blister backing label	<input type="checkbox"/> Consumer Information Leaflet (CIL)	<input type="checkbox"/> Physician sample	<input type="checkbox"/> Consumer sample	<input type="checkbox"/> Other (specify)
	YES	NO	NA	Comment				
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>								
Are annotated specifications submitted for all stock keeping units (SKUs)?								

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): August 17, 2007 <i>If yes, distribute minutes before filing meeting</i>	X			The meeting correspondence refers to it as a Pre-IND meeting although the focus of the meeting was largely about the Phase 3 development program.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 15, 2012 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): December 1, 2007 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 16, 2012

BLA/NDA/Supp #: NDA 204410

PROPRIETARY NAME: Opsumit

ESTABLISHED/PROPER NAME: macitentan

DOSAGE FORM/STRENGTH: tablets / 10 mg

APPLICANT: Actelion Pharmaceuticals, Ltd.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Pulmonary Arterial Hypertension

BACKGROUND: Actelion submitted this New Molecular Entity (NME) New Drug Application (NDA) for the use of Opsumit (macitentan) for the treatment of patients with pulmonary arterial hypertension (PAH).

Opsumit (macitentan) is a dual ET_A and ET_B endothelin receptor antagonist that would be available as a 10 mg film-coated tablets for once daily oral administration.

The IND for macitentan was submitted on June 3, 2008. A Pre-IND/EOP2 meeting was held on August 17, 2007. DCRP sent Actelion an SPA agreement letter on December 1, 2007. A pre-NDA meeting was held on March 15, 2012, and a top-line results meeting occurred on July 11, 2012.

Tracleer (bosentan) and Letairis (ambrisentan), two endothelin receptor antagonists, are approved for PAH (largely idiopathic/heritable PH and PH associated with connected tissue disease [WHO Group 1]). Actelion markets Tracleer (approved 2001) and Gilead markets Letairis (approved 2007).

(b) (4)

A multicenter, double blind, placebo controlled, parallel group, event driven, Phase 3 outcome study (AC-055-302/SERAPHIN) was conducted in 742 patients with symptomatic pulmonary arterial hypertension (PAH) who were randomized to three treatment groups [placebo (N=250), 3 mg macitentan (N=250) or 10 mg OPSUMIT (N=242) once daily], to assess the long-term effect on morbidity or mortality. At baseline, the majority of enrolled patients (64%) were treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%). The primary study endpoint was the time to first occurrence of a morbidity or mortality event up to end of double-blind treatment (EOT), defined as death, or atrial septostomy, or lung transplantation, or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or other worsening of PAH. Other worsening of

PAH was defined as the presence of all of the three following components: a sustained decrease in 6-minute walk distance (6MWD) of at least 15% from baseline; worsening of PAH symptoms (worsening of WHO FC or right heart failure); and need for new treatment for PAH. All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

The median treatment duration was 101, 116, and 118 weeks in the placebo, macitentan 3 mg and 10 mg groups, respectively, up to a maximum of 188 weeks on macitentan.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dan Brum	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Abraham Karkowsky		Y
Clinical	Reviewer:	Maryann Gordon	Y
	TL:	CDTL	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Hsien “Jim” Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	William “Tim” Link	Y
	TL:	Albert DeFelice	Y
Statistics (carcinogenicity)	Reviewer:	Mohammad Rahman	N
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Thomas Wong	
	TL:	Kasturi Srinivasachar	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kimberly Defronzo	
	TL:	Irene Chan	
OSE/DRISK (REMS)	Reviewer:	Jason Bunting	
	TL:	Reema Mehta	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	John Duan (biopharm), Dhananjay Marathe (biometrics)		
Other attendees	Ellis Unger (office director), Norman Stockbridge (director), Steve Grant (deputy director), Joshua Barton (panorama), Susan Lu (OSE)		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <ul style="list-style-type: none"> <i>this drug is not the first in its class</i>

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application probably will not raise significant safety or efficacy issues</i> ○ <i>the application probably will not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL</p>	<input type="checkbox"/> Not Applicable

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger, M.D.	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 14, 2013	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

DANIEL BRUM
12/01/2012