

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204410Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

Individual Study Reviews

NDA:	204410
Submission Date:	10/19/2012
Submission Type:	Original NDA (NME – Standard Review)
Brand Name:	OPSUMIT [®]
Generic Name:	macitentan
Drug Class:	Endothelin Receptor Antagonist (ERA)
Dosage Form & Strength:	Tablets, 10 mg
Proposed Indication:	Long term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) in adults (b) (4)
Sponsor:	Actelion Pharmaceuticals Ltd.
Review Division:	DCP1 & DCRP
Reviewers:	Sreedharan Sabarinath, PhD Ping Zhao, PhD
Team Leader:	Rajanikanth Madabushi, PhD

This review is an addendum to the original clinical pharmacology review submitted to DARRTS on 6/29/2013. The purpose of this review is to summarize the individual studies described in the question based review (QBR).

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Bioanalytical Method Validation

Study: SBA_S_04081 Period: 2005	Validation of a method for the determination of ACT-064992 and its metabolite ACT-132577 in human plasma by LC-MS/MS		
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\sba-s-04081			
Study: SBA_S_09020 Period: 2009	Validation of a method for the determination of ACT-373898 in human plasma by LC-MS/MS		
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\sba-s-09020			
Objective: To develop and validate LC-MS/MS methods for determining the plasma concentrations of ACT-064992 and its metabolites ACT-132577 (active) and ACT-373898 (inactive).			
Methods: The analysis was done using reversed phase chromatography with MS/MS detection in positive ion mode using water containing 0.1% v/v formic acid and acetonitrile containing 0.1 % v/v formic acid as mobile phase with gradient elution. The sample clean-up was by protein precipitation with acetonitrile and ethanol (1:1 mixture). The sample injection volume was 20 µL. The assay validation was performed as per FDA Guidance for Industry – Bioanalytical Method Validation, May 2001. The validation parameters included accuracy, precision, selectivity, stability (including freeze-thaw stability, short term room temperature stability, long term storage stability, stock solution stability, post preparative stability, re-injection reproducibility), recovery, and effect of dilution.			
Results & Discussion:			
Highlights of the assay methods			
Analytes	Macitentan (ACT-064992)	M6 (ACT-132577)	M5 (ACT-373898)
Matrix	Human Plasma		
Sample Volume	100 µL		
Sample Preparation	Protein precipitation (acetonitrile : ethanol in 50:50 ratio)		
Detection Technique	ESI+ LC-MS/MS		
LLOQ	1 ng/mL	1 ng/mL	0.5 ng/mL
ULOQ	2000 ng/mL	2000 ng/mL	500 ng/mL
The quality control (QC) samples used were 1 ng/mL (LOQ), 3 ng/mL (low), 100 ng/mL (medium) and 1500 ng/mL (high) for both ACT-064992 and ACT-132577. The QC samples for ACT-373898 were 0.5 ng/mL (LOQ), 1.5 ng/mL (low), 50 ng/mL (medium) and 400 ng/mL (high).			
The intra-day and inter-day coefficients of variations (CV) were 9.9 % and 10.4 % or less, respectively for ACT-064992 and 13.1 % and 10.4 % or less, respectively for ACT-132577 for all QC samples during the 3-			

day validation. The highest values for CV are reported for LOQ where $\pm 20\%$ deviation is permitted. The coefficient of variation for the intra-day and inter-day run were $\leq 17.2\%$ and 16.2% at LOQ (less than 10.5% and 14.3% at other QC levels) for ACT-373898. At other QC levels the intra-day CV were general less than 6% , except for run-3 where it was 14.3% . The inter-day % CV at other QC levels was less than 10.5% . The intra-day and inter-day inaccuracies were -6% to 13.6% and 1.5% to 4.3% , respectively for ACT-373898. The inaccuracy in the intra-day and inter-day runs was 14% and 5% or less for ACT-064992 and 8.7% and 5.5% or less for ACT-132577, respectively.

All the analytes ACT-064992, ACT-132577 and ACT-373898 were stable during at least 3 freeze-thaw cycles (for low and high QCs the % remaining was within $\pm 15\%$ of their nominal values). The recoveries were $>70\%$, $>95\%$ and $>92\%$ for ACT-064992, ACT-132577 and ACT-373898 respectively with the sample clean-up procedure. The analytes were stable at room temperature for 17 hours, at -25°C for 34 days, in auto-sampler for 20 hours at 8°C . ACT-373898 was stable at room temperature for 19 hours and for at least 36 days on storage at -25°C .

Reviewer's Comments:

The two assays were validated for ACT-064992, ACT-132577 and ACT-373898 as per FDA guidance and the accuracy and precision of the assays during the 3-day validation were within acceptable limits. Unless specified otherwise the bioanalytical conduct was acceptable in the clinical pharmacology studies described in this review.

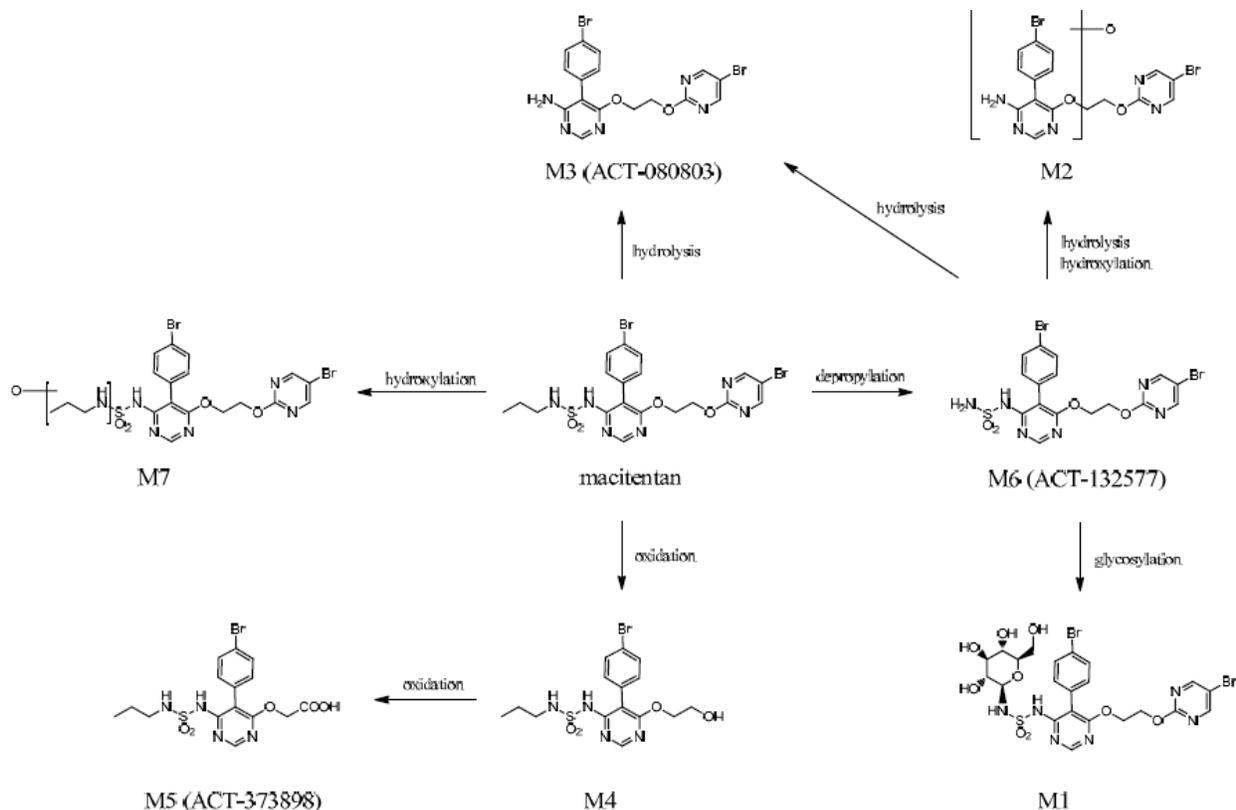
Conclusion: LC-MS/MS assays were developed and validated for ACT-064992, ACT-132577 and ACT-373898 as per FDA Guidance for Industry-Bioanalytical method validation, May 2001

In Vitro Studies

Metabolite Identification (microsomes and hepatocytes)

Studies: B-04.022, B-04-093 Study Period: 2003-04	Title: ACT-064992B - Metabolism in microsomes and hepatocytes from rat, mouse, dog, monkey, minipig and man
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4224-metab\b-04-022 EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4224-metab\b-04-093	
Objective: To identify number and proportions of the <i>in vitro</i> metabolites of ^{14}C -labelled macitentan in incubations with liver microsomes and hepatocytes from preclinical species and humans.	
Study Design: Incubations with fresh hepatocytes were carried out in monolayer culture and liver cells of two human donors were used. All incubations were conducted at $10\mu\text{M}$ concentration level (2-4 hours for hepatocytes and 40 minutes for microsomes) and samples were analyzed, once the incubations were terminated with methanol, using radio-chromatographic methods.	

Results: Formation of up to seven metabolites was observed across species in incubations with liver microsomes and hepatocytes. The proposed metabolic pathway for macitentan in human liver preparations are shown below:



Ref. Dc No D-12.345, 2.6.4 Pharmacokinetics Written Summary, Figure 1

Conclusions:

- Macitentan undergoes depropylation to form its active metabolite M6 (ACT-132577), which then undergoes glycosylation to form M1
- Both macitentan and M6 undergo non-enzymatic hydrolysis to M3 (ACT-080803).

Metabolite Identification (liver S9 fraction)

Studies: B-04.099

Study Period: 2004

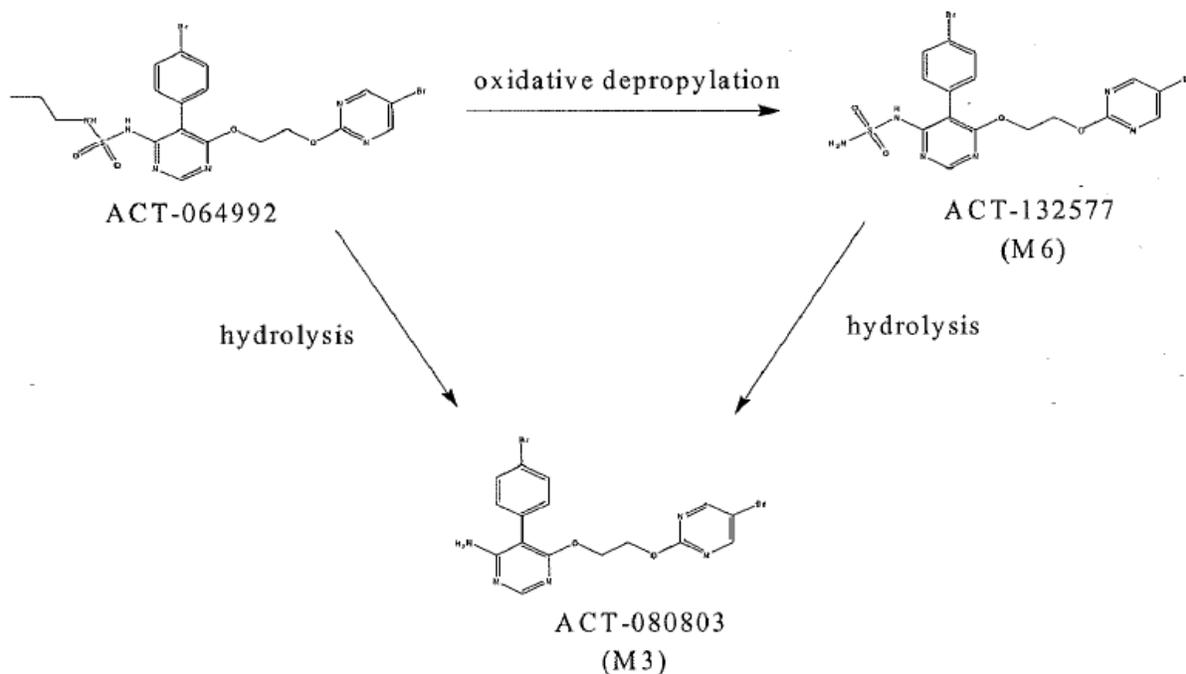
Title: Metabolic profiles of the endothelin receptor antagonist ACT-064992 with rat and human liver S9 fractions

EDR: <\\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4224-metab\b-04-099>

Objective: To investigate the metabolic profiles of ACT-064992 in liver S9 fractions from rat and human.

Study Design: The human and rat liver S9 fractions was purchased from (b) (4) and the microsomal protein concentrations were adjusted to 20 mg/ml. The concentration of ACT-064992 was 10 μ M and the incubation duration was 40 minutes. Ice cold acetonitrile was used to terminate the incubations before HPLC analyses.

Results: The incubation with human liver S9 fraction resulted in the formation of two metabolites M3 and M6. Rat liver S9 fraction showed small amounts of metabolite M3 in addition to M3 and M6 seen with human liver S9 fractions. The proposed metabolic scheme for ACT-064992 from these experiments are shown below:



Ref: B-04.099 Study report, Page 12, Scheme 1

Conclusions:

- The metabolites observed with rat and human liver S9 fractions are similar to those observed with liver microsomes and hepatocytes.

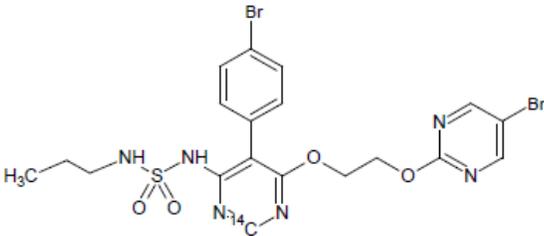
Identification of CYP enzymes

Studies: B-06.219 Study Period: 2007	Title: Identification of the cytochrome P450 enzymes catalyzing the formation of ACT-132577													
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4224-metab\b-06-219														
Objective: To identify the rat, dog and human CYP P450 enzymes involved in the catalysis of oxidative depropylation of ACT-064992 to the pharmacologically active metabolite ACT-132577 (M6).														
<p>Study Design: Two different designs were used; (1) incubation of ACT-064992 with human liver microsomes in the presence or absence of specific P450 isoform inhibitors and (2) incubation of ACT-064992 with recombinant human P450s expressed in baculo-virus infected Sf9 cells.</p> <p>The P450 isoform specific inhibitors used were furafylline (1A2), 8-methylpsoralene (2A6), ticlopidine (2B6/2C19), omeprazole (2C19), sulfaphenazole (2C9), quinidine (2D6), 4-methylpyrazole (2E1) and ketoconazole (3A4). Pooled human liver microsomes and the recombinant cytochrome P450 enzymes were sourced from (b) (4). ACT-064992 concentration used was 10 µM and the incubation period was 40 minutes for human liver microsomes and recombinant P450 systems. The reactions were initiated by the addition of 10 µL of the NADPH-regenerating system and incubations were terminated with acetonitrile before sample analysis.</p>														
<p>Results: In control experiments, in the absence of liver microsomes or NADPH regenerating system, a small amount of metabolite M3 (ACT-080803) was formed. M3 is a common hydrolysis product of ACT-064992 and ACT-132577. Only ketoconazole was able to reduce the formation of ACT-132577 in experiments with human microsomes, however the inhibition was not complete even at 1 µM concentration level for ketoconazole suggesting the involvement of other enzyme systems.</p> <p>In incubations with recombinant P450 enzymes expressed by Sf9 cells only CYP3A4 and CYP2C19 catalyzed the formation of ACT-132577. Enzyme kinetics of ACT-132577 formation and derived intrinsic clearances from human test systems are shown below:</p>														
<table border="1"> <thead> <tr> <th>Enzyme</th> <th>Km (µM)</th> <th>Vmax*</th> </tr> </thead> <tbody> <tr> <td>Liver microsomes</td> <td>27</td> <td>591</td> </tr> <tr> <td>CYP2C19</td> <td>58</td> <td>0.4</td> </tr> <tr> <td>CYP3A4</td> <td>71</td> <td>44</td> </tr> </tbody> </table>			Enzyme	Km (µM)	Vmax*	Liver microsomes	27	591	CYP2C19	58	0.4	CYP3A4	71	44
Enzyme	Km (µM)	Vmax*												
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CYP3A4	71	44												
<p>*pmol/min.mg protein for liver microsomes, and pmol/min.pmol P450 enzyme for recombinant enzyme experiments</p>														
<p>The ratios of intrinsic clearances of human CYP2C19 and CYP3A4 at different concentrations of ACT-064992 were 99:1 in favor of CYP3A4 in these experiments (see below).</p>														
<table border="1"> <thead> <tr> <th>ACT-064992 (µM)</th> <th>Clint CYP3A4*</th> <th>Clint CYP2C19*</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>0.611</td> <td>0.007</td> </tr> <tr> <td>10</td> <td>0.543</td> <td>0.006</td> </tr> <tr> <td>100</td> <td>0.256</td> <td>0.003</td> </tr> </tbody> </table>			ACT-064992 (µM)	Clint CYP3A4*	Clint CYP2C19*	1	0.611	0.007	10	0.543	0.006	100	0.256	0.003
ACT-064992 (µM)	Clint CYP3A4*	Clint CYP2C19*												
1	0.611	0.007												
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100	0.256	0.003												
<p>*ul/min.pmol</p>														
<p>Ref: B-06.219 Study Report</p>														

Conclusions:

- In humans the CYP3A4 was identified as the major enzyme contributing to the metabolism (99%) of ACT-064992 with negligible role for CYP2C19. Formation of M3 (ACT-080803) is considered non-enzymatic because of its formation without CYP involvement in these experiments.

Structural Elucidation of Metabolites

Studies: B-07.372 Study Period: 2012	Title: Structural elucidation of metabolites of the endothelin receptor antagonist ACT-064992 by liquid chromatography combined with high resolution mass spectrometry
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4224-metab\b-07-372	
Objective: To elucidate the structure of the metabolites of ACT-064992.	
Study Design: ACT-064992 was incubated with human hepatocytes and liver microsomes and selected samples were analyzed by LC-MS/MS. ¹⁴ C labeled analogue of ACT-064992 with radiolabel in the pyrimidine ring was used (denoted as ACT-064992B below).	
 ACT-064992B	
Results: Incubations with human liver microsomes for 40 minutes showed M6 (ACT-132577) as a prominent metabolite. Metabolites M2, M4 and M7 were formed in smaller amounts. After incubation with human hepatocytes for 6 hours, M6 was the main metabolite and M2, M4, M5 and M7 were formed to a lesser extent.	
Conclusions: <ul style="list-style-type: none">• The LC-MS/MS analysis confirmed the proposed metabolic profile of ACT064992 after incubation with human liver microsomes and hepatocytes. The proposed metabolic pathway is described in the study reviews for B-04.022 and B-04-093.	

Intestinal Permeability

Studies: B-05.040 Study Period: 2005	Title: <i>In vitro</i> intestinal permeation studies with endothelin receptor antagonist ACT-064992 using Caco-2 model			
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4222-absorp\b-05-040				
Objective: To determine the apparent permeability coefficients of ACT-064992 in the Caco-2 cell system and to test its effect on the permeability of the known MDR-1 substrates digoxin and rhodamine 123.				
Study Design: Caco-2 cells were sourced from (b) (4) and transport experiments were performed on day 27 post seeding. The integrity of cell monolayers were checked by measuring transepithelial electrical resistance and functional measurements with radiolabelled D-mannitol. Radiolabelled ACT-064992 at 1 and 10 µM concentrations were used. The incubation period was 3-4 hours at 37°C. Verapamil (20 µM) was used to assess the effect of known P-gp inhibitor on the permeability of ACT-064992.				
Results: The apparent permeation coefficients (P_{app}) of ACT-064992 were 11×10^{-6} cm/s and 13×10^{-6} cm/s at concentrations of 1 and 10 µM respectively (See Table below for P_{app} for ACT-064992 in the presence or absence of verapamil). There was no effect of MDR-1 inhibitor verapamil on the permeation of ACT-064992. ACT-064992 did not affect the permeation of two MDR-1 substrates digoxin and rhodamine 123.				
Apparent permeability coefficients (P_{app}) of ACT-064992 in the presence/absence of verapamil				
Transport direction	ACT-064992B [µM]	Verapamil [µM]	$P_{app}^{(1)}$ [10^{-6} cm/s]	Recovery [%]
A-B ⁽²⁾	1	--	11 ± 1	82
B-A	1	--	21 ± 0	90
A-B	1	20	9 ± 1	75
A-B	10	--	13 ± 0	81
B-A	10	--	22 ± 0	87
A-B	10	20	13 ± 0	76
(1) mean ± SD (n = 3); (2) A = apical compartment, B = basolateral compartment				
The effect of ACT-064992 on the permeability of MDR-1 substrates digoxin and rhodamine 123 are summarized in the tables below:				

Apparent permeability coefficients (P_{app}) of digoxin¹ in the presence/absence of ACT-064992

transport direction	ACT-064992 [μ M]	P_{app} [10^{-6} cm/s]		recovery [%]
		series 1 ⁽²⁾	series 2 ⁽²⁾	
A-B ⁽³⁾	0	5 \pm 1	6 \pm 1	82 / 80 ⁽⁴⁾
B-A	0	25 \pm 1	ND ⁽⁶⁾	87 / ND
A-B ⁽⁵⁾	0	19 \pm 3	ND	83 / ND
A-B	3	4 \pm 1	ND	76 / ND
A-B	10	5 \pm 0	5 \pm 0	77 / 80
A-B	30	4 \pm 1	4 \pm 0	74 / 80
A-B	100	5 \pm 0	6 \pm 0	75 / 79

(1) ³H-digoxin concentration: 1.0 μ M; (2) mean \pm SD of n = 3; (3) A = apical compartment; B = basolateral compartment; (4) recovery of series 1 and 2; (5) plus verapamil at 20 μ M; (6) ND = not determined

Apparent permeability coefficients (P_{app}) of rhodamine 123¹ in the presence/absence of ACT-064992

transport direction	ACT-064992 [μ M]	P_{app} [10^{-6} cm/s]	recovery [%]
A-B ⁽²⁾	0	3 \pm 0 ⁽³⁾	82
B-A	0	16 \pm 1	84
A-B ⁽⁴⁾	0	13 \pm 0	73
A-B	10	3 \pm 0	76
A-B	30	3 \pm 0	76
A-B	100	3 \pm 0	74

(1) rhodamine 123 concentration 10 μ M; (2) A = apical compartment; B = basolateral compartment ; (3) mean \pm SD of n = 3; (4) plus verapamil at 20 μ M

Ref: Study report B-05-040

Conclusions:

- The PK of ACT-064992 is less likely to be affected by substrates/inhibitors of MDR-1.
- ACT-064992 is unlikely to affect the permeability of compounds that are MDR-1 substrates.

CYP Inhibition Studies

Studies: B-04-024 Study Period: 2004	Title: Assessment of the inhibition potential of human cytochrome P450 enzymes by the endothelin receptor antagonist ACT-064992 <i>in vitro</i>																														
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\b-04-024																															
Objective: To assess the potential for inhibition of ACT-064992 on the activity of human CYP P450 isoforms <i>in vitro</i> .																															
Study Design: Pooled human liver microsomes and recombinant CYP P450 enzymes were sourced from (b) (4). The microsomal protein concentration was adjusted to 20 mg/ml and total CYP P450 concentrations were in the range of 420 to 490 pmol/mg respectively. The inhibition of CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 2A4 was tested using human liver microsomes and isoform specific marker transformations. The inhibition of CYP2B6 and 2C19 was done with recombinant enzymes expressed in Sf9 cells. The inhibitory potential on CYP3A4 activity was tested on midazolam 1'-hydroxylation and testosterone 6 β-hydroxylation. For determining IC ₅₀ values, all marker substrates were used at a single concentration around their respective K _m values. ACT-064992 concentrations up to 50 μM were used for CYP inhibition.																															
Results: An over view of the CYP inhibition of ACT-064992 are listed below:																															
<table border="1" data-bbox="383 1041 1240 1411"> <thead> <tr> <th>CYP isoform</th> <th>marker transformation</th> <th>IC₅₀ (μM)</th> </tr> </thead> <tbody> <tr> <td>1A2</td> <td>phenacetin-O-deethylation</td> <td>> 50⁽¹⁾</td> </tr> <tr> <td>2A6</td> <td>coumarin 7-hydroxylation</td> <td>> 50⁽²⁾</td> </tr> <tr> <td>2B6</td> <td>(S)-mephenytoin N-demethylation</td> <td>> 50⁽¹⁾</td> </tr> <tr> <td>2C9</td> <td>diclofenac 4'-hydroxylation</td> <td>3.7-8.2 (5.0)⁽³⁾</td> </tr> <tr> <td>2C19</td> <td>(S)-mephenytoin 4'-hydroxylation</td> <td>> 50⁽⁴⁾</td> </tr> <tr> <td>2D6</td> <td>dextromethorphan N-demethylation</td> <td>> 50⁽⁵⁾</td> </tr> <tr> <td>2E1</td> <td>chlorzoxazone 6-hydroxylation</td> <td>> 50</td> </tr> <tr> <td>3A4</td> <td>midazolam 1'-hydroxylation</td> <td>33-41⁽⁶⁾</td> </tr> <tr> <td>3A4</td> <td>testosterone 6β-hydroxylation</td> <td>24</td> </tr> </tbody> </table> <p data-bbox="383 1415 1240 1537">(1) 33% inhibition at 50 μM; (2) 23% inhibition at 50 μM; (3) three independent experiments with a mean of 5.6 μM; K_i value in parenthesis; (4) 18% inhibition at 50 μM; (5) 17% inhibition at 50 μM; (6) two independent experiments with a mean of 37 μM.</p>		CYP isoform	marker transformation	IC ₅₀ (μM)	1A2	phenacetin-O-deethylation	> 50 ⁽¹⁾	2A6	coumarin 7-hydroxylation	> 50 ⁽²⁾	2B6	(S)-mephenytoin N-demethylation	> 50 ⁽¹⁾	2C9	diclofenac 4'-hydroxylation	3.7-8.2 (5.0) ⁽³⁾	2C19	(S)-mephenytoin 4'-hydroxylation	> 50 ⁽⁴⁾	2D6	dextromethorphan N-demethylation	> 50 ⁽⁵⁾	2E1	chlorzoxazone 6-hydroxylation	> 50	3A4	midazolam 1'-hydroxylation	33-41 ⁽⁶⁾	3A4	testosterone 6β-hydroxylation	24
CYP isoform	marker transformation	IC ₅₀ (μM)																													
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3A4	midazolam 1'-hydroxylation	33-41 ⁽⁶⁾																													
3A4	testosterone 6β-hydroxylation	24																													
Conclusions: <ul style="list-style-type: none"> • ACT-064992 had the strongest effect on CYP2C9 activity with IC₅₀ values ranging from 3.7-8.2 μM. • The effect on CYP3A4 activity was considered moderate with IC₅₀ values of 33-41 μM using midazolam and 24 μM with testosterone as substrates. 																															

CYP Inhibition Studies (parent and metabolite)

Studies: B-12-103 Study Period: 2012	Title: Assessment of the inhibition potential of the endothelin receptor antagonist ACT-064992 and its metabolite ACT-132577 on the major human cytochrome P450 enzymes <i>in vitro</i>
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\b-12-103	
Objective: To assess the effects of ACT-064992 and its pharmacologically active metabolite ACT-132577 to inhibit human CYP isoforms 2C8, 2C9, 2D6 and 3A4 using human liver microsomes and isoform specific marker reactions. Competitive inhibition of CYP2C8 and time dependent inhibition of CYP2C9, 2D6 and 3A4 were to be investigated.	
Study Design: The CYP2C8 inhibition assay was performed using human liver microsomes and paclitaxel 6 alpha-hydroxylation as a P450 isoform-specific marker. The time-dependent inhibition of CYP2C9 activity was performed using human liver microsomes and diclofenac 4'-hydroxylation as P450 isoform-specific marker reaction. The time-dependent inhibition of CYP2D6 activity (dextromethorphan-O-demethylation as P450 isoform-specific marker reaction) and CYP3A4 activity (testosterone 6 β-hydroxylation as P450 isoform-specific marker reaction) was also performed using human liver microsomes.	
Results: ACT-064992 and ACT-132577 were inhibitors of CYP2C8 activity with IC ₅₀ values of 21 and 23 uM respectively. ACT-064992 and ACT-132577 did not exhibit time dependent inhibition on CYP2C9, 2D6 and 2A4 enzymes. The positive controls used, mibefradil, tienilic acid and paroxetine exhibited measurable time dependent inhibition in these experimental conditions.	
Reviewer's Comments: <i>It should be noted that ACT-064992 did not replicate the findings for CYP2C9 and 3A4 inhibition potential that was reported in the previous study (Study B-04-024). The IC₅₀ value without pre-incubation in this study was 30 μM for CYP2C9. Also the IC₅₀ for CYP3A4 inhibition reported in this study was higher >100 μM. A factor of ~5X difference in the IC₅₀ can be noted across these two studies.</i>	
Conclusions: <ul style="list-style-type: none">• There was no time dependent inhibition on CYP2C9, 2D6 and 3A4 activities with ACT-064992 and ACT-132577. Both moieties showed inhibitory effects on CYP2C8.	

CYP Induction Studies

Studies: B-05-107 Study Period: 2007	Title: Assessment of the human cytochrome P450 induction potential by the endothelin receptor antagonist ACT-064992 and its metabolite ACT-132577 <i>in vitro</i> .
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\b-05-107	
Objective: To assess the potential of ACT-064992 and ACT-132577 to induce the expression of human CYP isoforms such as CYP3A4, 2C9 and 1A2.	
Study Design: Both compounds were tested for their potential to activate the human nuclear receptor PXR in a transcriptional activation assay in CV-1 cells (green monkey kidney cells). Their potential to modulate mRNA expression and protein activity of CYP3A4, 2C9 and 1A2 was assessed in primary human hepatocytes. Nifedipine, diclofenac and phenacetin were used as marker substrates to quantify CYP3A4, 2C9 and 1A2 activities, respectively. Rifampin, a known inducer of CYP3A4 and activator of PXR, was used as positive control. Omeprazole was used as the positive control for CYP1A2 activity.	
Results: The EC ₅₀ for rifampin on human PXR was 0.5-0.6 μM. The respective values for ACT-064992 and ACT-132577 were 1.1-1.2 μM and 7.2-8.7 μM respectively. These results suggest that ACT-064992 activates human PXR <i>in vitro</i> with an EC ₅₀ value twice higher than that of rifampin. Also, both ACT-064992 and ACT-132577 increased CYP3A4 mRNA levels in a concentration dependent manner. ACT-064992 and ACT-132577 showed small increase in 1A2 enzyme activity at 10 μM concentration level, but did not exceed 25% of the maximal effect elicited by the positive control omeprazole. ACT-132577 did not activate CYP2C9 mRNA or CYP2C9 activity, while ACT-064992 showed moderate increase in activity especially at higher concentrations.	
Conclusions: <ul style="list-style-type: none"> • Both ACT-064992 and ACT-132577 can induce CYP3A4 enzymes <i>in vitro</i>. • The effects of both compounds on CYP2C9 and 1A2 are not considered significant. Reviewer's Comments: <i>It should be noted that in vivo PK studies of ACT-064992 did not show evidence for CYP3A4 induction. This could be because of the relatively lower systemic exposure obtained with clinical doses compared to the concentrations tested in the in vitro closed systems and the very high plasma protein binding (>99.5%) of both ACT-064992 and ACT-132577.</i>	

Transporter Studies

Studies: B-10.642 Study Period: 2012	Title: <i>In vitro</i> interaction studies with macitentan, its active metabolite ACT-132577 and organic anion transporting polypeptides OATP
EDR: \\cdsesub1\evsprod\NDA204410\0000\m4\42-stud-rep\422-pk\4226-pk-drug-interact\b-10-642	
Objective: To assess whether macitentan and its metabolite ACT-132577 are substrates and/or inhibitors of OATP1B1, 1B3 and 2B1 using CHO cells expressing these human transporters.	
Study Design: Chinese hamster ovary (CHO) cells expressing human transporters OATP1B1, 1B3 and 2B1 and respective wild type CHO cells were used. Prior to the transport experiments, the time dependence of cellular uptake was individually determined in order to optimize experimental conditions. The effect of the OATP inhibitors cyclosporine A and rifampicin on the uptake of ACT-064992 was investigated at a single concentration of 1 μM ACT-064992 for all three transporters. The inhibitory potential of ACT-064992 and ACT-132577 on the cellular uptake of OATP model substrates was investigated at a single substrate concentration ($\leq K_m$) of 1 μM atorvastatin for OATP1B1, and 5 μM E3S for OATP1B3 and OATP2B1. The inhibition experiments were performed in an ACT-064992 concentration range of 0.01 μM to 100 μM and in an ACT-132577 concentration range of 0.1 μM to 300 μM .	
Results: <ul style="list-style-type: none">• No apparent difference in the uptake of ACT-064992 between wild-type and OATP1B1 or OATP2B1 cells was observed. The uptake of ACT-064992 into OATP1B3 cells was maximally 20 % higher than into wild-type cells. Neither cyclosporine A nor rifampicin decreased the net uptake rate of ACT-064992 into any of the OATP-expressing cells.• No apparent difference in the uptake of ACT-132577 between wild-type and OATP1B1 cells was observed. The uptake of ACT-132577 into the OATP1B3 and OATP2B1 cells at concentrations below 4 μM was maximally 40 % higher than into wild-type cells.• The assessment of the inhibitory potential of ACT-064992 and ACT-132577 on the human OATP transporters was investigated by measuring their effect on the cellular uptake of OATP model substrates. Atorvastatin was used for OATP1B1, whereas 3HE3S was used for both, OATP1B3 and OATP2B1. Macitentan and ACT-132577 both inhibited OATP1B1-mediated uptake of atorvastatin, as well as OATP1B3- and OATP2B1-mediated uptake of E3S. The mean IC_{50} value of ACT-064992 for OATP1B1 was 6.9 μM, for OATP1B3 was 14 μM, and 0.8 μM for OATP2B1, respectively. The corresponding values for ACT-132577 were 21 μM, 56 μM and 15 μM, respectively.	
Conclusions: <ul style="list-style-type: none">• Hepatic uptake of macitentan and its active metabolite ACT-132577 does not depend on human OATP transporters as the uptake of both compounds into wild-type as well as OATP1B1-,	

OATP1B3- and OATP2B1-expressing CHO cells was comparably high. The cellular uptake of both compounds could be mainly driven by passive diffusion. Small contributions of active transport to the overall hepatic uptake cannot be excluded based on the present in vitro data. However, co-administration of OATP inhibitors in a clinical setting is unlikely to change the pharmacokinetic profile of ACT-064992 and ACT-132577.

- Macitentan and ACT-132577 both inhibited OATP1B1-mediated uptake of atorvastatin, as well as OATP1B3- and OATP2B1-mediated uptake of E3S.

Reviewer's Comments:

The total peak plasma concentrations of ACT-064992 and ACT-132577 at steady-state in healthy subjects are around 0.6 μ M and 1.5 μ M, respectively, with a 10 mg dose. Binding of ACT-064992 and ACT-132577 to human plasma proteins in vitro was reported as 99.6 % and 99.5 %, respectively. Therefore, the systemic exposure to macitentan or its active metabolite at clinical doses (10 mg once daily) is less likely to provide clinically significant impact on the PK of drugs that are OATP substrates.

Pharmacokinetic Studies

Mass Balance Study

Studies: AC-055-104 Study Period: 2007	Title: A single-center, open-label study with ¹⁴ C-labeled ACT-064992 to investigate the mass balance, pharmacokinetics, and metabolism following single oral administration to healthy male subjects																																								
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ac-055-104																																									
Objective: The primary objective was to investigate the rate and routes of excretion of ACT-064992 and the mass balance in urine and feces.																																									
Study Design: <ul style="list-style-type: none">Phase 1 study, open-label, single dose, single group design, N=6 healthy male subjectsScreening evaluation between 2 weeks and 3 days before dose administration, single dose treatment followed by at least 14 days of observation period and end of study examination(b) (4) formulation containing 10 mg ¹⁴C-labeled ACT-064992																																									
Results: <p>The cumulative radioactivity recovered from feces and urine was ~74 % of the administered dose. Approximately 50 % from urine and 24 % from feces was recovered with none in the form of unchanged drug or the active metabolite ACT-132577. The average plasma concentration-time profiles of total radioactivity (as ng equivalents/ml), ACT-064992 and ACT-132577 (as ng/ml) after a single 10 mg ¹⁴C-labeled dose (N=6) is shown below:</p> <table border="1"><caption>Estimated data from Figure 1</caption><thead><tr><th>Time (hr)</th><th>Concentration_ACT-064992 (ng/mL)</th><th>Concentration_ACT-132577 (ng/mL)</th><th>Radioactivity (ng-mL equiv.)</th></tr></thead><tbody><tr><td>0</td><td>1</td><td>1</td><td>1</td></tr><tr><td>10</td><td>150</td><td>100</td><td>250</td></tr><tr><td>50</td><td>40</td><td>100</td><td>150</td></tr><tr><td>100</td><td>5</td><td>50</td><td>100</td></tr><tr><td>150</td><td>1</td><td>20</td><td>50</td></tr><tr><td>200</td><td>-</td><td>10</td><td>25</td></tr><tr><td>250</td><td>-</td><td>5</td><td>15</td></tr><tr><td>300</td><td>-</td><td>3</td><td>10</td></tr><tr><td>320</td><td>-</td><td>2</td><td>10</td></tr></tbody></table>		Time (hr)	Concentration_ACT-064992 (ng/mL)	Concentration_ACT-132577 (ng/mL)	Radioactivity (ng-mL equiv.)	0	1	1	1	10	150	100	250	50	40	100	150	100	5	50	100	150	1	20	50	200	-	10	25	250	-	5	15	300	-	3	10	320	-	2	10
Time (hr)	Concentration_ACT-064992 (ng/mL)	Concentration_ACT-132577 (ng/mL)	Radioactivity (ng-mL equiv.)																																						
0	1	1	1																																						
10	150	100	250																																						
50	40	100	150																																						
100	5	50	100																																						
150	1	20	50																																						
200	-	10	25																																						
250	-	5	15																																						
300	-	3	10																																						
320	-	2	10																																						
Summary of the PK parameters are described below:																																									
Ref: AC-055-104 Study report, Page 50, Figure 1																																									

Matrix	t _{max} (h)	C _{max} (ng/ml)	t _{1/2} (h)	AUC _∞ (ng.h/ml)
Whole blood*	14 (6-24)	131 (119-144)	43 (32-58)	11385 (10405-12457)
Plasma*	12 (7-24)	235 (208-266)	103 (94-113)	21885 (18971-25248)
ACT-064992	6 (5-10)	170 (134-214)	15 (14-17)	5494 (4903-6156)
ACT-132577	48 (all 48)	121 (108-135)	44 (38-51)	12924 (11455-14581)

*Radioactivity (ng equivalent)

values are median (range) for t_{max} and geometric mean (95% CI) for others

Ref: AC-055-104 Study report, Page 51, Table 6

The table below describes the relative contribution of various moieties identified relative to the administered radioactive dose.

Percentage of radioactive dose recovered from urine and feces and relative contribution of various moieties. Note: 26.4% of the total radioactivity is unaccounted.

Moiety	Urine (49.7% of dose)		Feces (23.9% of dose)	
	% in Urine	% of Dose	% in Feces	% of Dose
Macitentan	0	0	16.9	4
Active (ACT-132577)	0	0	14	3.3
Inactive (ACT-373898)	22.9	11.4	3.6	0.9
ACT-080803	7	3.5	37.7	9
M323 u	26	12.9	13.1	3.1
M602 u	0	0	2	0.5
M706 u	24.8	12.3	0	0
Unidentified moieties	19.1	9.5	12.7	3

- The hydrolysis product ACT-080803 and a conjugate of ACT-132577 with glucose (M706u) accounted for 7 % and 25 % of radioactivity excreted in urine. Other moieties identified in urine were ACT-373898 and its hydrolysis product M323u, accounting for 23 % and 26 % of radioactivity excreted in urine, respectively.
- The five entities identified in feces were macitentan, ACT-132577, ACT-373898, M323u, and ACT-080803. ACT-080803 was the major product in feces, accounting for 37.7% of radioactivity excreted in feces. Macitentan and ACT-132577 represented 17 % and 14 % of radioactivity excreted in feces.

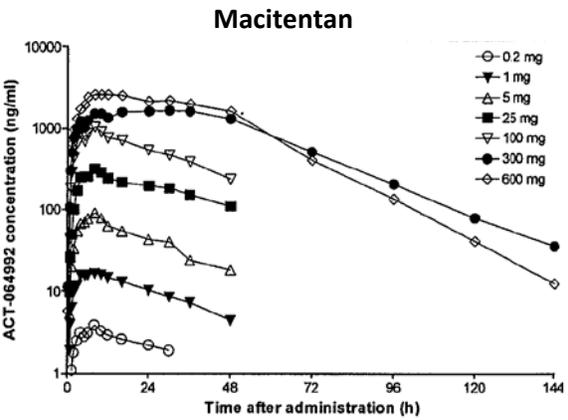
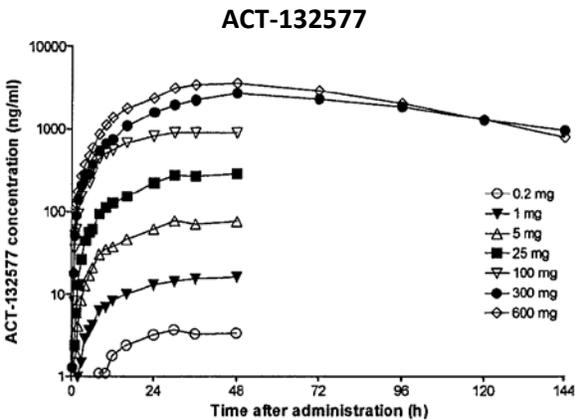
Conclusions:

- About 50 % of radio activity was recovered in urine, followed by 24% from feces.

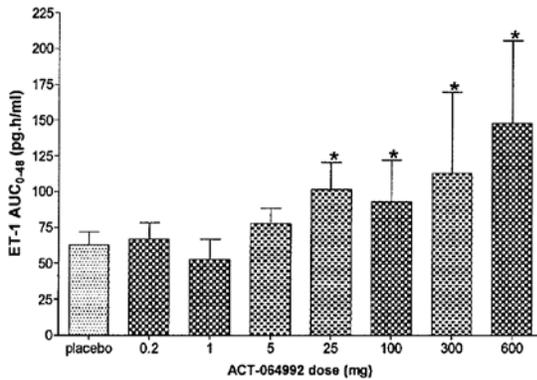
Reviewer's Comments:

The mass balance study accounted for only about 74 % of the total radioactivity, which is not optimal, and about 19 % and 13 % of the radioactivity detected in urine and feces are not characterized.

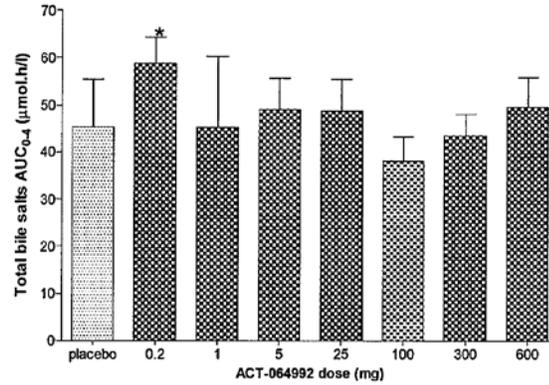
Single Ascending Dose PK Study

Study: AC-055-101 Study Period: 2004	Title: Investigation of the single ascending dose tolerability, PK and PD of ACT-064992 in healthy male subjects
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ac-055-101\ac-055-101-legacy.pdf	
Objective: To assess the PK, safety and tolerability of single doses of macitentan in healthy subjects	
Study Design: Single center, double blind, randomized, placebo controlled, SAD phase 1 study in healthy male volunteers (20-50 years of age, N~6 per dose group). Macitentan doses: Single dose of 0.2, 1, 5, 25, 100, 300 and 600 mg Test product/Route: 0.2, 1, 10 and 100 mg oral (b) (4) or matching placebo Bioanalysis: LC-MS/MS for macitentan and its active metabolite ACT-132577. Plasma ET-1 and total bile salts were also monitored.	
Results: The maximum plasma concentrations of macitentan and ACT-132577 were reached in about 8-12 h and 33-48 h respectively. The elimination half-life of macitentan was 13.4-17.5 h and that for ACT-132577 was 40-65.6 h (estimated only in 300 and 600 mg doses). The PK of macitentan and ACT-132577 were not dose proportional over the dose range studied. The average plasma concentration-time profiles of macitentan and its active metabolite ACT-132577 as well the effects on plasma ET-1 levels and bile salts are shown below:	
	

Effect on Plasma ET-1 (as AUC_{0-48h})



Effect on Plasma Bile Salts (as AUC_{0-4h})



* denotes statistical significance $P < 0.05$ compared placebo

Macitentan increased the plasma ET-1 levels, especially at higher doses while no significant effects were seen on total bile salts in plasma within 4 hours post dose (See Figures below). Metabolic profiling indicated that neither macitentan nor its metabolite ACT-132577 was present in urine.

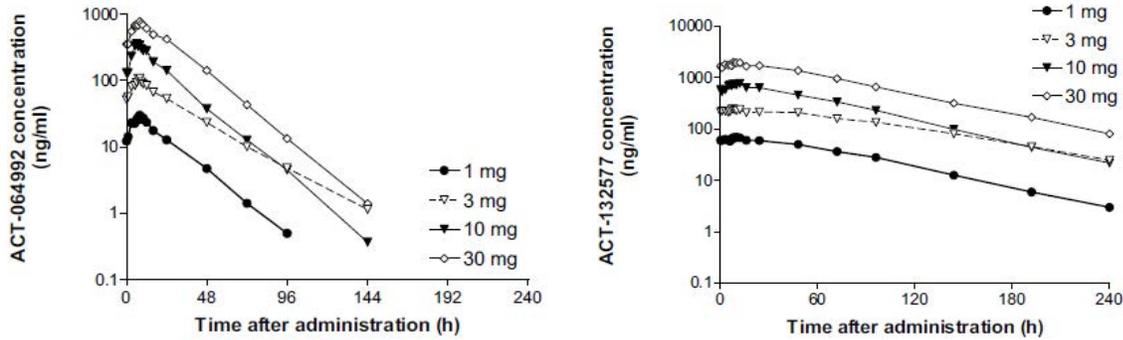
Conclusions:

- Single dose up to 300 mg was tolerated in healthy male subjects.
- Macitentan is absorbed slowly with a t_{max} of about 8 hours.
- The active metabolite ACT-132577 has a long elimination half-life of about 40-66 hours and will accumulate on repeat dosing.
- The sampling for total bile salts were done only up to 4 hours post dose and single dose of macitentan had no significant effects on bile salt levels (as measured as AUC_{0-4h}).
- Plasma ET-1 levels showed only an increasing trend with dose

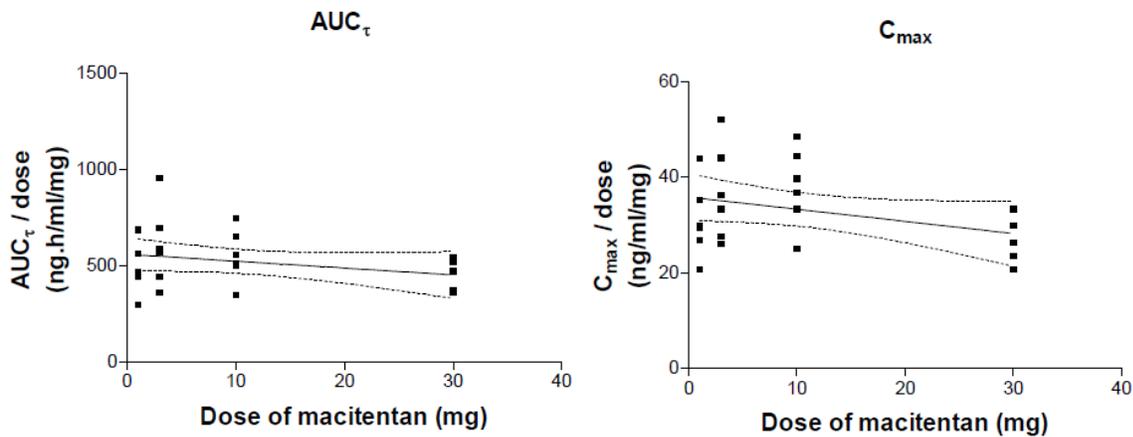
Multiple Ascending Dose PK Study

Study: AC-055-102 Study Period: 2005	Title: Investigation of the multiple ascending dose tolerability, pharmacokinetics and pharmacodynamics of ACT-064992 in healthy male subjects
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ac-055-102	
Objective: To evaluate the safety, tolerability and PK of multiple ascending doses of macitentan in healthy subjects	
Study Design: This was a single center, double-blind, placebo-controlled, randomized, ascending multiple dose study. Each dose level was investigated in a new group of 8 healthy male subjects (6 on active treatment and 2 on placebo). Macitentan doses: 1, 3, 10 and 30 mg once daily for 10 days Test product/Route: 1 and 10 mg oral (b) (4) or matching placebo Bioanalysis: <ul style="list-style-type: none">• Macitentan and its active metabolite ACT-132577 on days 1 and 10• Plasma ET-1 and bile salts levels• 6β-hydroxycortisol/cortisol ratio in 24 hr urine on days -1, 1 and last day (as an index for CYP3A enzyme induction) <i>Reviewer's Comment: The CYP3A induction potential of macitentan was evaluated in this study because a prior in vitro study suggested that macitentan and its active metabolite have the potential to induce CYP3A.</i>	
Results: The PK of macitentan was characterized by slow absorption ($t_{max} \sim 8$ h) and an average apparent elimination half-life of ~ 16 h. The PK of macitentan was almost dose proportional between 1 and 30 mg doses. After once daily multiple dosing the steady state concentrations of macitentan and its active metabolite ACT-132577 were reached after 3 days and 7 days respectively. The accumulation of macitentan at steady-state was approximately 1.5 fold while that of ACT-132577 was about 8.5 fold. The observed accumulation and that projected based on the half-life estimated following single dose are similar, indicating that there is no time-dependant pharmacokinetics for macitentan or its active metabolite. At steady state the metabolites ACT-132577 (active) and ACT-373898 (inactive) contributed to approximately 74% and 3% of total drug exposure, respectively.	

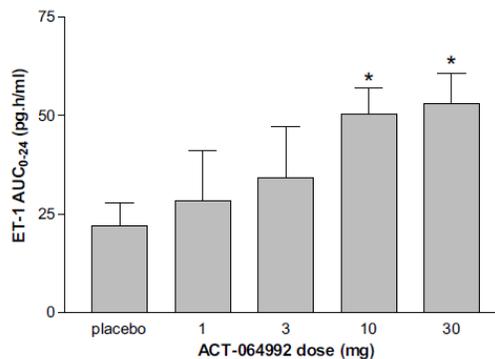
Average plasma concentration-time profiles of macitentan and ACT-132577



Dose normalized AUC and C_{max} of macitentan on Day 10



Plasma ET-1 levels (expressed as AUC_{24h} on day 10) showed an increasing trend with dose with 10 mg and 30 mg dose groups showing statistically significant increase compared to the placebo group (shown below with asterisks).



The urinary 6β-hydroxycortisol/cortisol ratios did not show statistically significant increase upon repeat dosing with macitentan. The plasma bile salts levels showed an increasing trend from day 1 to day 10, but were considered not clinically significant although the actual reasons are not known. Four subjects treated with macitentan had asymptomatic elevation in ALT or AST which were below 3xULN, but there were no effects on serum bilirubin, bile salts or alkaline phosphatases.

Conclusions:

- Macitentan is generally well tolerated in the study and the PK findings are consistent with the single ascending dose study
- Macitentan did not seem to affect urinary 6 β -hydroxycortisol/cortisol ratios on repeat dosing suggesting a lower potential for CYP3A induction
- There were incidence of ALT/AST elevations, but were not considered clinically significant

(b) (4) **vs. Tablet Relative Bioavailability Study**

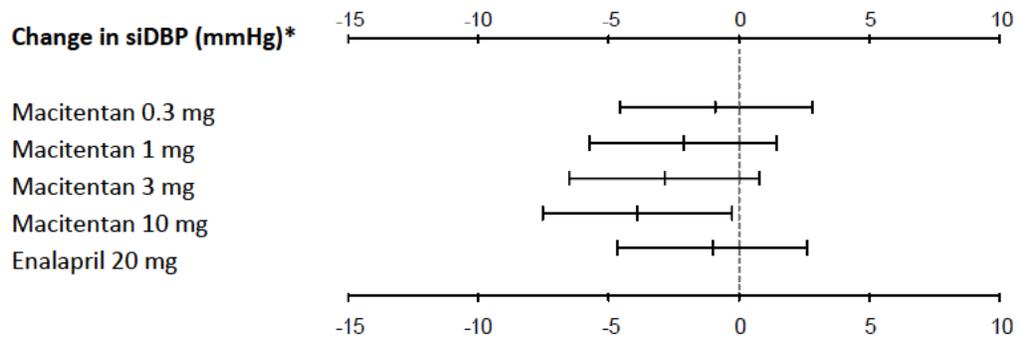
Study: AC-055-108 Study Period: 2007	Title: A single center, open label, randomized, two way cross over study to investigate the relative bioavailability of a single dose tablet and (b) (4) formulation of ACT-064992 in healthy male subjects												
EDR:\\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\ac-055-108													
<p>Objective: To evaluate the PK of macitentan from tablet and (b) (4) formulations after single dose treatment</p> <p><i>Reviewer's Comment: Earlier clinical pharmacology studies were conducted with the (b) (4) formulation. Rest of the clinical development program was conducted with the tablet dosage form. This study provided the bridging information between the two dosage forms.</i></p>													
<p>Study Design: The study was designed as a single center, open-label, randomized, two-way crossover, single-dose, Phase I study, involving about 12 healthy subjects.</p> <p>Treatment A: 10 mg single dose of ACT-064992 Tablet with 9 days observation period</p> <p>Treatment B: 10 mg single dose of ACT-064992 (b) (4) with 9 days observation period</p> <p>The washout period was 2 weeks. The subjects were fasted for at least 12 hours before study drug administration and 5 hours thereafter. Plasma concentrations of both macitentan and its active metabolite ACT-132577 were measured in this study.</p>													
<p>Results: The summary statistics of PK parameters of macitentan and ACT-132577 are shown below:</p> <table border="1" data-bbox="297 1356 1321 1493"> <thead> <tr> <th>Analyte*</th> <th>C_{max} (ng/ml)</th> <th>AUC_{0-t} (ng.h/ml)</th> <th>AUC_{0-∞} (ng.h/ml)</th> </tr> </thead> <tbody> <tr> <td>Macitentan</td> <td>0.81 (0.75-0.88)</td> <td>0.93 (0.87-0.99)</td> <td>0.93 (0.88-0.99)</td> </tr> <tr> <td>ACT-132577</td> <td>0.93 (0.86-1.0)</td> <td>0.94 (0.88-1.0)</td> <td>0.95 (0.89-1.0)</td> </tr> </tbody> </table> <p>*Ratio of geometric means of tablet/ (b) (4) and 90% confidence intervals are shown</p> <p>The apparent elimination half-life of macitentan and ACT-13257 were ~ 13 h and 46 h respectively.</p>		Analyte*	C _{max} (ng/ml)	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	Macitentan	0.81 (0.75-0.88)	0.93 (0.87-0.99)	0.93 (0.88-0.99)	ACT-132577	0.93 (0.86-1.0)	0.94 (0.88-1.0)	0.95 (0.89-1.0)
Analyte*	C _{max} (ng/ml)	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)										
Macitentan	0.81 (0.75-0.88)	0.93 (0.87-0.99)	0.93 (0.88-0.99)										
ACT-132577	0.93 (0.86-1.0)	0.94 (0.88-1.0)	0.95 (0.89-1.0)										
<p>Conclusions:</p> <ul style="list-style-type: none"> • The PK of macitentan and ACT-132577 were similar after 10 mg single dose administration as (b) (4) or tablet • The point estimates and 90% CI of AUC and C_{max} for macitentan were mostly within the acceptable BE range of 0.8-1.25 except that the lower 90 % CI for C_{max} (which was 0.75) • The same tablet formulation was used in the Phase III study and the final marketing image formulation is same as that used in Phase III. 													

Food Effect Study

Study: AC-055-103 Study Period: 2005	Title: Exploratory, open-label, randomized, 2-period, 2-treatment, cross-over study to investigate the effect of food on the pharmacokinetics of ACT-064992 in healthy male subjects												
EDR:\\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ac-055-103													
Objective: To evaluate the food effect on the PK of macitentan in healthy subjects													
<p>Study Design: This was a single center, open-label, randomized, 2-period, 2-treatment, cross-over study. About 10 healthy male Caucasian subjects participated in the study.</p> <p><u>Treatment A:</u> single 10 mg dose of macitentan (b) (4) in fasted state</p> <p><u>Treatment B:</u> single 10 mg dose of macitentan (b) (4) fed state (high fat, high calorie breakfast)</p> <p>The washout period was 3 weeks between treatments. For treatment A, subjects were fasted for at least 10 hours before dose administration and continued to fast for another 5 hours thereafter. During treatment B, subjects consumed a high calorie, high fat breakfast within 30 minutes prior to study drug administration. Both macitentan and its active metabolite ACT-132577 were monitored in this study.</p>													
Results: The summary statistics of PK parameters of macitentan and ACT-132577 are shown below:													
<table border="1"> <thead> <tr> <th>Analyte*</th> <th>C_{max} (ng/ml)</th> <th>AUC_{0-t} (ng.h/ml)</th> <th>AUC_{0-∞} (ng.h/ml)</th> </tr> </thead> <tbody> <tr> <td>Macitentan</td> <td>1.07 (0.96-1.21)</td> <td>0.98 (0.90-1.07)</td> <td>0.97 (0.89-1.07)</td> </tr> <tr> <td>ACT-132577</td> <td>1.04 (0.97-1.12)</td> <td>1.05 (1.02-1.08)</td> <td>1.05 (1.01-1.08)</td> </tr> </tbody> </table>		Analyte*	C _{max} (ng/ml)	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	Macitentan	1.07 (0.96-1.21)	0.98 (0.90-1.07)	0.97 (0.89-1.07)	ACT-132577	1.04 (0.97-1.12)	1.05 (1.02-1.08)	1.05 (1.01-1.08)
Analyte*	C _{max} (ng/ml)	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)										
Macitentan	1.07 (0.96-1.21)	0.98 (0.90-1.07)	0.97 (0.89-1.07)										
ACT-132577	1.04 (0.97-1.12)	1.05 (1.02-1.08)	1.05 (1.01-1.08)										
<p>*Ratio of geometric means of fed/fasted states and 90% confidence intervals are shown</p>													
<p>The apparent elimination half-life of macitentan and ACT-132577 were ~ 13-14 h and 42-44 h, respectively.</p>													
<p>Conclusions:</p> <ul style="list-style-type: none"> The PK of macitentan and ACT-132577 was not altered when administered with or without food. 													

Phase II Study in Hypertensive Patients

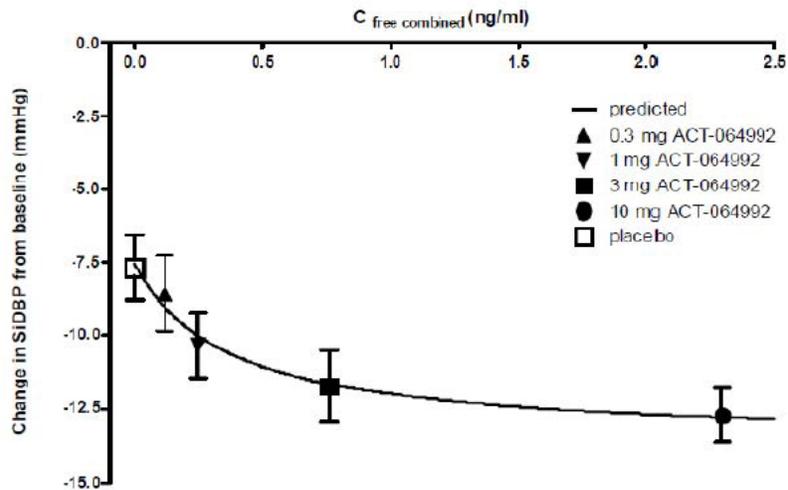
<p>Study: AC-055-201 Study Period: 2006</p>	<p>Title: A multicenter, double-blind, randomized, placebo and active controlled, parallel group, dose ranging study to evaluate the efficacy, safety and tolerability of ACT-064992 in subjects with mild to moderate essential hypertension</p>
<p>EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pah\5354-other-stud-rep\ac-055-201</p>	
<p>Objective: To evaluate the effect of a once daily oral regimen of 4 doses of macitentan on sitting diastolic blood pressure (SiDBP) at trough at 8 weeks of treatment</p>	
<p>Study Design: This was a multi-center, double-blind, randomized, parallel group, dose ranging Phase II study. Enalapril 20 mg was the active control.</p> <p>Study population: Subjects (N~379) with mild to moderate hypertension (Graeds 1 and 2 of the 1999 WHO hypertension classification)</p> <p>Macitentan doses studied: 0.3, 1, 3, and 10 mg (b) (4)</p> <p>The study design included a single-blind placebo run-in, wash out phase (Period 1) of 2 to 4 weeks. This was followed by an 8 week, double blind treatment phase (Period II). There was a 28 day follow up period starting after study drug discontinuation. All treatments (macitentan, placebo or enalapril) were administered in once daily regimen. Subjects who fulfilled all eligibility criteria and met none of the exclusion criteria at the end of Period 1 entered into Period 2 and were randomly assigned to treatment with one of the 4 doses of macitentan, enalapril or matching placebo in a 1:1:1:1:1 manner.</p> <p>Reviewer's Comments:</p> <p><i>The phase II study was conducted in subjects with mild to moderate hypertension and not in PAH patients. Hence, there is an uncertainty in extrapolating the findings from this study to a PAH population.</i></p>	
<p>Results:</p> <p>Macitentan treatment showed reduction in siDBP at trough and the BP effect was more pronounced at the highest dose group (See the figure below). However this study was not powered to compare the BP effects between dose groups or enalapril.</p>	



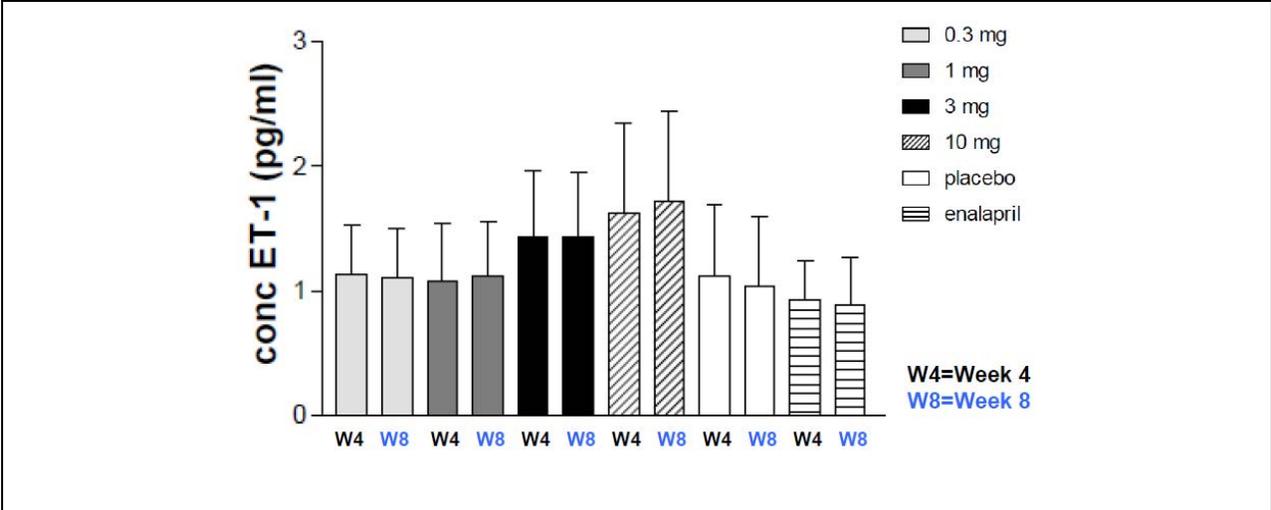
*Change in SiDBP from baseline to end of treatment (placebo corrected), per protocol set

Ref: Fig 3 of Study report

A PK/PD analysis using combined free fractions of macitentan and ACT-132577 in plasma suggested that the 10 mg dose may have provided the maximum pharmacological effect (SiDBP). The change in SiDBP (mean \pm SEM) versus combined free plasma concentrations of macitentan and its active metabolite ACT132577 at week 8 is shown below:



The plasma ET-1 levels also showed an increasing trend with macitentan dose but it should be noted that none of these increases were statistically significant. The average plasma ET-1 trough concentrations (+SD) at weeks 4 and 8 are shown below:



Conclusions:

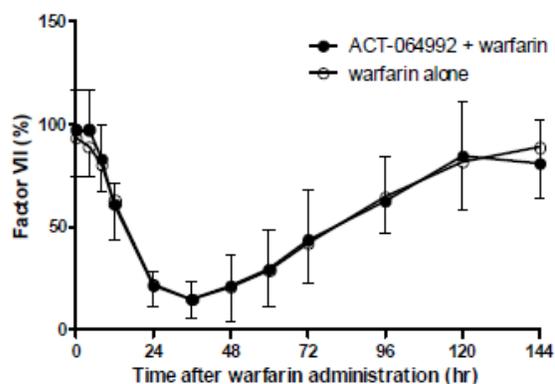
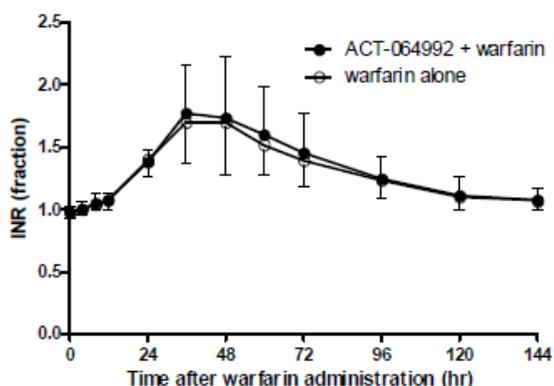
- A dose dependent decrease in SiDBP and increase in plasma ET-1 levels was observed. However, none of the findings are statistically significantly different either between the doses or the control.
- The highest and intermediate doses studied here (10 mg and 3 mg, respectively) were carried forward for further studies in PAH patients

Drug-Drug Interaction Studies

Warfarin

Study: AC-055-105 Study Period: 2007	Title: An open label study to investigate the effect of multiple dose ACT-064992 on the pharmacokinetics and pharmacodynamics of single dose warfarin in healthy male subjects									
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\ac-055-105										
Objective: To evaluate the drug interaction potential of multiple oral dose macitentan on single warfarin										
<p>Study Design: This was a single center, open label, randomized, two-way cross-over Phase I study in healthy subjects (N~12).</p> <p>Treatment A: Loading dose of 30 mg macitentan on day 1. Thereafter 10 mg macitentan once daily for 8 days. On Day 4, a single oral dose of 25 mg warfarin was administered together with macitentan. The total observation period was 9 days.</p> <p>Treatment B: A single dose of 25 mg warfarin on Day 1. The observation period was 6 days following warfarin dose.</p> <p>The two treatments were separated by a washout period of 2 to 3 weeks. The meals were standardized during treatment. Plasma concentrations of macitentan and ACT-132577 at trough and both R- and S-warfarin were measured in the study. INR and Factor VII activity were used as the pharmacodynamics measure for warfarin.</p> <p>Reviewer Comments:</p> <p><i>This study evaluated the potential for macitentan to inhibit CYP2C9. A 30 mg loading dose was used for macitentan to reach steady state conditions faster (by day 4 compared to day 7 without loading dose) for the active metabolite ACT-132577</i></p>										
<p>Results:</p> <p>The PK was similar with or without the concomitant administration of macitentan for both R- and S-warfarin.</p> <p>The geometric mean ratios and confidence intervals for warfarin in the presence or absence of macitentan are listed below (N=12):</p> <table border="1" data-bbox="428 1663 1192 1793"> <thead> <tr> <th>Analyte*</th> <th>C_{max} (ng/ml)</th> <th>AUC_{0-∞} (ng.h/ml)</th> </tr> </thead> <tbody> <tr> <td>S-warfarin</td> <td>0.94 (0.85-1.04)</td> <td>1.01 (0.96-1.05)</td> </tr> <tr> <td>R-Warfarin</td> <td>0.97 (0.92-1.03)</td> <td>1.0 (0.94-1.05)</td> </tr> </tbody> </table> <p>*Ratio of geometric means of trt-A/trt-B and 90% confidence intervals, trt-A: macitentan+warfarin, trt-B: warfarin only</p>		Analyte*	C _{max} (ng/ml)	AUC _{0-∞} (ng.h/ml)	S-warfarin	0.94 (0.85-1.04)	1.01 (0.96-1.05)	R-Warfarin	0.97 (0.92-1.03)	1.0 (0.94-1.05)
Analyte*	C _{max} (ng/ml)	AUC _{0-∞} (ng.h/ml)								
S-warfarin	0.94 (0.85-1.04)	1.01 (0.96-1.05)								
R-Warfarin	0.97 (0.92-1.03)	1.0 (0.94-1.05)								

It appears that macitentan did not alter the pharmacodynamics of warfarin, as measured by INR and Factor VII activity. The average INR and Factor VII activity over time with warfarin in the presence or absence of macitentan are shown below:



Macitentan regimen included a loading dose and the steady state was reached on Day 3 for macitentan in this study.

Reviewer's Comment:

The study showed that there is no PK interaction between macitentan and warfarin. However, it is not clear whether a single dose study is sensitive enough to rule out any potential pharmacodynamics interactions for warfarin.

Conclusions:

- Macitentan did not alter the PK and PD of warfarin in this study
- No dose adjustments are required for macitentan or warfarin on co-administration

Sildenafil

Study: AC-055-106 Study Period: 2007	Title: An open label, randomized, 3-treatment, 3-period, cross-over study to investigate mutual drug-drug interactions (DDI) between ACT-064992 and sildenafil in healthy male subjects
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\ac-055-106	
<p>Objective: To evaluate (1) the effect of macitentan on the PK of sildenafil and its desmethyl metabolite at steady state, (2) effect of sildenafil on the PK of macitentan and its metabolite ACT-132577 and (3) the tolerability macitentan and sildenafil on co-administration</p> <p><i>Reviewer's Comment: Macitentan is shown to have the potential to induce CYP3A4 in previous in vitro studies. Although multiple dose studies did not indicate any such possibility, the applicant assessed the PK interaction potential of macitentan at clinical dose level with sildenafil, a CYP3A4 substrate and more importantly a commonly used PAH drug.</i></p>	
<p>Study Design: Open label, randomized, 3-treatment, 3-period cross-over study.</p> <p><u>Treatment A:</u> Loading dose of 30 mg macitentan as single oral dose on day 1. Thereafter, 10 mg macitentan administered orally, once daily for 3 days.</p> <p><u>Treatment B:</u> Sildenafil 20 mg three times daily for 3 days and a single 20 mg dose on Day 4, administered orally.</p> <p><u>Treatment C:</u> Loading dose of 30 mg macitentan as single oral dose on day 1. Thereafter, 10 mg macitentan administered orally, once daily for 3 days. Concomitantly, orally administered sildenafil 20 mg three times daily for 3 days and a single 20 mg dose on Day 4.</p> <p>The washout period between treatments was at least 10 days. Plasma concentrations of macitentan, sildenafil and their major metabolites ACT-132577 and N-desmethyl sildenafil, respectively were measured in this study.</p>	
<p>Results:</p> <p>Sildenafil is a CYP3A4 substrate and is a commonly used drug for the treatment of PAH. In the presence of macitentan, the exposure to sildenafil and its metabolites were higher (~15% and 8%) than during monotherapy (See table below). The PK characteristics of macitentan were not affected but ACT-132577 showed a 15% reduction in its exposure when co-administered with sildenafil.</p>	

Analyte*	C _{max} (ng/ml)	AUC _τ (ng.h/ml)
Macitentan	0.99 (0.92-1.06)	1.06 (1.01-1.12)
ACT-132577	0.82 (0.76-0.89)	0.85 (0.80-0.91)
Sildenafil	1.26 (1.07-1.48)	1.15 (0.94-1.41)
N-desmethyl sildenafil	1.10 (0.99-1.22)	1.08 (0.96-1.22)

*Ratio of geometric means (presence/absence of interacting drug) and 90% confidence intervals, N=12

Conclusions:

- The PK of macitentan and ACT-132577 were not significantly affected by sildenafil
- Sildenafil and its metabolite showed a slight increase in exposure with macitentan, but is not considered significant
- The lack of DDI with sildenafil also suggests that CYP3A4 auto-induction is not expected at clinical doses for macitentan
- No dose adjustments are needed when macitentan and sildenafil are co-administered

Reviewer's Comments:

Approximately 58% of the study population in the SERAPHIN Phase III study was taking other PAH therapy, mainly sildenafil, as a co-medication. Macitentan also showed efficacy in patients taking concomitant PAH therapy at baseline (hazard ratio of 0.62 vs 0.45 in patients with no baseline PAH therapy for the occurrence of first morbidity or mortality event up to end of treatment plus 7 days).

Ketoconazole

Study: AC-055-107 Study Period: 2007	Title: A single center, open label, randomized, 2-period, cross-over, Phase I study to investigate the pharmacokinetic interaction between ACT-064992 and ketoconazole in healthy male subjects										
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\ac-055-107											
Objective: To evaluate the influence of concomitant ketoconazole, a strong CYP3A4 inhibitor, on the PK of macitentan and its metabolite ACT-132577 in healthy subjects											
<p>Study Design: This study was conducted as a single-center, open-label, randomized, two-way crossover, Phase 1 study involving about 12 subjects. After eligibility screening, the subjects were randomized to receive one of the two possible sequences (A/B and B/A) of the following treatments:</p> <p><u>Treatment A:</u> A single oral dose of 10 mg macitentan was to be administered on Day 1. The total observation period was to be 10 days following administration.</p> <p><u>Treatment B:</u> Ketoconazole was to be administered as multiple oral doses of 400 mg once daily for 24 days, starting on Day 1. On Day 5, a single oral dose of 10 mg macitentan was to be administered together with ketoconazole. The total observation period was to be 25 days following the administration of the first dose of ketoconazole.</p> <p>The two treatments were to be separated by a washout period of 3 weeks. The study measured plasma levels of both macitentan and ACT-132577.</p>											
<p>Results and Discussion:</p> <p>A single dose (10 mg) of macitentan when given with ketoconazole, administered as 400 mg once daily, increased the exposure (AUC_{∞}) and C_{max} to macitentan by about 2.3X and 1.3X respectively. The exposure and C_{max} of its active metabolite ACT-132577 decreased by ~ 26 % and ~ 51 % respectively. The elimination half-life of macitentan increased from 14.1 hours to 28.5 hours, while that of ACT-132577 showed a modest increase (46.7 hours versus 58.6 hours).</p> <p>The summary statistics of PK parameters of macitentan and ACT-132577 in the presence or absence of ketoconazole are shown below:</p> <table border="1" data-bbox="365 1617 1250 1759"> <thead> <tr> <th>Analyte*</th> <th>C_{max} (ng/ml)</th> <th>$AUC_{0-\infty}$ (ng.h/ml)</th> </tr> </thead> <tbody> <tr> <td>Macitentan</td> <td>1.28 (1.21-1.35)</td> <td>2.32 (2.15-2.50)</td> </tr> <tr> <td>ACT-132577</td> <td>0.49 (0.43-0.56)</td> <td>0.74 (0.66-0.84)</td> </tr> </tbody> </table> <p>*Ratio of geometric means in the presence/absence of ketoconazole and 90% confidence intervals. N=10</p>			Analyte*	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	Macitentan	1.28 (1.21-1.35)	2.32 (2.15-2.50)	ACT-132577	0.49 (0.43-0.56)	0.74 (0.66-0.84)
Analyte*	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)									
Macitentan	1.28 (1.21-1.35)	2.32 (2.15-2.50)									
ACT-132577	0.49 (0.43-0.56)	0.74 (0.66-0.84)									

Reviewer's Comments:

The observed DDI effects with ketoconazole could be attributed to its effects on the elimination phase of macitentan. The accumulation of macitentan on repeat dosing in presence of strong CYP3A4 inhibition could be much higher with an estimated accumulation index (R) of ~ 2.3 versus 1.4 when no CYP3A4 inhibition is present. Based on PBPK simulations using SimCYP® (described separately in a PBPK report) the exposure at steady state is expected to be approximately 3X to 4X higher with strong CYP3A4 inhibitors. The long term safety information on macitentan on doses higher than 10 mg is limited.

The applicant is seeking approval for only the 10 mg dose strength [REDACTED] (b) (4) [REDACTED]. Therefore, the option to reduce the dose of macitentan with strong CYP3A4 inhibitors is not considered. The use of macitentan 10 mg should therefore be avoided with strong CYP3A4 inhibitors like ketoconazole.

Two subjects in this study reported an increase in liver enzymes during the study, which were reported as AEs. One of the two subjects discontinued study drug treatment due to this AE. The elevations in liver enzymes were larger than 2 × ULN but did not exceed 4 × ULN and were asymptomatic and resolved without sequelae.

Conclusions:

- Strong CYP3A4 inhibition by ketoconazole resulted in significant increase in exposure to macitentan, a CYP3A4 substrate
- Two subjects in this DDI study reported increase in liver enzymes as an AE and one subject discontinued study treatment because of this AE
- The long term safety information on macitentan on doses higher than 10 mg is limited
- The use of macitentan 10 mg should therefore be avoided with strong CYP3A4 inhibitors like ketoconazole

Rifampin/Cyclosporine

Study: AC-055-111 Study Period: 2010	Title: A single-center, open-label, two-part, one-sequence crossover study to investigate the effect of cyclosporine and rifampicin on the pharmacokinetics of macitentan in healthy male subjects
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrinsic-factor-pk-stud-rep\ac-055-111	
Objective: To assess the effect of multiple dose cyclosporine (CYP3A4 and OATP inhibitor) and rifampin (strong CYP3A4 inducer) on the PK of macitentan and ACT-132577 <i>Reviewer Comments: Macitentan is a CYP3A substrate. Endothelin receptor antagonist (ERA) class to which macitentan belongs is known to be affected by OATP transporters. This study evaluated the effects of a strong CYP3A inducer (rifampin) and OATP inhibitor (cyclosporine).</i>	
Study Design: This was an exploratory, Phase 1, single-center, open-label, two-part, one-sequence crossover study to investigate the effect of cyclosporine and rifampicin on the pharmacokinetics of macitentan in healthy male subjects. This study had two parts, Part A and Part B. Part A for cyclosporine and Part B for rifampin. <u>Part A:</u> Each subject received multiple-dose treatment with macitentan, followed by multiple-dose co-administration of cyclosporine On the morning of Day 1, a loading dose of 30 mg of macitentan was administered orally. On the morning of Day 2 and thereafter, 10 mg of macitentan was administered orally, once daily for 16 days (Day 2 to Day 17) and a dose of 100 mg of cyclosporine was administered every 12 hours for 12 days, from the morning of Day 6 to Day 17. Both drugs were administered under fed conditions. <u>Part B:</u> Each subject received multiple-dose treatment with macitentan, followed by multiple-dose co-administration of rifampicin. On the morning of Day 1, a loading dose of 30 mg macitentan was administered orally. On the morning of Day 2 and thereafter, 10 mg of macitentan was administered orally, once daily for 11 days (from Day 2 to Day 12). An oral dose of 600 mg rifampicin was administered once daily for 7 days, from the morning of Day 6 to Day 12. Both study drugs were administered under fasted conditions (1 hour before a meal). The study measured plasma levels of both macitentan, ACT-132577 and inactive metabolite ACT-373898.	

Results & Discussion:

- In both Part A and part B, in the absence of cyclosporine or rifampin, steady state conditions for macitentan were reached on Day 5. The trough plasma levels of macitentan and its metabolites were similar in the absence of cyclosporine or rifampin.
- In the presence of cyclosporine, the exposure to macitentan and its metabolites did not change significantly (see table below).
- Rifampin, a strong CYP3A4 inducer, decreased the exposure to macitentan by about 80%. However the exposure to active metabolite ACT-132577 did not change much.

The summary statistics of PK parameters of macitentan, its active metabolite ACT-132577 and the inactive metabolite ACT-373898 in the presence or absence of cyclosporine/rifampin are shown below:

Perpetrator	Analyte*	C _{trough} (ng/ml)	AUC _t (ng.h/ml)
Cyclosporine	Macitentan	1.38 (1.06-1.81)	1.10 (0.91-1.33)
	ACT-132577	1.02 (0.87-1.19)	0.97 (0.85-1.11)
	ACT-373898	1.12 (0.81-1.55)	1.07 (0.79-1.45)
Rifampin	Macitentan	0.07 (0.05-0.1)	0.21 (0.17-0.26)
	ACT-132577	0.83 (0.73-0.94)	1.0 (0.89-1.12)
	ACT-373898	0.14 (0.09-0.20)	0.36 (0.27-0.50)

Ratio of geometric means in the presence/absence of cyclosporine or rifampin and 90% confidence intervals

Conclusions:

- Cyclosporine, an inhibitor of CYP3A4 and OATP, did not alter the PK of macitentan or its metabolites significantly. No dose adjustments are required for macitentan if co-administered with OATP inhibitors like cyclosporine.
- Rifampin, a strong CYP3A4 inducer, can significantly reduce the efficacy of macitentan. Therefore co-administration of macitentan with strong CYP3A4 inducers like rifampin should be avoided.

Reviewer's Comment:

Although the systemic exposure of ACT-132577 at steady state is about 3X higher than that of macitentan its potency at the ET receptors is assumed to be 5 to 8 times less than that of the parent drug. Therefore, there will be a consistent overall reduction (~ 50% or more) in the systemic availability of pharmacologically active moieties of macitentan when co-administered with rifampin. This may lead to reduced efficacy. The Phase III study SERAPHIN included 3 mg and 10 mg doses of macitentan (b) (4) the applicant is seeking approval only for the 10 mg strength.

Intrinsic Factor Studies

Japanese Vs. Caucasians

Study: AC-055-109 Study Period: 2008	Title: Single-center, open-label, parallel group study to evaluate the pharmacokinetics, tolerability, and safety of a single dose of 10 mg ACT-064992 in Japanese and Caucasian healthy subjects												
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ac-055-109													
Objective: To evaluate (1) the PK of macitentan in Japanese versus Caucasian healthy subjects after single dose treatment and (2) the tolerability of macitentan													
Study Design: This was a single-center, open-label, parallel group Phase 1 study. Ten healthy male and female Caucasian and ten healthy male and female Japanese subjects participated in this study. The Japanese and Caucasian subjects were matched for body weight ($\pm 5\%$) and gender. After an eligibility screening, the subjects received a single dose of 10 mg ACT-064992 as one tablet, administered in the fasting state on Day 1.													
Results: The absorption of macitentan was slow, with t_{max} occurring by 5 and 8.5 hours in Japanese and Caucasian subjects. The median apparent elimination half-life was 12.4 h (105-14.7) and 13.8 h (11.3-17.0) respectively in Japanese and Caucasians for macitentan. The median $t_{1/2}$ of ACT-132577 was slightly higher in Caucasians (52.6 vs. 41.4). Summary of the PK parameters are listed below: <table border="1" data-bbox="300 1165 1323 1291" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Analyte*</th> <th>C_{max} (ng/ml)</th> <th>AUC_{0-t} (ng.h/ml)</th> <th>$AUC_{0-\infty}$ (ng.h/ml)</th> </tr> </thead> <tbody> <tr> <td>Macitentan</td> <td>1.07 (0.91-1.25)</td> <td>0.85 (0.70-1.02)</td> <td>0.85 (0.71-1.02)</td> </tr> <tr> <td>ACT-132577</td> <td>1.02 (0.87-1.21)</td> <td>0.89 (0.77-1.03)</td> <td>0.85 (0.73-1.00)</td> </tr> </tbody> </table> <p style="text-align: center; margin-top: 5px;">*Ratio of geometric means of Japanese/Caucasians and 90% confidence intervals are shown</p>		Analyte*	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	Macitentan	1.07 (0.91-1.25)	0.85 (0.70-1.02)	0.85 (0.71-1.02)	ACT-132577	1.02 (0.87-1.21)	0.89 (0.77-1.03)	0.85 (0.73-1.00)
Analyte*	C_{max} (ng/ml)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)										
Macitentan	1.07 (0.91-1.25)	0.85 (0.70-1.02)	0.85 (0.71-1.02)										
ACT-132577	1.02 (0.87-1.21)	0.89 (0.77-1.03)	0.85 (0.73-1.00)										
Conclusions: <ul style="list-style-type: none"> • No clinically relevant differences were identified for the PK of macitentan between Japanese and Caucasian subjects 													

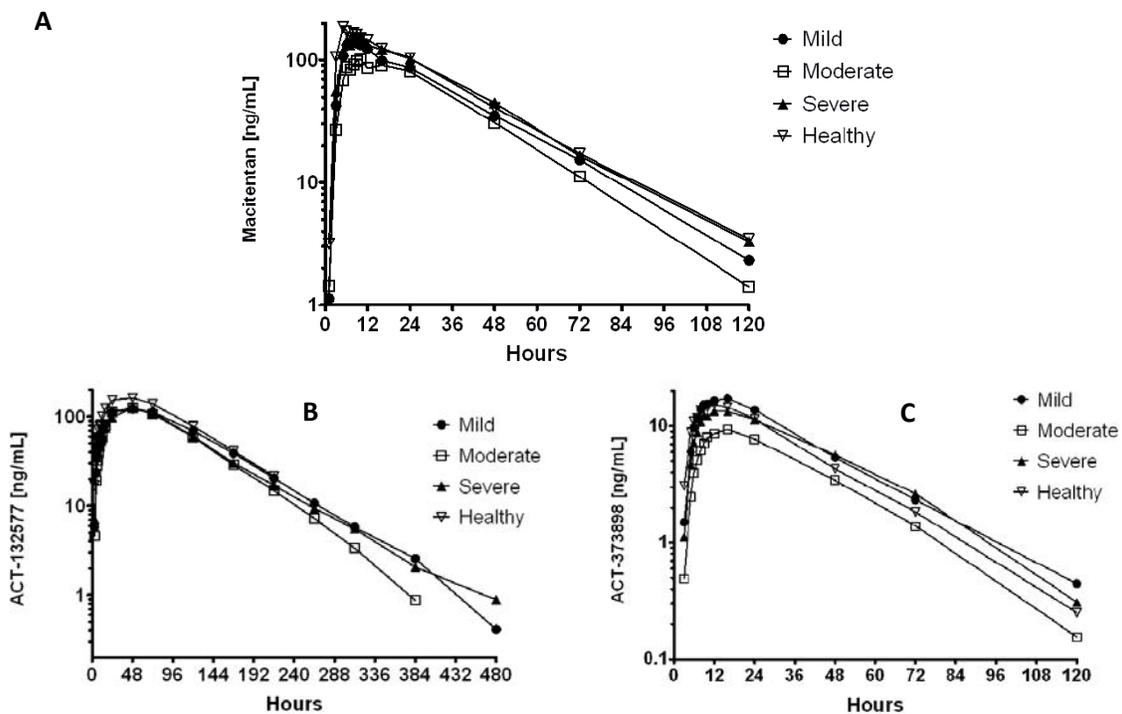
Hepatic Impairment Study

Study: AC-055-110 Study Period: 2009	Title: Single-center, open-label, single-dose study to investigate the pharmacokinetics, tolerability, and safety of ACT-064992 in subjects with mild, moderate, or severe hepatic impairment due to liver cirrhosis, and in healthy subjects															
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\ac-055-110\ac-055-110.pdf																
Objective: To assess the effect of mild, moderate or severe hepatic impairment due to liver cirrhosis on the PK of macitentan																
Study Design: Non-randomized, Open label, Single center, Single dose study <ul style="list-style-type: none"> • 24 subjects with hepatic impairment and 8 healthy normal subjects. • Child-Pugh classification for hepatic impairment, only hepatic impairment related to liver cirrhosis was included. • Subjects were to have normal renal function. • Co-administration of CYP3A4 inhibitors or inducers was not allowed. • Healthy subjects and subjects with hepatic impairment were not planned to be matched for age, sex or body weight. <p>Plasma concentrations of macitentan, active metabolite ACT-132577 and inactive metabolite ACT-373898 were measured in the study. Protein binding samples were collected at 8, 48 and 72 hours in all groups.</p>																
Results: Demographics of the study population is listed below: <table border="1" data-bbox="277 1289 1344 1415"> <thead> <tr> <th>Parameter</th> <th>Group A</th> <th>Group B</th> <th>Group C</th> <th>Group D</th> </tr> </thead> <tbody> <tr> <td>Age (years)</td> <td>46.4 (6.6)</td> <td>54.8 (8.5)</td> <td>48.9 (7.4)</td> <td>46.4 (8.8)</td> </tr> <tr> <td>BMI (Kg/m²)</td> <td>28.7 (2.5)</td> <td>25.9 (3.7)</td> <td>25.8 (3.3)</td> <td>25.9 (3.2)</td> </tr> </tbody> </table> <p>Groups A, B, C represent mild, moderate and severe hepatic impairment as per Child Pugh classification, Group D is healthy control, N=8 per group, Values are Mean (SD)</p> <p>Reviewer's Comment: <i>Although the protocol did not specify any criteria for matching of healthy subjects to subjects with hepatic impairment, the study groups were reasonably balanced.</i></p> <p>Validated HPLC-MS/MS assays were used to measure the total plasma concentrations from PK samples and unbound concentrations from protein binding samples. The assay sensitivities are listed below. The protein binding was determined using ultra filtration technique.</p>		Parameter	Group A	Group B	Group C	Group D	Age (years)	46.4 (6.6)	54.8 (8.5)	48.9 (7.4)	46.4 (8.8)	BMI (Kg/m ²)	28.7 (2.5)	25.9 (3.7)	25.8 (3.3)	25.9 (3.2)
Parameter	Group A	Group B	Group C	Group D												
Age (years)	46.4 (6.6)	54.8 (8.5)	48.9 (7.4)	46.4 (8.8)												
BMI (Kg/m ²)	28.7 (2.5)	25.9 (3.7)	25.8 (3.3)	25.9 (3.2)												

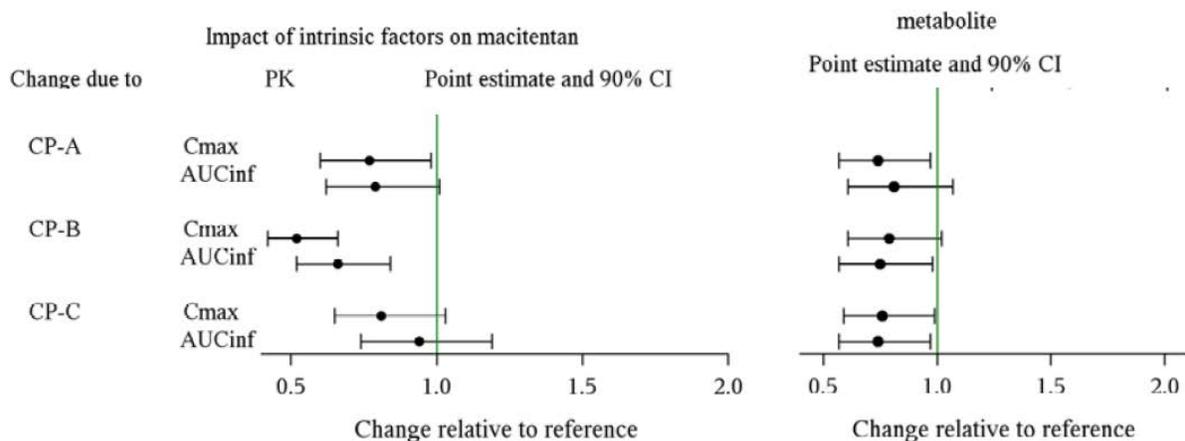
Analyte	Total Conc. in Plasma	Unbound Conc. in Plasma
Macitentan	1-2000 ng/ml	0.1-10 ng/ml
ACT-132577	1-2000 ng/ml	0.1-10 ng/ml
ACT-373898	0.5-500 ng/ml	0.1-10 ng/ml

The validation parameters for the assays and QC runs within sample analysis are within acceptable limits for total plasma concentrations. However, the free concentration measurements from protein binding samples by ultra-filtration failed to meet the requirements during incurred sample re-analysis (ISR). Only 14, 7 and 7% of the repeated samples for macitentan, ACT-132577 and ACT-373898 respectively were within the $\pm 20\%$ of reference value for unbound concentrations. The ISR for total concentrations resulted in 100, 100 and 90% samples within the acceptable limits for macitentan, ACT-132577 and ACT-373898 respectively.

The average plasma concentration-time profiles of (A) macitentan and its active metabolite (B) ACT-132577 and inactive metabolite (C) ACT-373898 are listed below:



The impact of hepatic function impairment (Child-Pugh A, B and C) on macitentan and ACT-132577 are shown below. The geometric mean ratios of PK parameters relative to subjects with normal hepatic function (reference) and 90% CI are plotted.



- The average plasma concentrations of macitentan and its active metabolite were generally lower in subjects with hepatic impairment than in healthy subjects (21, 34 and 6% reduction in AUC_∞ for Child-Pugh A, B and C classes respectively for macitentan, and 19-26% reduction for ACT-132577).
- There seems to be no significant changes in the elimination half-lives for macitentan or its metabolites in hepatic impairment but the maximum plasma concentrations were lower.
- The unbound concentrations of macitentan and its metabolites measured at their respective peak times were unreliable because of analytical variability on repeat analysis and cannot be used.
- There was no apparent correlation between severity of hepatic impairment or laboratory measurements such as albumin, bilirubin and prothrombin time with PK parameters.

Reviewer's Comment:

SERAPHIN Phase III study did not include patients with moderate or severe hepatic impairment. Even though there is a reduction in systemic exposure to macitentan and ACT-132577 in patients with impaired hepatic function, there was no correlation between liver function markers used in Child Pugh classification and PK parameters.

Conclusions:

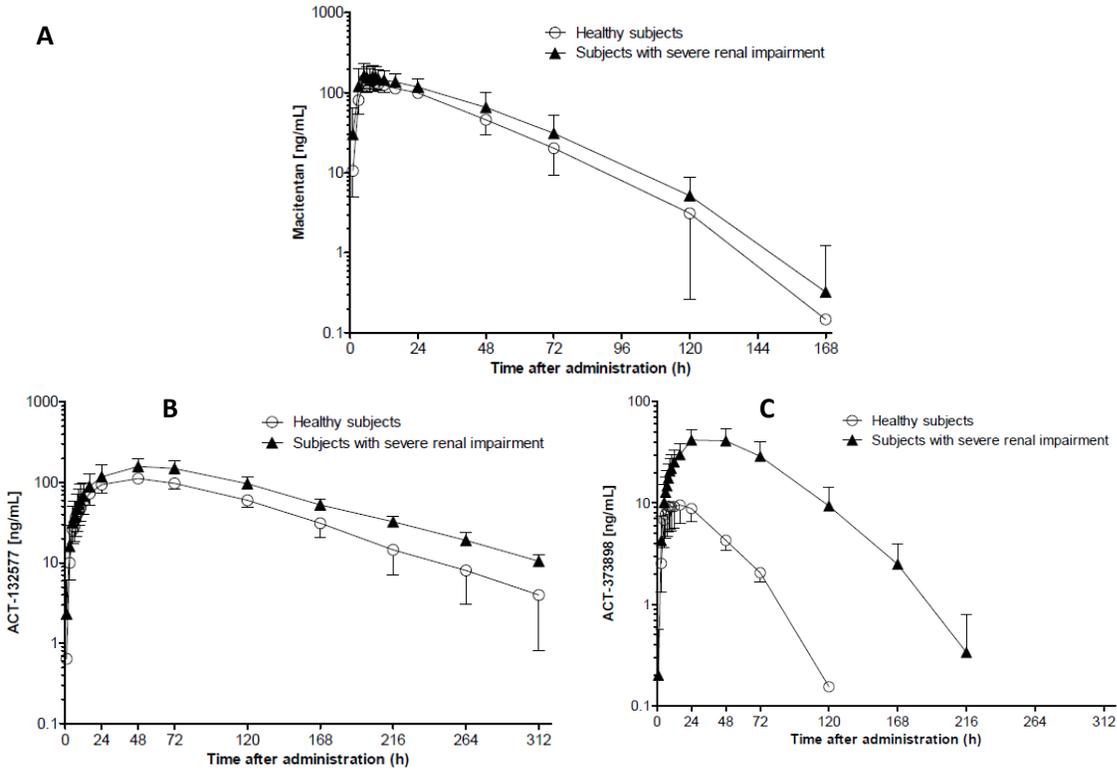
- Hepatic impairment resulted in up to 35% reduction in macitentan exposure.
- No dose adjustments are proposed in patients with mild, moderate or severe hepatic impairment.

Renal Impairment Study

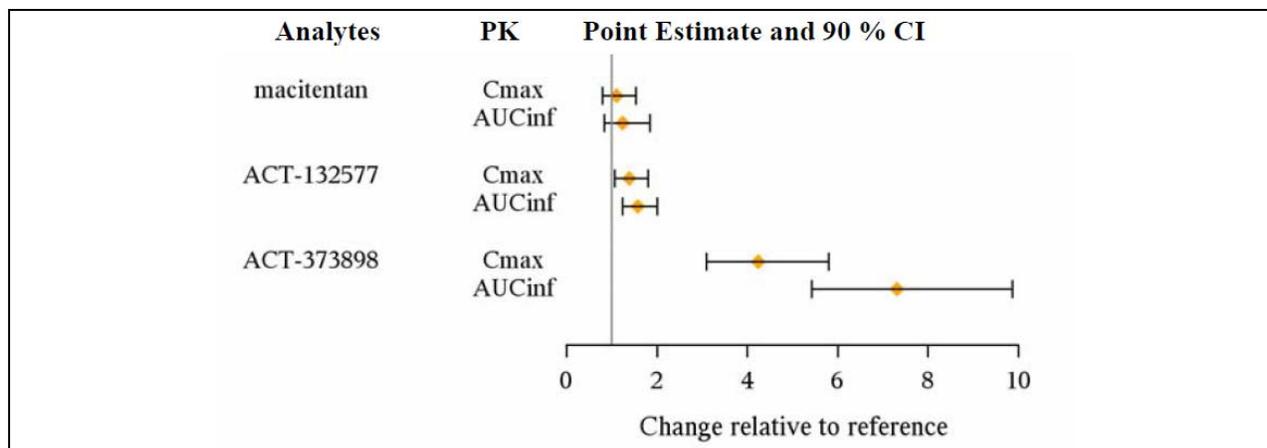
Study: AC-055-112 Study Period:	Title: Single-center, open-label, phase 1 study to investigate the pharmacokinetics (PK), tolerability, and safety of a single oral dose of macitentan in subjects with severe renal function impairment (SRFI)												
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrinsic-factor-pk-stud-rep\ac-055-112													
Objective: To evaluate the PK properties of a single dose of macitentan in subjects with severely impaired renal function compared to matched healthy subjects													
<p>Study Design:</p> <p>This was a prospective, single-center, parallel group, open-label, single-dose, Phase 1 study conducted in matched male and female subjects with either normal renal function or SRFI. Each subject with SRFI was matched with one healthy subject with regard to sex, age (± 5 years difference allowed), body weight and height ($\pm 10\%$ difference allowed), and both subjects were administered study drug within 5 days of one another.</p> <p>Before study drug administration, subjects were categorized in two groups based on mean creatinine clearance (CrCl) results and on age:</p> <p><u>Healthy Subjects:</u> CrCl > 80 ml/min for age <50 years or CrCl>70 ml/min for age 50-60 years</p> <p><u>SRFI:</u> CrCl 15-29 ml/min</p> <p>Creatinine clearance was derived from the creatinine plasma concentration using the Cockcroft-Gault formula. Mean creatinine clearance was calculated from results at screening and on Day -1, which were at least one week apart. A variability of up to 25% was allowed between measurements.</p> <p>Plasma concentrations of macitentan, active metabolite ACT-132577 and inactive metabolite ACT-373898 were measured in the study. Protein binding samples were collected at 8, 48 and 72 hours in all groups.</p>													
<p>Results:</p> <p>Validated HPLC-MS/MS assays were used to measure the total plasma concentrations from PK samples and unbound concentrations from protein binding samples. The assay sensitivities are listed below. The protein binding was determined using ultra filtration technique.</p> <table border="1" data-bbox="298 1640 1321 1803"> <thead> <tr> <th>Analyte</th> <th>Total Conc. in Plasma</th> <th>Unbound Conc. in Plasma</th> </tr> </thead> <tbody> <tr> <td>Macitentan</td> <td>1-2000 ng/ml</td> <td>0.1-10 ng/ml</td> </tr> <tr> <td>ACT-132577</td> <td>1-2000 ng/ml</td> <td>0.1-10 ng/ml</td> </tr> <tr> <td>ACT-373898</td> <td>0.5-500 ng/ml</td> <td>0.1-10 ng/ml</td> </tr> </tbody> </table>		Analyte	Total Conc. in Plasma	Unbound Conc. in Plasma	Macitentan	1-2000 ng/ml	0.1-10 ng/ml	ACT-132577	1-2000 ng/ml	0.1-10 ng/ml	ACT-373898	0.5-500 ng/ml	0.1-10 ng/ml
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The validation parameters for the assays and QC runs for sample analysis are within acceptable limits for total plasma concentrations. The unbound concentration measurements using ultra filtration technique had inter-run precision of 16.9% instead of 15% at certain QC levels for ACT-132577 and some QC samples for macitentan was outside the analytical range requiring extrapolation. The incurred sample reanalysis (ISR) results were within acceptable limits. Overall the bioanalysis for the total concentrations is acceptable and that for unbound concentrations can be considered as informative.

The average plasma concentration-time profiles of (A) macitentan (B) ACT-132577 and (C) ACT-373898 in subjects with SRFI and normal renal function are shown below:



The impact of severe renal function impairment on the PK of macitentan, ACT-132577 and ACT-373898 are shown below. Geometric mean ratios of PK parameters relative to subjects with normal renal function (reference) and 90% CI are plotted.



Reviewer's Comment:

The increase in exposure to macitentan and its active metabolite ACT-132577 in severe renal function impairment (~20% and 58% respectively) were not considered clinically significant. There was marked increase in exposure (~ 7.3 X) to the inactive metabolite ACT-3738989. There are no safety issues identified at this related to this metabolite (Ref. Nonclinical review in DARRTS dated 06/14/2013). Macitentan is considered as a low extraction drug with high protein binding and small changes to its protein binding may not have significant impact on its clinical efficacy, requiring dose adjustments.

Conclusions:

- No dose adjustments are proposed for subjects with severe renal function impairment
- Same recommendation applies to mild and moderate renal impairment categories

PBPK Analysis Summary

Studies: B-12.490, B-13.086	Title: Physiologically based pharmacokinetic (PBPK) modeling of macitentan
EDR: \\cdsesub1\evsprod\NDA204410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\b-12-490	
EDR: \\cdsesub1\evsprod\NDA204410\0012\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\b-13-086	
Background: <p>Macitentan is a CYP3A4 substrate. Clinical drug-drug interaction (DDI) studies were conducted for macitentan with ketoconazole (a strong CYP3A4 inhibitor) and rifampin (a strong CYP3A4 inducer). Ketoconazole, administered as 400 mg once daily, increased the exposure (AUC) and C_{max} to macitentan (single oral dose of 10 mg) by about 2.3X and 1.3X, respectively. The AUC and C_{max} of its active but 5-8 times less potent metabolite ACT-132577 decreased by ~ 26 % and ~ 51 % respectively. The elimination half-life of macitentan increased from 14.1 hours to 28.5 hours, while that of ACT-132577 showed a modest increase (46.7 hours versus 58.6 hours). Because of this change in elimination, the accumulation of macitentan on repeat dosing in presence of strong CYP3A4 inhibition could be higher (accumulation index $R \sim 2.3$ versus 1.4 with and without ketoconazole).</p> <p>Rifampin 600 mg once daily regimen, decreased the exposure to macitentan by approximately 80%, but did not significantly affect the exposure of ACT-132577.</p> <p>PAH is prevalent in patients with HIV and the SERAPHIN Phase III study included only less than 1% of such patients. So the review team requested information to understand the impact of various HIV treatments on the exposure to macitentan. Ritonavir, a strong CYP3A4 inhibitor, is one of the commonly used drugs for HIV treatment. The applicant had a PBPK model developed and qualified for macitentan using SimCYP® software and the review team used the same model and SimCYP® library compound ritonavir to simulate DDI trials.</p>	
Objective: <p>To assess drug-drug interaction potential of macitentan on repeat dosing with strong CYP3A4 inhibitors ketoconazole and HIV drugs like ritonavir.</p>	
Methods: <p>SimCYP® software, version 12 and its library drug models were used along with the applicant's model for macitentan (Ref. Study Report # B-12.490, B-13.086) in these simulations. The PBPK model submitted by the applicant assumed complete absorption of macitentan from the gut and CYP3A4 as the major metabolic pathway (96%). Since the CYP3A4 induction properties of lower doses of ritonavir are not well characterized we modified its PBPK model within SimCYP® library by considering only the inhibitory effects to represent a worst case scenario. All SimCYP® DDI simulations involved 10 clinical trials with 10 healthy Caucasian subjects (N=100). To simulate a concurrent clinical use scenario, ketoconazole was dosed at 400 mg once daily and macitentan at 10 mg once daily for 15 days. Trial simulations with ritonavir used 100 mg twice daily booster dose for 15 days and a single dose of macitentan 10 mg and also concurrent dosing of both drugs for 15 days.</p>	

Results & Discussion:

The PBPK model developed by the applicant was verified by comparing the predicted and observed clinical DDI results with ketoconazole (AC-055-107) and rifampin (AC-055-111). See Table below for the PBPK model performance.

AUC ratios (GM and 90%CI)	Macitentan		ACT-132577	
	Predicted	Observed	Predicted	Observed
Ketoconazole	2.7 (2.5-2.9)	2.3 (2.2-2.5)	0.6 (0.6-0.7)	0.7 (0.7-0.8)
Ketoconazole [⊗]	3.3 (3.0-3.5)	Not Applicable	Not included	
Rifampin	0.4 (0.3-0.4)	0.2 (0.2-0.3)	0.6 (0.5-0.6)	1.0 (0.9-1.1)
Ritonavir [*]	3.3 (3.0-3.5)	Not applicable	Not included	
Ritonavir ^{**}	4.1 (3.8-4.4)			

Ref: Applicant's PBPK reports for ketoconazole and rifampin predictions. All simulations are for 10 trials with 10 subjects each. AUC ratios are in the presence/absence of interacting drug. [⊗]Ketoconazole 400 mg once daily and macitentan 10 mg once daily for 15 days, ^{*}Ritonavir 100 mg twice daily till steady state and macitentan 10 mg single dose, ^{**}Ritonavir 100 mg twice daily and macitentan 10 mg once daily for 15 days, Rifampin 600 mg once daily

SimCYP[®] simulations resulted in about 3.3x increase in macitentan exposure when it was used concurrently with ketoconazole for 15 days. Strong CYP3A4 inhibition from ritonavir at its booster dose regimen showed 3-4X increase. The Phase III study included less than 1% HIV patients and was not adequate enough to characterize the safety and efficacy of macitentan. Also, there were concerns about limited data on long term safety of macitentan at doses higher than 10 mg. It should also be noted that two healthy subjects in the clinical DDI study with ketoconazole showed ALT/AST elevation and one of them discontinued treatment because of this adverse event.

Conclusions: Based on PBPK simulations, strong CYP3A4 inhibitors like ketoconazole and ritonavir can significantly increase the exposure (3 to 4x) to macitentan on repeat dosing, an exposure change that may not be represented by that observed after single dose macitentan co-administered with ketoconazole (about 2x).

Draft labeling recommendation:*Section 7.2: Strong CYP3A inhibitors*

Strong CYP3A inhibitors like ketoconazole significantly increase macitentan exposure. Many HIV drugs like ritonavir or ritonavir/lopinavir are strong inhibitors to CYP3A. Avoid concomitant use of OPSUMIT with strong CYP3A inhibitors.

Use other PAH treatment options when strong CYP3A inhibitors are needed as part of HIV treatment.

Rationale for the labeling recommendation:

- *Strong CYP3A inhibitors significantly increase exposure to macitentan*
- *There is limited data on the long term safety of macitentan at doses above 10 mg*
- *Macitentan has the potential to cause liver enzyme elevations at higher doses*
- *There is limited information on the safety and efficacy of macitentan in HIV patients*

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/s/

SREEDHARAN N SABARINATH
09/05/2013

PING ZHAO
09/05/2013

RAJANIKANTH MADABUSHI
09/06/2013

CLINICAL PHARMACOLOGY REVIEW

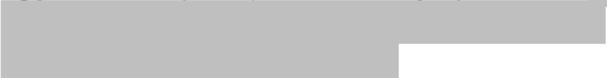
NDA:	204410
Submission Date:	10/19/2012
Submission Type:	Original NDA (NME – Standard Review)
Brand Name:	OPSUMIT®
Generic Name:	macitentan
Drug Class:	Endothelin Receptor Antagonist (ERA)
Dosage Form & Strength:	Tablets, 10 mg
Proposed Indication:	Long term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) in adults ^{(b) (4)} 
Applicant:	Actelion Pharmaceuticals Ltd.
Review Division:	Division of Cardiovascular and Renal Products
Primary Reviewers:	Sreedharan Sabarinath, PhD Dhananjay Marathe, PhD Ping Zhao, PhD
Team Leaders:	Rajanikanth Madabushi, PhD Yaning Wang, PhD

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1. EXECUTIVE SUMMARY

Actelion Pharmaceuticals Ltd has submitted an original new drug application (NDA 204410) for macitentan tablets (OPSUMIT[®]) for the long term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) in adult (b) (4)

Macitentan is an endothelin receptor antagonist (ERA) and acts on both ET_A and ET_B receptors. It is metabolized mainly by CYP3A4 and has a major circulating metabolite known as ACT-132577 which also possesses ERA activity. There are few other metabolites identified, but none of them are active at the endothelin (ET) receptors.

The clinical development program supporting this NDA included one pivotal efficacy study called SERAPHIN. There is an ongoing open label extension to this study called SERAPHIN-OL. SERAPHIN was a double blind, placebo controlled, parallel group, event driven, global study, which randomized 742 patients 1:1:1 to three treatment groups (10 or 3 mg macitentan once daily or placebo). The primary efficacy endpoint was the first occurrence of morbidity or mortality event during treatment. The composite primary efficacy endpoint included death, lung transplantation, initiation of prostanoids, atrial septostomy, and other worsening of PAH. Other worsening of PAH was defined as meeting three criteria: 15 % decrease in 6-minute walk distance (6MWD), worsening of PAH symptoms in terms of WHO functional class or right heart failure, and need for new PAH treatment. The study demonstrated a 45 % risk reduction versus placebo in favor of 10 mg macitentan treatment. In the primary time-to-event analysis taking the entire treatment period into account, the hazard ratio for occurrence of primary efficacy event versus placebo in the macitentan 3 mg group was 0.704 (97.5% CI 0.516-0.960, P=0.0108) and that for the 10 mg group was 0.547 (97.5% CI 0.392-0.762, P<0.0001) respectively. The major component of the primary efficacy endpoint that contributed to the results was other worsening of PAH. The placebo corrected median change in 6MWD from baseline to month 6 showed similar treatment effects versus placebo in the macitentan 3 mg (14 m, 97.5% CI 2-27, p=0.0122) and macitentan 10 mg groups (15 m, 97.5% CI 2-28, p=0.0078) respectively. The observed reduction in pulmonary vascular resistance (PVR) from baseline to month 6 with macitentan 10 mg was 36.5 % versus placebo. Although both 3 mg and 10 mg doses of macitentan showed efficacy compared to placebo, the applicant is seeking approval only for the higher 10 mg dose which showed greater efficacy compared to the 3 mg dose. There were no subgroups from SERAPHIN that were identified that could be benefited more with a dose lower than 10 mg.

The pivotal efficacy trial used the to-be-marketed commercial formulation and no pivotal BE study was required. A total of 14 clinical pharmacology studies were included in the application which formed the basis for characterizing the clinical pharmacology of macitentan and evaluating the impact of intrinsic and extrinsic factors.

1.1 Recommendations

The Office of clinical pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 204410. The CPB information provided is adequate to provide labeling recommendations for macitentan. The NDA can be approved from a clinical pharmacology perspective for the treatment of PAH.

The Office has 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

1.2 Post Marketing Requirements/Commitments

None.

2. SUMMARY OF OCP FINDINGS

2.1 Background

Actelion Pharmaceuticals Ltd is seeking approval for macitentan tablets (OPSUMIT[®]) for the long term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) in adult (b) (4)

Macitentan belongs to the class of ERAs used for the treatment of PAH. The other members of the ERA class are bosentan, ambrisentan and sitaxentan. The ERAs exert their action by preventing endogenous endothelin from binding to its receptors (ET_A or ET_B).

2.2 Current Submission

The current NDA is supported by a single pivotal efficacy study SERAPHIN. A total of 14 completed clinical pharmacology studies are included in the application. This includes ADME and PK studies in healthy subjects, studies in special populations (renal and hepatic impairment), a through QT study and drug-drug interaction studies. There was no population PK analysis included in the submission.

2.3 Pharmacokinetics

- Macitentan is an orally administered drug belonging to the ERA class
- The pharmacokinetics of macitentan is almost proportional from 1 to 30 mg dose
- Macitentan is metabolized mainly by CYP3A4 and one of its metabolites ACT-132577 is active at the ET receptors
- The average elimination half life of macitentan and ACT-132577 are 16 h and 48 h respectively
- The accumulation of macitentan upon repeat administration was approximately 1.5 fold while that of ACT-132577 was about 8.5 fold
- Both macitentan and ACT-132577 are highly bound to plasma proteins (>99 %)
- About 50% of the radioactive dose is eliminated by urine (none in the form of unchanged drug or as the active metabolite ACT-132577 as such) and about 24 % was recovered in feces
- No significant food effects

2.4 Exposure-Response Relationships

SERAPHIN study included two dose levels, 3 mg and 10 mg, for macitentan and placebo and was successful in demonstrating dose-response for the primary efficacy endpoint. The PK subset from SERAPHIN study provided a single PK sample from about 277 patients on macitentan and from about 120 patients on placebo. However, the PK subset had significantly lower event rates (~ 50 % lower) as the PK samples were collected at the end of treatment (EOT). Since the PK population was not representative of the intention to treat (ITT) population, a formal concentration-response analysis for efficacy or safety was not possible and hence not conducted.

2.5 Intrinsic Factors

2.5.1 Body weight, Sex, Age and Race

Body weight, sex, age and race did not seem to affect the exposure to macitentan or its metabolite significantly. Therefore, no dose adjustment is required based on body weight, sex, age or race.

2.5.2 Renal Impairment

An abbreviated renal impairment study showed that the increase in exposures to macitentan and its active metabolite ACT-132577 in severe renal function impairment (CrCL 15-29 mL/min) is ~ 20 % and 58 % respectively. However, the exposure to an inactive metabolite ACT-373898 increased by ~ 7.3X. There was no potential safety concern evident for this moiety in preclinical studies (Ref. Non-clinical Review, DARRTS dated 06/14/2013). Therefore, this finding is not considered clinically significant and no dose adjustments are proposed for subjects with severely impaired renal function. Consequently same recommendation applies to mild and moderately impaired renal function categories as well.

2.5.3 Hepatic Impairment

Impairment in hepatic function resulted in approximately 21 %, 34 % and 6 % reduction in macitentan exposure (AUC_{∞}) for Child-Pugh A, B and C classes respectively. There was no apparent correlation between severity of hepatic impairment or laboratory measurements of albumin, bilirubin and prothrombin time with PK parameters. The reduction in exposure seen with hepatic impairment (Child-Pugh A, B and C) is not considered as clinically significant. Therefore, no dose adjustments are proposed in patients with mild, moderate or severe hepatic impairment.

2.5.4 Pediatrics

The PK of macitentan in children has not been studied. The SERAPHIN study protocol allowed PAH patients who are 12 years and older to be enrolled but had only about 13 patients less than 18 years of age enrolled into the study (7 patients on 3 mg and 6 patients on 10 mg dose). There is no PK information from these patients from SERAPHIN.

2.6 Drug-Drug Interactions (DDI)

The current submission included *in vivo* DDI studies of macitentan with warfarin (metabolized by CYP2C9, 1A2 and to a smaller extent by 3A4), sildenafil (CYP3A

substrate and likely co-administered in PAH), cyclosporine-A (OATP1B1/1B3 and CYP3A inhibitor), ketoconazole (strong CYP3A inhibitor) and rifampin (strong CYP3A inducer). Warfarin, sildenafil (and its metabolite N-desmethyl sildenafil), and cyclosporine-A had no significant impact on the exposure to macitentan or its active metabolite ACT-132577 and vice versa. Therefore, no dose adjustments are required with sildenafil, warfarin and cyclosporine-A.

Rifampin, a strong CYP3A4 inducer, decreased the exposure to macitentan by approximately 80 % and could significantly reduce the efficacy of macitentan on co-administration. Therefore, rifampin should not be co-administered with macitentan.

A single dose (10 mg) of macitentan when given with ketoconazole, administered as 400 mg once daily, increased the exposure (AUC_{∞}) and C_{max} to macitentan by about 2.3X and 1.3X respectively. The exposure and C_{max} of its active metabolite ACT-132577 decreased by ~ 26 % and ~ 51 % respectively. The elimination half life of macitentan increased from 14.1 hours to 28.5 hours, while that of ACT-132577 showed a modest increase (46.7 hours versus 58.6 hours). The accumulation of macitentan on repeat dosing in presence of strong CYP3A4 inhibition could be higher (accumulation index $R \sim 2.3$ versus 1.4 with and without ketoconazole). Based on physiologically based pharmacokinetic (PBPK) modeling and simulation, the projected increase in steady state exposure is approximately 3X to 4X of that of macitentan alone. The long term safety information on macitentan on doses higher than 10 mg is limited. Therefore macitentan 10 mg should be avoided with strong CYP3A4 inhibitors like ketoconazole.

The drug interaction potential of booster doses of ritonavir or lopinavir/ritonavir or other HIV regimens that exhibit strong CYP3A inhibition was not studied. Since PAH is reported in HIV population, the review team requested information to understand the impact of various HIV treatments on the exposure to macitentan. Such an evaluation was not possible from the SERAPHIN study as it included less than 1% HIV patients. Hence, PBPK simulations were used to predict the potential impact of ritonavir (100 mg twice daily) on macitentan exposure. Multiple dosing with 100 mg twice daily ritonavir and a single dose of 10 mg macitentan resulted in ~ 3X increase in macitentan exposure. Concurrent dosing of both drugs for 15 days showed ~ 4X increase in macitentan exposure at steady state. This observation is in agreement with the *in vivo* DDI results with ketoconazole, a strong CYP3A4 inhibitor. Since ritonavir treatment for HIV will be for long term and there is no long term safety information on macitentan at doses above 10 mg, the predicted 4X increase in exposure with strong CYP3A4 inhibitors like ritonavir is considered clinically significant. Therefore macitentan 10 mg dose should be avoided if co-administration of strong CYP3A4 inhibitor drugs is desired for HIV treatment.

2.7 Biopharmaceutics

The phase III program for macitentan employed the final marketing image formulation and therefore no pivotal BE study is required.

When administered with a high calorie, high fat breakfast, the PK of macitentan and its active metabolite ACT-132577 are not affected. Therefore, macitentan can be administered once daily, with or without food (as administered in SERAPHIN study)

3. QUESTION BASED REVIEW

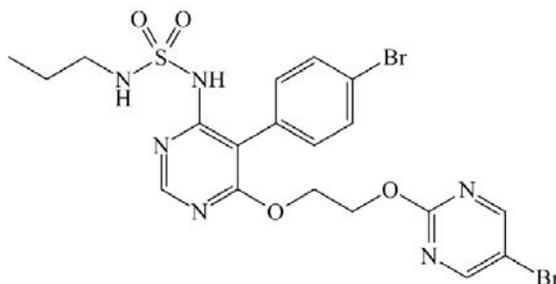
3.1 General Attributes

Macitentan (ACT-064992) is a fourth-in-class, endothelin receptor antagonist (ERA). Other ERAs used for the treatment of pulmonary arterial hypertension (PAH) include bosentan (approved in 2001), ambrisentan (approved in 2007) and sitaxentan (not approved in US, and withdrawn from market worldwide). Macitentan is orally active and acts on both ET_A and ET_B receptors. It has an active metabolite circulating in plasma called ACT-132577.

3.1.2 Drug Substance

Macitentan is a crystalline powder that is insoluble in water. The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide. It has a molecular formula of C₁₉H₂₀Br₂N₆O₄S and a molecular weight of 588.27.

Macitentan is achiral and has the following structural formula:



3.1.3 What are the proposed mechanism of action and therapeutic indication?

Endothelin (ET)-1 and its receptors (ET_A and ET_B) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy and inflammation. In PAH, the local ET system is up-regulated and is involved in vascular hypertrophy and in organ damage. The ET-1 may play a causative role in the development of PAH and further aiding in its progression. Macitentan is a dual ET_A and ET_B receptor antagonist that prevents the binding of ET-1 to its receptors.

The applicant is seeking approval for macitentan for the long term treatment of pulmonary arterial hypertension (PAH, WHO Group 1) in adult (b) (4)

3.1.4 What are the current treatments available for the proposed indication?

Available pharmacological therapies for PAH include endothelin receptor antagonists (ERAs), prostacyclin analogs and phosphodiesterase (PDE)-5 inhibitors.

The ERAs (eg. bosentan and ambrisentan) inhibit the effects of elevated ET-1 levels, reduce vasoconstriction, smooth muscle proliferation and pulmonary vessel fibrosis. Prostacyclin analogs such as epoprostenol, treprostinil and iloprost relax and reduce

proliferation of vascular smooth muscles. The PDE-5 inhibitors (eg. sildenafil, tadalafil) potentiate the antiplatelet, antiproliferative and vasodilatory effects of nitric oxide.

3.1.5 What are the proposed dosages and route of administration?

The proposed therapeutic dose of macitentan is 10 mg as film coated tablets. The dose should be taken once daily, with or without food.

3.2 General Clinical Pharmacology

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

The current NDA is supported by a pivotal efficacy trial SERAPHIN (AC-055-302) in PAH patients. The clinical development program has 14 completed clinical pharmacology studies. The submission includes a mass balance study (AC-055-104), PK (AC-055-101, AC-055-102) and food effect studies (AC-055-103), studies in renal and hepatic impairment (AC-055-110, AC-055-112), drug-drug interaction studies (with warfarin, sildenafil, ketoconazole, cyclosporine, and rifampin) and a thorough QT study (AC-055-114). In addition, there is an active controlled, dose-ranging Phase II study in patients with mild to moderate hypertension (AC-055-201) evaluating the effect of macitentan on sitting diastolic blood pressure (BP) and plasma ET-1 levels. The design features of the phase III study is described in Section 3.2.3.

3.2.2 Were the correct moieties identified and properly measured to assess clinical pharmacology?

The applicant measured macitentan (ACT-064992) and its active metabolite (ACT-132577) in plasma. They also measured an inactive metabolite ACT-373989 in some of the PK studies. ACT-132577 is approximately 8X less potent than macitentan on ET_A and 2X less potent on ET_B receptors *in vitro*. At steady state the systemic exposure to ACT-132577 was about 3X higher than that to macitentan. Validated HPLC-MS/MS methods were employed for quantifying these moieties.

3.2.3 What are the key features of the phase III trials of macitentan?

The pivotal efficacy trial SERAPHIN was a randomized, double blind, placebo controlled, parallel group, event driven clinical study in patients with symptomatic PAH (WHO FC II-IV), that compared oral once daily treatment with 3 mg and 10 mg doses of macitentan versus placebo. A schematic of the SERAPHIN study design is shown below (**Figure 1**). Patients aged 12 years or over were enrolled if diagnosed with WHO FC II-IV idiopathic PAH, familial PAH, or PAH associated with connective tissue disease, or HIV infection or drug and toxin use, PAH associated with simple congenital systemic to pulmonary shunts at least 1 year post surgical repair. Participants were required to have a baseline 6 minute walk distance (6MWD) of at least 50 meters.

A total of 742 patients were randomized to macitentan 3 mg, 10 mg or placebo in 1:1:1 ratio. Median age was about 45 years. Approximately 3 % were adolescents (12-17 years) and 14% were elderly (over 65 years). Only about 1 % of the study population was HIV patients. About 46% of the patients were WHO FC III. Treatments approved for PAH, including oral or inhaled prostanoids or oral PDE-5 inhibitors were allowed if they had

been taken at a stable dose for at least 3 months before randomization and remained unchanged during the study.

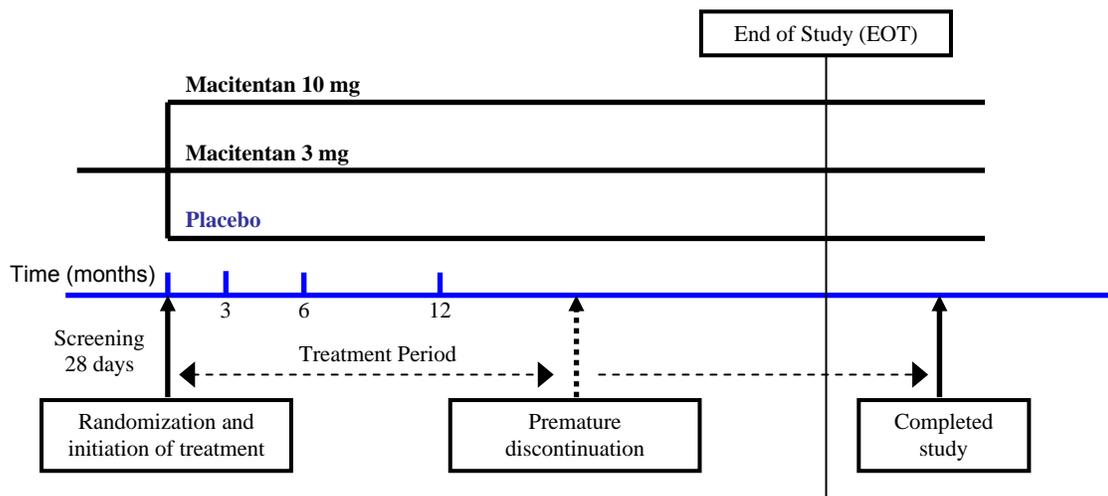


Figure 1: A schematic representation of SERAPHIN Phase III study design. Ref. AC-055-302 study report/Figure 1/Page 48

SERAPHIN study included a PK/PD subset where PK samples were collected at month 6 (N=81 on macitentan). A single PK sample was also collected at EOT (N=277 on macitentan). The primary efficacy endpoint was time to first occurrence of morbidity or mortality event up to EOT plus 7 days. Safety assessments included proportion of deaths, SAEs and AEs up to EOT plus 28 days or AEs leading to premature discontinuation.

3.2.4 How was the Phase III doses selected?

It should be noted that dose selection was not performed in PAH patients, which is the population of interest. Macitentan clinical development program included a Phase II study in patients with mild to moderate essential hypertension, which formed the applicant’s basis for Phase III dose selection. The phase II study evaluated macitentan doses from 0.3 mg to 10 mg once daily for 8 weeks and included a placebo group and enalapril (20 mg once daily) as an active comparator for the BP lowering effects. The dose selection for Phase III was based on the effects of macitentan on plasma ET-1 levels and sitting diastolic BP response. Macitentan showed a trend in increase in plasma ET-1 levels with dose. A similar trend for exposure dependent decrease in sitting diastolic BP was also observed. A PK/PD analysis indicated that the exposures associated with macitentan 10 mg were close to the plateau for BP reduction. Based on these results, the applicant chose 3 mg and 10 mg doses for Phase III trials. The **Figures 2** and **3** below show a comparison of plasma ET-1 levels from different treatment groups at week 4 and week 8, and combined free plasma concentration-BP relationship with macitentan and its active metabolite ACT-132577.

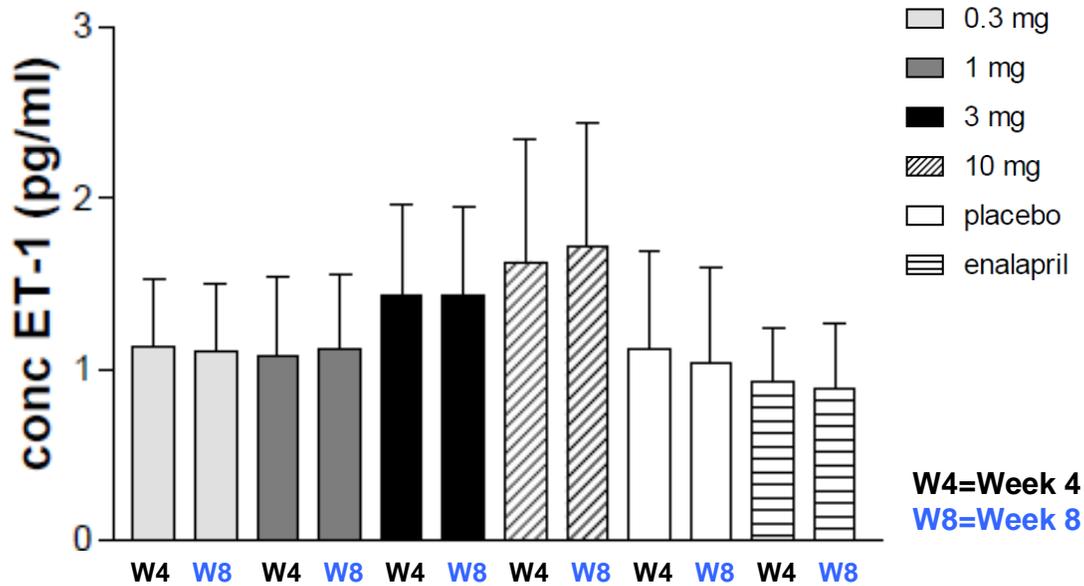


Figure 2: Average plasma ET-1 concentrations (+SD) at weeks 4 and 8 from phase II study AC-055-201 in patients with mild to moderate essential hypertension. Ref. Summary of clinical pharmacology studies/Figure 3/Page 42

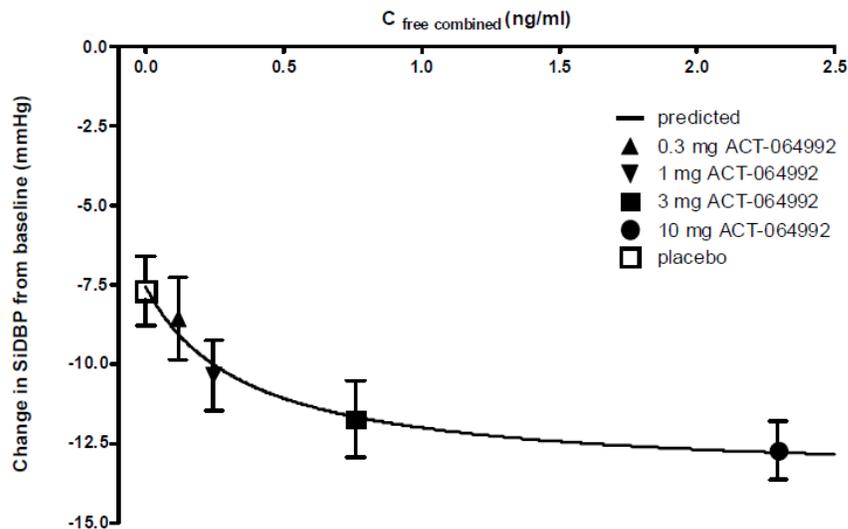


Figure 3: Change in sitting diastolic BP (mean±SEM) versus combined plasma concentrations (free fraction) of macitentan and ACT-132577 at week 8 from the Phase II study AC-055-201 in patients with mild to moderate essential hypertension. Ref. Summary of clinical pharmacology studies/Figure 5/Page 44

3.2.5 What are the characteristics of the exposure/dose-response relationships for efficacy or safety?

SERAPHIN study included two dose levels, 3 mg and 10 mg, for macitentan and placebo and was successful in demonstrating dose-response for the primary efficacy endpoint (See **Figure 4** below).

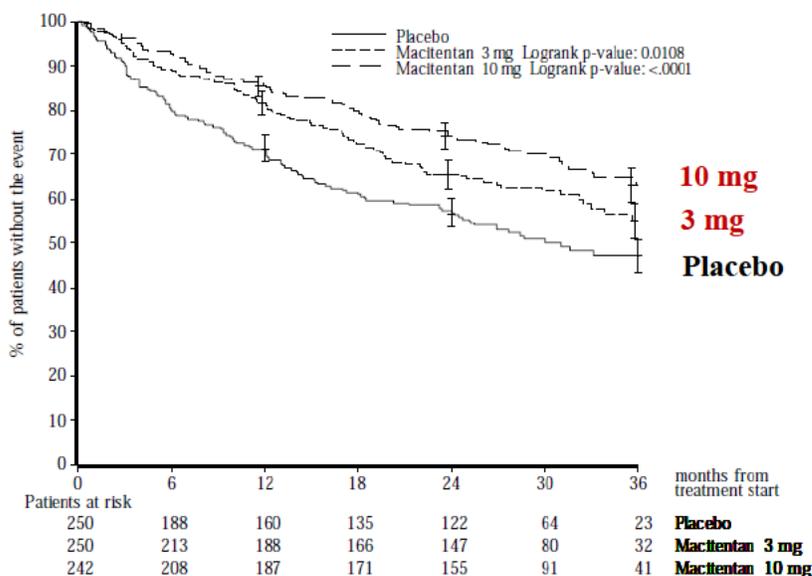


Figure 4: Kaplan-Meier curves for the first confirmed morbidity or mortality event up to EOT plus 7 days, All randomized set, KM estimates with standard error bars. Ref. Summary of Clinical Efficacy/Figure 2/Page 22

The PK subset from SERAPHIN study provided a single PK sample from ~ 277 patients on macitentan and from ~ 120 patients on placebo. However, the PK subset had significantly lower event rates as the PK samples were collected at the EOT (See **Table 1** below). Since the PK population was not representative of the ITT population a concentration-response analysis for efficacy or safety was not possible.

Table 1: Comparison of IIT and PK datasets for primary efficacy events in SERAPHIN

Treatment	Macitentan 3 mg		Macitentan 10 mg		Placebo	
	ITT	PK	ITT	PK	ITT	PK
Number of patients	250	134	242	143	250	120
Patients with efficacy events	95 (38.0%)	22 (16.4%)	76 (31.4%)	24 (16.8%)	116 (46.4%)	33 (27.5%)

3.2.6 Does macitentan prolong the QT or QTc interval?

The applicant performed a thorough QT study (Study # AC-055-114) to assess the electrophysiological effects of repeated daily doses of 10 mg and 30 mg doses of macitentan in healthy male and female subjects. As per the QT-IRT review macitentan did not show significant QTc prolongation (Ref. DARRTS date 03/05/2013).

3.3 PK Characteristics of the Drug and Metabolite(s)

Macitentan has one pharmacologically active metabolite (ACT-132577) and one metabolite inactive at ET receptors (ACT-373898) detected in plasma.

3.3.1 What are the single dose and multiple dose PK parameters?

Single doses of up to 600 mg and multiple doses up to 30 mg once daily for 10 days were evaluated in healthy subjects in phase I studies (Studies AC-055-101, AC-055-102). The PK profile of macitentan is characterized by relatively slow absorption with maximum plasma concentrations achieved by about 8 hours post dose and an apparent elimination half life of approximately 16 hours. The active metabolite ACT-132577 is formed slowly with a t_{max} of about 40 hours and eliminated with a half life of about 48 hours. The PK characteristics of ACT-373898 are similar to that of its parent macitentan. The **Figure 5** below shows the average plasma concentration time profile of macitentan and ACT-132577 from single and multiple dose PK studies.

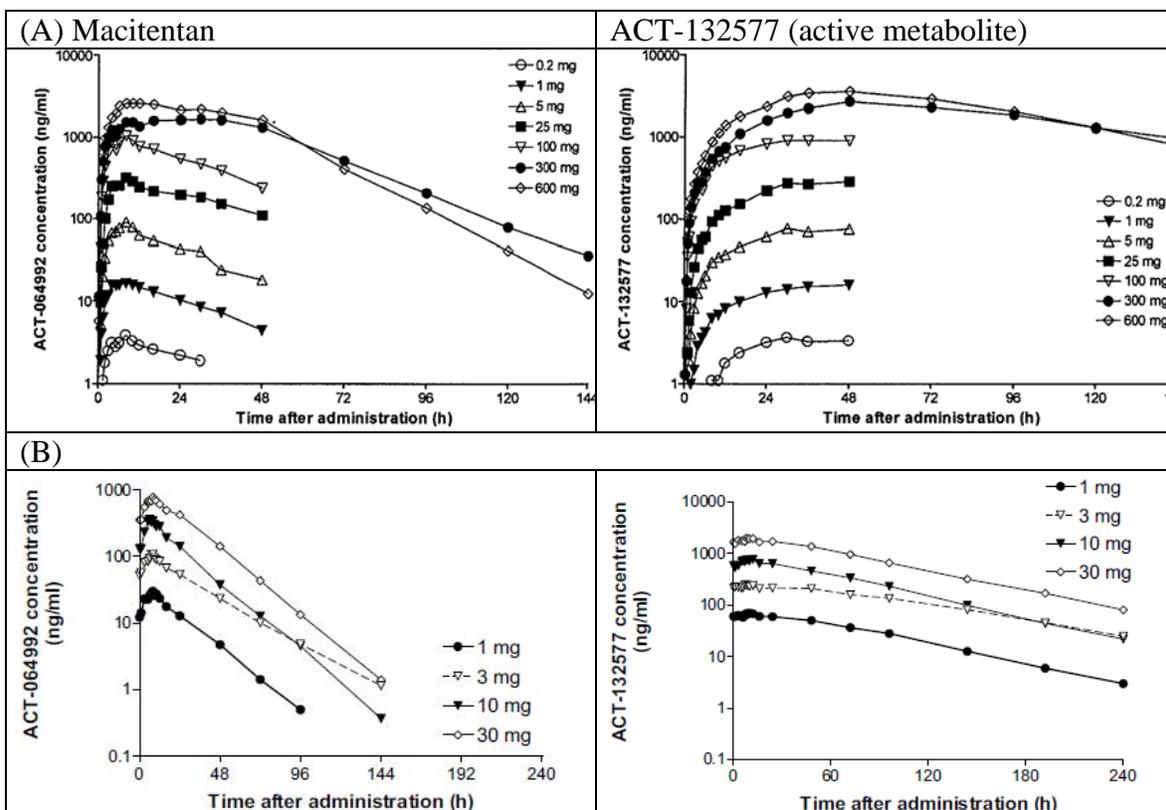


Figure 5: Mean plasma concentration time profiles of macitentan (ACT-064992) and its active metabolite ACT-132577 in healthy subjects from the single ascending dose study AC-055-101 (Panel A) and from multiple dose study AC-055-102 on Day 10 (Panel B). Ref. Figure 1/AC-055-101 Final Study Report/Page 36 and Figure 2/AC-055-102 Final Study Report/Page 47.

The steady state concentrations of macitentan and its active metabolite ACT-132577 were reached after 3 days and 7 days respectively up on once-daily multiple dosing. The accumulation of macitentan at steady-state was approximately 1.5X while that of ACT-

132577 was about 8.5X. The observed accumulation and that projected based on the half-life estimated following single dose are similar, indicating that there is no time-dependant pharmacokinetics for macitentan or its active metabolite. At steady state the metabolites ACT-132577 (active) and ACT-373898 (inactive) contributed to approximately 74 % and 3 % of total drug exposure, respectively.

3.3.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

PK data from patients with PAH were generated in a PK/PD sub-study in the Phase III study SERAPHIN. Macitentan median C_{trough} for both the 3 mg and 10 mg dose groups in PAH patients was approximately 2X higher than that observed in healthy subjects. The plasma concentrations of ACT-132577 in PAH patients were approximately 1.5X of those observed in healthy subjects.

3.3.3 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The AUC_{0-24h} and C_{max} for macitentan from Phase I studies were dose linear and were nearly dose proportional between 1 mg and 30 mg dose levels. A similar finding was reported over this dose range following repeat administration to steady state as shown in the **Figure 6** below.

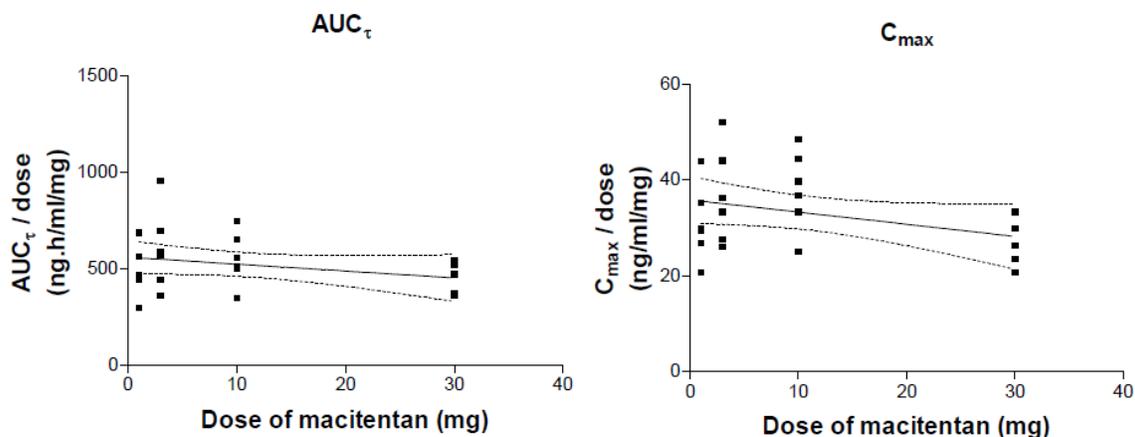


Figure 6: Dose normalized AUC_{τ} and C_{max} of macitentan on day 10 from multiple dose study. Ref. Figure 4/Study Report for AC-055-102/Report No. D-06.044/Page 51

3.3.4 What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

The inter subject variability (% CV) for AUC_{τ} at steady state in Phase I studies ranged from 24-30 % and 15-23 % for macitentan and ACT-132577 respectively. PAH patients showed higher inter subject variability for the trough plasma concentrations at month 6 from the Phase III study. The % CV was approximately 55 % for macitentan and 40 % for ACT-132577 in PAH patients. Although no population PK analyses were conducted, the PK/PD subset from the Phase III study did not indicate significant effect of intrinsic

factors on the exposure to macitentan and its metabolite. The impact of renal and hepatic impairment on macitentan is described separately.

3.3.5 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

3.3.5.1 Body weight, Sex, Age and Race

There was no population PK analysis performed to evaluate the effects of covariates. The PK data (C_{trough}) for macitentan and ACT-132577 at Month 6 and end-of-treatment (EOT) from the PK/PD sub-study within the Phase 3 study SERAPHIN was employed to evaluate any clinically relevant effects of body weight, sex, race or age. There was no significant effect of these covariates on the PK of macitentan and its active metabolite. The PK of macitentan and its metabolite was similar in Caucasian and Japanese healthy subjects in a single dose study. No dose adjustments are required based on body weight, sex, age or race.

3.3.5.2 Renal Impairment

The ADME study indicated that about 50 % of the radiolabelled dose is excreted in the urine. The current NDA includes a renal impairment study (AC-055-112) in subjects with severe renal function impairment (SRFI, CrCL 15-29 mL/min) and in healthy subjects (CrCL>80 mL/min for age <50 years or CrCL>70 mL/min for age 50-60 years). The increase in macitentan and its active metabolite ACT-132577 exposures in severe renal function impairment (~ 20 % and 58 % respectively) were not considered clinically significant. However, there was a marked increase in exposure (~ 7.3X) to the inactive metabolite ACT-373898 in SRFI (See **Figure 7**). ACT-373898 is inactive at ET receptors and there are no safety issues identified at this time related to this metabolite (Ref. Non-Clinical Review, DARRTS dated 06/14/2013). The bioanalysis of unbound concentrations of macitentan did not pass all necessary acceptability criteria making it less reliable. Nevertheless, macitentan is considered as a low extraction drug with high protein binding and small changes to its protein binding may not have significant impact on clinical efficacy requiring dose adjustments.

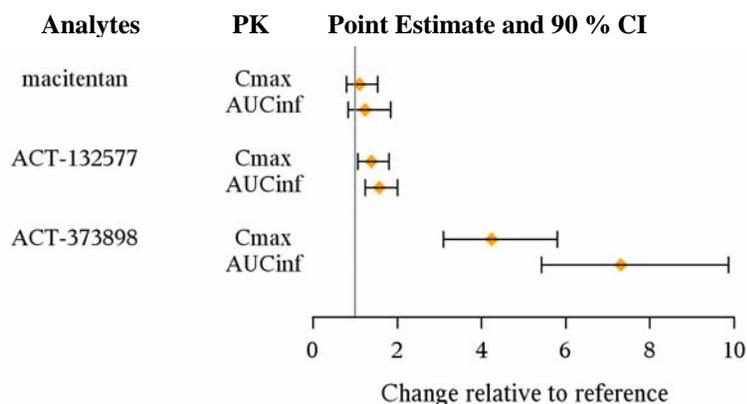


Figure 7: Impact of severe renal function impairment (SRFI) on macitentan, its active metabolite ACT-132577 and inactive metabolite ACT-373898. Geometric mean ratios of PK parameters relative to subjects with normal renal function (reference) and 90 % CI are plotted.

No dose adjustments are proposed for subjects with severely impaired renal function. Consequently same recommendation applies to mild and moderately impaired renal function categories.

3.3.5.3 Hepatic Impairment

The radio-labeled study in healthy humans showed that about 23.9 % of the radioactive material is excreted in feces. There was no PK study by intravenous route but the PK profiles of macitentan or its active metabolite after oral administration did not indicate significant enterohepatic re-circulation usually evident by multiple peaks. The current NDA included a hepatic impairment study in subjects with mild, moderate or severe hepatic impairment (Child-Pugh A, B and C respectively) due to liver cirrhosis compared to healthy subjects.

The average plasma concentrations of macitentan and its active metabolite were generally lower in subjects with hepatic impairment than in healthy subjects (See Figure 8 below). Hepatic impairment resulted in 21 %, 35 % and 6 % reduction in macitentan exposure in Child-Pugh A, B and C classes respectively. Exposures to ACT-132577 also decreased by 19-26 % across the hepatic impairment classes. There was no apparent correlation between severity of hepatic impairment or laboratory measurements of albumin, bilirubin and prothrombin time with PK parameters. There seems to be no significant changes in the elimination half-lives for macitentan or its metabolites in hepatic impairment. The unbound concentrations of macitentan and its metabolites measured at their respective peak times were unreliable because of analytical variability on repeat analysis and can not be used. But macitentan is considered as a low extraction drug with high protein binding and small changes to its protein binding may not have significant impact on clinical efficacy requiring dose adjustments.

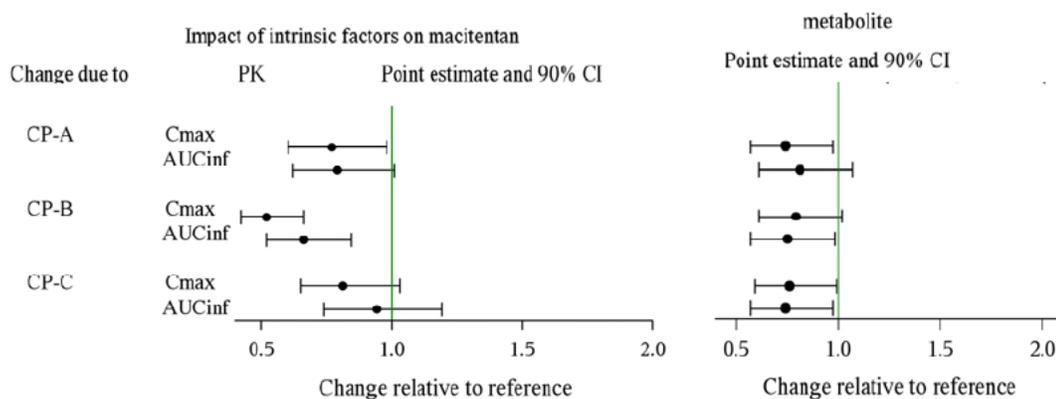


Figure 8: Impact of hepatic function impairment (Child-Pugh classes A, B and C) on macitentan and its active metabolite ACT-132577. Geometric mean ratios of PK parameters relative to subjects with normal hepatic function (reference) and 90 % CI are plotted.

Although the Phase III study SERAPHIN did not include patients with moderate and severe hepatic impairment, macitentan was shown to be effective at 3 mg and 10 mg dose levels compared to placebo. The reduction in exposure seen in the hepatic impairment study may not result in any significant loss in efficacy. Therefore, no dose adjustments are proposed in patients with mild, moderate or severe hepatic impairment.

3.3.6 What are the characteristics of drug absorption (possible transporters and pH impact)?

Macitentan is absorbed slowly with a t_{max} of about 8 hours after oral administration. The absolute bioavailability after oral administration is not known, but a PBPK method estimated it to be about 74%. The exposure to macitentan and its active metabolite ACT-132577 is unchanged in the presence of food.

3.3.7 What are the characteristics of drug distribution, including plasma protein binding?

Macitentan and ACT-132577 are well distributed with apparent volume of distribution (V_{ss}/F) of about 50 L and 40 L respectively. Macitentan and its metabolites are highly bound (> 99 %) to plasma proteins, mainly to albumin. The free fraction of macitentan in plasma is estimated to be 0.4 %. The average blood to plasma ratio was 0.5 for both macitentan and ACT-132577 indicating limited partitioning to red blood cells.

3.3.8 What are the characteristics of drug metabolism?

The metabolism of macitentan was characterized in the ADME study (AC-055-104) and metabolite identification and characterization were performed using *in vitro* experiments with human liver microsomes, hepatocytes and S9 fractions.

Macitentan undergoes metabolism by CYP3A4 and to a minor extent by CYP2C19. The active metabolite ACT-132577 and inactive metabolite ACT-373898 are the only metabolites of macitentan detected in plasma. The proposed metabolic pathway is shown below in Figure 9:

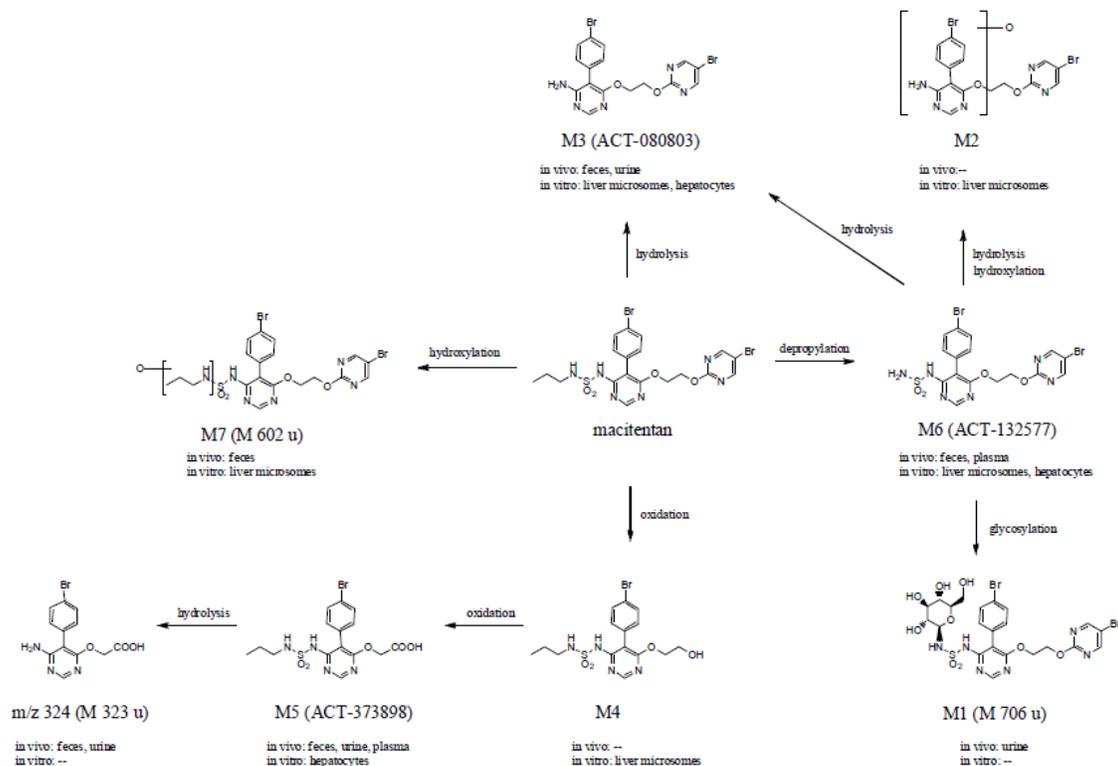


Figure 9: Proposed metabolic pathway for macitentan (Ref. Summary of clinical pharmacology studies/figure 21/page 82)

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

In the human ADME study (AC-055-104) where a single 10 mg dose of ^{14}C labeled macitentan was administered in healthy subjects, the mean cumulative recovery of radioactivity was 73.6 % and approximately 49.7 % of radioactive drug material was eliminated in urine (none in the form of unchanged drug or the active metabolite ACT-132577 as such). The hydrolysis product ACT-08083 and a conjugate of ACT-132577 with glucose (M706u) accounted for 7 % and 24.8 % of radioactivity excreted in urine. Other moieties identified in urine were ACT-373898 and its hydrolysis product M323u, accounting for 22.9 % and 26 % of radioactivity excreted in urine, respectively.

About 23.9 % of the radioactive drug material was recovered from feces. The five entities identified in feces were macitentan, ACT-132577, ACT-373898, M323u, and ACT-08083. ACT-08083 was the major product in feces, accounting for 37.7 % of radioactivity excreted in feces. Macitentan and ACT-132577 represented 16.9 % and 14 % of radioactivity excreted in feces. The Table 2 below describes the relative contribution of various moieties identified relative to the administered radioactive dose.

Table 2: Percentage of radioactive dose recovered from urine and feces and relative contribution of various moieties. Note: 26.4 % of the total radioactivity is unaccounted.

Moiety	Urine (49.7% of dose)		Feces (23.9% of dose)	
	% in Urine	% of Dose	% in Feces	% of Dose
Macitentan	0	0	16.9	4
Active (ACT-132577)	0	0	14	3.3
Inactive (ACT-373898)	22.9	11.4	3.6	0.9
ACT-080803	7	3.5	37.7	9
M323 u	26	12.9	13.1	3.1
M602 u	0	0	2	0.5
M706 u	24.8	12.3	0	0
Unidentified moieties	19.1	9.5	12.7	3

The mass balance study accounted for only about 74 % of the total radioactivity, which is not optimal, and about 19 % and 12.7 % of the radioactivity detected in urine and feces are not characterized.

3.3.10 What is the drug-drug interaction (DDI) potential for macitentan?

In vitro studies

The *in vitro* evaluation of DDI potential focused on CYP inhibition, CYP induction and effects on transporters for macitentan and its active metabolite ACT-132577. The biotransformation of macitentan to ACT-132577 predominantly involves CYP3A4 with CYP2C19 playing a very minor role.

Macitentan had no significant inhibitory effects on human CYP enzymes including 1A2, 2A6, 2B6, 2C19, 2D6 and 2E1 (Study B-05-024). Macitentan inhibited CYP3A4 (IC₅₀ 24-37 μ M), CYP2C8 (IC₅₀ 21 μ M) and CYP2C9 (5.6 μ M). The CYP inhibition pattern was similar for ACT-132577 (Study B-05-130). The inhibitory effects of macitentan and ACT-132577 were not time dependent for CYP2C9, 2D6 and 3A4 (Study B-12-103).

Macitentan and ACT-132577 activated human pregnane X receptor (PXR) with EC₅₀ values of 1.1-1.2 μ M and 7.2-8.7 μ M respectively (Study B-05-107). *In vitro* studies with human hepatocytes also showed increased CYP3A4 mRNA activity. These studies suggest that macitentan and ACT-132577 has the potential for CYP3A4 induction at the concentration levels tested. But they did not elicit changes in CYP1A2 or 2C9 expression in human hepatocytes.

In vitro studies (B-05-040) using Caco-2 cells indicate that macitentan is not an inhibitor of P-gp mediated efflux. Similarly, macitentan and ACT-132577 were shown not to be influenced with OATP inhibitors or inducers significantly (Study B-10-642). But macitentan and ACT-132577 inhibited OATP1B1 and OATP1B3 mediated uptake of respective substrates with IC₅₀ values of 6.9 μ M and 14 μ M respectively.

Macitentan and ACT-132577 inhibited NTCP mediated uptake of taurocholate (a prototypical bile salt) with IC₅₀ values of 19 μM and 14 μM respectively (Study B-05-044). The BSEP mediated efflux of taurocholate was also inhibited by macitentan and its metabolite (IC₅₀ values of 18 μM and 50 μM respectively).

In summary, the *in vitro* studies indicate that macitentan and its active metabolite will be susceptible to significant DDI with potent CYP3A4 inhibitors, but not so with P-gp or OATP inducers or inhibitors. At the same time, macitentan and ACT-132577 has the potential to induce CYP3A4 and inhibit hepatic transporters, although at concentrations higher than that expected with therapeutic doses. It should also be noted that macitentan and ACT-132577 have very high plasma protein binding (> 99 %) and the free fraction available at therapeutic concentrations may be much lower than that is required to cause potential induction or inhibition effects.

***In vivo* studies**

To address DDI potentials seen in *in vitro* studies the applicant conducted *in vivo* DDI studies using warfarin (metabolized by CYP2C9, 1A2 and to a smaller extent by 3A4, Study AC-055-105), ketoconazole (a potent CYP3A4 inhibitor, Study AC-055-107), cyclosporine A (a CYP3A4 and OATP inhibitor, Study AC-055-111 Part A), rifampin (a potent CYP3A4 inducer, Study AC-055-111 part B) and sildenafil (CYP3A4 substrate and likely to be co-administered in PAH, Study AC-055-106). Also, the SERAPHIN phase III study allowed concomitant stable therapy with other PAH drugs including sildenafil without any significant increase in safety events. Figure 10 shows the impact of extrinsic factors on the PK of macitentan and ACT-132577.

It was observed that warfarin, sildenafil (and its metabolite N-desmethyl sildenafil), and cyclosporine-A had no significant impact on the exposure to macitentan or its active metabolite ACT-132577 and vice versa. The lack of DDI with sildenafil also suggests that CYP3A4 auto-induction is not expected at clinical doses. Similarly, the lack of DDI with cyclosporine-A suggests that OATP may not have a significant role in the hepatic uptake of macitentan or its metabolite.

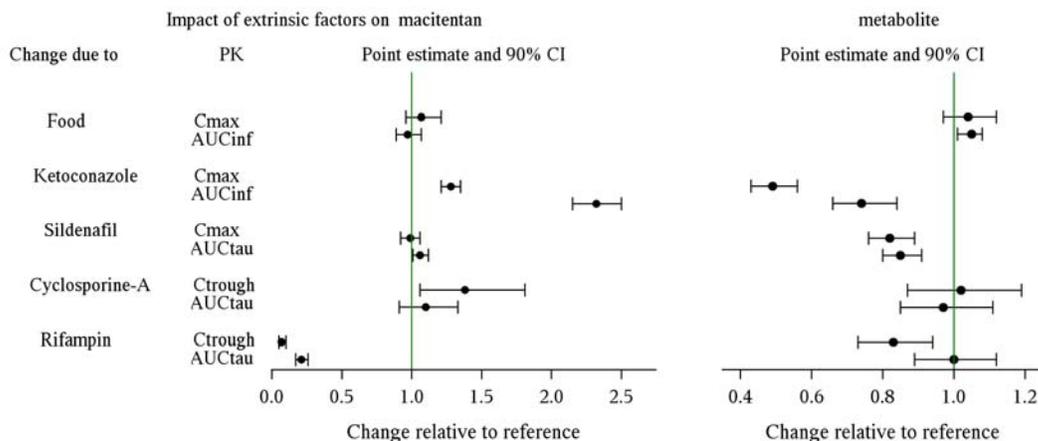


Figure 10: Impact of extrinsic factors on macitentan and its active metabolite ACT-132577. Geometric mean ratios of PK parameters and 90 % CI are plotted. Macitentan PK when used alone is the reference for DDI studies. Macitentan PK in fasted state is the

reference for food effect study. Doses used: Ketoconazole 400 mg once daily, sildenafil 20 mg three times daily, cyclosporine-A 100 mg twice daily and rifampin 600 mg once daily.

Rifampin, a potent CYP3A4 inducer, however decreased the exposure to macitentan by approximately 80%, which could significantly reduce the efficacy. Therefore rifampin should not be co-administered with macitentan.

A single dose (10 mg) of macitentan when given with Ketoconazole, administered as 400 mg once daily, increased the exposure (AUC_{∞}) and C_{max} to macitentan by about 2.3X and 1.3X respectively. The exposure and C_{max} of its active metabolite ACT-132577 decreased by ~ 26 % and ~ 51 % respectively. The elimination half life of macitentan increased from 14.1 hours to 28.5 hours, while that of ACT-132577 showed a modest increase (46.7 hours versus 58.6 hours). The observed DDI effects with ketoconazole could therefore be attributed to its effects on the elimination phase of macitentan. The accumulation of macitentan on repeat dosing in presence of strong CYP3A4 inhibition could be much higher with an estimated accumulation index of ~ 2.3 versus 1.4 when no CYP3A4 inhibition is present. The exposure at steady state is expected to be approximately 3 to 4X higher with strong CYP3A4 inhibitors. The long term safety information on macitentan on doses higher than 10 mg is limited. The use of macitentan 10 mg should therefore be avoided with strong CYP3A4 inhibitors like ketoconazole.

Even though PAH is prevalent in HIV infection the SERAPHIN phase III study included less than 1 % of patients with HIV. Therefore the safety and efficacy data on macitentan in HIV patients is very limited. Macitentan was not studied with lopinavir/ritonavir or other ritonavir containing HIV regimens. Ritonavir is a strong CYP3A4 inhibitor and has some reported induction properties on CYP3A4 system. We conducted physiologically based pharmacokinetic (PBPK) simulations using the applicant's model to predict the potential impact of ritonavir (100 mg twice daily) on macitentan exposure. The applicant verified the PBPK model in SimCYP[®] software using the results from ketoconazole and rifampin DDI studies (See Table 3). Since the CYP3A4 induction properties of lower doses of ritonavir is not well characterized we modified the PBPK model within SimCYP[®] library by considering only its inhibitory effects for the PBPK simulations for macitentan to represent a worst case scenario. Multiple dosing with 100 mg twice daily ritonavir resulted in ~ 3X increase in macitentan exposure after single dose of 10 mg macitentan. Concurrent dosing of both drugs for 15 days showed ~ 4X increase in macitentan exposure at steady state. This observation, although does not consider CYP3A4 induction effects of ritonavir, if any, is in agreement with the *in vivo* DDI observation with ketoconazole, a strong CYP3A4 inhibitor. CYP3A inhibitors like ketoconazole are expected to prolong the elimination half life of macitentan thus increasing its accumulation on repeat dosing. Since ritonavir treatment for HIV will be for long term and there is no long term safety information on macitentan at doses above 10 mg, the predicted 4X increase in exposure with strong CYP3A4 inhibitors like ritonavir is considered clinically significant. Therefore macitentan 10 mg dose should be avoided if co-administration of strong CYP3A4 inhibitor drugs is desired.

Table 3: Performance of the PBPK model for macitentan

AUC ratios (GM and 90%CI)	Macitentan		ACT-132577	
	Predicted	Observed	Predicted	Observed
Ketoconazole	2.7 (2.5-2.9)	2.3 (2.2-2.5)	0.6 (0.6-0.7)	0.7 (0.7-0.8)
Ketoconazole [⊗]	3.3 (3.0-3.5)	Not Applicable	Not included	
Rifampin	0.4 (0.3-0.4)	0.2 (0.2-0.3)	0.6 (0.5-0.6)	1.0 (0.9-1.1)
Ritonavir [*]	3.3 (3.0-3.5)	Not applicable	Not included	
Ritonavir ^{**}	4.1 (3.8-4.4)			

Ref: Sponsor's PBPK study report for ketoconazole and rifampin predictions, 10 trials with 10 subjects each, [⊗]Ketoconazole 400 mg QD and macitentan 10 mg QD for 15 days *Ritonavir 100 mg BID till study state and macitentan as 10 mg single dose, **Ritonavir 100 mg BID and macitentan 10 mg QD were given simultaneously for 15 days, Rifampin 600 mg QD

3.4 Biopharmaceutics

3.4.1 What are the characteristics of the bioanalytical method(s) used in the clinical pharmacology studies?

Validated HPLC-MS/MS methods were used for measuring the concentrations of macitentan, ACT-132577 and ACT-373898 in plasma. The linearity ranges of the assays are listed in Table 4. The accuracy and precision of the assays were within the acceptable limits ($\leq 20\%$ at LOQ and $\leq 15\%$ at all other QC levels) and the reported validation parameters are acceptable.

Table 4: Assay Linearity from the method validation program

Analytes/Parameter	Macitentan	ACT-132577	ACT-373898
LLOQ	1.0 ng/mL	1.0 ng/mL	0.5 ng/mL
ULQ	2000 ng/mL	2000 ng/mL	500 ng/mL

LLOQ: Lower limit of quantification, ULQ: Upper limit of quantification

Ref: Method validation reports: SBA_S_04081 and SBA_S_09020

While estimation of total plasma concentrations are acceptable, the sample analysis for free concentrations (unbound) of these analytes for estimating plasma protein binding from hepatic impairment study (AC-055-110) showed unacceptable variability on incurred sample re-analysis. Only 14.3 % of the repeats for macitentan, 7.1 % of the repeats for ACT-132577 and 7.1 % of the repeats for ACT-373898 were within $\pm 20\%$ of the reference values for and therefore did not pass the acceptance criteria. This could be because the established LLOQs may not be sufficient enough for estimating the unbound fraction of these analytes. The reported protein binding values for these analytes from the hepatic impairment study are therefore unreliable.

3.4.2 How is the final marketing image formulation bridged to the Phase III formulation?

The phase III formulation is same as the final marketing image (FMI) formulation and therefore no pivotal bioequivalence study was required.

The exposure to macitentan was not affected in a food effect study (AC-055-103, Figure 9) and so the clinical doses can be administered once daily with or without food as done in SERAPHIN study. The early PK studies were performed using a (b) (4) formulation. A comparison study (AC-055-108) between the (b) (4) formulation and final tablet formulation showed that the point estimates and 90 % CI of AUC and C_{\max} for macitentan were mostly within the acceptable BE range of 0.8-1.25 except that the lower 90 % CI for C_{\max} (which was 0.75).

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/s/

SREEDHARAN N SABARINATH
06/28/2013

DHANANJAY D MARATHE
06/28/2013

PING ZHAO
06/28/2013

YANING WANG
06/28/2013

RAJANIKANTH MADABUSHI
06/29/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	204-410
Submission Date:	10/19/2012, 1/22/2013, 3/29/2013
Drug Name:	Opsumit (Macitentan) Tablets
Formulation:	Tablets
Strength:	10 mg
Applicant:	Actelion Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA 505(b)(1)

SYNOPSIS

Submission: NDA 204-410 Opsumit (macitentan) Tablets submitted on 10/19/2012, is proposed for the indication of the treatment of pulmonary arterial hypertension. Justifications for the proposed dissolution methodology and acceptance criterion are provided for the quality control. In addition, the proposed specification of the particle size distribution is supported by a physiologically based model using GastroPlus software.

Review: The Biopharmaceutics review is focused on the effect of the particle size on bioavailability and the proposed dissolution methodology and acceptance criterion.

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 $Q = (b) (4)$ 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.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the information provided in NDA 204-410 for Opsumit (macitentan) Tablets and found it acceptable. From the Biopharmaceutics perspective this NDA is recommended for approval.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

Date

cc: NDA 204-410 *DARRTS, RLostritto*

BIOPHARMACEUTICS EVALUATION

1. Introduction

This is an NME NDA application for macitentan 10 mg film coated tablets. Macitentan is an orally active, nonpeptide, dual endothelin (ET A and ET B) receptor antagonist proposed for the indication of the treatment of pulmonary arterial hypertension. Macitentan is proposed to be administered orally with a once daily (o.d.) regimen. The doses of 3 mg and 10 mg were selected for the pivotal study AC-055-302 in patients with PAH.

2. Physiological properties of the drug substance

Macitentan is soluble in many nonalcoholic solvents, slightly soluble in methanol and ethanol, and insoluble in aqueous media with pH in the range 1.2 to 9 as shown in the following table.

Solvent	Solubility	Solubility in mg/mL
pH 1.2 Simulated gastric fluid	not soluble	-
pH 4 Merck	not soluble	-
pH 6.8 Simulated gastric fluid	not soluble	-
pH 7 Merck	not soluble	-
pH 9 Merck	not soluble	-
Water	not soluble	-

Macitentan was reported as BCS class II i.e. low solubility and high permeability by the Applicant.

Reviewer's Comments: The solubility of the drug substance is low, which justifies the usage of surfactant when dissolution method is developed. Although the Applicant claimed a BCS class II drug, the data supporting high permeability were not provided.

3. The Pharmacokinetics of Macitentan

To compensate for the lack of a traditional absolute bioavailability study, the bioavailability of macitentan was simulated using a physiologically-based PK (PBPK) computer model. The performance of this model was validated by comparing predicted and observed plasma concentration time-courses from a clinical DDI study with ketoconazole. The predicted plasma concentration vs. time profiles matched the observed profiles well and allowed an estimation of oral bioavailability of macitentan of 74% (95% CL 72–77%).

The PK profile of macitentan is characterized by relatively slow absorption with maximum plasma concentrations achieved about 8 hours after drug administration, and an apparent elimination half-life ($t_{1/2}$) of approximately 16 hours. The active metabolite

ACT-132577 is formed slowly and eliminated with a $t_{1/2}$ of approximately 48 hours. The metabolite ACT-373898 has a PK profile similar to that of macitentan. The PK parameters of macitentan are similar after single- and multiple-dosing.

After multiple dosing, steady-state conditions of macitentan and ACT-132577 were obtained after 3 days and 7 days, respectively. The AUC₀₋₂₄ and C_{max} of macitentan were dose-proportional over the tested dose range (1 to 30 mg o.d.). As anticipated from the observed $t_{1/2}$, the accumulation of macitentan was minimal (approximately 1.5-fold) whereas that of ACT-132577 was about 8.5-fold. At steady-state, the metabolites ACT-132577 and ACT-373898 contributed to approximately 74% and 3% of total drug exposure, respectively. Macitentan and its circulating metabolites are highly bound ($\geq 99\%$) to plasma proteins, mainly albumin, in all species, including man. The exposure to macitentan and ACT-132577 is unchanged in the presence of food.

Macitentan undergoes metabolism by CYP3A4 and CYP2C19. The contribution of CYP2C19 is too limited to be relevantly affected by drug-drug interactions (DDIs) or genetic polymorphism. The active metabolite ACT-132577 and the inactive ACT-373898 are the only metabolites of macitentan detected in plasma. In the human ADME study, approximately 50% of radioactive drug material was eliminated in urine, none in the form of unchanged drug or the active metabolite. Conjugated products of macitentan and ACT-132577 excreted in the bile may be reconverted into their active forms by intestinal bacterial action, but there are no indications of relevant enterohepatic recirculation in either animals or man.

Reviewer's Comments: *The slower absorption with a T_{max} about 8 hours is consistent with the low solubility. The predicted bioavailability (74%) may indicate a relatively high permeability.*

4. The Composition

The composition (mg) of the Macitentan film-coated tablets used in clinical studies is shown in the following table.

Ingredients	3 mg	10 mg
Macitentan	3.00	10.00
Lactose monohydrate		(b) (4)
Microcrystalline cellulose		
Sodium starch glycollate type A		
Povidone		
Magnesium Stearate		
Polysorbate 80		
(b) (4)		
Total	72.80	72.80

Reviewer's Comments: *The two strengths can be considered (b) (4) and both were used in clinical trials. However, 10 mg strength was selected as the to-be-marketed formulation.*

5. The formulation development

The following scheme shows the formulation changes during the development.



A (b) (4) formulation was initially developed and was used in early Phase 1 studies as well as in the Phase 2 study AC-055-201 in essential hypertension. (b) (4)

The film-coated tablets were used in clinical Phases 1, 2 and 3. The human pharmacokinetic profile of the (b) (4) formulation was compared to the tablet formulation in a clinical study (AC-055-108). The study showed that absorption of macitentan was slow with a median t_{max} of 8 hours and 10 hours for the (b) (4) and tablet respectively, and a terminal half-life of approximately 13 hours for both formulations. Mean C_{max} was approximately 19% lower after ingestion of the tablet compared to the (b) (4) formulation with its lower 90% confidence limit below the usually accepted bioequivalence range of 0.80-1.25.

The dosage strength of 10 mg macitentan was chosen for the market formulation based on the results of the pivotal Phase 3 study. The composition of the commercial film-coated 10 mg tablet is the same as that used in clinical studies, including the pivotal Phase 3 study.

Reviewer's Comments: Although there were formulation changes during the development (b) (4) the to-be-marketed formulation is the same as that used in the pivotal clinical trials.

6. Dissolution method development

1. *Proposed dissolution conditions*

Apparatus: USP 2 (paddle)
Temperature: 37.0 ± 0.5 °C
Speed: 75 ± 2 rpm
Volume: 900 mL
Medium: Buffer pH=6.8 with 0.1% of Cetrimonium bromide (CTAB)
Sampling volume: 12 mL

2. *Justification of the dissolution medium*



The dissolution profile of macitentan tablets when using a buffer pH 6.8 with 0.1% CTAB as dissolution medium is provided in the following figure.



The dissolution was above (b) (4) after 30 minutes. Buffer solution pH 6.8 with 0.1% CTAB was selected as the dissolution medium for the macitentan 10 mg film-coated tablets.

Reviewer's Comments: The selected dissolution medium seems reasonable.

3. Justification of the rotation speed

Per FDA request, a rationale for the choice of 75 rpm as rotation speed for the dissolution testing was added to section 3.2.P.2.2.3 Pharmaceutical Development.



The Reviewer's Comments: The results demonstrated that the dissolution method using 0.1% CTAB provides ability to distinguish drug product manufacturing changes and the discriminating ability on tablets which were exposed to inappropriate storage conditions.

5. Acceptance criterion of dissolution testing

An acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes was proposed by the Applicant. After reviewing the data, the following information request was conveyed to the Applicant on December 12, 2012.

“The dissolution data provided (including the stability data) appear to support tightening of the dissolution acceptance criterion to $Q = \text{(b) (4)}$ at 30 minutes. We recommend that you implement this criterion and provide the revised specification table for your drug product.”

In the response dated January 22, 2013, the Applicant acknowledged that currently available release and stability data could support a revision of the acceptance criterion from $Q = \text{(b) (4)}$ to $Q = \text{(b) (4)}$ at 30 minutes. (b) (4)

During the Mid-Cycle review phase, the following information request was conveyed to the Applicant on 3/21/2013.

The provided dissolution data fully support an acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes for your product. Therefore, your proposal to keep the currently proposed $Q = \text{(b) (4)}$ at 30 minutes is not acceptable. Implement the dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes and provide the updated specifications table for your drug product with the revised acceptance criterion for the dissolution test.

In the response dated 3/29/2013, the Applicant accepted the recommendation and updated the drug product's specifications table.

The Reviewer's Comments: The Applicant accepted the FDA recommendation and implemented the dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes. The pending issue has been resolved.

6. Particle size effect on bioavailability

[REDACTED] (b) (4)
[REDACTED]. The current specification of the drug substance has been established as follows.

Particle size distribution:

10th percentile: [REDACTED] (b) (4)
50th percentile: [REDACTED]
90th percentile: [REDACTED]

The effect of the particle size distribution of the drug substance on the bioavailability was investigated by a parameter sensitivity analysis with a physiologically-based pharmacokinetic (PBPK) software (GastroPlus™).

With the input parameters, the effect of drug substance particle size on the percentage absorbed was investigated in a parameter sensitivity analysis. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Further, the software simulated the plasma concentration-time curves of macitentan following administration of an oral dose of 10 mg with different particle size. The results are shown in the following table and figure.

During the Mid-Cycle review's phase, the following information request was conveyed to the Applicant on 3/21/2013.

1. *The following requests are regarding Table 3 of the PBPK Modeling Research Report (page 14).*
 - a. *Confirm that the 4th to 7th columns are referred to radius of uniform particle size distribution.*
 - b. *Clarify what particle size distribution was used for the 2nd (baseline) and 3rd (specification) columns. If uniform distribution was used, provide the radius value used in simulations and its justification. If distributions based on the 10th, 50th and 90th percentiles were used, provide justification for inconsistent particle size distributions used in the simulations.*

In the response dated 3/29/2013, the Applicant clarified that the particle size distribution was used in the simulation.

7. **Reviewer's Comments:** *The proposed drug substance specification for particle size is acceptable. This Reviewer used GastroPlus to perform a simulation investigating the effect of particle size distribution on the in vivo performance as shown in the following figure. The results showed that the formulation with the particle size of the worst scenario (the green line, the higher limits of the specification) is bioequivalent*

to the clinical formulation (the red line) with the green and pink areas for 90% confidence intervals, respectively. Therefore, the Applicant's provided data using GastroPlus to evaluate the particle size effect on bioavailability is acceptable.



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/s/

JOHN Z DUAN
06/18/2013

ANGELICA DORANTES
06/18/2013

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

NDA Number	204-410
Submission Date	Oct 19, 2012
Product name, generic name of the active	OPSUMIT (macitentan)10 mg tablet
Dosage form and strength	Tablets, 10 mg
Applicant	Actelion Pharmaceuticals
Clinical Division	Division of Cardioresenal Drug Products
Type of Submission	Original NDA 505(b)1
Biopharmaceutics Primary Reviewer	John Duan, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

BIOPHARMACEUTICS INITIAL ASSESSMENT
Biopharmaceutics Summary
<p>This submission is a New Drug Application (NDA 204-410) for the use of OPSUMIT (macitentan) tablets in the treatment of patients with pulmonary arterial hypertension (PAH).</p> <p>A (b) (4) formulation was initially developed (b) (4). This formulation was used in early Phase 1 studies as well as in the Phase 2 study AC-055-201 in essential hypertension. (b) (4)</p> <p>(b) (4) The film-coated tablets were used in clinical Phases 1, 2 and 3. The human pharmacokinetic profile of the (b) (4) formulation was compared to the tablet formulation in a biocomparison study (AC-055-108) as shown in the following scheme.</p>

ONDQA - BIOPHARMACEUTICS

Initial Product Quality Assessment and Filing Review

(b) (4)

The dosage strength of 10 mg macitentan was chosen for the market formulation based on the results of the pivotal Phase 3 study. The composition of the commercial film-coated 10 mg tablet is the same as that used in clinical studies, including the pivotal Phase 3 study.

(b) (4)

The effect of the particle size distribution of the drug substance on the bioavailability was investigated by performing a parameter sensitivity analysis with a physiologically-based pharmacokinetic (PBPK) software (GastroPlus™). From the analysis, it concluded that (b) (4)

However, the details have not been provided.

(b) (4)

Furthermore, investigations were carried out in order to identify an appropriate dissolution method for the commercial macitentan 10 mg film-coated tablets as shown below.

(b) (4)

ONDQA - BIOPHARMACEUTICS

Initial Product Quality Assessment and Filing Review

Apparatus: USP 2 (paddle)
Temperature: 37.0 ± 0.5 °C
Speed: 75 ± 2 rpm
Volume: 900 mL
Medium: Buffer pH=6.8 with 0.1% of Cetrimonium bromide (CTAB)
Sampling volume: 12 mL
Sampling time point: 30 min

A dissolution acceptance criterion of $Q = \text{[redacted]}^{(b)(4)}$ was set initially. This criterion was used during the entire clinical development. Based on the release data from the clinical batches of film-coated tablets, the dissolution criterion was tightened to $Q = \text{[redacted]}^{(b)(4)}$ at 30 minutes and will be applied to the registration and commercial batches.

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution information/data and the effect of particle size on the bioavailability of the proposed product.

Critical Review Issues

Critical review issues identified during filing are as follows.

- Suitability of the proposed dissolution method and acceptance criterion.
- Suitability of the Applicant's conclusion regarding the effect of particle size on the bioavailability.

Comments for Day 74-Letter

The following comments should be conveyed to the Applicant:

- Provide the rationale of selecting a rotation speed of 75 rpm for the dissolution testing. Provide the dissolution data using $\text{[redacted]}^{(b)(4)}$
- The dissolution data provided (including the stability data), support the tightening of the dissolution acceptance criterion to $Q = \text{[redacted]}^{(b)(4)}$ at 30 minutes. Implement this criterion and provide the revised specification table for your drug product.
- Provide the details of the parameter sensitivity analysis using GastroPlus to support the conclusion regarding the effect of particle size on the bioavailability, including the model chosen, the parameter selected and the parameter ranges.

ONDQA - BIOPHARMACEUTICS

Initial Product Quality Assessment and Filing Review

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
1.	Does the application contain dissolution data?	X		
2.	Is the dissolution test part of the DP specifications?	X		
3.	Does the application contain the dissolution method development report?	X		
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		In vivo PK data will be reviewed by the Office of Clinical Pharmacology.
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		X	Not applicable

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
11.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
13.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Please convey the Applicant in the 74-Day letter the comments listed in pages 3 of this filing review.

Administrative Block: *{See appended electronic signature page}*

John Duan, Ph.D.
 Biopharmaceutics Primary Reviewer
 Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
 Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

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/s/

JOHN Z DUAN
11/18/2012

ANGELICA DORANTES
11/18/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Macitentan is a new orally active, dual endothelin receptor antagonist. The sponsor is seeking approval for macitentan for the long term treatment of pulmonary arterial hypertension (PAH) ^(b)
[REDACTED] ⁽⁴⁾ Clinical evidence for the efficacy and safety of macitentan in the treatment of patients with PAH is derived from a pivotal, placebo controlled, double-blind, phase III study called SERAPHIN (Study # AC-055-302), which enrolled 742 patients with symptomatic PAH, randomized in a 1:1:1 ratio to once daily macitentan 3 mg, 10 mg or placebo. An open label extension study is ongoing. Details of the clinical pharmacology studies included in the submission are listed below.

	Information		Information
NDA Number	204410	Brand Name	OPSUMIT [®]
OCP Division	I	Generic Name	Macitentan
Medical Division	DCRP	Drug Class	Endothelin receptor antagonist
OCP Reviewer	Sreedharan Sabarinath	Indication(s)	Pulmonary arterial hypertension (PAH)
OCP Team Leader	Rajanikanth Madabushi	Dosage Form	Tablet
Pharmacometrics Reviewer	Dhananjay Marathe	Dosing Regimen	10 mg Once daily
Date of Submission	19-Oct-2012	Route of Administration	Oral
Estimated Due Date of OCP Review	19-Jun-2013	Sponsor	Actelion
PDUFA Due Date	19-Oct-2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	3	3	3 Stand-alone validation reports
I. Clinical Pharmacology				
Mass balance:	X	1	1	Study # AC-055-104
Isozyme characterization:	X	5	5	Microsomes/hepatocytes/P450 Study # B-04-022, B-04-093, B-04-099, B-06-219, B-07-372
Blood/plasma ratio:	X	2		
Plasma protein binding:	X	3	3	
Intestinal Permeability	X	1	1	Study # B-05.040
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	SAD - Study # AC-055-101
multiple dose:	X	1	1	MAD - Study # AC-055-102
Patients-				
single dose:	-			
multiple dose:	X	1	1	Study # AC-055-201 Phase 2, Dose range, in Mild/Moderate Hypertension
Dose proportionality -				
fasting / non-fasting single dose:	X	1		SAD - Study # AC-055-101

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting multiple dose:	X	1		MAD – Study # AC-055-102
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4	4	# AC-055-105 Warfarin # AC-055-106 Sildenafil # AC-055-107 Ketoconazole # AC-055-111 Cyclosporin A # AC-055-111 Rifampin
In-vitro/Pre-clinical	X	5	5	P450 inhibition, induction and transporters. Study # B-04-024, B-12-203, B-05-107, B-10-642, B-05-044
Subpopulation studies -				
ethnicity:	X	1	1	Study # AC-055-109 Japanese Vs. Caucasians (Korean Vs. Caucasian ongoing)
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	Study # AC-055-112
hepatic impairment:	X	1	1	Study # AC-055-110
PD -				
Phase 2:	X	1		Study # AC-055-201
Phase 3:	X	1		Phase 3 Study: SERAPHIN
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	4	3	#AC-055-113 <i>Spermatogenesis</i> #AC-055-114 TQT # AC-055-201 BP # AC-055B-201 IPF
Phase 3 clinical trial:	X	1	1	PK/PD report
Population Analyses -	X	1	1	Population PK analyses report
II. Biopharmaceutics				
Absolute bioavailability	X	1	1	PBPK Report (SimCYP)
Relative bioavailability -				
solution as reference:	-			
alternate formulation as reference:	X	1	1	Study # AC-055-108 10 mg Tablet Vs. 10 mg (b) (4)
Bioequivalence studies -				
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies	X	1	1	Study # AC-055-103 Fasted Vs. Fed for 10 mg (b) (4)
Bio-waiver request based on BCS	-			
BCS class	-			
Dissolution study to evaluate alcohol induced dose-dumping	-			
III. Other CPB Studies	-			
Genotype/phenotype studies	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Not applicable. Granted Orphan drug status.
Literature References	X			
Total Number of Studies		43	36	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used			X	The tablets used in the pivotal Phase 3 study are

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
	in the pivotal clinical trials?				the same as the final market formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			<i>Based on D-R in hypertension and Phase 1 SAD/MAD on ET-1 levels</i>
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
	section of the label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the NDA is fileable. There are no potential review issues identified at this time. We have the following information request to the Sponsor:

- Please provide the SimCYP[®] workspaces, compound and output files from the PBPK analyses used for absolute bioavailability estimation.

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

/s/

SREEDHARAN N SABARINATH
11/16/2012

RAJANIKANTH MADABUSHI
11/16/2012