

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204410Orig1s000

MEDICAL REVIEW(S)

Division Director Review

Date	15 October 2013
From	Norman Stockbridge
Subject	Division Director memo
NDA/BLA # Supplement#	204410 000
Applicant	Actelion
Date of Submission	19 October 2012
PDUFA Goal Date	19 October 2013
Proprietary Name / Established (USAN) names	Opsumit Macitentan
Dosage forms / Strength	Oral tablets; 10 mg
Proposed Indication(s)	1.  (b) (4)
Recommended:	Approval

I refer to reviews of CMC (Wang; 24 May 2013), biopharmaceutics (Duan; 18 June 2013), pharmacology/toxicology (Link; 14 June and 26 August 2013), clinical pharmacology (Sabarinath, Marathe, and Zhao; 29 June and 6 September 2013), clinical (Gordon; 19 June 2013), and statistics (Zhang; 18 June 2013 and 4 October 2013). There is also a CDTL memo (Southworth; 19 September 2013), with which I am in complete agreement.

CMC site inspections are complete. There are no other CMC issues.

There are no outstanding issues with biopharmaceutics.

The non-clinical work-up is consistent with macitentan being a mixed endothelin ETA and ETB receptor antagonist. There is one long-lived active metabolite. Typical of these drugs, macitentan shows toxicity at seminiferous tubules, decreases hematocrit, and causes craniofacial abnormalities in fetuses exposed in utero. There is no identified off-target toxicity. There was no genotoxicity finding; two-year carcinogenicity studies in two species were unremarkable.

In man, the long half-life results in about 50% accumulation of the parent, and about 8-fold of the active metabolite, with once daily dosing. Plasma levels are about 50-100% higher in PAH patients than in normal volunteers. Both parent and metabolite are highly protein bound. Macitentan is subject to metabolism by multiple CYPs; inhibition or induction of 3A merits dose adjustment. Dose adjustment is also not needed for hepatic or renal impairment.

A single study supports approval. SERAPHIN was a parallel study in which 742 subjects with pulmonary arterial hypertension (77% female; 55% idiopathic, 31% connective tissue disorders; WHO functional class II-III; 60% on background PDE5 inhibitor) were randomized to placebo or to macitentan 3 or 10 mg and followed for up to about 4 years (median of about 2).

The primary end point was fairly conventional, clinical worsening as evidenced by all-cause mortality, need for atrial septostomy, lung transplantation, IV or SC prostanoids, or clinical worsening (confirmed 15% decrease in 6MW plus increase in functional class or right heart failure plus new oral or other therapy for PAH) to end of treatment + 7 days. Both doses were allocated alpha=0.005, so the overall alpha was 0.01, deemed by the Division and ODEI as an adequate basis for one-study approval.

Statistical significance was achieved at 10 mg (HR=0.55; p=0.0001), but not quite at 3 mg (HR=0.7; p=0.011). Most of the events and all of the treatment effect are, predictably, on worsening PAH.

The effect on 6MW at 6 months was about 22 m (p=0.008). Similar results are obtained on both end points for the observed data and including the imputed data for withdrawals.

Reviews describe similar effects on the composite end point and on 6MW in various subsets. Analysis by background PDE5 inhibitor is a particular concern considering how hard it has been to show consistent effects of one vasodilator on top of another one.

The table below shows effects on the composite end point by baseline use of PDE5 inhibitor:

PDE5 inhibitor	Macitentan		Placebo		HR	97.5% CI
	N	# events	N	# events		

None	88	26	95	48	0.45	0.26	0.77
BERAPROST	6	3	4	2	1.03	0.13	8.09
ILOPROST	10	3	3	2	0.59	0.08	4.69
SILDENAFIL	140	46	140	62	0.60	0.39	0.94
TADALAFIL	2	1	2	0			
VARDENAFIL	8	1	8	3	0.35	0.03	4.61

The effect is similar on no PDE5 inhibitor and on sildenafil (where the bulk of the experience is), and even statistically significant in both subsets.

This table shows effects on 6MW at 6 months:

PDE5 inhibitor	Placebo				Macitentan 10 mg			
	N	Mean	STD	Median	N	Mean	STD	Median
None	95	-12.2	122.4	0	88	3.1	85.4	13.5
BERAPROST	4	-52.8	127.1	-13.5	6	-43.2	57.6	-47
ILOPROST	3	31.3	62.9	39	10	-4.8	49.2	-8.5
SILDENAFIL	140	-6.3	85.1	4	140	20.0	82.6	17.5
TADALAFIL	2	3.0	17.0	3	2	19.0	48.1	19
VARDENAFIL	8	-9.9	71.3	4.5	8	4.8	95.5	-15.5

Again, there are, at least, similar median effects on sildenafil or no PDE5 inhibitor.

In addition, there are at least favorable trends on functional class and hospitalization.

Deaths were similar across groups¹.

The only clear “safety” signal is anemia; as an AE, the counts are <1% on placebo, 2% on 3 mg, and 3% on 10 mg. This is consistent with effects seen with all the drugs approved for PAH, and I suspect that it contributes to benefit.

There is no hint of hepatotoxicity, but the baggage for endothelin receptors is such that the review team favors labeling similar to ambrisentan’s, with additional clinical information obtained through a post-marketing commitment.

I concur with the entire review team in recommending approval.

¹ The accounting is a little confusing. For all subjects throughout the entire study, there were 28 deaths on placebo and 30 on macitentan 10 mg. For adjudicated events as part of the primary end point (EOT+7), the numbers are 17 and 16 as first events, and they are 18 and 16 as adjudicated events at any time up to EOT+7. However, the adjudicators liberally interpreted the window; unadjudicated counts are 19 and 14 for EOT+7.

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/s/

NORMAN L STOCKBRIDGE
10/15/2013

NDA#204410

Drug: macitentan

Sponsor: Actelion

Medical Reviewer: Maryann Gordon, MD

Re: liver toxicity review

Summary

Macitentan is an agent developed for the treatment of patients with pulmonary arterial hypertension (PAH). Because this drug is chemically similar to bosentan, a drug associated with liver transaminase elevations, and the Canadian Health Authorities were concerned about the liver toxicities reported by patients who received macitentan during the clinical trials, I, as the primary reviewer decided to re-examine the known effects of macitentan on the liver.

In my re-review, I have found, at best, only a weak link between possible liver injury and the use of this agent. However, there is still need for vigilance because

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

Background

The findings that led me to this conclusion are:

- 1) [REDACTED] ^{(b) (4)} hypertension study AC-055-201 because of signs of liver toxicity [REDACTED] ^{(b) (4)}

A total of 379 subjects were randomized to placebo (n = 54), ACT-064992 doses 0.3 mg (n = 54), 1 mg (n = 60); 3 mg (n = 57); 10 mg (n = 56) or enalapril (n = 56).

Safety outcome: There were five cases of increased liver enzyme (LFT) elevation $> 3 \times$ ULN in the ACT-064992 treatment groups (1, 2, 1 and 1 in the ACT-064992 0.3, 1, 3, 10 mg groups, respectively), and none in placebo or the enalapril groups.

There were three subjects, randomized to macitentan in the study who were discontinued because of elevated LFTs:

-#202-1024, macitentan 1 mg, 51 year old white female, concomitant medications included aspirin, pipemidic acid, bromazepam, diclofenac, avamigran, ibuprofen, omeprazole, ranitidine and sertraline. She reported mild ALT elevations and a urinary tract infection needing treatment with an antibiotic.

-#204-1011, macitentan 3 mg, diagnosed during study with pancreatic cancer with obstruction of the papilla of Vateri.

-#119-1429, macitentan 10 mg, 70 year old white male was receiving atorvastatin and warfarin at baseline. Reported mild ALT elevations and was hospitalized for benign prostate hyperplasia with urinary retention leading to prostatectomy. He received Ampicillin 2g IV and gentamycin.

There was one subject with pancreatic cancer and the other two had mild increases in ALT in association with antibiotic use.

2) Study AC-055-102 was a single center, double blind, placebo-controlled, randomized, ascending dose study in healthy male subjects. The subjects received 1, 3, 10 or 30 mg dose of macitentan or placebo for 10 days. There was a trend for small increases in mean levels of the liver aminotransferases ASAT and ALAT compared to baseline in the groups treated with 10 and 30 mg macitentan, mainly caused by four subjects. However, all cases of elevated liver aminotransferases were asymptomatic, resolved within 2 weeks and there were no reported changes in serum bile salts, bilirubin, or AP reported. The sponsor apparently decided at this point to limit exposure to macitentan in PAH patients to no more than 10 mg once daily.

3) Health Canadian received a list of 38 macitentan treated subjects who reported at least one event using the preferred term “drug-related hepatic disorders” and then later died. I concluded that these patients died of PAH progression and their liver toxicities were probably the result of PAH progression.

4) The long term placebo-controlled trial in PAH (SERAPHIN) did not demonstrate that macitentan had an adverse effect on the liver. However, there is a case of drug rechallenge that is discussed below.

Patient 8401-11587 (macitentan 10 mg)

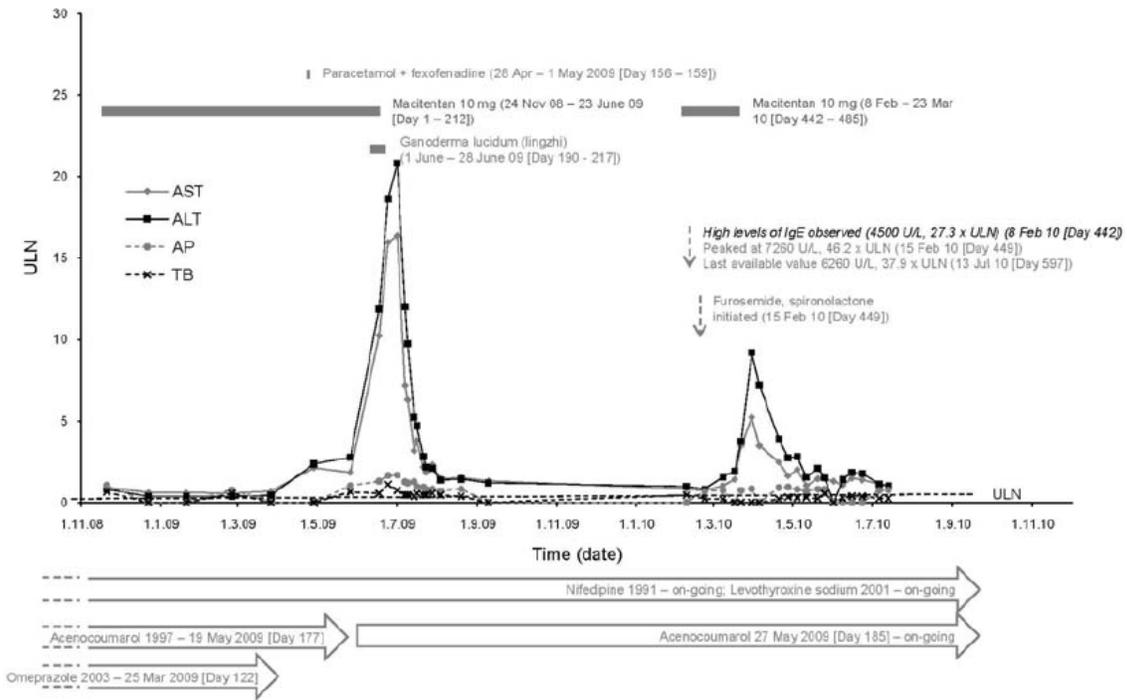
This 26 year old female patient with idiopathic PAH had a medical history of hypothyroidism, upper abdominal pain, headache, human papilloma virus infection, and cutaneous tuberculosis. The patient reported a history of liver disease with increases of liver enzymes on at least at two occasions and a past history of receiving sitaxentan.

On Day 190, the patient started drinking a “natural” coffee containing ‘*Ganoderma lucidum*’ (the lingzhi or reishi mushroom) followed by elevations of ALT and AST > 10 x ULN with slight elevation of AP and no significant elevation of TBIL were observed. Study treatment was permanently discontinued and the *Ganoderma lucidum*-containing beverage was stopped on Day 217.

This patient was rechallenged with macitentan (without the coffee drink) 10 mg starting 7.5 months after study treatment discontinuation. ALT and AST were within the normal range prior to rechallenge. IgE at this time was reported to be 4500 IU/mL (normal 1-165 IU/mL). During the rechallenge, her PAH grew worse with signs of hepatic congestion.

After five week of macitentan aminotransferases were elevated and continued to increase. Macitentan was discontinued on Day 486 and LFTs eventually normalized.

8401-11587 F. 26, MEX, SERAPHIN DB



5) There are 2 studies in patients with digital ulcers. Although there are some patients with increased transaminases, they are complex cases and it is hard to identify a direct link between liver toxicity and use of macitentan.

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/s/

MARYANN GORDON
07/25/2013

CLINICAL REVIEW

Application Type NDA
Application Number(s) 204410
Priority or Standard S

Submit Date(s) October 19, 2012
Received Date(s) October 19, 2012
PDUFA Goal Date October 19, 2013
Division / Office ODEI/DCRDP

Reviewer Name(s) Maryann Gordon, MD
Review Completion Date June 21, 2013

Established Name Macitentan
(Proposed) Trade Name Opsumit®
Therapeutic Class Endothelin receptor antagonist
Applicant Actelion

Formulation(s) Tablets
Dosing Regimen Once daily
Indication(s) Pulmonary arterial hypertension (PAH)
Intended Population(s) PAH, WHO Group 1

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

The results of the single large, well-controlled efficacy trial in patients with PAH showed that macitentan 10 mg once daily reduces the risk of the occurrence of worsening PAH symptoms. There was neither a survival benefit nor a mortality risk with doses 10 mg once daily or less. Other benefits included improvements in 6MWD, WHO functional class, health-related Quality of Life (QoL), and fewer days of hospitalizations.

The identified risks include numerous reports of usually mild anemia that infrequently resulted in the need for transfusions. There may be increased risk of liver enzyme elevations with doses about 10 mg.

1.1 Recommendation on Regulatory Action

Approval of the 10 mg tablet for once daily use in patients with PAH, WHO Group 1.

1.2 Risk Benefit Assessment

The benefit of this agent in delaying the worsening of symptoms in patients with PAH probably outweighs the risks of macitentan 10 mg once daily.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Exploration of doses above 10 mg once daily for improved efficacy should be considered.

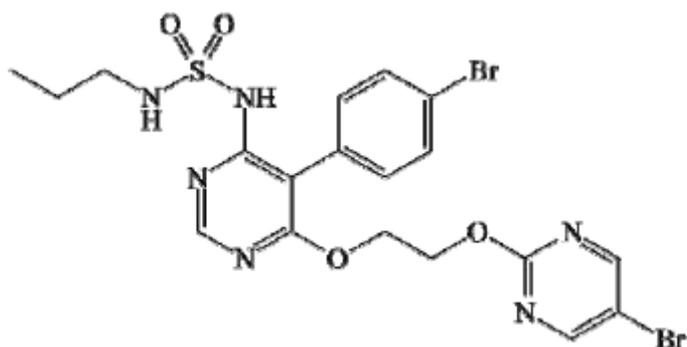
2 Introduction and Regulatory Background

Macitentan is being proposed for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) [REDACTED] (b) (4). The safety and efficacy of this application is based mainly on the outcome of the Seraphin trial for which the study design, endpoints, and analysis strategy were discussed with the Division of Cardiovascular Drug Products at the US FDA. The protocol for this study was based on an agreement between the FDA and the sponsor within Special Protocol Assessment (SPA).

2.1 Product Information

PHARMACOLOGIC CLASS

Macitentan is a dual ETA and ETB endothelin receptor antagonist and has the following structural formula:



MODE OF ACTION

Macitentan is an orally active, dual ETA and ETB receptor antagonist that prevents the binding of ET-1 to its receptors. Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is up regulated and is involved in vascular hypertrophy and in organ damage.

2.2 Tables of Currently Available Treatments for Proposed Indications

Drugs approved for PAH are shown below.

bosentan (Tracleer)

ambrisentan (Letairis)

sildenafil (Revatio)

tadalafil (Adcirca)

treprostinil injection (Remodulin)

treprostinil inhalation (Tyvaso)

iloprost (Ventavis)

epoprostenol (Flolan)

2.3 Availability of Proposed Active Ingredient in the United States

Available

2.4 Important Safety Issues with Consideration to Related Drugs

- 1) Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with an endothelin receptor blocker (bosentan).
- 2) Based on animal data, endothelin receptor blockers are likely to cause major birth defects if used during pregnancy (class labeling).
- 3) Decreased sperm counts (class effect).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See FDA reviewer's guide to NDA 204410 for complete submissions and communications with FDA regarding the development of macitentan under IND 77,258.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

The Seraphin study includes the list of IECs / IRBs including center name of IEC/IRB chairperson, address, date of approval of initial protocol, date of approval of protocol amendments. The model for the informed consent was submitted.

3.1 Submission Quality and Integrity

The quality of this submission and the studies conducted in support of the NDA are as expected.

A routine DSI inspection was requested for study AC-055-302 with no major violations.

3.2 Compliance with Good Clinical Practices

The protocols used to support this NDA stated that the study was to be conducted in compliance with Good Clinical Practices. With the exception of minor protocol violations, there is no indication that good clinical practices were not followed by any investigator.

3.3 Financial Disclosures

FORM FDA 3455: See documents for the information regarding the sixteen investigators with financial interests to disclose for the major efficacy study AC-055-302 in section 1.3.4 of the sponsor's NDA. The remaining investigators were without financial interests and are listed in

Clinical Review
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NDA 204410, Opsumit® (macitentan)

FORM FDA 3454. There is no indication that financial compensations compromised the integrity of the data used in support of this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See individual review

4.2 Clinical Microbiology

NA

4.3 Preclinical Pharmacology/Toxicology

See individual review

4.4 Clinical Pharmacology

See individual review

5 Sources of Clinical Data

Materials used for the clinical review of this NDA include the original submission dated 10-19-2012 and the safety update dated 1-31-2013.

5.1 Tables of Studies/Clinical Trials

See NDA 5.2 Tabular listings of all clinical trials.

The NDA consists of data from

- 14 clinical pharmacology studies,
- one study in patients with essential hypertension (AC-055-201),
- one study in patients with PAH (AC-055-302/SERAPHIN)
- one open label study in patients with PAH (AC-055-303)
- other indications include idiopathic pulmonary fibrosis, glioblastoma, digital ulcers.

See attachment to this NDA review for reviewer's comments about Phase 1 studies, terminated studies, PK studies, and studies in indications other than PAH.

5.2 Review Strategy

This is a primary review by a single medical officer. The focus of the review was on the large Seraphin trial. The other trials were reviewed and included in this document as deemed appropriate by the reviewer. All necessary safety discussions are included as well.

5.3 Discussion of Individual Studies/Clinical Trials

The complete review for clinical trial AC-055-302 (Seraphin) is in the attachment.

6 Review of Efficacy

In the single efficacy in PAH study AC-055-302 the incidence rate of patients with confirmed PAH events was lower for the macitentan 10 mg group (31%) compared to macitentan 3 mg (38%) and placebo (46%) groups. The reporting of death was slightly more frequent for macitentan 3 mg (8%) compared to placebo (7%) and macitentan 10 mg (7%). There were more IV/SC prostanoids initiations in the placebo group (2%) compared to the macitentan groups (0.4% each). The largest cause of a CEC confirmed endpoint for all groups was worsening of PAH. There was a higher incidence rate of placebo patients (37%) reporting this portion of the primary endpoint compared to macitentan 3 mg (29%) and macitentan 10 mg (24%).

6.1 Indication

OPSUMIT® is indicated for the long-term treatment of pulmonary arterial hypertension (PAH,WHO Group I) to reduce symptoms.

6.1.1 Methods

The indication for this NDA is supported by a single, large, multi-center, randomized, double-blind, placebo-controlled study (AC-055-302/SERAPHIN) designed to evaluate the effect of macitentan compared to placebo on morbidity and mortality in patients with symptomatic PAH.

6.1.2 Demographics

The table below shows the demographics for the SERAPHIN trial.

Table 4 Summary of demographic and baseline characteristics, SERAPHIN study, All-randomized set

Characteristic	Placebo (N = 250)	Macitentan 3 mg (N = 250)	Macitentan 10 mg (N = 242)	All patients (N = 742)
Female sex — no. (%)	184 (73.9)	187 (75.4)	194 (80.2)	565 (76.5)
Age — years	46.7 ± 17.03	44.5 ± 16.26	45.5 ± 14.99	45.6 ± 16.13
Race — no. (%)				
Caucasian/White	131 (52.6)	137 (55.2)	135 (55.8)	403 (54.5)
Black	8 (3.2)	5 (2.0)	6 (2.5)	19 (2.6)
Asian	71 (28.5)	69 (27.8)	65 (26.9)	205 (27.7)
Hispanic	37 (14.9)	37 (14.9)	35 (14.5)	109 (14.7)
Other	2 (0.8)	—	1 (0.4)	3 (0.4)
Time from PAH diagnosis — years	2.6 ± 3.73	3.0 ± 4.54	2.6 ± 3.63	2.7 ± 3.99
PAH etiology — no. (%)				
Idiopathic	126 (51.0)	144 (58.3)	134 (55.6)	404 (55.0)
Heritable	3 (1.2)	8 (3.2)	2 (0.8)	13 (1.8)
Connective tissue disease	81 (32.8)	70 (28.3)	73 (30.3)	224 (30.5)
Congenital shunts	26 (10.5)	15 (6.1)	21 (8.7)	62 (8.4)
HIV infection	3 (1.2)	1 (0.4)	6 (2.5)	10 (1.4)
Drugs and toxins	8 (3.2)	9 (3.6)	5 (2.1)	22 (3.0)
6-Minute walk distance — m	352.4 ± 110.6	364.1 ± 95.5	362.6 ± 93.2	359.6 ± 100.2
WHO functional class — no. (%)				
I	0	0	1 (0.4)	1 (0.1)
II	129 (51.8)	138 (55.6)	120 (49.6)	387 (52.4)
III	116 (46.6)	105 (42.3)	116 (47.9)	337 (45.6)
IV	4 (1.6)	5 (2.0)	5 (2.1)	14 (1.9)
Hemodynamics				
mRAP (mmHg)	8.8 ± 5.59	9.2 ± 5.32	9.2 ± 6.03	9.1 ± 5.64
mPAP (mmHg)	53.1 ± 18.13	55.1 ± 16.74	53.5 ± 17.63	53.9 ± 17.50
PCWP (mmHg)	9.5 ± 3.38	9.8 ± 3.30	9.5 ± 3.44	9.6 ± 3.37
CI (L/min/m ²)	2.44 ± 0.80	2.36 ± 0.79	2.36 ± 0.78	2.39 ± 0.79
PVR (dyn.sec/cm ⁵)	996 ± 784.3	1044 ± 624.2	1040 ± 672.5	1026 ± 693.7
Background PAH therapy — no. (%)				
Yes	154 (61.8)	163 (65.7)	154 (63.6)	471 (63.7)
No	95 (38.2)	85 (34.3)	88 (36.4)	268 (36.3)
Background PAH therapy — no. (%)				
PDE-5	150 (60.2)	154 (62.1)	150 (62.0)	454 (61.4)
Oral/inhaled prostanoids	7 (2.8)	18 (7.3)	16 (6.6)	41 (5.5)
Anticoagulants — no. (%)	123 (49.2)	134 (53.6)	123 (50.8)	380 (51.2)

Plus-minus values are means ± SD; 6MWD = 6-minute walk distance; CI = cardiac index; HIV = human immunodeficiency virus; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase type 5; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

Source [D-12.425](#)

Patients aged 12 years or over were enrolled if diagnosed with WHO FC II–IV idiopathic PAH, familial PAH, PAH associated with connective tissue disease, PAH associated with simple congenital systemic-to-pulmonary shunts at least 1 year post surgical repair, or PAH associated with HIV infection, or drug and toxin use. Participants were required to have a baseline 6MWD of at least 50 m.

Overall, the subjects in SERAPHIN were predominantly female (77%), white, living outside the US (mostly in Europe or Asia), and had a mean age of 45.6 years (3% of subjects were less than 18 years of age). Differences between treatment groups were small indicating that randomization was successful in patient distribution.

In addition, mean time from PAH diagnosis to randomization in the study population was 2.7 years, idiopathic PAH was the most common etiology (55%) followed by collagen vascular disease (30%), congenital shunts (8%), drugs and toxins (3%), and HIV infection (1%), baseline mean 6MWD was approximately 360 m, mean Borg dyspnea index was approximately 3.5 across the groups, most patients were WHO FC II (52%) or WHO FC III (46%).

Around one third of subjects had at least one sign of heart failure with peripheral edema being the most common. The majority (approximately 64%) of patients were receiving concomitant PAH therapy with sildenafil being the most common (58%)¹. The percentages of patients taking sildenafil at baseline were similar across treatment groups. Other commonly used drugs included furosemide and spironolactone. The most frequently reported concomitant diseases were ventricular failure, hypertension, and scleroderma. The treatment groups were balanced.

6.1.3 Subject Disposition

A total of 590 patients (80%) completed the study as planned and 22%, 17% and 22% of patients withdrew prematurely in the macitentan 3 mg, macitentan 10 mg, and placebo groups, respectively. The reasons for withdrawal are shown below by treatment group.

Table 60 Summary of reasons for premature discontinuation from the study, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of reasons for premature discontinuation from the study
 Analysis set: All randomized

Reason for discontinuation	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one reason	55	22.0%	56	22.4%	41	16.9%
Death	44	17.6%	47	18.8%	34	14.0%
Withdrawal of subject's consent	3	1.2%	6	2.4%	4	1.7%
Lost to follow-up	7	2.8%	3	1.2%	2	0.8%
Administrative reason	1	0.4%	-	-	1	0.4%

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A total of three patients (two in the macitentan 3 mg group -5702/15103, 1901/10606, 1 patient in the placebo group- 6002/11080) who did not follow appropriate ICF procedure are not included in this Table. These patients discontinued study due to administrative reasons (placebo) and loss-to follow-up (macitentan 3 mg).

Death was the main reason for patient withdrawal (19% macitentan 3 mg, 14% macitentan 10 mg, 18% placebo). Other reasons for premature discontinuation from the study included

¹ Endothelin receptor antagonists were prohibited as were IV or SQ prostanoids.

withdrawal of consent (2% macitentan 3 mg, 2% macitentan 10 mg, 1% placebo) and loss to follow up (1% macitentan 3 mg, 1% macitentan 10 mg, 3% placebo).

6.1.4 Analysis of Primary Endpoint(s)

Pre-IND communication / Response to proposed composite endpoint dated October 3, 2007: In response to a 27 August 2007 Pre-IND submission containing a description of the proposed composite endpoint for study AC-055-302, the Division, upon consultation and review with Dr. Robert Temple, agreed that the proposed composite endpoint appeared to be acceptable.

The primary objective was assessed as the time from start of study treatment to the first morbidity or mortality event (primary endpoint) up to end of treatment plus 7 days and was a composite including the following components:

- death, or onset of a treatment-emergent AE with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or,
- atrial septostomy or hospitalization for atrial septostomy, or,
- lung transplantation or hospitalization for lung transplantation, or,
- initiation of i.v. or s.c. prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of i.v. or s.c. prostanoids, or,
- other worsening of PAH.

Other worsening of PAH was defined by the combined occurrence in a patient of all the following three events:

- at least 15% decrease in the 6MWD from baseline, confirmed by two 6MWTs, performed on separate days, within 2 weeks of each other.

AND,

- worsening of PAH symptoms that included at least one of the following:
 - o increase in WHO FC, or no change in patients in WHO FC IV at baseline,
 - o appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy,

AND,

- need for new treatment(s) for PAH that included the following:
 - o oral or inhaled prostanoids (e.g., iloprost),
 - o oral phosphodiesterase inhibitors (e.g., sildenafil),
 - o ERAs (e.g., bosentan, ambrisentan) only after discontinuation of the study treatment,
 - o intravenous diuretics.

Adjudication of all events by the independent Clinical Endpoints Committee (CEC) was done in a blinded manner. The CEC adjudicated the type of primary endpoint event and confirmed whether a primary event of mortality up to EOT + 7 days was due to PAH. The CEC had the right to override strict protocol definitions to adjudicate an event.

The function of the clinical endpoints committee (CEC) was to review all mortality and morbidity events in a blinded fashion and to qualify or disqualify events. The table below shows the number and percent of patients by treatment group with at least one CEC confirmed event².

Table 20 Summary of causes of primary endpoint events (CEC-confirmed), All-randomized set

	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	No.	%	No.	%	No.	%
Total PATIENTS with at least one confirmed event	116	46.4%	95	38.0%	76	31.4%
First confirmed event						
WORSENING OF PAH*	93	37.2%	72	28.8%	59	24.4%
DEATH	17	6.8%	21	8.4%	16	6.6%
IV/SC PROSTANOID INITIATION	6	2.4%	1	0.4%	1	0.4%
LUNG TRANSPLANTATION	-	-	1	0.4%	-	-

* Corresponds to 'Other worsening of PAH'
 CEC = Clinical Event Committee, EOT = End of treatment.
 Events confirmed by Independent CEC.
 Source: Table 89

The hazard ratio versus placebo for the occurrence of a morbidity or mortality event in the macitentan 3 mg group was 0.704 (97.5% CLs 0.516, 0.960, log rank p = 0.0108). In the macitentan 10 mg dose group, the effect versus placebo was highly statistically significant as measured by the hazard ratio of 0.547 (97.5% CLs 0.392, 0.762, log rank p < 0.0001).

The Kaplan-Meier curves are shown below. The placebo separates from the macitentan groups about 12 months and all groups are separated from one another at 24 months. At 36 months the macitentan 10 mg is still distinct from placebo.

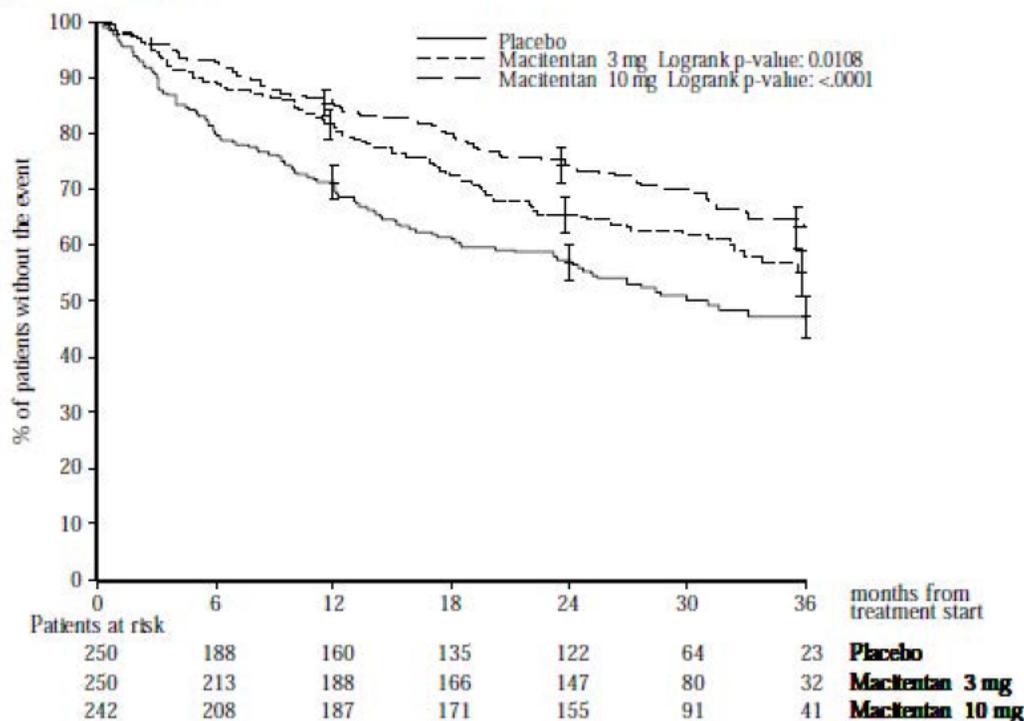
² The numbers of unconfirmed events were 20 for placebo, 16 for macitentan 3 mg and 9 for macitentan 10 mg.

Figure 3 Kaplan-Meier curves of the first confirmed morbidity or mortality event up to EOT + 7 days, All-randomized set (Kaplan-Meier estimate)

ACT-064992, Protocol AC-055-302

Time to first confirmed morbidity/mortality event up to EOT+7 days (CEC) (Kaplan-Meier estimate with standard error bars)

Analysis set: All-randomized



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Statistical tests are performed including all data available during the follow-up period.
 Figure MMTBG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

A total of 94 (26 macitentan 3 mg, 34 macitentan 10 mg and 34 placebo) patients discontinued study treatment without experiencing events for the primary endpoint. Of these, 29 (7 macitentan 3 mg, 9 macitentan 10 mg and 13 placebo) did not experience a primary endpoint event even though they showed signs of PAH worsening.

The groups of patients discontinuing treatment showing or not showing signs of PAH worsening are displayed below.

Table 22 Summary of reasons for discontinuation from the treatment for patients without a primary endpoint event by signs of PAH worsening at the time of study drug discontinuation, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of reasons for discontinuation from the treatment for patients without a primary endpoint event by signs of PAH worsening at the time of study drug discontinuation
 Analysis set: All randomized

Preferred term	Placebo N=134		Macitentan 3 mg N=155		Macitentan 10 mg N=166		All patients N=455	
	No.	%	No.	%	No.	%	No.	%
Patients discontinuing treatment showing signs of PAH worsening	13	9.7%	7	4.5%	9	5.4%	29	6.4%
ADVERSE EVENT	6	4.5%	2	1.3%	8	4.8%	16	3.5%
DISEASE PROGRESSION NOT LEADING TO OL**	4	3.0%	-	-	1	0.6%	5	1.1%
WITHDRAWAL FROM TREATMENT	3	2.2%	4	2.6%	-	-	7	1.5%
TREATMENT FAILURE	2	1.5%	1	0.6%	-	-	3	0.7%
WITHDRAWAL OF CONSENT	1	0.7%	-	-	1	0.6%	2	0.4%
ADMINISTRATION OF FORBIDDEN DRUG	1	0.7%	-	-	-	-	1	0.2%
Patients discontinuing treatment showing NO sign of PAH worsening	21	15.7%	19	12.3%	25	15.1%	65	14.3%
WITHDRAWAL FROM TREATMENT	7	5.2%	3	1.9%	12	7.2%	22	4.8%
ADVERSE EVENT	6	4.5%	9	5.8%	6	3.6%	21	4.6%
ADMINISTRATIVE/OTHER	5	3.7%	2	1.3%	4	2.4%	11	2.4%
WITHDRAWAL OF CONSENT	-	-	3	1.9%	3	1.8%	6	1.3%
LOST TO FOLLOW-UP	3	2.2%	2	1.3%	-	-	5	1.1%

**Patients who terminated the treatment due to a mortality/morbidity event
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The results are consistent with the primary analysis when the patients showing signs of PAH worsening are considered to have reached an endpoint and are included in the analysis.

There was an additional analysis using all morbidity and mortality events that were reported by the investigator whether or not the CEC confirmed the event. The hazard ratio for macitentan 3 mg versus placebo for the occurrence of a morbidity or mortality event was 0.689 (0.513, 0.925, logrank p = 0.0044). Regarding the macitentan 10 mg versus placebo, the hazard ratio was 0.506 (0.367, 0.698, logrank p < 0.0001).

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints included change in 6MWD from baseline to Month 6, proportion of patients with improvement in modified WHO FC from baseline to Month 6, time to death due to PAH or hospitalization for PAH up to end of treatment (death due to PAH as identified by CEC up to end of treatment plus 7 days, or onset of a treatment-emergent adverse event with a fatal outcome due to PAH occurring up to 4 weeks after end of treatment, or hospitalization for PAH up to end of treatment plus 7 days), time to death of all causes up to end of treatment (death from all causes up to end of treatment plus 7 days, or onset of a treatment-emergent adverse event with a fatal outcome occurring up to 4 weeks after end of treatment, and time to death from all causes up to end of study).

Change in 6MWD from baseline to Month 6

The 6MWT was performed at screening, randomization (Day 1), Month 3, Month 6, and every 6 months thereafter, and at EOT/event visit.

Baseline walk distances were longest for placebo (352 m) compared to macitentan 3 mg and 10 mg (364 m and 363 m, respectively). Most study subjects did not use supplemental oxygen (>90%). However, supplemental oxygen was used less by macitentan 10 mg (3.3%) compared to placebo (7.2%) and macitentan (8.5%), indicating that subjects in the macitentan group were less sick.

After 6 months of treatment, the placebo group had a mean decrease of 9.4 m compared to a mean increase of 7.4 m for the macitentan 3 mg group and 12.5 m for the macitentan 10 mg group in walk distance.

The placebo-corrected mean change (\pm SD) from baseline at month 6 in 6MWD was
16.8 m (\pm 96.95) in the macitentan 3 mg group and
22.0 m (\pm 92.58) in the macitentan 10 mg group.

Missing walk data

There were 52 (20.9%) placebo subjects, 32 (12.9%) macitentan 3 mg subjects and 30 (12.4%) macitentan 10 mg subjects who did not have 6 month walk data.

6MWD at all assessed time points

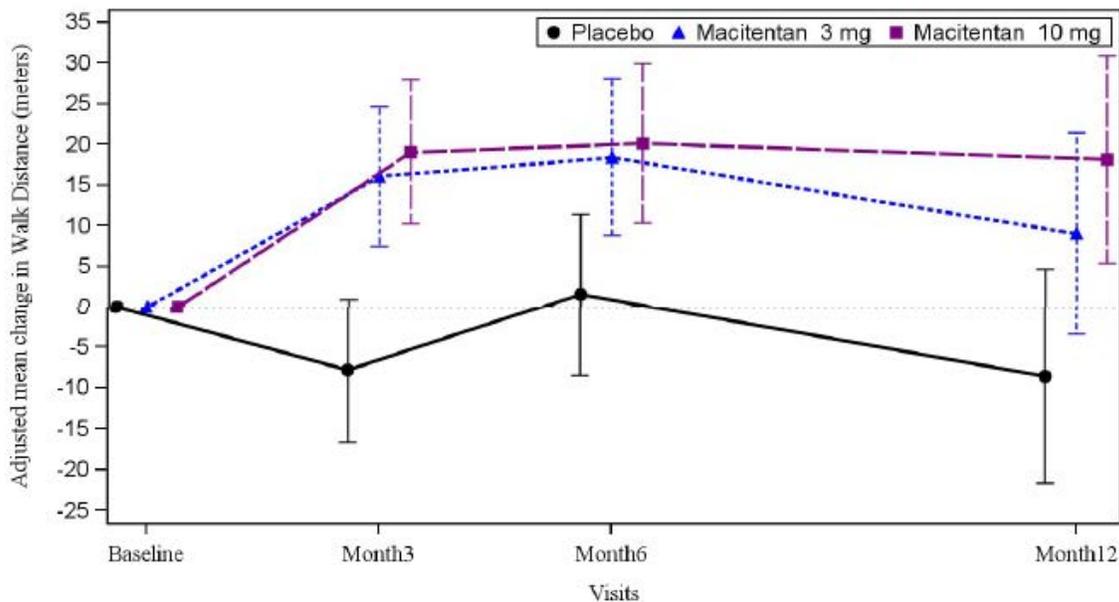
The figure below shows the change from baseline in the walk distance up to month 12.

Figure 17 Change from baseline in 6MWD at all visits up to Month 12, All-randomized set

ACT-064992, Protocol: AC-055-302

Plot of adjusted mean (95% CL) changes from baseline in Walk Distance values (meters) by visit up to Month 12

Analysis set: All-randomized



95% confidence limits of adjusted mean are displayed.

While the adjusted mean changes in 6MWD improved for patients in the macitentan groups (10 mg tended to be better than 3 mg), the walk distance for the placebo patients tended to drop below baseline values.

Additional efficacy endpoints

Improvements in WHO functional class

At baseline, most patients were WHO class II or III. At month 6, most patients did not change class. However, those randomized to macitentan 3 mg and 10 mg were more likely to have improved (20% and 22%, respectively) compared to placebo (13%).

Regarding those that became worse,

- Placebo: 3% changed from class II at baseline to IV and 12% from class III at baseline to IV.
- Macitentan 3 mg: 3% changed from class II at baseline to IV and 5% from class III at baseline to IV.
- Macitentan 10 mg <1% changed from class II at baseline to IV and 3% from class III at baseline to IV.

Deaths caused by PAH or hospitalizations caused by PAH (end of treatment)

There was a lower incidence rate of subjects with a cause of death linked to PAH in the macitentan 10 mg group (3%) compared to macitentan 3 mg (6%) and placebo (6%).

There was a lower incidence rate of subjects with at least one hospitalization for PAH in the macitentan 10 mg group (20%) compared to macitentan 3 mg (23%) and placebo (33%).

Hospitalizations

The table below shows the number per year of all-cause hospitalizations and number per year of in-patient hospital days by treatment group.

Table 151 Number per year of all-cause hospitalizations and number per year of in-patient hospital days for all causes from baseline up to EOT + 28 days, All treated set

ACT-064992, Protocol: AC-055-302
 Number per year of all-cause hospitalizations and number per year of in-patient hospital days for all causes from baseline up to EOT + 28 days
 Analysis set: All treated

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Number per year of all-cause hospitalizations			
n	249	250	242
Mean	1.0	0.6	0.5
Standard deviation	2.27	1.22	1.81
Standard error	0.14	0.08	0.12
Median	0.0	0.0	0.0
Q1 , Q3	0.0 , 1.0	0.0 , 0.8	0.0 , 0.4
Min , Max	0.0 , 24.4	0.0 , 10.0	0.0 , 24.4
Number per year of in-patient hospital days for all causes			
n	249	250	242
Mean	12.2	7.5	5.7
Standard deviation	37.57	21.12	19.38
Standard error	2.38	1.34	1.25
Median	0.0	0.0	0.0
Q1 , Q3	0.0 , 9.0	0.0 , 4.2	0.0 , 3.3
Min , Max	0.0 , 340.9	0.0 , 172.7	0.0 , 182.6

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The mean number of hospitalizations (all causes) per year was similar across treatment groups (0.6 in the macitentan 3 mg group, 0.5 in the macitentan 10 mg group, 1.0 in the placebo group).

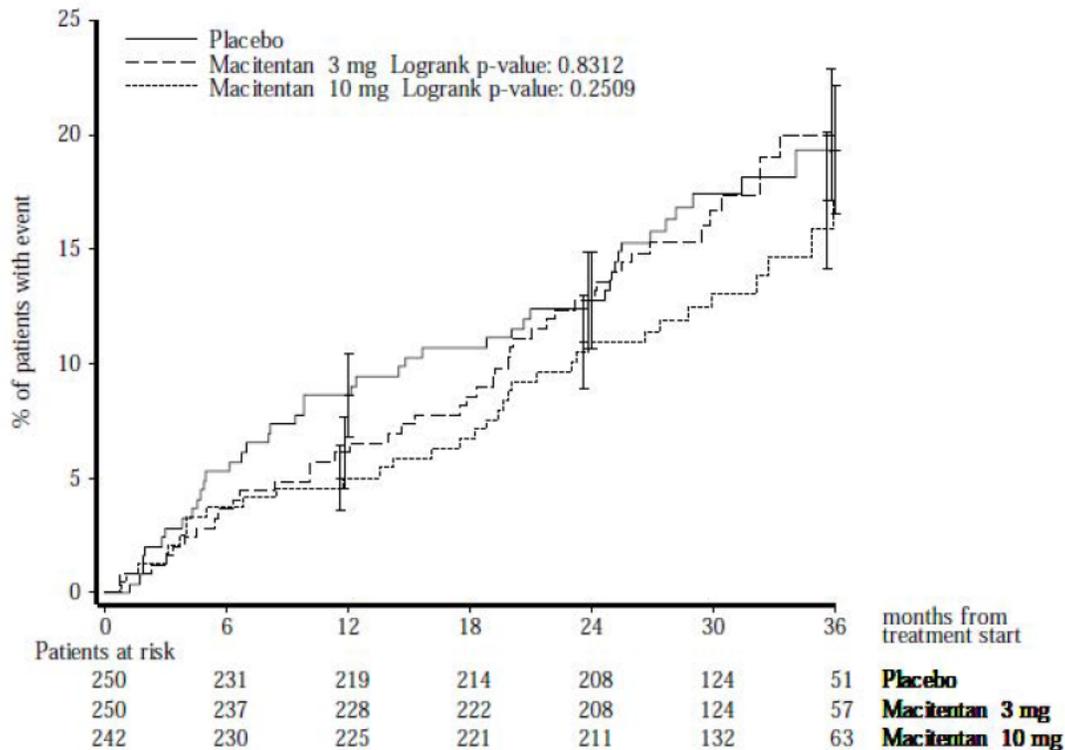
The numbers of in-patient hospital days for all causes were lower for macitentan 10 mg (5.7 days) compared to macitentan 3 mg (7.5 days) and placebo (12.2 days).

Deaths from all causes end of study (EOS)

There was a lower incidence rate of death resulting from any cause in the macitentan 10 mg group (14%) compared to macitentan 3 mg (19%) and placebo (18%). The Kaplan-Meier curves are shown below.

Figure 16 Kaplan-Meier curves of death of all causes up to EOS, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to death of all causes up to EOS (CRF) (Kaplan-Meier estimate with standard error bars)
 Analysis set: All-randomized



CRF = Case report form, EOS = End of study; deaths reported on CRF.
 Includes one patient who died after EOS following a confirmed (CEC) adverse event with a fatal outcome.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Statistical tests are performed including all data available during the follow-up period.
 Figure DTEOBG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

Borg dyspnea index

Regarding changes from baseline at month 6 in the Borg index by treatment group, there was some improvement in the index for the macitentan dose groups (-0.7 for 3 mg and -0.5 for 10 mg). The placebo group grew a little worse. These changes for the treatment groups were consistent at all clinic visits.

Quality of life questionnaire

The SF-36 questionnaire was used to assess quality of life. A higher score for the individual domains and summary component scores indicated a better condition of the patient.

There were indications that the patients in the macitentan groups showed improvement compared to the patients in placebo.

Hemodynamic variables

Hemodynamic endpoints (change in PVR and CI from baseline to Month 6) were analyzed in a sub-set of the SERAPHIN population who participated in the PK/PD sub-study (n = 187). Macitentan was associated with a clear treatment effect on pulmonary hemodynamics compared to placebo. There was no clear difference between the 3 mg and 10 mg doses on any of the hemodynamic variables collected.

Table 37 Treatment effect of macitentan (median changes vs placebo) on hemodynamic variables from baseline to Month 6, All-randomized set, patients participating in the PK/PD sub-study

	Placebo	Macitentan 3 mg	Macitentan 10 mg
PVR (dyn × sec/cm⁵)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 504 (±919)	Mean: -122 (±308)	Mean: -25 (±688)
Median [Range]	Median: 58 (-279, 3623)	Median: -61 (-1223, 587)	Median: -168 (-1690, 2668)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean percent change*: 62.2 (52.8, 73.3) Median percent change: 70.0 (56.0, 82.1)	Mean percent change*: 61.8 (49.9, 76.5) Median percent change: 63.5 (50.8, 78.3)
mRAP (mmHg)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 7.4 (±18.68)	Mean: 11.1 (±38.53)	Mean: 7.8 (±27.62)
Median [Range]	Median: 0 (-8, 75)	Median: 0 (-16, 182)	Median: 0 (-11, 119)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: 3.7 (-8.3, 15.6) Median: -0.6 (-3.0, 1.0)	Mean: 0.4 (-9.1, 9.9) Median: -1.0 (-3.0, 1.0)
mPAP (mmHg)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 6.6 (±14.37)	Mean: -0.4 (±10.17)	Mean: 3.9 (±28.39)
Median [Range]	Median: 2.0 (-15, 57)	Median: 0 (-19.3, 2802)	Median: -2.0 (-33.0, 116.1)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: -6.9 (-12.0, -1.9) Median: -5.0 (-9.0, -1.0)	Mean: -2.7 (-11.7, 6.3) Median: -7.0 (-12.0, -2.0)
CI (L/min/m²)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: -0.48 (±0.701)	Mean: 0.20 (±0.598)	Mean: 0.13 (±0.887)
Median [Range]	Median: -0.21 (-2.53, 0.44)	Median: 0.10 (-0.89, 1.76)	Median: 0.23 (-2.97, 1.99)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: 0.68 (0.41, 0.94) Median: 0.53 (0.27, 0.86)	Mean: 0.61 (0.28, 0.93) Median: 0.58 (0.28, 0.93)

* Mean percent change over placebo = ratio of geometric means × 100

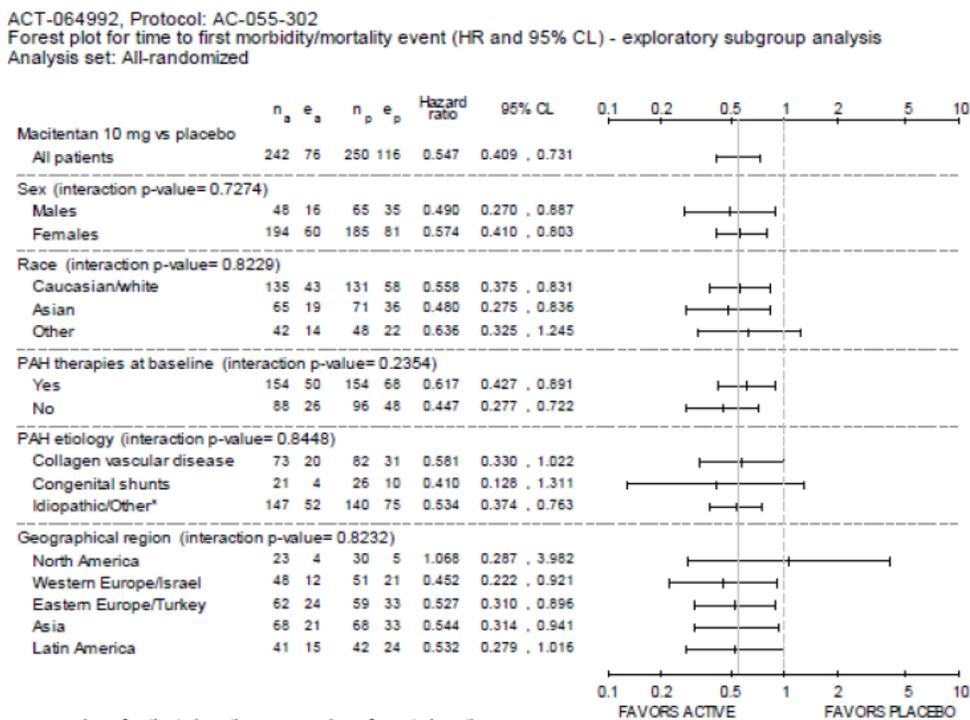
6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

The figure below is a Forest plot for the time to first morbidity/mortality event (confirmed by CEC) by subgroups for macitentan 10 mg vs. placebo.

Figure 5 Occurrence of the first morbidity or mortality event (CEC-confirmed) up to EOT + 7 days by subgroups (macitentan 10 mg versus placebo), All-randomized set



n_a = number of patients in active; e_a = number of events in active
 n_p = number of patients in placebo; e_p = number of events in placebo

*Other etiology consists of idiopathic or familial PAH, or PAH related to HIV infection or drugs and toxins.

Figure MMT_HR_SG_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12

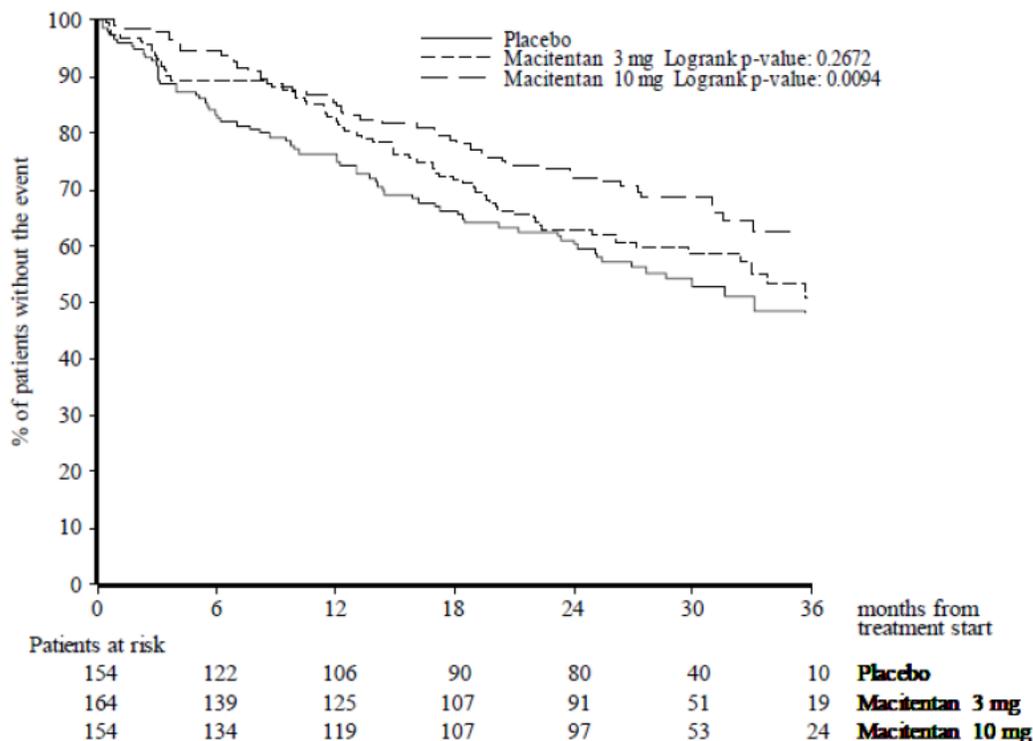
Efficacy of the 10 mg dose was shown regardless of sex and race. The 10 mg dose was effective whether the patients were receiving background PAH therapies or PAH etiologies (except for congenital shunts which included few patients). However, there was no demonstration of efficacy for patients living in North America.

PAH background therapy at baseline

The figure below shows the Kaplan-Meier curves of the confirmed morbidity or mortality events for subjects receiving PAH therapy at baseline.

Figure 7 Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events for patients with concomitant PAH therapy at baseline, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by concomitant PAH therapy at baseline
 Analysis set: All-randomized
 Concomitant PAH therapy at baseline: Yes



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Figure MMT_PAHPG_A - Produced by (b) (4) on 24AUG12 - Data dump of 26APR12

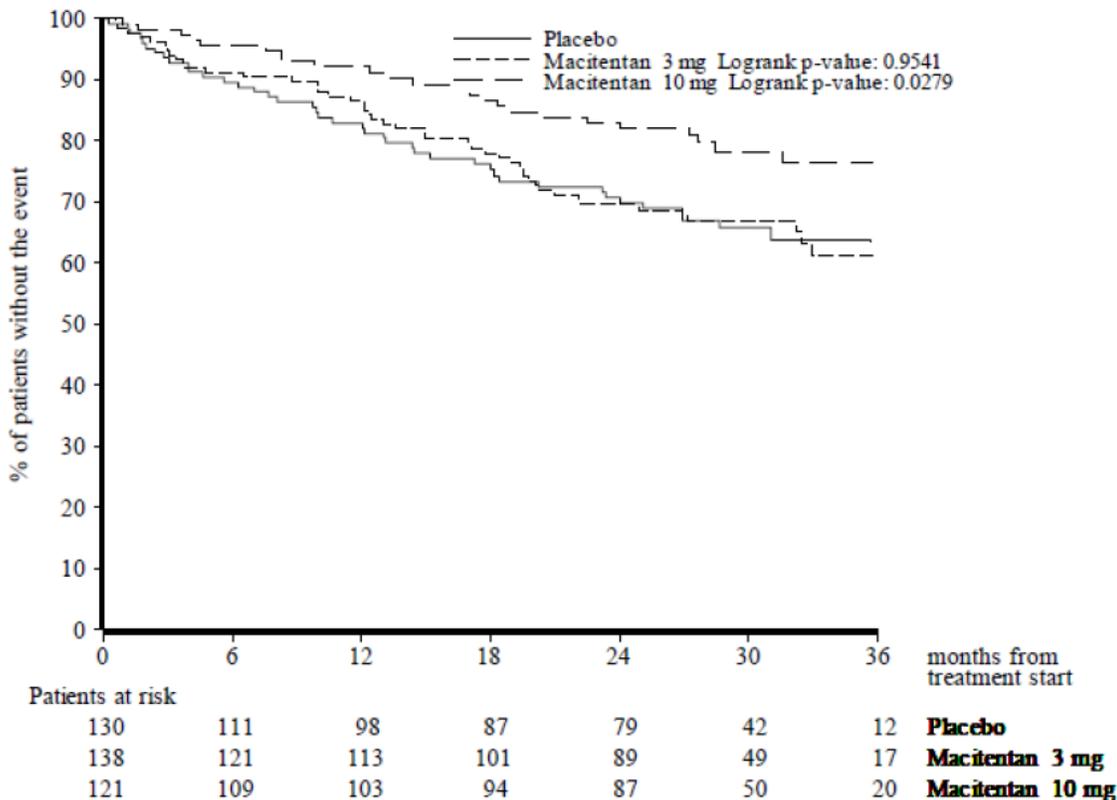
While the macitentan 3 mg group was not statistically different from placebo, the subjects who were on background PAH therapy and macitentan 10 mg showed a significant effect.

WHO functional classification at baseline

The two figures below show the Kaplan Meier curves by WHO functional class.

Figure 8 Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events up to EOT + 7 days by WHO FC I/II at baseline, All-randomized set

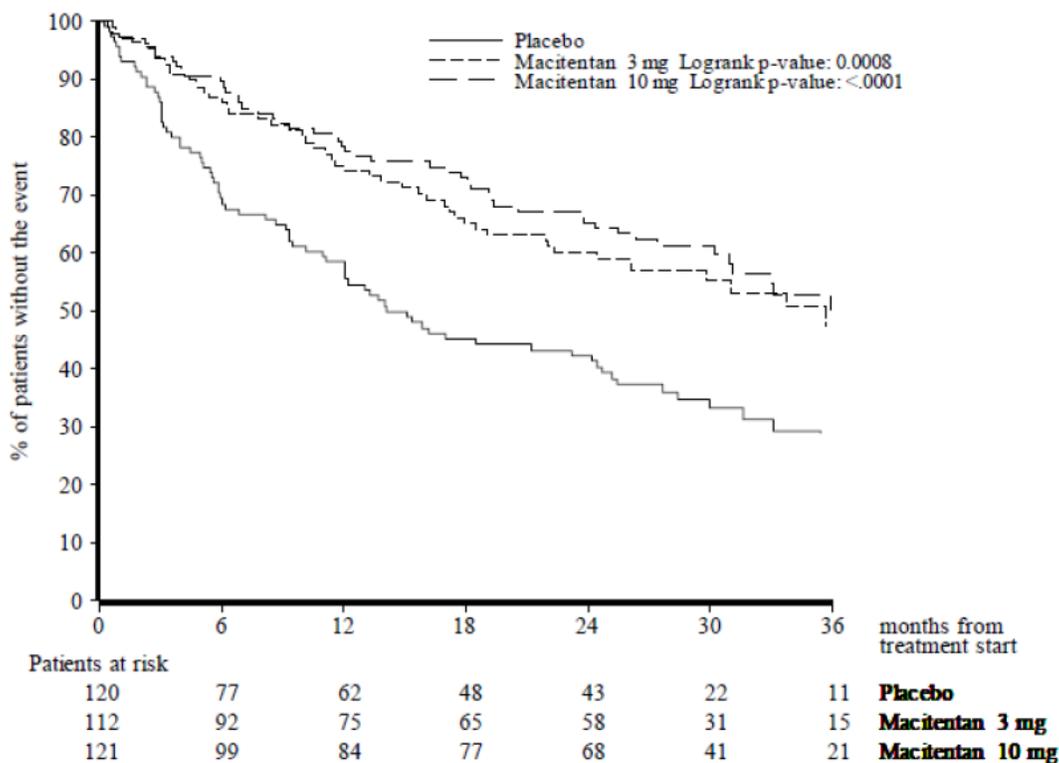
ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by WHO FC at baseline
 Analysis set: All-randomized
 WHO class at baseline: I/II



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Figure MMT_WHOPG_A - Produced by (b)(4) on 24AUG12 - Data dump of 26APR12

Figure 9 Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events up to EOT + 7 days by WHO FC III/IV at baseline, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by WHO FC at baseline
 Analysis set: All-randomized
 WHO class at baseline: III/IV



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Figure MMT_WHOPG_A - Produced by (b) (4) on 24AUG12 - Data dump of 26APR12

The two doses of macitentan were equally effective compared to placebo in the sicker patients (i.e., WHO classes III/IV), but only macitentan 10 mg showed efficacy in the less sick patients (i.e., WHO classes I/II).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Doses of macitentan used in the Seraphin study were probably limited because of liver function test abnormalities in the early studies. Perhaps the use of higher doses would have produced greater efficacy, especially regarding the 6MWD.

Macitentan doses up to 600 mg were used in the single-ascending dose study AC-055-101.

One case of increased liver transaminases was observed in subject 704, who had received 600 mg of ACT-064992, and the other in subject 708, who had received placebo. Both cases occurred 7 days after drug administration whereas 3 days after administration liver enzymes were normal. In subject 704, an increase in ALAT of about 2 times the upper limit of normal was observed accompanied by a small increase in ASAT. In subject 708, the increase in ALAT was less pronounced, returned more quickly to baseline and was not accompanied by an increase in ASAT. In neither subject a change in bilirubin or alkaline phosphatase was noted. Both cases of increased liver transaminases were reported as an AE by the investigator (see Table 5). These abnormalities resolved within 2 weeks or less (Appendix 16.4.7).

Study AC-055-102 was a single center, double blind, placebo-controlled, randomized, ascending dose study in healthy male subjects. The subjects received 1, 3, 10 or 30 mg dose of macitentan or placebo for 10 days. The study raised the question of macitentan's adverse effect on LFT.

There was a trend for increased mean levels of the liver aminotransferases ASAT and ALAT compared to baseline in the groups treated with 10 and 30 mg macitentan, mainly caused by four subjects. In the group treated with 10 mg macitentan, three cases of single elevated liver enzymes were reported.

- Subject 301 (10 mg) presented with an isolated increase of ALAT values of 1.1 times the upper limit of normal (ULN) (2.3-fold increase from baseline) the day after the last drug intake.
- Subject 307 (10 mg) presented with an isolated increase in ALAT of 1.2 x ULN (a 1.4-fold increase from baseline) 10 days after the last drug intake.
- Subject 304 (10 mg) had an increase in ASAT of 1.8 x ULN (2.6-fold increase from baseline) and ALAT levels just above the ULN (1.3-fold increase from baseline) 10 days after the last drug intake.

In the group treated with 30 mg macitentan, there was one subject reporting elevated LFTs.

- Subject 401 (30 mg) experienced increases in ASAT of about 2 x ULN and in ALAT of about 2.5 x ULN on day 10.

One placebo subject reported abnormal LFTs.

- Subject 308 (placebo) reported on Day 4 of treatment with ASAT levels just above the ULN (1.3 fold-increase from baseline) and an increase in ALAT of 1.1 x ULN (1.4-fold increase from baseline).

However, all cases of elevated liver aminotransferases were asymptomatic, resolved within 2 weeks and there were no reported changes in serum bile salts, bilirubin, or AP reported

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Clinical Review
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NDA 204410, Opsumit® (macitentan)

6.1.10 Additional Efficacy Issues/Analyses

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7 Review of Safety

Safety Summary from Seraphin

The main focus of this safety summary is study AC-055-302/Seraphin. The complete review of the study is the attachment.

Important findings:

-the incidence rates of reported deaths were similar for the 3 treatment groups: placebo (8%), macitentan 3 mg (9%), and macitentan 10 mg (7%). Most deaths were attributed to right ventricular failure or PAH.

-the adverse events reported more often in the macitentan groups compared to placebo included anemia, headache, thrombocytopenia, hypotension and various infections (URTI, nasopharyngitis, bronchitis, UTI, and others).

-liver function test abnormalities were reported more often in the placebo group (perhaps a result of worsening PAH in the placebo group). However, the dose of macitentan was limited to 10 mg or less.

-anemia reported as a serious adverse events was more frequent in the macitentan 3 and 10 mg groups (2% and 3%, respectively) compared to placebo (<1%). Anemia was given as the reason for drop outs in 2 patients (1 for each macitentan group). Marked hematology abnormalities are shown below.

Table 46 Incidence of marked hematology abnormalities up to 28 days after treatment discontinuation, All-treated set

Laboratory Abnormality	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
HEMATOLOGY						
Hemoglobin	HH	3 /237 1.3%	2 /241 0.8%	2 /230 0.9%		
	LL	9 /237 3.8%	19 /241 7.9%	32 /230 13.9%		
Hematocrit	HH	2 /237 0.8%	2 /241 0.8%	1 /230 0.4%		
	LL	5 /237 2.1%	15 /241 6.2%	15 /230 6.5%		
Leukocytes	HH	2 /236 0.8%	1 /241 0.4%	1 /229 0.4%		
	LL	0 /236	2 /241 0.8%	12 /229 5.2%		
Platelets	HH	0 /235	0 /240	0 /230		
	LL	8 /235 3.4%	6 /240 2.5%	19 /230 8.3%		

Incidence of pre-defined treatment-emergent laboratory abnormalities up to 28 days after treatment discontinuation

Hemoglobin <= 8 g/dl	1 /237 0.4%	4 /241 1.7%	10 /230 4.3%
Hemoglobin > 8 g/dl and <= 10 g/dl	7 /237 3.0%	11 /241 4.6%	10 /230 4.3%

Values given are the number of patients with at least one abnormality/number of patients (%).
 HH and LL denote values above or below the Arctelion marked reference range and having a clinically relevant change in the same direction.
 Source: Table 174 and Table 177

Abnormally low hematocrit, leukocytes, and platelets were more common in macitentan 10 mg compared to the other two groups.

-of the 4 reports of serious acute or relapsing pancreatitis, all were by patients in the macitentan groups (3 and 1, macitentan 3 mg and 10 mg, respectively).

Safety findings from additional studies

Pool 1 (3 completed double blind, placebo controlled phase 2/3 studies) :

-adverse events associated with infection (especially URTI and bronchitis), headache, anemia, hypotension, thrombocytopenia and insomnia were more common in the macitentan groups compared to placebo.

-incidence rates of reported deaths from any cause were similar across treatment groups.

-serious adverse events reported more frequently in macitentan compared to placebo includes anemia.

-incidence rates for drop outs because of an adverse event included ALT/AST increases (1% macitentan any dose compared to 0 placebo). LFT abnormalities are shown in the table below.

Table 46 Incidence of liver function abnormalities occurring from treatment start up to 28 days after EOT in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
ALT or AST > 3 x ULN n n (%)	125 3 (2.4)	307 11 (3.6)	414 13 (3.1)	846 27 (3.2)	360 14 (3.9)
ALT or AST > 5 x ULN n n (%)	125 1 (0.8)	307 4 (1.3)	414 8 (1.9)	846 13 (1.5)	360 7 (1.9)
ALT or AST > 8 x ULN n n (%)	125 1 (0.8)	307 4 (1.3)	414 6 (1.4)	846 11 (1.3)	360 2 (0.6)
ALT or AST > 3 x ULN and TBIL > 2 x ULN at any time n n (%)	125 0	301 5 (1.7)	398 5 (1.3)	824 10 (1.2)	349 5 (1.4)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = end of treatment, TBIL = total bilirubin, ULN = upper limit of the normal range

Note: Denominator for percentages based on number of non-missing observations for each treatment group and total. Incidence based on the number of patients with at least one post-baseline abnormality for each category.

Patient 1406/11104 (placebo) is not counted in source table since TBIL > 2 x ULN as reported by a local laboratory was not included in the clinical database. Patient 9103/12093 (macitentan 3 mg) was incorrectly included in source table, despite TBIL < 2 x ULN. Patient 204-1011 (3 mg group) was not classified in the ALT/AST > 3 x ULN and TBIL > 2 x ULN in source table, since TBIL > 2 x ULN was observed more than 28 days after treatment discontinuation.

Studies AC-055-201, AC-055B201, AC-055-302

Source: [Appendix 5, Table 167](#), and, [D-12.559: Annex 1, narratives](#)

Clinical pharmacology studies

Clinically relevant LFT abnormalities reported in these studies are cited below:

- a) In study AC-055-102, one subject treated with macitentan 30 mg had an increase in ALT to $3.1 \times \text{ULN}$. The elevations resolved spontaneously after the end of treatment;
- b) In study AC-055-106, one subject treated with sildenafil had increases in AST ($4.5 \times \text{ULN}$) and ALT ($1.6 \times \text{ULN}$) 11 days after EOT, with a macitentan 30 mg loading dose followed by 10 mg o.d. for 3 days.
- c) In study AC-055-107, one subject had increases in AST ($1.6 \times \text{ULN}$), ALT ($4.0 \times \text{ULN}$) and GGT ($2.7 \times \text{ULN}$) during treatment with ketoconazole (18 days) and 13 days after a single dose of macitentan 10 mg.
- c.) In study AC-055-110, one subject with mild impairment of hepatic function had clinically significant increases in ALT ($8.1 \times \text{ULN}$), AST ($7.3 \times \text{ULN}$) and GGT ($3.3 \times \text{ULN}$) at EOS from baseline elevated levels of $4.1 \times \text{ULN}$, $3.9 \times \text{ULN}$ and $1.9 \times \text{ULN}$, respectively.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical evidence for the efficacy and safety of macitentan in the treatment of patients with PAH is derived from study AC-055-302/SERAPHIN.

The long-term safety data in patients with PAH are derived from the open label study AC-055-303.

The application also contains information from 14 completed Phase 1 clinical pharmacology studies. Three additional Phase 1 studies are ongoing.

Two Phase 2 studies in other indications have been completed:

- AC-055-201 (moderate essential hypertension)
- AC-055B201 (idiopathic pulmonary fibrosis)

7.1.2 Categorization of Adverse Events

As stated by the sponsor, adverse events were collected on the case report form adverse event page. Investigator verbatim terms were coded to MedDRA preferred terms using the most recent MedDRA dictionary available at the time. The pooled AE data were coded according to MedDRA v. 14.0 and, therefore, the results of the pooled safety analyses do not necessarily match the results provided in the individual CSRs, where previous versions may have been used.

Serious adverse events (SAE) during the screening period that were considered by the investigator to be related to study-mandated procedures were collected on the SAE form and entered only into the Actelion drug safety database (Argus™ Safety). All SAEs during the treatment period and up to 28 days after study drug discontinuation were collected on SAE forms

as well as on the CRF AE page. For patients from study AC-055-302 who continued into the open-label

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pool 1 (three completed, double blind, placebo controlled phase 2/3 studies)

The table below shows the overall reporting of adverse events in study AC-055-201 (hypertension), AC-005B201 (IPF), and AC-055-302 (PAH). These studies were fairly large, double blind, placebo controlled, randomized trials.

Table 27 Overview of adverse events in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
No. of patients with any AE	42 (32.6)	253 (81.4)	363 (85.8)	658 (76.2)	317 (85.7)
No. of patients with SAEs	4 (3.1)	132 (42.4)	148 (35.0)	284 (32.9)	158 (42.7)
No. of patients with any AE leading to premature discontinuation of treatment	12 (9.3)	35 (11.3)	43 (10.2)	90 (10.4)	46 (12.4)
No. of patients who died [†]	0	22 (7.1)	25 (5.9)	47 (5.4)	25 (6.8)

Note: Denominator for percentages based on number of patients in Safety Population for each treatment group and total.

[†] Includes deaths during study up through 28 days from end of treatment.

Studies AC-055-201, AC-055B201, AC-055-302

Reports of any adverse event, serious adverse event, and adverse event leading to study drug discontinuation are lower for the combined macitentan dose groups (equivalent for macitentan 10 mg) compared to the placebo groups.

The table below shows the reporting of adverse events in the large, placebo controlled trial AC-055-302.

Table 28 Overview of adverse events in the double-blind PAH population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
No. of patients with any AE	240 (96.0)	229 (94.6)	469 (95.3)	240 (96.4)
No. of patients with any SAE	130 (52.0)	109 (45.0)	239 (48.6)	137 (55.0)
Number of patients with any AE leading to premature discontinuation of treatment	34 (13.6)	26 (10.7)	60 (12.2)	31 (12.4)
No. of patients who died [†]	22 (8.8)	16 (6.6)	38 (7.7)	21 (8.4)

AE = adverse event, SAE = serious adverse event

Note: Denominator for percentages based on number of patients in Safety Population for each treatment group and total.

[†] Includes deaths during study up through 28 days from end of treatment.

Study AC-055-302

Reports of any adverse event, serious adverse event, and adverse event leading to study drug discontinuation are lower or equivalent for the combined macitentan dose groups compared to the placebo groups.

Pool 2 (AC-055-302 plus the open label extension AC-055-303)

Regarding the ongoing study AC-055-303, patients received macitentan 10 mg per day and data are included up to the cut-off date of 26 April 2012. By the cut-off date, 550 patients from study AC-055-302 had initiated treatment and had data entered in study AC-055-303.

7.2 Adequacy of Safety Assessments

The safety analysis includes 863 patients who received macitentan treatment and 370 patients who received placebo in Phase 2 and 3 randomized, double-blind, placebo-controlled studies for up to 188 weeks. There is also safety review of the 14 clinical pharmacology studies that includes a total of 356 subjects.

For the indication pulmonary arterial hypertension, there were 492 patients exposed to macitentan treatment and 249 exposed to placebo treatment during the double-blind study Seraphin. Of the patients who received double-blind macitentan treatment in the Seraphin trial, 367 continued into an open-label extension study, as of to receive macitentan 10 mg once daily treatment, along with 183 patients who switched from placebo treatment to macitentan 10 mg once daily (as of 4-26-2012).

There were 317 subjects who received macitentan in either a study of essential hypertension (AC-055-201) or idiopathic pulmonary fibrosis (AC-055B201). The doses ranged from < 3 mg up to 10 mg one daily. There are two ongoing trials in digital ulcers AC-055C301 and AC-055C302 with 33 patients and 9 patients, respectively.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the 14 completed Phase 1 clinical pharmacology studies (AC-055-101 to AC-055-114), a total of 356 subjects, including 324 healthy subjects, 24 subjects with hepatic impairment, and 8 subjects with renal impairment were exposed to macitentan. Of the 356 subjects, 149 were exposed to single doses of macitentan and 207 received multiple doses of macitentan.

Safety data from three completed double-blind, placebo-controlled Phase 2/3 studies (AC-055-201, AC-055B201, and AC-055-302) were pooled in order to evaluate the safety of macitentan compared to placebo in patients, using the largest available dataset.

Table 5 Patients included in Pool 1

Analysis set	Study number (acronym)	Numbers of patients, Safety set					Placebo
		Macitentan (mg)				All	
		< 3 mg pool (0.3 mg)	3 mg (1 mg)	10 mg	All		
Pool 1	3 DB, controlled studies (pooled)						
	AC-055-302 (SERAPHIN)	NA	NA	250	242	492	249
	AC-055B201 (MUSIC)	NA	NA	NA	119	119	59
	AC-055-201	63	66	61	62	252	62
	Total		129 ^a	311	423	863	370

DB = double-blind, NA = not applicable

^a Data for the macitentan 0.3 mg- and 1 mg-treated patients were combined due to the small number of patients who received these doses.

The studies in pool 2 include AC-055-302 and AC-055-303, by dose.

Table 6 Patients included in Pool 2

Analysis set	Study number (acronym)	Numbers of patients, Safety set					
		3 mg/ none	10 mg/ none	Placebo/ 10 mg	3 mg/ 10 mg	10 mg/ 10 mg	Total macitentan
Pool 2	Double-blind/ open-label treatment AC-055-302/AC-055-303	65	60	183	185	182	675

The table below shows the combined pools 1 and 2 by dose and type of study.

Table 8 Overall exposure in Pool 1 and Pool 2

Treatment	Double-blind PAH		Double-blind other indications		Total double-blind Pool 1		Open label PAH		Overall total	
	N	Years	N	Years	N	Years	N	Years	N	Years
Macitentan										
< 3mg	-	-	129	15	129	15	-	-	129	15
3 mg	250	477	61	8	311	484	-	-	311	484
10 mg	242	482	181	138	423	620	550 ^a	362	606	982
All	492	959	371	161	863	1120	550 ^a	362	1046 ^b	1482
Placebo	249	407	121	76	370	484	-	-	370	484

Years = Patient years based on total days on Macitentan/365.25 for patients who took study drug for at least 1 day

DB = double-blind, PAH = pulmonary arterial hypertension, OL = open-label

^a Previous treatment in double-blind study: placebo = 183 patients, macitentan 3 mg = 185 patients, macitentan 10 mg = 182 patients

^b 1046 exposed to macitentan = 863 patients in phase 2-3 DB studies + 183 patients in OL exposed to placebo in DB study

The table below shows the exposure of the Pool 1 group.

Table 9 Exposure to study medication in the pooled double-blind safety set (Pool 1)

	< 3 mg (N=129)	3 mg (N=311)	10 mg (N=423)	Total Macitentan (N=863)	placebo (N=370)
Exposure (weeks) ¹					
n	129	311	423	863	370
Mean (SD)	6.10 (2.463)	81.28 (58.664)	76.50 (54.112)	67.70 (57.832)	68.21 (53.238)
Median	7.00	92.57	67.57	56.14	57.57
Min, Max	0.3, 9.7	0.7, 188.0	0.1, 188.0	0.1, 188.0	0.3, 184.9
Exposure, n (%)					
n	129	311	423	863	370
< 24 weeks	129 (100.0)	95 (30.5)	106 (25.1)	330 (38.2)	116 (31.4)
24 - < 48 weeks	0	27 (8.7)	59 (13.9)	86 (10.0)	55 (14.9)
48 - < 72 weeks	0	21 (6.8)	70 (16.5)	91 (10.5)	51 (13.8)
72 - < 96 weeks	0	20 (6.4)	33 (7.8)	53 (6.1)	24 (6.5)
96 - < 120 weeks	0	73 (23.5)	67 (15.8)	140 (16.2)	66 (17.8)
≥ 120 weeks	0	75 (24.1)	88 (20.8)	163 (18.9)	58 (15.7)
Patient Years Exposure ²					
n	129	311	423	863	370
Exposure (years)	15	484	620	1120	484

Note: Denominator for percentages based on number of patients in Safety Population for each treatment group and total.

¹ Duration of exposure is defined as the time (days/7) elapsing between the start and the end of treatment, inclusive.

² Patient year is based on total days on study drug/365.25 for patients who took study drug for at least 1 day.

Studies AC-055-201, AC-055B201, AC-055-302

Source: Appendix 5, Table 4

The mean duration was 68 weeks for total macitentan groups and the placebo groups.

The table below shows the duration of treatment for the large, placebo controlled trial AC-055-302.

Table 10 Exposure to study medication in the double-blind PAH population

	3 mg (N=250)	10 mg (N=242)	Total Macitentan (N=492)	Placebo (N=249)
Exposure (weeks) ¹				
n	250	242	492	249
Mean (SD)	99.51 (50.824)	103.89 (52.443)	101.67 (51.621)	85.33 (53.648)
Median	115.64	118.36	116.93	101.29
Min, Max	0.7, 188.0	0.3, 188.0	0.3, 188.0	0.3, 184.9
Exposure, n (%)				
n	250	242	492	249
< 24 wks	34 (13.6)	34 (14.0)	68 (13.8)	53 (21.3)
24 - < 48 weeks	27 (10.8)	20 (8.3)	47 (9.6)	35 (14.1)
48 - < 72 weeks	21 (8.4)	18 (7.4)	39 (7.9)	22 (8.8)
72 - < 96 weeks	20 (8.0)	15 (6.2)	35 (7.1)	15 (6.0)
96 - < 120 weeks	73 (29.2)	67 (27.7)	140 (28.5)	66 (26.5)
≥ 120 weeks	75 (30.0)	88 (36.4)	163 (33.1)	58 (23.3)
Patient Years Exposure ²				
n	250	242	492	249
Exposure (years)	477	482	959	407

Note: Denominator for percentages based on number of patients in Safety Population for each treatment group and total.

¹ Duration of exposure is defined as the time (days/7) elapsing between the start and the end of treatment, inclusive.

² Patient year is based on total days on study drug/365.25 for patients who took study drug for at least 1 day.

Study AC-055-302

Demographics

In the 14 completed Phase 1 clinical pharmacology studies, 91.8% of those treated were healthy subjects and 8.2% were subjects with hepatic or renal impairment. A total of 82.6% were male and 89% were Caucasian. The age range of the subjects was 19 to 66 years.

The demographics for the studies in pool 1 studies are shown in the table below.

Table 18 Demographics in the pooled double-blind safety set (Pool 1)

	< 3 mg (N=129)	3 mg (N=311)	10 mg (N=423)	Total Macitentan (N=863)	Placebo (N=370)
Age (years)					
n	129	311	423	863	370
Mean (SD)	56.5 (9.87)	46.8 (16.04)	52.9 (15.50)	51.2 (15.40)	51.3 (16.41)
Median	56.0	47.0	55.0	53.0	53.0
Min, Max	26, 84	12, 83	13, 84	12, 84	13, 85
Age Group (years), n (%)					
n	129	311	423	863	370
< 18	0	7 (2.3)	6 (1.4)	13 (1.5)	7 (1.9)
18 - 64	107 (82.9)	259 (83.3)	302 (71.4)	668 (77.4)	275 (74.3)
≥ 65	22 (17.1)	45 (14.5)	115 (27.2)	182 (21.1)	88 (23.8)
Sex, n (%)					
n	129	311	423	863	370
Male	81 (62.8)	98 (31.5)	174 (41.1)	353 (40.9)	140 (37.8)
Female	48 (37.2)	213 (68.5)	249 (58.9)	510 (59.1)	230 (62.2)
Race, n (%)					
n	129	311	423	863	370
White	128 (99.2)	198 (63.7)	311 (73.5)	637 (73.8)	249 (67.3)
Asian	0	70 (22.5)	65 (15.4)	135 (15.6)	72 (19.5)
Other	1 (0.8)	43 (13.8)	47 (11.1)	91 (10.5)	49 (13.2)
BMI (kg/m²)					
n	129	311	423	863	370
Mean (SD)	29.87 (4.188)	26.29 (6.060)	27.33 (5.782)	27.34 (5.791)	26.87 (5.585)
Median	29.40	25.60	26.60	27.00	26.30
Min, Max	21.1, 51.1	15.3, 61.9	15.8, 52.5	15.3, 61.9	14.8, 49.0
Location¹, n (%)					
n	129	311	423	863	370
North America	0	30 (9.6)	70 (16.5)	100 (11.6)	53 (14.3)
Western Europe	87 (67.4)	82 (26.4)	136 (32.2)	305 (35.3)	117 (31.6)
Eastern Europe	42 (32.6)	84 (27.0)	90 (21.3)	216 (25.0)	81 (21.9)
Asia	0	71 (22.8)	86 (20.3)	157 (18.2)	77 (20.8)
Latin America	0	44 (14.1)	41 (9.7)	85 (9.8)	42 (11.4)
Renal impairment n (%)					
n	129	308	418	855	365
None	81 (62.8)	136 (44.2)	192 (45.9)	409 (47.8)	163 (44.7)
Mild	40 (31.0)	128 (41.6)	167 (40.0)	335 (39.2)	145 (39.7)
Moderate-Severe	8 (6.2)	44 (14.3)	59 (14.1)	111 (13.0)	57 (15.6)

Note: Denominator for percentages based on number of non-missing observations for each treatment group and total

¹ North America includes Canada, Western Europe includes South Africa and Israel, Eastern Europe includes Turkey, Asia includes Australia.

No renal impairment = creatinine clearance ≥ 90 mL/min, mild = 60–90 mL/min, moderate–severe = <60 mL/min.

Studies AC-055-201, AC-055B201, AC-055-302

Source: Appendix 5, Table 13

The table below shows the demographic data for the large, placebo controlled study AC-055-302.

Table 19 Demographics in the double-blind PAH population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Age (years)				
n	250	242	492	249
Mean (SD)	44.3 (16.29)	45.5 (14.99)	44.9 (15.66)	46.8 (17.09)
Median	43.0	45.0	44.0	46.0
Min, Max	12, 80	13, 76	12, 80	13, 85
Age Group (years), n (%)				
n	250	242	492	249
<18	7 (2.8)	6 (2.5)	13 (2.6)	7 (2.8)
18 - 64	210 (84.0)	209 (86.4)	419 (85.2)	198 (79.5)
>= 65	33 (13.2)	27 (11.2)	60 (12.2)	44 (17.7)
Sex, n (%)				
n	250	242	492	249
Male	61 (24.4)	48 (19.8)	109 (22.2)	65 (26.1)
Female	189 (75.6)	194 (80.2)	383 (77.8)	184 (73.9)
Race, n (%)				
n	250	242	492	249
White	137 (54.8)	135 (55.8)	272 (55.3)	130 (52.2)
Asian	70 (28.0)	65 (26.9)	135 (27.4)	71 (28.5)
Other	43 (17.2)	42 (17.4)	85 (17.3)	48 (19.3)
BMI (kg/m ²)				
n	250	242	492	249
Mean (SD)	25.73 (6.347)	25.62 (6.053)	25.67 (6.198)	25.15 (5.117)
Median	24.80	24.40	24.60	24.40
Min, Max	15.3, 61.9	15.8, 52.5	15.3, 61.9	14.8, 49.0
Location ¹ , n (%)				
n	250	242	492	249
North America	30 (12.0)	23 (9.5)	53 (10.8)	30 (12.0)
Western Europe	42 (16.8)	48 (19.8)	90 (18.3)	50 (20.1)
Eastern Europe	63 (25.2)	62 (25.6)	125 (25.4)	59 (23.7)
Asia	71 (28.4)	68 (28.1)	139 (28.3)	68 (27.3)
Latin America	44 (17.6)	41 (16.9)	85 (17.3)	42 (16.9)
Renal impairment n (%)				
n	247	238	485	244
None	102 (41.3)	100 (42.0)	202 (41.6)	103 (42.2)
Mild	105 (42.5)	94 (39.5)	199 (41.0)	95 (38.9)
Moderate-Severe	40 (16.2)	44 (18.5)	84 (17.3)	46 (18.9)

Note: Denominator for percentages based on number of non-missing observations for each treatment group and total
¹ North America includes Canada, Western Europe includes South Africa and Israel, Eastern Europe includes Turkey, Asia includes Australia.

No renal impairment = creatinine clearance \geq 90 mL/min, mild = 60–90 mL/min, moderate–severe = <60 mL/min.
 Study AC-055-302

As expected with a PAH population, there were more females than males and the median age of approximately 45 years. Approximately 12% of the macitentan-treated patients were elderly and 3% were adolescents. The patients were predominantly white or Asian. A total of 58.3% of the macitentan-treated patients had renal impairment with >17% in the moderate–severe category. The groups were reasonably well balanced profiles across the treatment groups.

Disease characteristics

The baseline disease characteristics of the patient sin the large, placebo controlled trial AC-055-302 (Seraphin) are shown in the table below.

Table 21 Disease characteristics of the double-blind PAH population (All-randomized set)

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
Time from PAH diagnosis (days)				
n	247	247	241	735
Mean	942	1079	951	991
Standard deviation	1362.0	1659.1	1325.1	1456.9
Standard error	86.7	105.6	85.4	53.7
Median	460	425	476	462
Q1, Q3	180, 1279	178, 1230	174, 1090	178, 1225
Min, Max	6, 13267	1, 11957	2, 10199	1, 13267
Etiology of PAH [n (%)]				
n	247	247	241	735
Idiopathic	126 51.0%	144 58.3%	134 55.6%	404 55.0%
Familial	3 1.2%	8 3.2%	2 0.8%	13 1.8%
Collagen vascular disease	81 32.8%	70 28.3%	73 30.3%	224 30.5%
Congenital shunts	26 10.5%	15 6.1%	21 8.7%	62 8.4%
HIV infection	3 1.2%	1 0.4%	6 2.5%	10 1.4%
Drugs and toxins	8 3.2%	9 3.6%	5 2.1%	22 3.0%
WHO functional class [n (%)]				
n	249	248	242	739
I	-	-	1 0.4%	1 0.1%
II	129 51.8%	138 55.6%	120 49.6%	387 52.4%
III	116 46.6%	105 42.3%	116 47.9%	337 45.6%
IV	4 1.6%	5 2.0%	5 2.1%	14 1.9%
6 min Walk Test (m) (absolute)				
n	249	248	242	739
Mean	352.4	364.1	362.6	359.6
Standard deviation	110.62	95.52	93.21	100.15
Standard error	7.01	6.07	5.99	3.68
Median	360.0	378.0	378.0	372.0
Q1, Q3	284.0, 428.0	311.0, 425.0	300.0, 434.0	300.0, 430.0
Min, Max	65.0, 650.0	80.0, 610.0	90.0, 578.0	65.0, 650.0
Signs of right heart failure [n (%)]				
n	249	248	242	739
Patients with at least one sign	78 31.3%	76 30.6%	76 31.4%	230 31.1%
Concomitant PAH therapy [n (%)]				
n	249	248	242	739
No	95 38.2%	85 34.3%	88 36.4%	268 36.3%
Yes	154 61.8%	163 65.7%	154 63.6%	471 63.7%
Sildenafil	140 56.2%	146 58.9%	140 57.9%	426 57.6%
Tadalafil	2 0.8%	3 1.2%	2 0.8%	7 0.9%
Vardenafil	8 3.2%	5 2.0%	8 3.3%	21 2.8%
Iloprost	3 1.2%	13 5.2%	10 4.1%	26 3.5%
Beraprost	4 1.6%	5 2.0%	6 2.5%	15 2.0%
Treprostinil	-	1 0.4%	-	1 0.1%

HIV = human immunodeficiency virus, PAH = pulmonary arterial hypertension, WHO = World Health Organization

The mean time from PAH diagnosis to randomization was 2.6 to 2.9 years across the three treatment groups. Idiopathic PAH was the most common etiology in the study population (approximately 51–58%) followed by PAH resulting from collagen vascular disease (approximately 30%) and PAH following surgery for congenital shunts (6 to 11%). Familial PAH and PAH resulting from HIV infection, drugs, or toxins ranged from <1% to 4% of patients in any group.

Most patients were WHO functional class II/III; only 2% were class IV.

The mean baseline 6 minute walk test ranged from 352 to 364 meters. About 31% of all patients had at least one sign of heart failure.

The majority of patients were receiving concomitant PAH medication (64%), predominantly sildenafil (approximately 58%). There was an increase in the number of patients receiving sildenafil during the trial in all treatment groups, more in the placebo group than the macitentan groups.

Number and (percent) of patients

sildenafil	Macitentan 3 mg	Macitentan 10 mg	placebo
at baseline	147 (58.8)	140 (57.9)	139 (55.8)
at endpoint	154 (61.1)	150 (62)	154 (61.8)
No. of patients adding drug during study	7	10	15

The use of furosemide, spironolactone and iloprost also increased both in the macitentan and placebo groups as did antibacterials for systemic use (56.0% and 52.9% of patients in the macitentan 3 mg and 10 mg groups, compared to 43.4% of patients in the placebo group).

7.2.2 Explorations for Dose Response

Drug effect on liver function tests (LFT)

Study AC-055-102 was a single center, double blind, placebo-controlled, randomized, ascending dose study in healthy male subjects. The subjects received 1, 3, 10 or 30 mg dose of macitentan or placebo for 10 days. The study raised the question of macitentan's adverse effect on LFT.

There was a trend for increased mean levels of the liver aminotransferases ASAT and ALAT compared to baseline in the groups treated with 10 and 30 mg ACT-064992, mainly caused by four subjects. In the group treated with 10 mg ACT-064992, three cases of single elevated liver enzymes occurred.

- Subject 301 (10 mg) presented with an isolated increase of ALAT values of 1.1 times the upper limit of normal (ULN) (2.3-fold increase from baseline) the day after the last drug intake.
- Subject 307 (10 mg) presented with an isolated increase in ALAT of 1.2 x ULN (a 1.4-fold increase from baseline) 10 days after the last drug intake.
- Subject 304 (30 mg) had an increase in ASAT of 1.8 x ULN (2.6-fold increase from baseline) and ALAT levels just above the ULN (1.3-fold increase from baseline) 10 days after the last drug intake.
- Subject 401 (30 mg) experienced increases in ASAT of about 2 x ULN and in ALAT of about 2.5 x ULN on day 10.
- Subject 308 (placebo) reported on Day 4 of treatment with ASAT levels just above the ULN (1.3 fold-increase from baseline) and an increase in ALAT of 1.1 x ULN (1.4-fold increase from baseline).

The results of ASAT and ALAT levels of these subjects during the study are shown in the table below.

Table 7 ASAT and ALAT levels for subjects in the 10-mg, 30-mg, and placebo group with observed values outside the normal range

Subject number	Visit	Date	ASAT (U/L)	ALAT (U/L)
<i>10 mg ACT-064992</i>				
301	Screening	02.Mar.05	20	16
	Day -1	21.Mar.05	21	22
	Day 4	25.Mar.05	26	20
	Day 11	01.Apr.05	34	50 H
	End of Study	10.Apr.05	31	36
304	Screening	02.Mar.05	28	31
	Day -1	21.Mar.05	24	36
	Day 4	25.Mar.05	23	31
	Day 11	01.Apr.05	21	30
	End of Study	10.Apr.05	62 H	46 H
	Re-check	18.Apr.05	42 H	36
	Re-check	22.Apr.05	22	30
307	Screening	15.Mar.05	21	37
	Day -1	21.Mar.05	21	38
	Day 4	25.Mar.05	22	38
	Day 11	01.Apr.05	27	36
	End of Study	10.Apr.05	24	53 H
	Re-check	18.Apr.05	21	38
<i>30 mg ACT-064992</i>				
401	Screening	24.Mar.05	38 H	51 H
	Re-check	30.Mar.05	25	45
	Day -1	04.Apr.05	26	40
	Day 4	08.Apr.05	34	46 H
	Day 11	15.Apr.05	71 H	115 H
	Re-check	18.Apr.05	59 H	141 H
	Re-check	20.Apr.05	56 H	140 H
	End of Study	24.Apr.05	28	82 H
Re-check	29.Apr.05	25	47 H	
<i>Placebo</i>				
308	Screening	15.Mar.05	24	30
	Day -1	21.Mar.05	27	35
	Day 4	25.Mar.05	36 H	48 H
	Day 11	01.Apr.05	25	36
	End of Study	10.Apr.05	23	35

H and L denote values above or below the normal range. Normal range AST: 0-35 U/L. Normal range ALT: 0-45 U/L

All cases of elevated liver aminotransferases were asymptomatic, resolved within 2 weeks and had no concurrent changes in serum bile salts, bilirubin, or alkaline phosphatase.

Abnormally low hemoglobin/reports of anemia

There was a higher incidence rate of reporting anemia and/or hemoglobin decrease as an adverse event with patients receiving macitentan 10 mg compared to lower doses of macitentan and placebo. The table below shows the results for the Pool 1 studies.

Table 58 Anemia/ hemoglobin decrease SAEs and AEs leading to discontinuation in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any Anemia/hemoglobin decrease AE	3 (2.3)	28 (9.0)	53 (12.5)	84 (9.7)	14 (3.8)
SAEs	0	6 (1.9)	8 (1.9)	14 (1.6)	2 (0.5)
AEs leading to discontinuation of treatment	1 (0.8)	1 (0.3)	1 (0.2)	3 (0.3)	1 (0.3)

AE = adverse event, SAE = serious adverse event
 Studies AC-055-201, AC-055B201, AC-055-302
 Source: Derived from [Appendix 5, Listing 14](#) and [Listing 15](#)

Deaths and serious adverse events

Compared to placebo, there is no obvious effect of the dose of macitentan (3 mg and 10 mg) on the incidence rates of reported deaths or serious adverse events (study AC-055-302).

Table 34 Deaths up to 28 days after end of treatment in the double-blind PAH population by preferred term

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients who died	22 (8.8)	16 (6.6)	38 (7.7)	21 (8.4)

Table 35 SAEs up to 28 days after end of treatment in the pooled double-blind safety set (Pool 1) by preferred term (≥ 2 patients in the total macitentan column)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with SAEs	4 (3.1)	132 (42.4)	148 (35.0)	284 (32.9)	158 (42.7)

7.2.3 Special Animal and/or In Vitro Testing

The *in vitro* data showed that macitentan is a CYP3A4 substrate and, therefore, there is a potential of either macitentan or its active metabolite (ACT-132577) to elicit drug-drug interactions with concomitantly administered substrates.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

7.2.4 Routine Clinical Testing

Central laboratories were used for the completed Phase 2 and Phase 3 clinical studies, with each study using a different central laboratory. In addition, abnormal liver test data (AST and/or ALT > 3 × ULN) from local laboratory investigations not reported via the central laboratories but brought to the attention of the sponsor were entered into a separate database and are used in the analysis. All laboratory variables reported in different units by the central and local laboratories were converted to the standard international (SI) units defined in the ‘Actelion Laboratory Ranges’. Both central and local laboratory data are included in the pooled safety analyses.

In the ongoing open-label extension study (AC-055-303), laboratory data are designated as ‘abnormal’ based on local laboratory ranges. Laboratory values were neither collected nor recorded in the study database and, therefore, no laboratory data are provided for Pool 2.

7.2.5 Metabolic, Clearance, and Interaction Workup

The *in vitro* data showed that macitentan is a CYP3A4 substrate and, therefore, there is a potential of either macitentan or its active metabolite (ACT-132577) to elicit drug-drug interactions with concomitantly administered substrates.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events associated with other endothelin receptor antagonists include liver function test abnormalities, anemia, hypotension and edema.

7.3 Major Safety Results

7.3.1 Deaths

Pool 1

The table below shows the deaths reported in the studies making up Pool 1, by treatment group.

Table 33 Deaths up to 28 days after end of treatment in the pooled double-blind safety set (Pool 1) by preferred term

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients who died	0	22 (7.1)	25 (5.9)	47 (5.4)	25 (6.8)
RIGHT VENTRICULAR FAILURE	0	4 (1.3)	6 (1.4)	10 (1.2)	6 (1.6)
PULMONARY ARTERIAL HYPERTENSION	0	6 (1.9)	2 (0.5)	8 (0.9)	3 (0.8)
RESPIRATORY FAILURE	0	2 (0.6)	3 (0.7)	5 (0.6)	2 (0.5)
SUDDEN DEATH	0	1 (0.3)	2 (0.5)	3 (0.3)	0
ACUTE RESPIRATORY FAILURE	0	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.5)
HYPOXIA	0	0	2 (0.5)	2 (0.2)	0
IDIOPATHIC PULMONARY FIBROSIS	0	0	2 (0.5)	2 (0.2)	4 (1.1)
PULMONARY EMBOLISM	0	0	2 (0.5)	2 (0.2)	1 (0.3)
SUDDEN CARDIAC DEATH	0	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.5)
ACUTE MYOCARDIAL INFARCTION	0	0	1 (0.2)	1 (0.1)	0
ACUTE RESPIRATORY DISTRESS SYNDROME	0	0	1 (0.2)	1 (0.1)	0
ANGIOSARCOMA	0	1 (0.3)	0	1 (0.1)	0
ARRHYTHMIA	0	0	1 (0.2)	1 (0.1)	0
BACTERIAL SEPSIS	0	0	1 (0.2)	1 (0.1)	0
CARDIAC ARREST	0	1 (0.3)	0	1 (0.1)	0
CARDIO-RESPIRATORY ARREST	0	0	1 (0.2)	1 (0.1)	0
DEATH	0	0	1 (0.2)	1 (0.1)	1 (0.3)
DIARRHOEA INFECTIOUS	0	1 (0.3)	0	1 (0.1)	0
GASTROINTESTINAL HAEMORRHAGE	0	1 (0.3)	0	1 (0.1)	0
HAEMATEMESIS	0	0	1 (0.2)	1 (0.1)	0
HEAD AND NECK CANCER	0	0	1 (0.2)	1 (0.1)	0
HYPVOLAEMIC SHOCK	0	1 (0.3)	0	1 (0.1)	0
MALIGNANT MEDIASTINAL NEOPLASM	0	0	1 (0.2)	1 (0.1)	0
METABOLIC ACIDOSIS	0	1 (0.3)	0	1 (0.1)	0
METASTATIC NEOPLASM	0	1 (0.3)	0	1 (0.1)	0
MULTI-ORGAN DISORDER	0	1 (0.3)	0	1 (0.1)	0
MULTI-ORGAN FAILURE	0	0	1 (0.2)	1 (0.1)	0
OESOPHAGEAL VARICES HAEMORRHAGE	0	1 (0.3)	0	1 (0.1)	0
PNEUMONIA	0	0	1 (0.2)	1 (0.1)	1 (0.3)
PNEUMONIA INFLUENZAL	0	1 (0.3)	0	1 (0.1)	0
ROAD TRAFFIC ACCIDENT	0	1 (0.3)	0	1 (0.1)	0
SEPTIC SHOCK	0	1 (0.3)	0	1 (0.1)	0
SYSTEMIC SCLEROSIS	0	0	1 (0.2)	1 (0.1)	0
ACUTE LEFT VENTRICULAR FAILURE	0	0	0	0	1 (0.3)
CARDIAC FAILURE CONGESTIVE	0	0	0	0	1 (0.3)
CARDIOGENIC SHOCK	0	0	0	0	2 (0.5)
CARDIOPULMONARY FAILURE	0	0	0	0	1 (0.3)
LEFT VENTRICULAR FAILURE	0	0	0	0	1 (0.3)
PANCREATIC MASS	0	0	0	0	1 (0.3)
RENAL FAILURE	0	0	0	0	1 (0.3)
SEPSIS	0	0	0	0	1 (0.3)
SYSTEMIC LUPUS ERYTHEMATOSUS	0	0	0	0	1 (0.3)

Note: Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count. Cause of Death is from the Disposition CRF, where coded

Preferred terms may have more than one cause of death for any 1 patient.

A patient is counted once if one or more events in that category.

Studies AC-055-201, AC-055B201, AC-055-302

There were 47 deaths (5%) in patients treated with any dose of macitentan and 25 deaths (7%) in patients treated with placebo in the double blind controlled studies grouped into Pool 1.

SERAPHIN

Most of the deaths in the Pool 1 group were reported in the AC-055-302 SERAPHIN study. These deaths are shown in the table below.

Table 34 Deaths up to 28 days after end of treatment in the double-blind PAH population by preferred term

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients who died	22 (8.8)	16 (6.6)	38 (7.7)	21 (8.4)
RIGHT VENTRICULAR FAILURE	4 (1.6)	6 (2.5)	10 (2.0)	6 (2.4)
PULMONARY ARTERIAL HYPERTENSION	6 (2.4)	2 (0.8)	8 (1.6)	3 (1.2)
SUDDEN DEATH	1 (0.4)	2 (0.8)	3 (0.6)	0
RESPIRATORY FAILURE	2 (0.8)	0	2 (0.4)	1 (0.4)
SUDDEN CARDIAC DEATH	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)
ACUTE MYOCARDIAL INFARCTION	0	1 (0.4)	1 (0.2)	0
ACUTE RESPIRATORY FAILURE	1 (0.4)	0	1 (0.2)	1 (0.4)
ANGIOSARCOMA	1 (0.4)	0	1 (0.2)	0
ARRHYTHMIA	0	1 (0.4)	1 (0.2)	0
BACTERIAL SEPSIS	0	1 (0.4)	1 (0.2)	0
CARDIAC ARREST	1 (0.4)	0	1 (0.2)	0
CARDIO-RESPIRATORY ARREST	0	1 (0.4)	1 (0.2)	0
DEATH	0	1 (0.4)	1 (0.2)	1 (0.4)
DIARRHOEA INFECTIOUS	1 (0.4)	0	1 (0.2)	0
GASTROINTESTINAL HAEMORRHAGE	1 (0.4)	0	1 (0.2)	0
HAEMATEMESIS	0	1 (0.4)	1 (0.2)	0
HYPOVOLAEMIC SHOCK	1 (0.4)	0	1 (0.2)	0
METABOLIC ACIDOSIS	1 (0.4)	0	1 (0.2)	0
METASTATIC NEOPLASM	1 (0.4)	0	1 (0.2)	0
MULTI-ORGAN DISORDER	1 (0.4)	0	1 (0.2)	0
MULTI-ORGAN FAILURE	0	1 (0.4)	1 (0.2)	0
OESOPHAGEAL VARICES HAEMORRHAGE	1 (0.4)	0	1 (0.2)	0
PNEUMONIA INFLUENZAL	1 (0.4)	0	1 (0.2)	0
PULMONARY EMBOLISM	0	1 (0.4)	1 (0.2)	1 (0.4)
ROAD TRAFFIC ACCIDENT	1 (0.4)	0	1 (0.2)	0
SEPTIC SHOCK	1 (0.4)	0	1 (0.2)	0
SYSTEMIC SCLEROSIS	0	1 (0.4)	1 (0.2)	0
ACUTE LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (0.4)
CARDIOGENIC SHOCK	0	0	0	2 (0.8)
CARDIOPULMONARY FAILURE	0	0	0	1 (0.4)
LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
PANCREATIC MASS	0	0	0	1 (0.4)
RENAL FAILURE	0	0	0	1 (0.4)
SEPSIS	0	0	0	1 (0.4)
SYSTEMIC LUPUS ERYTHEMATOSUS	0	0	0	1 (0.4)

Note: Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

Cause of Death is from the Disposition CRF, where coded

Preferred terms may have more than one cause of death for any 1 patient. A patient is counted once if the patient had one or more events in that category.

Study AC-055-302

There was a slightly higher incidence of reported deaths in the placebo group (8%) compared to the macitentan 10 mg group (7%). The incidence rate was slightly higher for the macitentan 3 mg (9%).

Right heart failure and PAH were the two most frequently cited causes of death.

Open label study AC-055-303 OL

A total of 15 patients died during the 120 Day safety update period. These deaths are shown in the table below.

Table 16 Deaths up to 28 days after end of treatment by preferred term reported during the 120 Day safety update period in Pool 2

Treatment DB/OL	Patient No.	Age/sex	OL Day	Cause of Death
Placebo/ 10 mg	1415-10348	73/F	749	Acute right ventricular failure following trauma (Reported as PTs of "Acute right ventricular failure, humerus fracture, radius fracture")
	3805-13594	36/F	1099	Pulmonary arterial hypertension
	3811-13596	26/F	631	Acute right ventricular failure, Pulmonary embolism
	5501-13737	28/F	1070	Right ventricular failure
	5601-15615	56/F	73	Worsening of the underlying disease (Reported as PT "death")
3 mg/ 10 mg	1001-10960	69/M	1118	Recurrence of a rectosigmoid tumor with multiple metastases (Reported as PTs of "decreased appetite, Diarrhea, vomiting")
	3805-14853	52/F	1092	Pulmonary arterial hypertension
	3901-12857	17/F	1360	Pulmonary hypertension
	4102-13344	16/F	1232	During the night, patient developed acute shortness of breath, became unconscious and died (Reported as PT "sudden death")
	4102-13346	54/F	1385	RIGHT VENTRICULAR FAILURE
	5107-15853	35/F	916	PULMONARY ARTERIAL HYPERTENSION
	8402-11846	43/F	1145	RIGHT VENTRICULAR FAILURE
10 mg/ 10 mg	3805-13350	42/F	1240	PULMONARY ARTERIAL HYPERTENSION
	3805-14852	42/F	982	PULMONARY ARTERY ANEURYSM
	5502-11222	45/F	1144	PULMONARY ARTERIAL HYPERTENSION

DB = double-blind, OL = open-label, M = male, F = female
 The patient's age, is that reported at baseline.
 Studies AC-055-302, AC-055-303

The causes of deaths are not unexpected in this PAH patient population.

Other studies

There were no deaths in the essential hypertension population. In the double-blind IPF population (Study AC-055B201), a total of 9 (8%) patients in the macitentan group and 4 (7%) patients in the placebo group died. There were no deaths reported in the completed or ongoing clinical pharmacology studies or the ongoing digital ulcer studies.

7.3.2 Nonfatal Serious Adverse Events

Pool 1

The serious adverse events reported by patients in pool 1 are shown below by treatment group.

Table 35 SAEs up to 28 days after end of treatment in the pooled double-blind safety set (Pool 1) by preferred term (≥ 2 patients in the total macitentan column)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with SAEs	4 (3.1)	132 (42.4)	148 (35.0)	284 (32.9)	158 (42.7)
PULMONARY ARTERIAL HYPERTENSION	0	48 (15.4)	32 (7.6)	80 (9.3)	57 (15.4)
RIGHT VENTRICULAR FAILURE	0	21 (6.8)	23 (5.4)	44 (5.1)	40 (10.8)
PNEUMONIA	0	7 (2.3)	10 (2.4)	17 (2.0)	10 (2.7)
ANEMIA	0	6 (1.6)	6 (1.4)	11 (1.3)	1 (0.3)
SYNCOPE	0	7 (2.3)	4 (0.9)	11 (1.3)	6 (1.6)
IDIOPATHIC PULMONARY FIBROSIS	0	0	10 (2.4)	10 (1.2)	6 (1.6)
RESPIRATORY FAILURE	0	3 (1.0)	7 (1.7)	10 (1.2)	4 (1.1)
CHEST PAIN	1 (0.8)	4 (1.3)	4 (0.9)	9 (1.0)	4 (1.1)
ATRIAL FLUTTER	0	2 (0.6)	5 (1.2)	7 (0.8)	0
HAEMOPTYSIS	0	4 (1.3)	3 (0.7)	7 (0.8)	2 (0.5)
RENAL FAILURE ACUTE	0	4 (1.3)	2 (0.5)	6 (0.7)	0
GASTROENTERITIS	0	3 (1.0)	3 (0.7)	6 (0.7)	0
PREGNANCY	0	1 (0.3)	0	1 (0.1)	0
ACUTE RESPIRATORY FAILURE	0	2 (0.6)	0	2 (0.2)	0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	4 (1.3)	0	4 (0.5)	0
DYSNOEA	0	2 (0.6)	2 (0.5)	4 (0.5)	1 (0.3)
HYPOXIA	0	0	4 (0.9)	4 (0.5)	2 (0.5)
PANCREATITIS ACUTE	0	3 (1.0)	1 (0.2)	4 (0.5)	0
PULMONARY EMBOLISM	0	1 (0.3)	3 (0.7)	4 (0.5)	3 (0.8)
ACUTE MYOCARDIAL INFARCTION	0	1 (0.3)	2 (0.5)	3 (0.3)	1 (0.3)
BRONCHITIS	0	3 (0.9)	1 (0.2)	4 (0.5)	0
CARDIAC ARREST	0	3 (1.0)	0	3 (0.3)	0
CHOLELITHIASIS	0	1 (0.3)	2 (0.5)	3 (0.3)	1 (0.3)
HYPOTENSION	0	1 (0.3)	2 (0.5)	3 (0.3)	0
LIVER FUNCTION TEST ABNORMAL	0	3 (1.0)	2 (0.5)	5 (0.6)	1 (0.3)
LOWER RESPIRATORY TRACT INFECTION	0	1 (0.3)	1 (0.2)	2 (0.2)	0
MEINORRHAGIA	0	2 (0.6)	1 (0.2)	3 (0.3)	0
PYREXIA	0	2 (0.6)	1 (0.2)	3 (0.3)	0
SKIN ULCER	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SUDDEN DEATH	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SUPRAVENTRICULAR TACHYCARDIA	0	1 (0.3)	3 (0.7)	4 (0.5)	0
THROMBOCYTOPENIA	0	0	3 (0.7)	3 (0.3)	1 (0.3)
UPPER RESPIRATORY TRACT INFECTION	0	3 (1.0)	0	3 (0.3)	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	1 (0.2)	1 (0.1)	0
ANGINA PECTORIS	0	1 (0.3)	1 (0.2)	2 (0.2)	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	1 (0.2)	1 (0.1)	0
ATRIAL TACHYCARDIA	0	0	1 (0.2)	1 (0.1)	0
BRADYCARDIA	0	0	1 (0.2)	1 (0.1)	0
CARDIO-RESPIRATORY ARREST	0	0	1 (0.2)	1 (0.1)	0
CHOLECYSTITIS	0	0	1 (0.2)	1 (0.1)	0
COLON CANCER	0	0	1 (0.2)	1 (0.1)	0
CORONARY ARTERY DISEASE	0	0	1 (0.2)	1 (0.1)	0
DEVICE MALFUNCTION	0	0	1 (0.2)	1 (0.1)	0
DIARRHOEA	0	0	1 (0.2)	1 (0.1)	0
DYSFUNCTIONAL UTERINE BLEEDING	0	0	1 (0.2)	1 (0.1)	0
EPISTAXIS	0	0	1 (0.2)	1 (0.1)	0
ERYSIPELAS	0	2 (0.6)	0	2 (0.2)	0
GASTRIC ULCER HAEMORRHAGE	0	1 (0.3)	1 (0.2)	2 (0.2)	0
GENERAL PHYSICAL HEALTH DETERIORATION	0	1 (0.3)	1 (0.2)	2 (0.2)	0
HAEMATEMESIS	0	1 (0.3)	1 (0.2)	2 (0.2)	0
HEADACHE	1 (0.8)	0	1 (0.2)	2 (0.2)	0
HEPATIC ENZYME INCREASED	0	1 (0.3)	1 (0.2)	2 (0.2)	0
OVARIAN CYST	0	1 (0.3)	1 (0.2)	2 (0.2)	0
OVARIAN NEOPLASM	0	1 (0.3)	1 (0.2)	2 (0.2)	0
PNEUMONIA ASPIRATION	0	1 (0.3)	1 (0.2)	2 (0.2)	0
PULMONARY FIBROSIS	0	1 (0.3)	1 (0.2)	2 (0.2)	0
RESPIRATORY TRACT INFECTION	0	0	2 (0.5)	2 (0.2)	0
SUBDURAL HAEMATOMA	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SUDDEN CARDIAC DEATH	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SYSTEMIC LUPUS ERYTHEMATOSUS	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SYSTEMIC SCLEROSIS	0	0	2 (0.5)	2 (0.2)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	0	2 (0.6)	0	2 (0.2)	0
UPPER LIMB FRACTURE	1 (0.8)	1 (0.3)	0	2 (0.2)	0
URINARY TRACT INFECTION	0	0	2 (0.5)	2 (0.2)	0
UTERINE LEIOMYOMA	0	1 (0.3)	1 (0.2)	2 (0.2)	0

SAE = serious adverse event

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

Studies AC-055-201, AC-055B201, AC-055-302

There were higher incidence rates of reporting these serious events in the macitentan 3 mg (42%) and placebo (43%) groups compared to macitentan 10 mg (33%).

Clinical Review
Maryann Gordon, M.D.
NDA 204410, Opsumit® (macitentan)

Serious anemia was more often reported by macitentan 3 mg (2%), macitentan 10 mg (1%) compared to placebo (<1%) as was **acute renal failure** (macitentan 3 mg (1%), macitentan 10 mg (1%) compared to placebo (<1%)).

Serious adverse events PAH and right ventricular failure were most often reported by placebo patients (15% and 11%) compared to macitentan 10 mg (8% and 5%).

SERAPHIN

The serious adverse events reported in the Seraphin trial are shown below by treatment group.

Table 36 SAEs up to 28 days after the end of treatment in the double-blind PAH population (≥ 2 patients in the total macitentan column)

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients with SAEs	130 (52.0)	109 (45.0)	239 (48.6)	137 (55.0)
PULMONARY ARTERIAL HYPERTENSION	48 (19.2)	32 (13.2)	80 (16.3)	56 (22.5)
RIGHT VENTRICULAR FAILURE	21 (8.4)	23 (9.5)	44 (8.9)	40 (16.1)
ANAEMIA	5 (2.0)	6 (2.5)	11 (2.2)	1 (0.4)
PNEUMONIA	7 (2.8)	4 (1.7)	11 (2.2)	8 (3.2)
SYNCOPE	7 (2.8)	4 (1.7)	11 (2.2)	6 (2.4)
CHEST PAIN	4 (1.6)	3 (1.2)	7 (1.4)	1 (0.4)
HAEMOPTYSIS	4 (1.6)	3 (1.2)	7 (1.4)	4 (1.6)
ATRIAL FLUTTER	2 (0.8)	4 (1.7)	6 (1.2)	2 (0.8)
RESPIRATORY FAILURE	3 (1.2)	3 (1.2)	6 (1.2)	2 (0.8)
GASTROENTERITIS	3 (1.2)	2 (0.8)	5 (1.0)	2 (0.8)
PREGNANCY	5 (2.0)	0	5 (1.0)	2 (0.8)
RENAL FAILURE ACUTE	4 (1.6)	1 (0.4)	5 (1.0)	0
DYSPNOEA	2 (0.8)	2 (0.8)	4 (0.8)	1 (0.4)
PANCREATITIS ACUTE	3 (1.2)	1 (0.4)	4 (0.8)	0
BRONCHITIS	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.4)
CARDIAC ARREST	3 (1.2)	0	3 (0.6)	1 (0.4)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	3 (1.2)	0	3 (0.6)	0
MEMORRHAGIA	2 (0.8)	1 (0.4)	3 (0.6)	0
PULMONARY EMBOLISM	1 (0.4)	2 (0.8)	3 (0.6)	1 (0.4)
SKIN ULCER	2 (0.8)	1 (0.4)	3 (0.6)	0
SUDDEN DEATH	1 (0.4)	2 (0.8)	3 (0.6)	0
SUPRAVENTRICULAR TACHYCARDIA	1 (0.4)	2 (0.8)	3 (0.6)	0
UPPER RESPIRATORY TRACT INFECTION	3 (1.2)	0	3 (0.6)	1 (0.4)
ACUTE MYOCARDIAL INFARCTION	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)
ACUTE RESPIRATORY FAILURE	2 (0.8)	0	2 (0.4)	1 (0.4)
ALANINE AMINOTRANSFERASE INCREASED	0	2 (0.8)	2 (0.4)	1 (0.4)
ASPARTATE AMINOTRANSFERASE INCREASED	0	2 (0.8)	2 (0.4)	1 (0.4)
ATRIAL TACHYCARDIA	1 (0.4)	1 (0.4)	2 (0.4)	0
BRADYCARDIA	1 (0.4)	1 (0.4)	2 (0.4)	0
CARDIO-RESPIRATORY ARREST	1 (0.4)	1 (0.4)	2 (0.4)	0
CHOLECYSTITIS	1 (0.4)	1 (0.4)	2 (0.4)	0
CHOLELITHIASIS	1 (0.4)	1 (0.4)	2 (0.4)	0
COLON CANCER	2 (0.8)	0	2 (0.4)	0
DIARRHOEA	0	2 (0.8)	2 (0.4)	1 (0.4)
DYSFUNCTIONAL UTERINE BLEEDING	2 (0.8)	0	2 (0.4)	0
EPISTAXIS	1 (0.4)	1 (0.4)	2 (0.4)	0
ERYSIPELAS	2 (0.8)	0	2 (0.4)	0
GASTRIC ULCER HAEMORRHAGE	1 (0.4)	1 (0.4)	2 (0.4)	0
GENERAL PHYSICAL HEALTH DETERIORATION	1 (0.4)	1 (0.4)	2 (0.4)	0
HAEMATEMESIS	1 (0.4)	1 (0.4)	2 (0.4)	0
HEPATIC ENZYME INCREASED	1 (0.4)	1 (0.4)	2 (0.4)	0
HYPOTENSION	1 (0.4)	1 (0.4)	2 (0.4)	3 (1.2)
LIVER FUNCTION TEST ABNORMAL	0	2 (0.8)	2 (0.4)	1 (0.4)
LOWER RESPIRATORY TRACT INFECTION	2 (0.8)	0	2 (0.4)	1 (0.4)
OVARIAN CYST	1 (0.4)	1 (0.4)	2 (0.4)	0
OVARIAN NEOPLASM	1 (0.4)	1 (0.4)	2 (0.4)	0
PULMONARY FIBROSIS	1 (0.4)	1 (0.4)	2 (0.4)	0
PYREXIA	2 (0.8)	0	2 (0.4)	0
RESPIRATORY TRACT INFECTION	0	2 (0.8)	2 (0.4)	2 (0.8)
SUBDURAL HAEMATOMA	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)
SUDDEN CARDIAC DEATH	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.8)
SYSTEMIC LUPUS ERYTHEMATOSUS	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.4)
SYSTEMIC SCLEROSIS	0	2 (0.8)	2 (0.4)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	2 (0.8)	0	2 (0.4)	2 (0.8)
URINARY TRACT INFECTION	0	2 (0.8)	2 (0.4)	3 (1.2)
UTERINE LEIOMYOMA	1 (0.4)	1 (0.4)	2 (0.4)	0

PAH = pulmonary arterial hypertension, SAE = serious adverse event

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

Study AC-055-302

More patients in the placebo (55%) and macitentan 3 mg (52%) groups reported a serious adverse event compared to macitentan 10 mg (45%).

Clinical Review
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NDA 204410, Opsumit® (macitentan)

Serious anemia was reported more frequently in the macitentan 3 mg (2%) and macitentan 10 mg (3%) groups compared to placebo (<1%). Chest pain, but **not** acute MI, was also reported more frequently in the macitentan 3 mg (2%) and macitentan 10 mg (1%) than placebo (<1%).

Worsening PAH and right ventricular failure were the most frequently reported serious adverse events and both were reported at lower frequencies in the macitentan groups than in the placebo group.

Completed clinical pharmacology studies

No serious adverse events were reported during macitentan treatment in any of the clinical pharmacology studies.

Ongoing Phase 3 digital ulcer studies

No serious adverse events were reported in the ongoing digital ulcer studies

Other ongoing studies

In the glioblastoma study (AC-055-115) 1 patient reported a convulsion. In the Japanese (AC-055-116) and Korean (AC-055-117) studies, no serious adverse events were reported.

7.3.3 Dropouts and/or Discontinuations

Pool 1

The adverse events leading to discontinuation of treatment are shown below by treatment group.

Table 37 AEs leading to discontinuation of study treatment in the pooled double-blind safety set (Pool 1)

	< 3 mg (N=125) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients permanently Discontinued from study treatment Due to AEs	12 (9.3)	35 (11.3)	43 (10.2)	90 (10.4)	46 (12.4)
PULMONARY ARTERIAL HYPERTENSION	0	6 (1.9)	4 (0.9)	10 (1.2)	10 (2.7)
ALANINE AMINOTRANSFERASE INCREASED	0	3 (1.0)	5 (1.2)	8 (0.9)	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	3 (1.0)	5 (1.2)	8 (0.9)	0
RIGHT VENTRICULAR FAILURE	0	3 (1.0)	4 (0.9)	7 (0.8)	6 (1.6)
HEADACHE	2 (1.6)	0	3 (0.7)	5 (0.6)	3 (0.8)
IDIOPATHIC PULMONARY FIBROSIS	0	0	5 (1.2)	5 (0.6)	4 (1.1)
HYPERTENSION	3 (2.3)	0	1 (0.2)	4 (0.5)	2 (0.5)
LIVER FUNCTION TEST ABNORMAL	0	1 (0.3)	3 (0.7)	4 (0.5)	2 (0.5)
ANAEMIA	1 (0.8)	1 (0.3)	1 (0.2)	3 (0.3)	0
PREGNANCY	0	3 (1.0)	0	3 (0.3)	1 (0.3)
CHEST PAIN	1 (0.8)	0	1 (0.2)	2 (0.2)	0
COLON CANCER	0	2 (0.6)	0	2 (0.2)	0
DIZZINESS	0	1 (0.3)	1 (0.2)	2 (0.2)	1 (0.3)
SYNCOPE	1 (0.8)	0	1 (0.2)	2 (0.2)	1 (0.3)
TACHYCARDIA	2 (1.6)	0	0	2 (0.2)	0
TRANSAMINASES INCREASED	1 (0.8)	1 (0.3)	0	2 (0.2)	0
ABDOMINAL PAIN	0	0	1 (0.2)	1 (0.1)	2 (0.5)
ACUTE RIGHT VENTRICULAR FAILURE	0	1 (0.3)	0	1 (0.1)	0
ALCOHOLISM	0	1 (0.3)	0	1 (0.1)	0
ANGIOSARCOMA	0	1 (0.3)	0	1 (0.1)	0
BLOOD PRESSURE INCREASED	1 (0.8)	0	0	1 (0.1)	0
CARDIAC ARREST	0	1 (0.3)	0	1 (0.1)	0
CARDIOGENIC SHOCK	0	0	1 (0.2)	1 (0.1)	1 (0.3)
COLITIS ISCHAEMIC	0	1 (0.3)	0	1 (0.1)	0
DIARRHOEA INFECTIOUS	0	1 (0.3)	0	1 (0.1)	0
DIPLOPIA	1 (0.8)	0	0	1 (0.1)	0
DRUG INTOLERANCE	0	0	1 (0.2)	1 (0.1)	0
DYSPNOEA	0	0	1 (0.2)	1 (0.1)	0
ECZEMA	0	1 (0.3)	0	1 (0.1)	0
GASTRIC ULCER HAEMORRHAGE	0	0	1 (0.2)	1 (0.1)	0
HEAD AND NECK CANCER	0	0	1 (0.2)	1 (0.1)	0
HEART AND LUNG TRANSPLANT	0	1 (0.3)	0	1 (0.1)	0
HEPATIC ENZYME INCREASED	0	0	1 (0.2)	1 (0.1)	0
HEPATITIS	0	0	1 (0.2)	1 (0.1)	1 (0.3)
HYPERBILIRUBINAEMIA	0	0	1 (0.2)	1 (0.1)	0
HYPERSENSITIVITY	1 (0.8)	0	0	1 (0.1)	0
HYPOTENSION	0	0	1 (0.2)	1 (0.1)	0
HYPOVOLAEMIC SHOCK	0	1 (0.3)	0	1 (0.1)	0
HYPOXIA	0	0	1 (0.2)	1 (0.1)	0
INTERSTITIAL LUNG DISEASE	0	1 (0.3)	0	1 (0.1)	0
JAUNDICE	0	1 (0.3)	0	1 (0.1)	1 (0.3)
LIP SWELLING	0	0	1 (0.2)	1 (0.1)	0
MALIGNANT MEDIASTINAL NEOPLASM	0	0	1 (0.2)	1 (0.1)	0
METASTATIC NEOPLASM	0	1 (0.3)	0	1 (0.1)	0
MIGRAINE	1 (0.8)	0	0	1 (0.1)	0
MULTI-ORGAN DISORDER	0	1 (0.3)	0	1 (0.1)	0
OEDEMA PERIPHERAL	0	0	1 (0.2)	1 (0.1)	1 (0.3)
OESOPHAGEAL VARICES HAEMORRHAGE	0	1 (0.3)	0	1 (0.1)	0
PNEUMONIA	0	1 (0.3)	0	1 (0.1)	0
PNEUMONIA INFLUENZAL	0	1 (0.3)	0	1 (0.1)	0
PULMONARY EMBOLISM	0	0	1 (0.2)	1 (0.1)	0
RESPIRATORY FAILURE	0	0	1 (0.2)	1 (0.1)	1 (0.3)
SEPTIC SHOCK	0	1 (0.3)	0	1 (0.1)	0
SUBDURAL HAEMATOMA	0	0	1 (0.2)	1 (0.1)	0
TEMPORAL ARTERITIS	1 (0.8)	0	0	1 (0.1)	0
THROMBOCYTOPENIA	0	0	1 (0.2)	1 (0.1)	1 (0.3)
TREATMENT FAILURE	0	0	1 (0.2)	1 (0.1)	0
URTICARIA	1 (0.8)	0	0	1 (0.1)	0
VERTIGO	1 (0.8)	0	0	1 (0.1)	0
VISUAL IMPAIRMENT	1 (0.8)	0	0	1 (0.1)	0
VOMITING	0	0	1 (0.2)	1 (0.1)	0
ACUTE RESPIRATORY FAILURE	0	0	0	0	1 (0.3)
ANAEMIA MEGALOBlastic	0	0	0	0	1 (0.3)
ASCITES	0	0	0	0	1 (0.3)

	< 3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
CARDIAC FAILURE CONGESTIVE	0	0	0	0	1 (0.3)
CARDIOPULMONARY FAILURE	0	0	0	0	1 (0.3)
CEREBROVASCULAR ACCIDENT	0	0	0	0	1 (0.3)
COCCIDIOIDOMYCOSIS	0	0	0	0	1 (0.3)
DISTURBANCE IN ATTENTION	0	0	0	0	1 (0.3)
GASTROENTERITIS	0	0	0	0	1 (0.3)
HAEMOPTYSIS	0	0	0	0	1 (0.3)
HYPERTENSIVE CRISIS	0	0	0	0	1 (0.3)
INCOHERENT	0	0	0	0	1 (0.3)
LEFT VENTRICULAR FAILURE	0	0	0	0	1 (0.3)
LEUKOCYTOCLASTIC VASCULITIS	0	0	0	0	1 (0.3)
LUNG SQUAMOUS CELL CARCINOMA STAGE	0	0	0	0	1 (0.3)
UNSPECIFIED	0	0	0	0	1 (0.3)
RENAL FAILURE	0	0	0	0	1 (0.3)
SEPSIS	0	0	0	0	1 (0.3)
TREMOR	0	0	0	0	1 (0.3)

AE = adverse event

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

Studies AC-055-201, AC-055B201, AC-055-302

Source: [Appendix 5, Table 157](#)

A higher frequency of placebo subjects dropped out because of an adverse event (12%) than patients in the macitentan 10 mg group (10%).

A higher frequency of macitentan 10 mg patients dropped out for elevated ALT (1%) and/or AST (1%) compared to none in the placebo group.

SERAPHIN

The table below shows the patients who dropped out of the Seraphin study because of an adverse event.

Table 38 AEs leading to discontinuation of study treatment in the double-blind PAH safety population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
Number of patients withdrawn from treatment due to AEs	34 (13.6)	26 (10.7)	60 (12.2)	31 (12.4)
PULMONARY ARTERIAL HYPERTENSION	6 (2.4)	4 (1.7)	10 (2.0)	10 (4.0)
RIGHT VENTRICULAR FAILURE	3 (1.2)	4 (1.7)	7 (1.4)	6 (2.4)
ALANINE AMINOTRANSFERASE INCREASED	3 (1.2)	2 (0.8)	5 (1.0)	0
ASPARTATE AMINOTRANSFERASE INCREASED	3 (1.2)	2 (0.8)	5 (1.0)	0
HEADACHE	0	3 (1.2)	3 (0.6)	0
LIVER FUNCTION TEST ABNORMAL	0	3 (1.2)	3 (0.6)	2 (0.8)
PREGNANCY	3 (1.2)	0	3 (0.6)	1 (0.4)
ANAEMIA	1 (0.4)	1 (0.4)	2 (0.4)	0
COLON CANCER	2 (0.8)	0	2 (0.4)	0
ACUTE RIGHT VENTRICULAR FAILURE	1 (0.4)	0	1 (0.2)	0
ALCOHOLISM	1 (0.4)	0	1 (0.2)	0
ANGIOSARCOMA	1 (0.4)	0	1 (0.2)	0
CARDIAC ARREST	1 (0.4)	0	1 (0.2)	0
CARDIOGENIC SHOCK	0	1 (0.4)	1 (0.2)	1 (0.4)
CHEST PAIN	0	1 (0.4)	1 (0.2)	0
COLITIS ISCHAEMIC	1 (0.4)	0	1 (0.2)	0
DIARRHOEA INFECTIOUS	1 (0.4)	0	1 (0.2)	0
DIZZINESS	1 (0.4)	0	1 (0.2)	0
DRUG INTOLERANCE	0	1 (0.4)	1 (0.2)	0
DYSPNOEA	0	1 (0.4)	1 (0.2)	0
ECZEMA	1 (0.4)	0	1 (0.2)	0
GASTRIC ULCER HAEMORRHAGE	0	1 (0.4)	1 (0.2)	0
HEART AND LUNG TRANSPLANT	1 (0.4)	0	1 (0.2)	0
HEPATIC ENZYME INCREASED	0	1 (0.4)	1 (0.2)	0
HEPATITIS	0	1 (0.4)	1 (0.2)	1 (0.4)
HYPERBILIRUBINAEMIA	0	1 (0.4)	1 (0.2)	0
HYPOTENSION	0	1 (0.4)	1 (0.2)	0
HYPOVOLAEMIC SHOCK	1 (0.4)	0	1 (0.2)	0
INTERSTITIAL LUNG DISEASE	1 (0.4)	0	1 (0.2)	0
JAUNDICE	1 (0.4)	0	1 (0.2)	1 (0.4)
METASTATIC NEOPLASM	1 (0.4)	0	1 (0.2)	0
MULTI-ORGAN DISORDER	1 (0.4)	0	1 (0.2)	0
ESOPHAGEAL VARICES HAEMORRHAGE	1 (0.4)	0	1 (0.2)	0
PNEUMONIA	1 (0.4)	0	1 (0.2)	0
PNEUMONIA INFLUENZAL	1 (0.4)	0	1 (0.2)	0
SEPTIC SHOCK	1 (0.4)	0	1 (0.2)	0
SUBDURAL HAEMATOMA	0	1 (0.4)	1 (0.2)	0
SYNCOPE	0	1 (0.4)	1 (0.2)	1 (0.4)
TRANSAMINASES INCREASED	1 (0.4)	0	1 (0.2)	0
TREATMENT FAILURE	0	1 (0.4)	1 (0.2)	0
VOMITING	0	1 (0.4)	1 (0.2)	0
ANAEMIA MEGALOBLASTIC	0	0	0	1 (0.4)
ASCITES	0	0	0	1 (0.4)
CARDIAC FAILURE CONGESTIVE	0	0	0	1 (0.4)
CARDIOPULMONARY FAILURE	0	0	0	1 (0.4)
CEREBROVASCULAR ACCIDENT	0	0	0	1 (0.4)
GASTROENTERITIS	0	0	0	1 (0.4)
HAEMOPTYSIS	0	0	0	1 (0.4)
LEFT VENTRICULAR FAILURE	0	0	0	1 (0.4)
LEUKOCYTOCLASTIC VASCULITIS	0	0	0	1 (0.4)
OEDEMA PERIPHERAL	0	0	0	1 (0.4)
RENAL FAILURE	0	0	0	1 (0.4)
RESPIRATORY FAILURE	0	0	0	1 (0.4)
SEPSIS	0	0	0	1 (0.4)
THROMBOCYTOPENIA	0	0	0	1 (0.4)

AE = adverse event, PAH = pulmonary arterial hypertension

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

The drop outs rates in the macitentan 3 mg, macitentan 10 mg and placebo groups were 14%, 11% and 12 % respectively.

Adverse events associated with liver abnormalities that led to discontinuation of treatment included increased ALT and AST, abnormal liver function test, increased transaminases, hepatitis, hyperbilirubinemia and increased hepatic enzyme, and jaundice. On the basis of a

grouping of liver abnormality adverse events, 4% and 4% of patients in the macitentan 3 mg and 10 mg groups discontinued study treatment due to such events and 2% of placebo-treated patients discontinued treatment.

Anemia was rarely reported as a reason for dropping out of treatment (one patient in each of the macitentan 3 mg and 10 mg groups reported anemia and in one patient in the placebo group reported megaloblastic anemia).

Completed clinical pharmacology studies

In a drug interaction study with ketoconazole, one subject discontinued study treatment because of increased AST, ALT, and GGT during treatment with ketoconazole (18 days) and 13 days after a single dose of macitentan 10 mg.

Ongoing Phase 3 digital ulcer studies

One patient discontinued because of disease progression (worsening of digital ulcer). The patient's treatment allocation remains blinded.

Other ongoing studies

In the glioblastoma study, one patient discontinued treatment because of a convulsion at a macitentan 30 mg dose.

In the Japanese and Korean studies, there were no adverse events that resulted in discontinuation of study treatment.

7.3.4 Significant Adverse Events

Significant adverse events of concern include:

- 1) Decrease in hemoglobin/anemia

7.3.5 Submission Specific Primary Safety Concerns

Primary safety concerns include

- 1) Fetal toxicity (class effect)
- 2) Decrease in hemoglobin/anemia
- 3) Pulmonary veno-occlusive disease with pulmonary edema (class effect)
- 4) Liver function abnormalities
- 5) Decreased sperm count (class effect)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events reported in Pool 1 studies (the completed double-blind, placebo-controlled Phase 2/3 studies AC-055-201, AC-055B201, and AC-055-302) are shown below by dose.

Table 29 Adverse events in the pooled double-blind safety set (Pool 1) by preferred term (at least 3.0% in the total macitentan group)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with AEs	42 (32.6)	253 (81.4)	363 (85.8)	658 (76.2)	317 (85.7)
PULMONARY ARTERIAL HYPERTENSION	0	75 (24.1)	53 (12.5)	128 (14.8)	88 (23.8)
UPPER RESPIRATORY TRACT INFECTION	1 (0.8)	50 (16.1)	58 (13.7)	109 (12.6)	46 (12.4)
HEADACHE	19 (14.7)	35 (11.3)	45 (10.6)	99 (11.5)	38 (10.3)
OEDEMA PERIPHERAL	0	40 (12.9)	58 (13.7)	98 (11.4)	49 (13.2)
NASOPHARYNGITIS	1 (0.8)	40 (12.9)	39 (9.2)	80 (9.3)	27 (7.3)
ANAEMIA	3 (2.3)	22 (7.1)	46 (10.9)	71 (8.2)	9 (2.4)
DYSPNOEA	2 (1.6)	26 (8.4)	42 (9.9)	70 (8.1)	31 (8.4)
RIGHT VENTRICULAR FAILURE	0	37 (11.9)	32 (7.6)	69 (8.0)	56 (15.1)
DIZZINESS	4 (3.1)	24 (7.7)	38 (9.0)	66 (7.6)	34 (9.2)
BRONCHITIS	0	20 (6.4)	44 (10.4)	64 (7.4)	23 (6.2)
COUGH	1 (0.8)	20 (6.4)	43 (10.2)	64 (7.4)	51 (13.8)
CHEST PAIN	3 (2.3)	20 (6.4)	28 (6.6)	51 (5.9)	23 (6.2)
DIARRHOEA	0	14 (4.5)	30 (7.1)	44 (5.1)	22 (5.9)
INSOMNIA	1 (0.8)	17 (5.5)	25 (5.9)	43 (5.0)	13 (3.5)
URINARY TRACT INFECTION	0	16 (5.1)	24 (5.7)	40 (4.6)	16 (4.3)
HYPOTENSION	0	14 (4.5)	21 (5.0)	35 (4.1)	13 (3.5)
NAUSEA	1 (0.8)	13 (4.2)	21 (5.0)	35 (4.1)	15 (4.1)
SYNCOPE	1 (0.8)	21 (6.8)	12 (2.8)	34 (3.9)	21 (5.7)
ARTHRALGIA	0	16 (5.1)	17 (4.0)	33 (3.8)	12 (3.2)
INFLUENZA	1 (0.8)	11 (3.5)	19 (4.5)	31 (3.6)	7 (1.9)
PNEUMONIA	0	10 (3.2)	21 (5.0)	31 (3.6)	17 (4.6)
FATIGUE	3 (2.3)	11 (3.5)	15 (3.5)	29 (3.4)	18 (4.9)
BACK PAIN	0	16 (5.1)	12 (2.8)	28 (3.2)	28 (7.6)
PHARYNGITIS	0	11 (3.5)	17 (4.0)	28 (3.2)	8 (2.2)
HYPOKALAEMIA	0	13 (4.2)	14 (3.3)	27 (3.1)	14 (3.8)
SINUSITIS	0	11 (3.5)	16 (3.8)	27 (3.1)	8 (2.2)
HYPERTENSION	6 (4.7)	10 (3.2)	10 (2.4)	26 (3.0)	12 (3.2)
PALPITATIONS	0	14 (4.5)	12 (2.8)	26 (3.0)	13 (3.5)

AE = adverse event

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

Preferred terms are sorted in descending order of the Total Macitentan frequency count.

Studies AC-055-201, AC-055B201, AC-055-302

Hematology

-anemia: 2%, 7%, 11%, 2% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively

Infection

(All) Respiratory infections³: 2%, 46%, 45%, 39% for macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;

³ Pool 1 studies AC-055-201, AC-055B201, AC-055-302

-upper respiratory tract infection: 1%,16%, 14%, 12% for macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-nasopharyngitis: 1%, 13%, 9%, 7% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-bronchitis: 0%, 6% 10%, 6% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-influenza: 1%, 4%, 5%, 2% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-pharyngitis: 0%, 4%, 4%, 2% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-sinusitis: 0%, 4%, 4%, 2% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively.

Other

-dyspnea: 2%, 8%, 10%, 8% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively;
-hypotension: 0%, 5%, 5%, 4% macitentan < 3 mg, macitentan 3 mg, macitentan 10 mg and placebo, respectively.

The following table shows the adverse events that were reported by at least 3% of patients in the macitentan 10 mg group and reported more than those in the placebo group.

Number and (percent) of subjects

Adverse event	Macitentan 10 mg N=423	Placebo N=370	Placebo subtracted %
<u>Any event</u>	<u>363 (81)</u>	<u>317 (86)</u>	<u>-5</u>
Anemia	46 (11)	9 (2)	9
Bronchitis	44 (10)	23 (6)	4
Influenza	19 (5)	7 (2)	3
URTI	58 (14)	46 (12)	2
headache	45 (11)	38 (10)	1
Peripheral edema	58 (14)	49 (13)	1
Nasopharyngitis	39 (9)	27 (7)	2
Dyspnea	42 (10)	31 (8)	2
Chest pain	28 (7)	23 (6)	1
Diarrhea	30 (7)	22 (6)	1
Insomnia	25 (6)	13 (4)	2
URI	24 (6)	16 (4)	2
Hypotension	21 (5)	13 (4)	1
Nausea	21 (5)	15 (4)	1
Pharyngitis	17 (4)	8 (2)	2
Sinusitis	16 (4)	8 (2)	2

From table 29

7.4.2 Laboratory Findings

Hematology

Anemia/decreased hemoglobin

Pool 1

There were decreases in hemoglobin and reports of anemia as well as decreases in platelets and leukocyte counts in the pool 1 studies. The reports of these abnormalities in the pool 1 studies are shown below.

Table 57 Anemia/ hemoglobin decrease AEs in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any SMQ Anaemia/Hb decrease AE	3 (2.3)	28 (9.0)	53 (12.5)	84 (9.7)	14 (3.8)
Anemia AEs per 100 patient-years	19.9	5.8	8.5	7.5	2.9
Number of AEs	3	36	79	118	17
Crude incidence					
ANAEMIA	3 (2.3)	22 (7.1)	46 (10.9)	71 (8.2)	9 (2.4)
HAEMATOCRIT DECREASED	0	1 (0.3)	6 (1.4)	7 (0.8)	0
HAEMOGLOBIN DECREASED	0	1 (0.3)	6 (1.4)	7 (0.8)	1 (0.3)
IRON DEFICIENCY ANAEMIA	0	5 (1.6)	2 (0.5)	7 (0.8)	2 (0.5)
RED BLOOD CELL COUNT DECREASED	0	0	3 (0.7)	3 (0.3)	0
ERYTHROPENIA	0	1 (0.3)	0	1 (0.1)	0
HAEMOLYTIC ANAEMIA	0	0	1 (0.2)	1 (0.1)	0
MYELODISPLASTIC SYNDROME	0	0	1 (0.2)	1 (0.1)	0
PANCYTOPENIA	0	1 (0.3)	0	1 (0.1)	0
ANAEMIA HAEMOLYTIC AUTOIMMUNE	0	0	0	0	1 (0.3)
ANAEMIA MACROCYTIC	0	0	0	0	1 (0.3)
ANAEMIA MEGALOBLASTIC	0	0	0	0	1 (0.3)

AE = adverse event, PT = preferred term

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

AEs per 100 patient-years Exposure derived as (%) = 100(incidence/[total treatment duration days/365]).

Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.

PTs are sorted in descending order of the Total Macitentan frequency count.

Studies AC-055-201, AC-055B201, AC-055-302

Source: [Appendix 5, Table 72](#) and [Table 98](#)

The incidence rates of anemia reported as an adverse event were greater for the macitentan groups (2%, 7%, and 11% for macitentan < 3mg, macitentan 3 mg, and macitentan 10 mg, respectively) compared to placebo (2%) and there is a dose response.

The table below shows the reports of anemia that were considered serious and/or led to withdrawal.

Table 58 Anemia/ hemoglobin decrease SAEs and AEs leading to discontinuation in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any Anemia/hemoglobin decrease AE	3 (2.3)	28 (9.0)	53 (12.5)	84 (9.7)	14 (3.8)
SAEs	0	6 (1.9)	8 (1.9)	14 (1.6)	2 (0.5)
AEs leading to discontinuation of treatment	1 (0.8)	1 (0.3)	1 (0.2)	3 (0.3)	1 (0.3)

AE = adverse event, SAE = serious adverse event

Studies AC-055-201, AC-055B201, AC-055-302

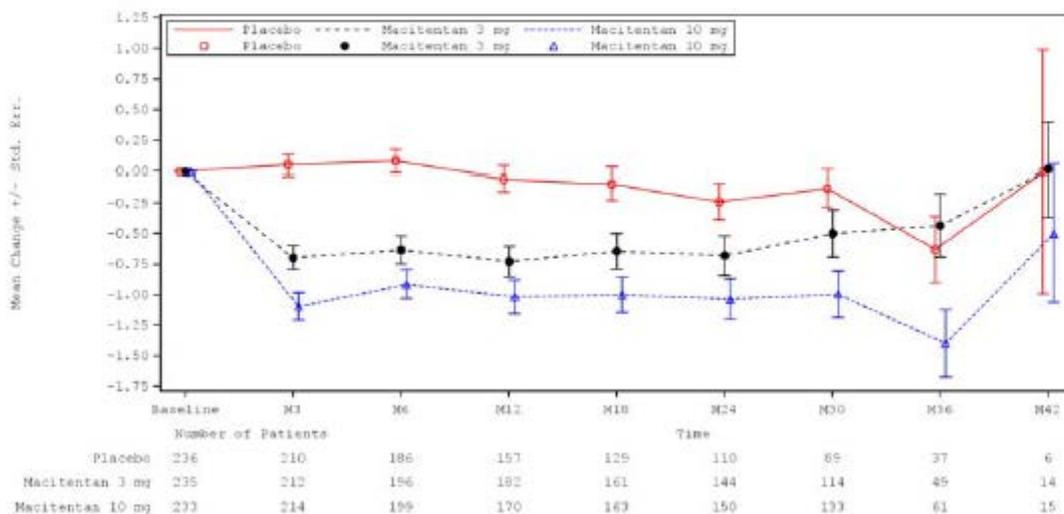
Source: Derived from Appendix 5, Listing 14 and Listing 15

The incidence rates of anemia reported as a serious adverse event were greater for the macitentan groups (0%, 2%, and 2% for macitentan < 3mg, macitentan 3 mg, and macitentan 10 mg, respectively) compared to placebo (1%) and there is a dose response. The incidence rates for drop outs because of anemia were similar across treatment groups (<1%). Transfusions, in some cases, were required.

The figure below shows mean hemoglobin and hematocrit data for the double-blind PAH population (Studies AC-055-201, AC-055B201, AC-055-302).

Figure 1 Change from baseline in hemoglobin and hematocrit over time in the double-blind PAH population

Hemoglobin (g/dL)



Decreases were generally reported within the first 3 months of the start of study treatment and then leveled off. In the macitentan 3 mg and 10 mg groups, hemoglobin at month 3 had median decreases of 0.75 g/dL and 1.0 g/dL from baseline, respectively, but only 0.06 g/dL in the placebo group. Other decreases in the macitentan groups included erythrocyte count.

Leukocyte counts

In Seraphin, there were small decreases from baseline in leukocyte counts for the macitentan groups compared to no change for placebo. These data are shown in the table below.

Table 94 Change from baseline in leukocyte counts and proportion of patients with markedly low leukocyte counts in the double-blind PAH population up to 28 days after treatment discontinuation (combined central and local laboratory data), All-treated set

HEMATOLOGY : Leukocytes (10e9/L)			
	Macitentan 3 mg N=250	Macitentan 10 mg N=242	Placebo N=249
Baseline			
n (missing)	221 (29)	218 (24)	220 (29)
Mean	7.9	7.5	7.5
Standard deviation	3.06	2.41	2.44
Median	7.3	7.2	7.2
Q1 , Q3	6.0, 9.2	5.7, 8.9	5.8, 8.9
Min , Max	2.7, 27.6	3.1, 16.5	2.8, 16.5
Last up to 28 days after treatment discontinuation			
n (missing)	221 (29)	218 (24)	220 (29)
Mean	6.9	6.7	7.5
Standard deviation	2.48	2.42	2.56
Median	6.6	6.4	7.1
Q1 , Q3	5.4, 8.0	4.9, 8.2	5.8, 8.8
Min , Max	2.6, 21.3	2.4, 15.0	2.4, 23.1
Change from baseline			
n (missing)	221 (29)	218 (24)	220 (29)
Mean	-0.9	-0.7	0.0
Standard deviation	2.78	2.27	2.57
Median	-0.6	-0.8	-0.2
Q1 , Q3	-2.2, 0.5	-2.0, 0.6	-1.5, 1.2
Min , Max	-11.9, 11.4	-6.6, 10.2	-8.1, 14.2
Patients with markedly low counts ^a	0 /221	2 /218 0.9%	0 /220

CTC = common toxicity criteria, PAH = pulmonary arterial hypertension

^a Patients with worsening of CTC grade from 0 or 1 at baseline to \geq grade 3 ($< 2.0 \times 10^9/L$) at any time during the study
 Study AC-055-302

Source: D-12.425, Table 171; Appendix 5, Table 164

A shift analysis showed that 19.6% of macitentan-treated PAH patients had a deterioration in common toxicity criteria grade from baseline at some time during the study, compared to 10.5% of placebo-treated patients. In the macitentan 3 mg and 10 mg groups, the proportions were 14.9% and 24.3%, respectively. Two patients in the macitentan 10 mg group had shifts to CTC grade 3 (1.0 to $< 2.0 \times 10^9/L$), one (5601- 10727) from grade 0 (within the normal range) and the other (5202-13720) from grade 1 ($3.0 \times 10^9/L$ to $< LLN$) at baseline.

Platelets

In the double-blind PAH population, there were similar small decreases in mean platelet count from baseline across treatment groups (Table 95).

Clinical Chemistry

Laboratory values indicating abnormalities include liver function tests (LFT) and creatinine.

Liver function tests

Pool 1

The incidence of liver abnormality AEs was 8.5% in the total macitentan pool and 11.9% in the placebo pool.

The table below shows the numbers and percentages of patients reporting liver associated serious and all adverse events.

Table 43 Liver abnormality SAEs and AEs leading to discontinuation in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any SMQ Liver abnormality AE	3 (2.3)	32 (10.3)	38 (9.0)	73 (8.5)	44 (11.9)
SAEs AEs leading to discontinuation of treatment	0	6 (1.9)	6 (1.4)	12 (1.3)	4 (1.1)
	1 (0.8)	7 (2.3)	11 (2.6)	19 (2.2)	4 (1.1)

AE = adverse event, SAE = serious adverse event, SMQ = standardized MedDRA query

Studies AC-055-201, AC-055B201, AC-055-302

Source: Derived from [Appendix 5](#), [Listing 14](#) and [Listing 15](#)

The data show little effect of macitentan on serious liver abnormalities. However, doses of macitentan are limited to 10 mg or less.

The table below shows the number and percentage of reports of abnormal LFTs in the Seraphin trial.

Table 47 Incidence of liver function abnormalities occurring from treatment start up to 28 days after EOT in the double-blind PAH safety population

	3 mg (N=250) n (%)	10 mg (N=242) n (%)	Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
ALT or AST > 3 x ULN				
n	247	236	483	244
n (%)	10 (4.0)	8 (3.4)	18 (3.7)	11 (4.5)
ALT or AST > 5 x ULN				
n	247	236	483	244
n (%)	4 (1.6)	6 (2.5)	10 (2.1)	5 (2.0)
ALT or AST > 8 x ULN				
n	247	236	483	244
n (%)	4 (1.6)	5 (2.1)	9 (1.9)	1 (0.4)
ALT or AST > 3 x ULN and TBIL > 2 x ULN at any time				
n	241	230	471	237
n (%)	4 (1.7)	4 (1.7)	8 (1.7)	5 (2.1)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = end of treatment, TBIL = total bilirubin, ULN = upper limit of the normal range

Note: Denominator for percentages based on number of non-missing observations for each treatment group and total. Incidence based on the number of patients with at least one post-baseline abnormality for each category.

Patient 1406/11104 (placebo) was not included in source table since TBIL > 2 x ULN as reported by a local laboratory was not included in the clinical database. Patient 9103/12093 (macitentan 3 mg) was incorrectly included in source table, despite TBIL < 2 x ULN.

Study AC-055-302

Source: [Appendix 5, Table 168](#), and [D-12.559, Annex 1: narratives](#)

Only the ALT or AST > 8 x ULN listings show the macitentan groups worse than placebo. The numbers of subjects reporting this event are small in all groups. However, the upper dose of macitentan is limited to 10 mg.

Ongoing PAH study (AC-055-303, continuation of Seraphin)

All patients who enrolled into this study receive macitentan 10 mg.

There were an additional 9 cases of aminotransferase elevations > 3 x ULN were reported up to the cut-off date of 26 April 26, 2012.

- 3 cases with ALT/AST > 3 x ULN and total bilirubin > 2 x ULN,
- 3 cases with ALT/AST > 8 x ULN (total bilirubin > 2 x ULN) and
- 3 cases with ALT/AST > 3 x ULN (total bilirubin > 2 x ULN).

After the cut-off date of 26 April 26, 2012, three additional cases of ALT/AST > 3 x ULN with total bilirubin < 2 x ULN were reported up to 31 July 31, 2012 (2 of the 3 cases normalized while treatment was continued or restarted).

Studies in other indications

In the ongoing AC-055-115 study, 13 patients with glioblastoma received doses up to 120 mg with no obviously detrimental effect on LFTs for up to 147 days.

Creatinine and renal adverse events

Laboratory data for the double-blind PAH population showed no mean or median increases in serum creatinine over the period of the study. There were eight patients reporting marked creatinine elevations, defined as ≥ 154 $\mu\text{mol/L}$ and 75% increase from baseline. These eight patients were four in the macitentan 3 mg group, three in the macitentan 10 mg group, and one in the placebo group and are shown below.

Table 69 Overview of patients with marked elevations in creatinine (i.e., ≥ 154 $\mu\text{mol/L}$ and 75% increase from baseline) in the double-blind PAH population

Treatment group	Patient No.	Likely/ possible cause of renal failure	Recovery*
Macitentan 3 mg	1413-10464	Medical history of renal failure – creatinine ≥ 154 $\mu\text{mol/L}$ at baseline – induced by contrast media	NA
	3405-15477	Low blood pressure	Yes
	3806-13467	Secondary to PAH progression	NA
	9105-12105	No confounding factors	NA
Macitentan 10 mg	5304-13115	Single dose – RHF – ischemic hepatitis – death	NA
	8009-12087	Secondary to right ventricular failure	NA
	3406-12601	Creatinine ≥ 154 $\mu\text{mol/L}$ at baseline	Yes
Placebo	8401-11588	Secondary to low cardiac output (hemodialysis and ultrafiltration)	NA

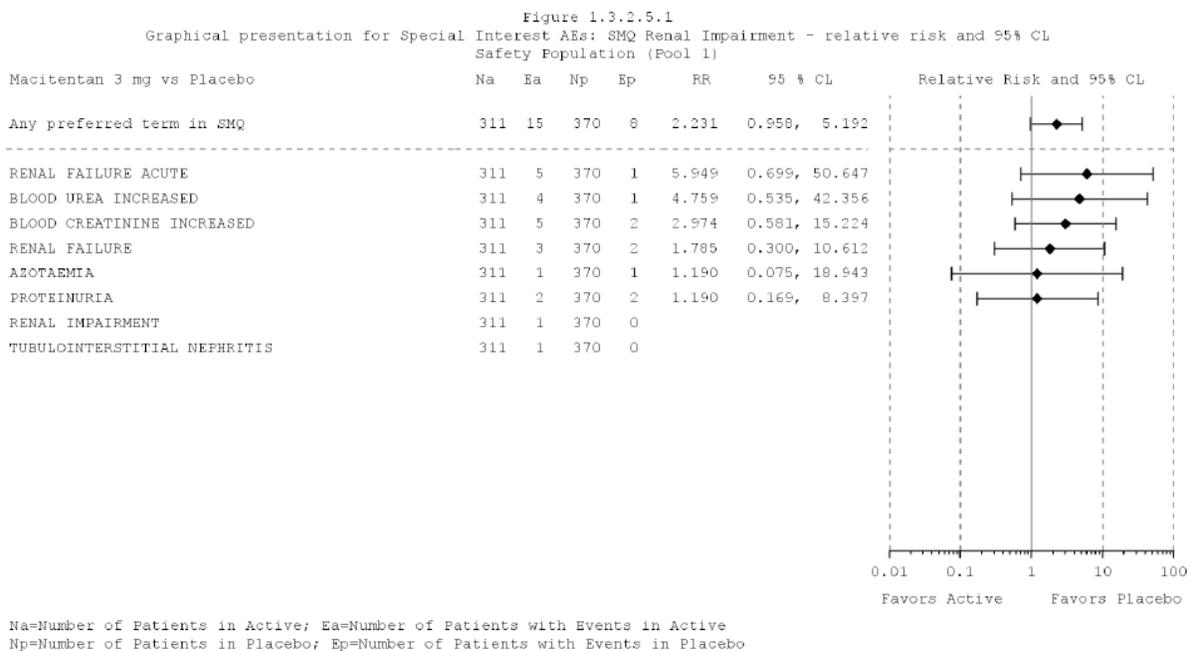
PAH = pulmonary arterial hypertension, NA: not available, RHF = right heart failure

* Recovery for creatinine increase was defined as a return to the normal range or baseline value.

Source: D-12.425, Table 53

Pool 1

In the pooled double-blind safety set, the incidences of renal impairment adverse events were 3.5% in the total macitentan pool and 2.2% in the placebo pool. The incidences in the macitentan 3 mg group and 10 mg group were 4.8% and 3.3%, respectively. The figure below shows the relative risk and 95% CL for adverse events indicative of renal abnormalities for macitentan 10 mg vs. placebo.



The table below shows the renal serious adverse events and renal adverse events leading to discontinuation by treatment group.

Table 64 Renal impairment SAEs and AEs leading to discontinuation in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any Renal impairment AE	1 (0.8)	15 (4.8)	14 (3.3)	30 (3.5)	8 (2.2)
SAEs leading to discontinuation of treatment	0	5 (1.6)	2 (0.5)	7 (0.8)	2 (0.5)
AEs leading to discontinuation of treatment	0	0	0	0	1 (0.3)

AE = adverse event, SAE = serious adverse event
 Studies AC-055-201, AC-055B201, AC-055-302
 Source: Derived from Appendix 5, Listing 14 and Listing 15

The incidence rates for patients who report a serious renal adverse event were 0, 1.6%, 0.5%, and 0.5% for macitentan < 3mg, 3 mg and 10 mg, and placebo respectively. Only one patient (placebo) discontinued treatment because of a renal adverse event.

7.4.3 Vital Signs

Blood pressure

In the double-blind PAH safety population, the incidence of hypotension adverse events are shown below.

Table 70 Hypotension AEs in the double-blind PAH safety population

	Macitentan		Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
	3 mg (N=250) n (%)	10 mg (N=242) n (%)		
Number of patients with any SMQ Hypotension AE	15 (6.0)	17 (7.0)	32 (6.5)	11 (4.4)
Hypotension AEs per 100 patient-years	3.1	3.5	3.3	2.7
Number of AEs	16	19	35	12
Crude incidence				
HYPOTENSION	14 (5.6)	15 (6.2)	29 (5.9)	11 (4.4)
ORTHOSTATIC HYPOTENSION	0	2 (0.8)	2 (0.4)	0
BLOOD PRESSURE SYSTOLIC DECREASED	1 (0.4)	0	1 (0.2)	0

AE = adverse event, PAH = pulmonary arterial hypertension, PT = preferred term, SMQ = standardized MedDRA query
 Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

AEs per 100 patient-years Exposure derived as (%) = 100(incidence/[total treatment duration days/365]).

Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.

PTs are sorted in descending order of the Total Macitentan frequency count.

Study AC-055-302

Source: [Appendix 5, Table 75](#) and [Table 101](#)

The incidences in the macitentan 3 mg group and 10 mg group were 6.0% and 7.0%, compared to 4.4% for placebo. Macitentan is a known vasodilator.

The incidence rates for reported serious adverse events related to hypotension are shown below by treatment group.

Table 71 Hypotension SAEs and AEs leading to discontinuation in the double-blind PAH safety population

	Macitentan		Total Macitentan (N=492) n (%)	Placebo (N=249) n (%)
	3 mg (N=250) n (%)	10 mg (N=242) n (%)		
Number of patients with any hypotension AE	15 (6.0)	17 (7.0)	32 (6.5)	11 (4.4)
SAEs	1 (0.4)	2 (0.8)	3 (0.6)	3 (1.2)
AEs leading to discontinuation of treatment	0	1 (0.4)	1 (0.2)	0

AE = adverse event, PAH = pulmonary arterial hypertension, SAE = serious adverse event

Study AC-055-302

Source: Derived from [Appendix 5, Listing 14](#) and [Listing 15](#)

Heart rate

There is no evidence that macitentan has an effect on heart rate.

Table 96 Change from baseline in heart rate in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129)	3 mg (N=311)	10 mg (N=423)	Total Macitentan (N=863)	Placebo (N=370)
Heart Rate (BEATS/MIN) ^a					
Baseline					
n	125	305	408	838	360
Mean (SD)	72.4 (9.96)	78.4 (11.98)	76.1 (12.61)	76.4 (12.17)	77.5 (12.04)
Median	71.0	78.0	76.0	76.0	78.0
Min, Max	50, 110	48, 120	47, 130	47, 130	50, 124
Last Visit					
n	125	305	408	838	360
Mean (SD)	72.0 (9.97)	77.9 (13.61)	77.1 (13.64)	76.6 (13.28)	78.9 (13.46)
Median	70.0	77.0	76.0	76.0	78.0
Min, Max	50, 104	49, 120	43, 125	43, 125	48, 150
Change from Baseline ^b					
n	125	305	408	838	360
Mean (SD)	-0.4 (7.41)	-0.5 (13.52)	1.1 (12.60)	0.3 (12.34)	1.4 (14.64)
Median	0.0	-2.0	0.0	0.0	1.0
Min, Max	-20, 20	-60, 46	-40, 51	-60, 51	-38, 77

^a Change from baseline to last visit up to 28 days post treatment discontinuation; where multiple assessments fell on the same day due to repeated assessments, the highest value was used.

^b For study AC-055-302, heart rate was based on assessment of pulse rate.

Data are presented for patients who had both a baseline and post-baseline value.

Studies AC-055-201, AC-055B201, AC-055-302

Source: [Appendix 5, Table 182](#)

Body weight

There is no evidence that macitentan has an effect on body weight.

Table 98 Change from baseline in body weight up to last visit in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129)	3 mg (N=311)	10 mg (N=423)	Total Macitentan (N=863)	Placebo (N=370)
Baseline					
n	125	305	408	838	358
Mean (SD)	85.8 (15.37)	70.5 (17.70)	75.3 (19.33)	75.1 (18.85)	73.6 (18.23)
Median	86.5	69.5	74.0	74.0	70.5
Min, Max	55, 136	37, 132	38, 134	37, 136	37, 126
Last Visit					
n	125	305	408	838	358
Mean (SD)	85.7 (15.63)	70.8 (17.17)	75.3 (18.97)	75.2 (18.49)	73.7 (18.48)
Median	87.0	68.2	74.4	74.3	70.9
Min, Max	56, 136	39, 130	37, 167	37, 167	36, 132
Change from Baseline ^a					
n	125	305	408	838	358
Mean (SD)	-0.1 (2.04)	0.3 (4.76)	0.1 (5.43)	0.1 (4.82)	0.1 (4.69)
Median	0.0	0.4	0.0	0.0	0.0
Min, Max	-6, 8	-24, 18	-29, 51	-29, 51	-19, 43

^a Change from baseline to last visit up to 28 days post treatment discontinuation; where multiple assessments fell on the same day due to repeated assessments, the highest value was used.

Data are presented for patients who had both a baseline and post-baseline value.

Studies AC-055-201, AC-055B201, AC-055-302

Source: [Appendix 5, Table 182](#)

7.4.4 Electrocardiograms (ECGs)

Pool 1

The overall incidence of treatment-emergent ECG findings was similar in the patients who were treated with macitentan and with placebo.

Table 102 Summary of treatment-emergent ECG abnormal findings by frequency in the pooled double-blind safety set (Pool 1)

	<3 mg (N=129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with treatment-emergent ECG findings	17 (13.2)	145 (46.6)	153 (36.2)	315 (36.5)	160 (43.2)
Number of ECG Findings	19	265	249	533	281

Evaluation of ECG variables showed no clinically relevant differences in HR, PR, QRS or QTcF between the worst/highest value obtained and baseline for any of the macitentan doses compared to baseline. There is no evidence that macitentan has pro arrhythmic potential.

7.4.5 Special Safety Studies/Clinical Trials

Effect on sperm

The testicular safety study (AC-055-113) conducted in healthy male subjects was poorly conducted and, therefore, uninformative. This agent will get a statement in the label that reflects the bosentan experience.

7.4.6 Immunogenicity

Immune system disorders were reported at a higher incidence rate in the macitentan groups than in the placebo group (2.3%, 20/863) for all macitentan doses in Pool 1 compared to placebo (0.8%, 3/370).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The adverse events possibly linked to dose include anemia and liver function test abnormalities.

7.5.2 Time Dependency for Adverse Events

The table below shows the number of reported adverse event by months of macitentan treatment.

Table 41 Proportion of patients with AEs, SAEs and AEs of special interest and who died over time from treatment start up to 28 days after EOT in the pooled DB and OL PAH safety set (Pool 2)

	Overall (N=675) n (%)	0-<6 (N=675) n (%)	Months of macitentan treatment				
			6-<12 (N=509) n (%)	12-<18 (N=478) n (%)	18-<24 (N=445) n (%)	24-<30 (N=405) n (%)	>=30 (N=292) n (%)
Number of patients with any AE	561 (83.1)	427 (63.3)	383 (75.2)	350 (73.2)	342 (76.9)	308 (76.0)	249 (85.3)
No. of patients with any AEs of special interest:							
Liver Abnormalities	74 (11.0)	25 (3.7)	27 (5.3)	27 (5.6)	29 (6.5)	27 (6.7)	15 (5.1)
Oedema	134 (19.9)	60 (8.9)	44 (8.6)	55 (11.5)	50 (11.2)	41 (10.1)	35 (12.0)
Anaemia/Hb Decreased	80 (11.9)	27 (4.0)	30 (5.9)	33 (6.9)	42 (9.4)	41 (10.1)	32 (11.0)
Hypotension	40 (5.9)	18 (2.7)	9 (1.8)	7 (1.5)	9 (2.0)	5 (1.2)	2 (0.7)
Renal Impairment	33 (4.9)	13 (1.9)	11 (2.2)	10 (2.1)	11 (2.5)	8 (2.0)	6 (2.1)
Respiratory Infections	332 (49.2)	144 (21.3)	130 (25.5)	106 (22.2)	110 (24.7)	91 (22.5)	64 (21.9)
Malignancies	12 (1.8)	5 (0.7)	4 (0.8)	4 (0.8)	4 (0.9)	3 (0.7)	1 (0.3)
MACE	13 (1.9)	5 (0.7)	3 (0.6)	4 (0.8)	4 (0.9)	4 (1.0)	1 (0.3)
MI	6 (0.9)	2 (0.3)	3 (0.6)	3 (0.6)	2 (0.4)	2 (0.5)	1 (0.3)
Cerebrovascular	7 (1.0)	3 (0.4)	0	1 (0.2)	2 (0.4)	2 (0.5)	0
Number of patients with any SAE	308 (45.6)	128 (19.0)	107 (21.0)	98 (20.5)	88 (9.8)	69 (17.0)	55 (18.8)
Number of patients who died ⁴	82 (12.1)	23 (3.4)	13 (2.6)	9 (1.9)	18 (4.0)	10 (2.5)	9 (3.1)

AE = adverse event, MACE = major adverse cardiovascular events, EOT = end of treatment, MI = myocardial infarction
 Note: Denominator for percentages is based on number of patients in the Safety Population for total macitentan that were present at the start of each interval (still on treatment period from day of treatment start to the day of treatment end plus 28 days, inclusive).

Months are defined as days elapsed since start of treatment/30.4375. An event is considered present in an interval by taking into account the relationship between the event onset and resolution date and the interval extremes. If a patient experiences one or multiple events of special interest across time intervals, then the patient is counted once for each of these intervals.

⁴ Includes deaths during study up to 28 days after end of treatment.
 Studies AC-055-302 and AC-055-303

It is difficult to draw conclusions from such data because most adverse events are reported more often the longer the patients are in the trials. That said, nothing seems to occur only after the patients had been on drug for more than a certain amount of time.

7.5.3 Drug-Demographic Interactions

Age

Patients ≥ 65 years with PAH reported more dyspnea in the macitentan 3 mg group (18%) and 10 mg group (15%) compared to placebo (11%). In the 18–64 age range, the incidences were similar across treatment groups.

Edema adverse events were also reported at a higher incidence in elderly PAH patients treated with macitentan compared to placebo. The incidence rates were 30%, 26% and 18% in the macitentan 10 mg, 3 mg and placebo groups, respectively.

Sex

There is no indication that adverse events are different for males and females.

Race

There is no indication that adverse events are different for different races. Study AC-055-109) showed exposure in white subjects to be approximately 18% higher than in Japanese subjects.

7.5.4 Drug-Disease Interactions

There were no obvious indications that there are differences in safety based on WHO functional class, PAH etiology, signs/symptoms of right heart failure, renal impairment, or hepatic impairment.

7.5.5 Drug-Drug Interactions

The *in vitro* data showed that macitentan is a CYP3A4 substrate.

Ketoconazole (AC-055-107)

In the presence of ketoconazole, exposure to macitentan was increased approximately 2-fold compared to when macitentan was administered alone. The geometric mean ratios (macitentan + ketoconazole: macitentan) for C_{max} and AUC were 1.28 and 2.32, with 90% CL of 1.21–1.35 and 2.15–2.50, respectively.

Rifampicin (AC-055-111)

Coadministration of rifampicin decreased exposure to macitentan. The geometric mean ratio (macitentan + rifampicin: macitentan) for AUC was 0.21 with 90% CL of 0.17–0.26. Reduced efficacy of macitentan in the presence of rifampicin is a possibility.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Pool 1

The table below shows the adverse events related to malignancies that were reported during the studies classified as pool 1.

Table 82 Malignancy AEs in the pooled double-blind safety set (Pool 1)

	< 3 mg (N = 129) n (%)	3 mg (N=311) n (%)	10 mg (N=423) n (%)	Total Macitentan (N=863) n (%)	Placebo (N=370) n (%)
Number of patients with any Malignancy AE	0	8 (2.6)	11 (2.6)	19 (2.2)	7 (1.9)
Malignancy AEs per 100 patient-years	0	1.7	1.8	1.7	1.4
Number of AEs	0	11	15	26	10
Crude incidence					
COLON CANCER	0	2 (0.6)	0	2 (0.2)	0
MALIGNANT TUMOUR EXCISION	0	1 (0.3)	1 (0.2)	2 (0.2)	0
OVARIAN NEOPLASM	0	1 (0.3)	1 (0.2)	2 (0.2)	0
SQUAMOUS CELL CARCINOMA	0	0	2 (0.5)	2 (0.2)	1 (0.3)
ADENOCARCINOMA	0	1 (0.3)	0	1 (0.1)	0
ANGIOSARCOMA	0	1 (0.3)	0	1 (0.1)	0
BASAL CELL CARCINOMA	0	0	1 (0.2)	1 (0.1)	1 (0.3)
BREAST CANCER	0	1 (0.3)	0	1 (0.1)	1 (0.3)
CARBOHYDRATE ANTIGEN 125 INCREASED	0	0	1 (0.2)	1 (0.1)	0
CARBOHYDRATE ANTIGEN 19-9 INCREASED	0	0	1 (0.2)	1 (0.1)	0
HEAD AND NECK CANCER	0	0	1 (0.2)	1 (0.1)	0
LUNG NEOPLASM	0	1 (0.3)	0	1 (0.1)	1 (0.3)
MALIGNANT MEDIASTINAL NEOPLASM	0	0	1 (0.2)	1 (0.1)	0
METASTATIC NEOPLASM	0	1 (0.3)	0	1 (0.1)	0
PITUITARY TUMOUR	0	0	1 (0.2)	1 (0.1)	0
PROSTATE CANCER	0	0	1 (0.2)	1 (0.1)	0
PROSTATECTOMY	0	0	1 (0.2)	1 (0.1)	0
RECTAL CANCER	0	0	1 (0.2)	1 (0.1)	1 (0.3)
RECTOSIGMOID CANCER	0	1 (0.3)	0	1 (0.1)	0
SUPERIOR VENA CAVA SYNDROME	0	0	1 (0.2)	1 (0.1)	0
LIVER SCAN ABNORMAL	0	0	0	0	1 (0.3)
LUNG SQUAMOUS CELL CARCINOMA	0	0	0	0	0
STAGE UNSPECIFIED	0	0	0	0	1 (0.3)
RENAL SCAN ABNORMAL	0	0	0	0	1 (0.3)
THYROID NEOPLASM	0	0	0	0	1 (0.3)

AE = adverse event, PT = preferred term

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for each treatment group.

AEs per 100 patient-years Exposure derived as (%) = 100(incidence/[total treatment duration days/365]).

Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.

PTs are sorted in descending order of the Total Macitentan frequency count.

Studies AC-055-201, AC-055B201, AC-055-302. Source: [Appendix 5, Table 80](#) and [Table 107](#)

There was a slightly higher incidence rate of patients reporting a malignancy in the 10 mg macitentan group (3%) compared to placebo (2%).

7.6.2 Human Reproduction and Pregnancy Data

There were 7 pregnancies (5 on macitentan 3 mg and 2 on placebo) reported in the clinical development program. Of the 5 patients in the macitentan 3 mg group, one had a therapeutic abortion and one had a spontaneous abortion. Both patients restarted macitentan treatment. One patient had an abortion scheduled, but died due to worsening of PAH before the scheduled date. For the other 2 macitentan-treated patients, both permanently discontinued treatment and continued the pregnancy. Both women gave birth prematurely. In one case the baby had hyaline membrane disease complicated by sepsis, a grade 4 intracranial hemorrhage and poor skin condition. Three days after birth, the baby died from persistent hypotension, due to extreme prematurity. No obvious abnormality was noted and the prenatal screening at Week 18 had shown no anomaly. In the second case, the baby had no neonatal abnormalities and survived.

7.6.3 Pediatrics and Assessment of Effects on Growth

Data are not available at this time.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

The highest single dose administered was 600 mg in study van Giersbergen 2005a. The reported adverse events are shown below.

Table 5. Summary of post-treatment AEs (including unrelated) by frequency

Group: All Subjects	ACT-064992 (mg)							Placebo	All
	0.2	1	5	25	100	300	600		
All system organ classes	N=6	N=6	N=6	N=6	N=6	N=6	N=6	N=14	N=56
Total subjects with at least one AE	-	-	-	2	3	2	5	4	16
Total number of AEs	-	-	-	3	3	3	14	5	28
Headache NOS	-	-	-	2	1	2	5	3	13
Back pain	-	-	-	-	-	1	-	1	2
Hepatic function abnormal NOS	-	-	-	-	-	-	1	1	2
Nausea	-	-	-	-	-	-	2	-	2
Rhinitis NOS	-	-	-	-	-	-	2	-	2
Vomiting NOS	-	-	-	-	-	-	2	-	2
Abdominal pain NOS	-	-	-	-	-	-	1	-	1
Flushing	-	-	-	-	-	-	1	-	1
Leucocytosis NOS	-	-	-	-	1	-	-	-	1
Nasopharyngitis	-	-	-	1	-	-	-	-	1
Neck pain	-	-	-	-	1	-	-	-	1

Note: only AEs with onset after start of treatment are included.
 NOS: Not otherwise specified

In the ongoing study in glioblastoma (AC-055-115), no cases of dose-limiting toxicity have been reported up to a dose of 90 mg/day.

Drug abuse

There is no indication of any potential for abuse from clinical studies or from current knowledge of ERAs in general.

Withdrawal and rebound

There were no studies evaluating the withdrawal and rebound potential of macitentan. was not specifically studied in patients with PAH.

7.7 Additional Submissions / Safety Issues

Safety Update

The cut-off date for the ISS was April 26, 2012 for the safety update it was August 26, 2012, and for ongoing studies in non-PAH indications it was July 31, 2012. Narratives for patients who had aminotransferase elevations > 3 X ULN are provided for events that were reported to the sponsor up to December 31, 2012.

Additional data were submitted for the Seraphin trial (AC-055-302) and additional 4 months of safety data from the Seraphin open-label extension study (AC-055-303). This includes a further 156 patient-years, bringing the total to 1477 patient-years exposure.

Table 2 Ongoing Phase 3 clinical trials in PAH

Study	Study objectives	Patients in safety population	Median treatment duration ^a (Weeks)	Treatment/dose (mg)	Type of control/blinding
AC-055-303 (SERAPHIN OL)	Long-term safety of macitentan in patients with PAH	550	Placebo/10 mg: 28.9 3 mg/10 mg: 159.0 10 mg/10 mg: 163.6	Macitentan 10 mg o.d.	Single-arm, open-label treatment, extension study

o.d. = once daily, OL = open-label, PAH = pulmonary arterial hypertension.

^a duration of exposure up to cut-off date of 26 August 2012. Treatment groups show DB/OL treatment allocation.

There is also information from the ongoing blinded digital ulcer studies (AC-055C301 and AC-055C302) shown below and the glioblastoma study AC-055-115.

Table 3 Ongoing Phase 3 clinical trials in other indications

Study	Study objectives	Patients in All-randomized/ safety population ^a	Planned treatment duration ^b	Treatment/dose (mg)	Type of control/blinding/ Design
AC-055C301	Efficacy and safety of macitentan in patients with ischemic DUs associated with SSc	112 patients	Treatment period 1: 16 weeks Treatment period 2: Week 16 to EOS	Treatment period 1: Macitentan 3 mg, 10 mg, or placebo Treatment period 2: Continuation of macitentan 3 mg, 10 mg or placebo for variable duration up to 2.5 years	Placebo-controlled, parallel-group, randomized, double-blind treatment Fixed 16-week duration followed by a long-term variable duration period
AC-055C302	Efficacy and safety of macitentan in patients with ischemic DUs associated with SSc	48 patients	Treatment period 1: 16 weeks Treatment period 2: Week 16 to EOS	Treatment period 1: Macitentan 3 mg, 10 mg, or placebo Treatment period 2: Continuation of macitentan 3 mg, 10 mg or placebo for variable duration up to 2.5 years	Placebo-controlled, parallel-group, randomized, double-blind treatment Fixed 16-week duration followed by a long-term variable duration period

DU = digital ulcer, EOS = end of study, SSc = systemic sclerosis.

^a Preliminary evaluation of ongoing study (treatment allocation remains blinded)

^b up to 31 July 2012, median duration of exposure was 10.6 and 9.9 weeks in Studies AC-055C301 and AC-055C302, respectively.

Information is also included from two completed Phase 1 studies conducted in Japan (AC-055-116) and South Korea (AC-055-117) shown below.

Table 4 Completed clinical pharmacology studies

Study [Document No.]	Study objectives	Subjects evaluable for safety	Treatment duration	Treatment/dose	Design/type of control/blinding
AC-055-116 [D-12.181]	Investigation of the PK, PD, safety and tolerability of macitentan in male Japanese subjects	16 healthy subjects	Once daily oral dose for 10 days	Macitentan (6 subjects/group): 3, 10 mg Placebo (2 subjects/group)	Multiple-ascending dose, placebo-controlled, double-blind
AC-055-117 [D-12.439]	Investigation of the PK, PD, safety and tolerability of macitentan in male Korean subjects	30 healthy subjects	Once daily oral dose for 10 days	Macitentan (8 subjects/group): 3, 10, 30 mg Placebo (2 subjects/group)	Multiple-ascending dose, placebo-controlled, double-blind

PD = pharmacodynamic, PK = pharmacokinetic.

Since no patient in either study reported a serious adverse event, an adverse event that led to study discontinuation, or markedly abnormal laboratory finding associated with liver enzyme elevation (ALT or AST > 3 X ULN) there is no further discussion of them in this review.

Duration of exposure (pool 2)

The number of subjects who took part in study AC-055-302 and the long term extension AC-055-303 was 675 (unchanged from the ISS). The comparison of the duration of exposure in the ISS and safety update are shown below.

Table 9 Comparison of the duration of exposure in Pool 2 at the cut-off dates of the ISS and the 120 Day safety update

	Total Macitentan (N=675) 26 April 2012	Total Macitentan (N=675) 26 August 2012
Exposure Duration (weeks) ¹		
n	675	675
Mean (SD)	102.15 (62.115)	114.21 (65.279)
Median	126.57	142.71
Min, Max	0.3, 202.3	0.3, 219.7
Exposure Distribution, n (%)		
n	675	675
< 6 months (<24 wks)	166 (24.6)	68 (10.1)
6 - < 12 months (24 - <48 wks)	31 (4.6)	125 (18.5)
12 - < 18 months (48 - <72 wks)	33 (4.9)	33 (4.9)
18 - < 24 months (72 - <96 wks)	40 (5.9)	38 (5.6)
24 - < 30 months (96 - <120 wks)	113 (16.7)	36 (5.3)
>=30 months (>=120 wks)	292 (43.3)	375 (55.6)
Patient Years Exposure ²		
n	675	675
Exposure (years)	1321	1477

Note: Denominator for percentages based on number of patients in Safety Population.

¹ Duration of exposure is defined as the time (days/7) elapsed between the start and the end of Macitentan treatment, inclusive. Time on placebo treatment is not counted

² Patient years is based on total days on Macitentan/365.25 for patients who have taken study drug for at least one day. Studies AC-055-302, AC-055-303

The mean exposure duration increased from 102 to 114 weeks. The number of subjects with at least 12 months of exposure increased from 478 to 482.

Deaths

There were 15 deaths reported during the 120 Day safety update period.

Table 16 Deaths up to 28 days after end of treatment by preferred term reported during the 120 Day safety update period in Pool 2

Treatment DB/OL	Patient No.	Age/sex	OL Day	Cause of Death
Placebo/ 10 mg	1415-10348	73/F	749	Acute right ventricular failure following trauma (Reported as PTs of "Acute right ventricular failure, humerus fracture, radius fracture")
	3805-13594	36/F	1099	Pulmonary arterial hypertension
	3811-13596	26/F	631	Acute right ventricular failure, Pulmonary embolism
	5501-13737	28/F	1070	Right ventricular failure
	5601-15615	56/F	73	Worsening of the underlying disease (Reported as PT "death")
3 mg/ 10 mg	1001-10960	69/M	1118	Recurrence of a rectosigmoid tumor with multiple metastases (Reported as PTs of "decreased appetite, Diarrhea, vomiting")
	3805-14853	52/F	1092	Pulmonary arterial hypertension
	3901-12857	17/F	1360	Pulmonary hypertension
	4102-13344	16/F	1232	During the night, patient developed acute shortness of breath, became unconscious and died (Reported as PT "sudden death")
	4102-13346	54/F	1385	RIGHT VENTRICULAR FAILURE
	5107-15853	35/F	916	PULMONARY ARTERIAL HYPERTENSION
	8402-11846	43/F	1145	RIGHT VENTRICULAR FAILURE
10 mg/ 10 mg	3805-13350	42/F	1240	PULMONARY ARTERIAL HYPERTENSION
	3805-14852	42/F	982	PULMONARY ARTERY ANEURYSM
	5502-11222	45/F	1144	PULMONARY ARTERIAL HYPERTENSION

DB = double-blind, OL = open-label, M = male, F = female
 The patient's age, is that reported at baseline.
 Studies AC-055-302, AC-055-303

The causes of the 15 deaths such as resulting from PAH and right ventricular failure are not unexpected considering the patient population. None of these deaths seems unexpected.

Deaths in other studies include one death from respiratory failure in the digital ulcer study AC-055C302 in a patient with a background of scleroderma and her course included anemia and aspiration pneumonia. There were no deaths reported in the glioblastoma study although there was one that occurred greater than 30 days after treatment was stopped.

Serious adverse events

Pool 2

A total of 326 (48%) of the 675 macitentan-treated patients reported, similar to the percentage reported in the ISS. The events reported by at least 3 patients are shown in the table below.

Table 17 SAEs reported from treatment start up to 28 days after end of treatment in the pooled PAH safety set (Pool 2) by preferred term (≥ 3 patients)

	Total Macitentan (N=675) n (%)
Number of patients with SAEs	326 (48.3)
PULMONARY ARTERIAL HYPERTENSION	108 (16.0)
RIGHT VENTRICULAR FAILURE	70 (10.4)
PNEUMONIA	18 (2.7)
ANAEMIA	16 (2.4)
SYNCOPE	14 (2.1)
ATRIAL FLUTTER	9 (1.3)
CHEST PAIN	9 (1.3)
RESPIRATORY FAILURE	9 (1.3)
DYSNOEA	8 (1.2)
GASTROENTERITIS	8 (1.2)
HAEMOPTYSIS	8 (1.2)
RENAL FAILURE ACUTE	8 (1.2)
SUDDEN DEATH	8 (1.2)
PULMONARY EMBOLISM	7 (1.0)
UPPER RESPIRATORY TRACT INFECTION	7 (1.0)
CARDIAC ARREST	6 (0.9)
ACUTE RIGHT VENTRICULAR FAILURE	5 (0.7)
BRONCHITIS	5 (0.7)
HYPOTENSION	5 (0.7)
PANCREATITIS ACUTE	5 (0.7)
PREGNANCY	5 (0.7)
UPPER GASTROINTESTINAL HAEMORRHAGE	5 (0.7)
ATRIAL FIBRILLATION	4 (0.6)
LOWER RESPIRATORY TRACT INFECTION	4 (0.6)
ACUTE MYOCARDIAL INFARCTION	3 (0.4)
BRADYCARDIA	3 (0.4)
CARDIO-RESPIRATORY ARREST	3 (0.4)
CHOLECYSTITIS	3 (0.4)
CHOLELITHIASIS	3 (0.4)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	3 (0.4)
EPISTAXIS	3 (0.4)
ERYSIPELAS	3 (0.4)
HAEMATEMESIS	3 (0.4)
LEFT VENTRICULAR FAILURE	3 (0.4)
LIVER FUNCTION TEST ABNORMAL	3 (0.4)
MENORRHAGIA	3 (0.4)
OVARIAN CYST	3 (0.4)
PLEURAL EFFUSION	3 (0.4)
PULMONARY OEDEMA	3 (0.4)
PYREXIA	3 (0.4)
SEPSIS	3 (0.4)
SKIN ULCER	3 (0.4)
SUDDEN CARDIAC DEATH	3 (0.4)
SUPRAVENTRICULAR TACHYCARDIA	3 (0.4)
SYSTEMIC LUPUS ERYTHEMATOSUS	3 (0.4)
URINARY TRACT INFECTION	3 (0.4)
UTERINE LEIOMYOMA	3 (0.4)
VOMITING	3 (0.4)

SAE = serious adverse event

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population.

Preferred terms are sorted in descending order of frequency.

Studies AC-055-302 AC-055-303

For comparison with a placebo group, the table below shows the reporting rates of the five most commonly reported serious adverse events in the base study Seraphin.

Table 169 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by frequency, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by frequency,
 Analysis set: All treated

System Organ Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	No.	%	No.	%	No.	%
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one SAE	137	55.0%	130	52.0%	109	45.0%
Total number of SAEs	246		246		189	
PULMONARY ARTERIAL HYPERTENSION	56	22.5%	48	19.2%	32	13.2%
RIGHT VENTRICULAR FAILURE	40	16.1%	21	8.4%	23	9.5%
PNEUMONIA	8	3.2%	7	2.8%	4	1.7%
SYNCOPE	6	2.4%	7	2.8%	4	1.7%
ANAEMIA	1	0.4%	5	2.0%	6	2.5%

Regarding the serious events reported by at least 2% of the patients in the uncontrolled trial:
 - pulmonary arterial hypertension, the reporting rate for placebo was 23% and the uncontrolled study macitentan rate was 16%;
 -right ventricular failure, the reporting rate for placebo was 16% and the uncontrolled study macitentan rate was 10%.
 -pneumonia, the reporting rate for placebo was 3% and the uncontrolled study macitentan rate was also 3%;
 -syncope, the reporting rate for placebo was 2% and the uncontrolled study macitentan rate was 2%; and
 -anemia, the reporting rates of all anemia in the placebo controlled base study (Seraphin) were 8.8% macitentan 3 mg, 13.2% macitentan 10 mg, 3.2% placebo. The reporting of serious anemia⁴ in the base study was 2% and 3% on macitentan 3 mg and 10 mg, respectively, versus 0.4% on placebo. In the open label long term study the reporting rate was 2%.

Other studies

Digital ulcer studies

During the 120 Day safety update period, serious adverse events were reported in 4 patients (3%) in Study AC-055C301. These included events related to disease progression (infected skin ulcer, skin ulcer, and skin pain), and reports of pneumonia, hysterectomy and bilateral avascular necrosis.

In Study AC-055C302, serious adverse events of renal failure and pulmonary alveolar hemorrhage leading to death were reported in one patient.

Clinical pharmacology studies

In the glioblastoma study (AC-055-115) 2 patients reported serious convulsions.

Adverse events leading to discontinuation

Pool 2

⁴ anemia led to discontinuation of treatment for 1 patient in each of the macitentan 3 mg and 10 mg groups, and megaloblastic anemia led to discontinuation of treatment for 1 patient in the placebo group in the Seraphin study.

The incidence rate for discontinuations from adverse events was 13%. The numbers and percentages of patients who withdrew by reported event (only those events reported by at least two patients) are shown below.

Table 19 AEs leading to discontinuation of study treatment in Pool 2

	Total Macitentan (N=675) n (%)
Number of patients withdrawn from treatment due to AEs	89 (13.2)
PULMONARY ARTERIAL HYPERTENSION	15 (2.2)
RIGHT VENTRICULAR FAILURE	12 (1.8)
ASPARTATE AMINOTRANSFERASE INCREASED	7 (1.0)
ALANINE AMINOTRANSFERASE INCREASED	6 (0.9)
LIVER FUNCTION TEST ABNORMAL	6 (0.9)
HEADACHE	5 (0.7)
PREGNANCY	3 (0.4)
ACUTE RIGHT VENTRICULAR FAILURE	2 (0.3)
ANAEMIA	2 (0.3)
BLOOD BILIRUBIN INCREASED	2 (0.3)
CARDIAC ARREST	2 (0.3)
COLON CANCER	2 (0.3)
DYSPNOEA	2 (0.3)
HYPOTENSION	2 (0.3)
PULMONARY OEDEMA	2 (0.3)

The table below shows discontinuations because of adverse events (limited to events reported by at least 3 macitentan 10 mg patients) in the placebo controlled Seraphin trial.

Table 45 Summary of adverse events (including unrelated) leading to permanent discontinuation of study drug, by frequency, All-treated set

ACT-064992, Protocol: AC-055-302

System Organ Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	N=249		N=250		N=242	
	No.	%	No.	%	No.	%
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one AE	31	12.4%	34	13.6%	26	10.7%
Total number of AEs	37		40		32	
PULMONARY ARTERIAL HYPERTENSION	10	4.0%	6	2.4%	4	1.7%
RIGHT VENTRICULAR FAILURE	6	2.4%	3	1.2%	4	1.7%
ALANINE AMINOTRANSFERASE INCREASED	-		3	1.2%	2	0.8%
ASPARTATE AMINOTRANSFERASE INCREASED	-		3	1.2%	2	0.8%
LIVER FUNCTION TEST ABNORMAL	2	0.8%	-		3	1.2%
PREGNANCY	1	0.4%	3	1.2%	-	
HEADACHE	-		-		3	1.2%

Between 11 and 14% of patients dropped out because of an adverse event in the Seraphin trial, similar to the drop outs rates for the Pool 2 patients.

Ongoing digital ulcer studies

In Study AC-055C301, five patients (4%) discontinued study treatment because of adverse events. Two patients discontinued due to disease progression (worsening of digital ulcer). Two patients discontinued because of increased ALT and AST. One patient discontinued because of nasal dryness. In study AC-055C302, one patient with pulmonary fibrosis related scleroderma discontinued because of pulmonary alveolar hemorrhage which resulted in death.

Ongoing clinical pharmacology studies

In the glioblastoma study (AC-055-115) 2 patients discontinued treatment because of convulsion (1) and aphasia (1) at a macitentan dose of 30 mg.

Liver abnormalities

Pool 2

The incidence of liver abnormality adverse events was 12% in the total macitentan pool, similar to 11% reported in the ISS. The incidence rate for the 375 patients who received at least 30 months of treatment and up to a maximum duration of approximately 50 months was 5%. In the safety update, there were 11 subjects who reported an abnormal liver adverse event and one patient dropping out of the study because of it.

Pt ID	Macitentan dose	Highest LFTs	comments
Seraphin open label			
9001-11105	10 mg	AST 5.5x ULN, ALT 8xULN. TBIL value unknown.	Hx travel to Cuba. Dx cholecystitis and cholelithiasis
3603-11727	10 mg	ALT 7.2xULN, AST 5.2xULN, Tbil 3.4xULN, AP 5.2xULN	Cholelithiasis. Study drug discontinued. Tests normalized after stone removal
5601-12097	10 mg	ALT 8.5xULN, AST 5.5xULN, AP 4.8x ULN, TBIL 1.9xULN	Gout with allopurinol Rx. Study drug discontinued
5306-11856	10 mg	AST 3.4 ULN, TBIL 2.0x ULN	Worsening PAH. Study drug discontinued
3812-11969	10 mg	ALT 5.1xULN, AST 7.0x ULN, AP 1.2xULN, TBIL 1.6xULN.	Reported atrial fib Rx amiodarone. Study drug discontinued
4101-12083	10 mg	ALT 2.5xULN, AST 3.6x ULN, AP 0.5xULN, and TBIL 0.8xULN.	Resolved without drug discontinuation
5307-13097	10 mg	ALT 7.2 × ULN, AST 7.3x ULN, AP 1.2x ULN, TBIL 1.5x ULN.	Reported TB. Resolved without drug discontinuation
6001-10968	10 mg	ALT 4.1xULN, AST 4.7x ULN, AP 0.6xULN, and	Worsening PAH. Resolved while

		TBIL 2.6xULN	remaining on drug.
6001-12963	10 mg	ALT 4.4xULN, AST 3.7x ULN, AP 0.9xULN, TBIL 0.5xULN	Increased alcohol intake. Drug discontinued and lab tests improved.
Digital ulcers			
3201-41015	Blinded (macitentan 3mg, 10 mg, placebo)	ALT 4.5xULN, AST 3.7x ULN, AP 1.3xULN	ALT above normal at baseline, history of gallstones
3400-41243	Blinded (macitentan 3mg, 10 mg, placebo)	ALT 6.2xULN, AST 3.5x ULN	Enzymes improved after discontinuation of study medication and methotrexate
9006-42521	Blinded (macitentan 3mg, 10 mg, placebo)	ALT 4.6 xULN, AST 2.5x ULN, AP 2.4xULN. TBIL UNL	Values fell after temp dc. Re-challenge was negative
2100-80643	10 mg	ALT 44.4xULN, AST 32.5x ULN, AP 1.3xULN, TBIL 1.5xULN	Discontinued acetaminophen, mycophenolate mofetil, macitentan
3801-81322	Blinded (macitentan 3mg, 10 mg, placebo)	ALT 8.4xULN, AST 4.4x ULN. APx1.6 ULN, TBIL UNL	Permanently discontinued. Dx chronic cholecystitis
5002-41883	placebo	ALT 4.5xULN, AST unknown APx1.1 ULN, TBIL UNL	Permanently discontinued placebo. Concomitant acetaminophen
8405-82687	Blinded (macitentan 3mg, 10 mg, placebo)	ALT 5.6xULN, AST 1.6xUNL, AP and TBIL UNL	Permanently discontinued. Taking methotrexate

Anemia

Pool 2

The incidence rate of adverse events indicative of anemia/ hemoglobin decrease was 12%, similar to the rate reported in the ISS.

Table 32 Anemia/ hemoglobin decrease AEs occurring from treatment start up to 28 days after end of treatment by preferred term in the overall safety population (Pool 2)

	Total Macitentan (N=675) n (%)
Number of patients with any AEs of special interest: SMQ Anaemia/Hb decreased	82 (12.1)
Number of AEs ¹	121
ANAEMIA	67 (9.9)
IRON DEFICIENCY ANAEMIA	12 (1.8)
HAEMOGLOBIN DECREASED	8 (1.2)
HAEMATOCRIT DECREASED	4 (0.6)
RED BLOOD CELL COUNT DECREASED	2 (0.3)
ERYTHROPENIA	1 (0.1)
HAEMOLYTIC ANAEMIA	1 (0.1)
PANCYTOPENIA	1 (0.1)

AE = adverse event, SMQ = standardised MedDRA query

Note: For each preferred term, a patient is counted once if the patient had one or more events in that category.

Denominators for percentages are based on number of patients in Safety Population for overall macitentan treatment group.

Preferred terms that were not reported (incidence = 0%) for any treatment are not displayed.

PT is sorted in descending order of frequency.

¹ Number of AEs represents the total number of reported AEs.

Studies AC-055-302, AC-055-303

Overall, there were 40 patients (6%) with decreases to > 8 and ≤ 10 g/dL and 18 patients (3%) with hemoglobin decreases to ≤ 8 g/dL (the incidence rates were the same in ISS).

Other studies

There was one subject who reported decreased hemoglobin in the two digital ulcer studies. No reports of anemia were received in the glioblastoma study (AC-055-115).

8 Postmarket Experience

Macitentan is not currently available in any country.

Clinical Review
Maryann Gordon, M.D.
NDA 204410, Opsumit® (macitentan)

9 Appendices

See attached list of clinical trials and complete review of study AC-055-302.

9.1 Literature Review/References

See NDA section 2.7.5

9.2 Labeling Recommendations

See draft label

9.3 Advisory Committee Meeting

Not recommended.

Clinical Review
Maryann Gordon, M.D.
NDA 204410, Opsumit® (macitentan)

ATTACHMENTS

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Attachment A

Phase I studies, terminated studies, PK studies, studies in indications other than PAH			
Study number/title	number of subjects/dose/study design	Number of deaths/serious adverse events	comments
AC-055-101 Investigation of the PK, PD, safety and tolerability of macitentan in male subjects.	56 healthy subjects Single oral dose Macitentan (6 subjects/group): 0.2, 1, 5, 25, 100, 300, 600 mg Placebo (2 subjects/group) Single ascending dose, placebo controlled, double-blind	0/0	MTD deemed to be 300 mg. Headache was the most often reported adverse event. QTc increase was reported with higher doses.
AC-055-102 Investigation of the PK, PD, safety and tolerability of macitentan in male subjects.	32 healthy subjects Once daily oral dose for 10 days Macitentan (6 subjects/group): 1, 3, 10, 30 mg Placebo (2 subjects/group) Multiple ascending dose, placebo controlled, double-blind	0/0	Headache was the most often reported adverse event. A trend for increased levels of ASAT and ALAT was observed in the groups treated with 10 and 30 mg ACT-064992, which was mainly caused by four subjects. When compared to baseline, three subjects in the 10-mg dose group had an increase in either ASAT or ALAT level that varied between 1.4 and 2.6-fold. However, these findings only marginally exceeded the ULN (varied between 1.1 and 1.8-fold) and were isolated cases (i.e., no effects on other liver enzymes such as AP and bilirubin were observed). In the 30-mg dose group a more prominent elevation in

			ASAT and ALAT was observed in one subject. The morning after the last drug intake, increases in ASAT of about 2 . ULN and ALAT of about 2.5 . ULN were observed, the latter increasing to approximately 3 . ULN, at the first follow-up measurement 3 days later. In the placebo group also one subject was identified with increased ASAT and ALAT levels that only marginally exceeded the ULN (1.1-fold). All cases of elevated liver aminotransferases were asymptomatic, resolved within 2 weeks, and were considered as not clinically relevant by the investigator. No change in serum bile salts, bilirubin, or AP was noted.
AC-055-103 Investigation of the effect of food on the PK of macitentan in male subjects. Safety and tolerability.	10 healthy subjects Single oral dose on two occasions Macitentan 10 mg Single dose (once in fed state and once in fasted state), 2-way cross-over, uncontrolled, open-label	0/0	
AC-055-104 Investigation of the mass balance, pharmacokinetics, metabolism and safety in healthy male subjects.	6 healthy subjects Single oral dose 14C-Macitentan 10 mg Open-label, uncontrolled	0/0	
AC-055-105 Investigation of the effect of macitentan on the PK and PD of warfarin in healthy male subjects. Safety and tolerability. 14 healthy subjects	Treatment A: Once daily oral macitentan for 8 days. Single dose of oral warfarin. Treatment B: Single oral warfarin dose. Treatment A: Macitentan 30 mg	0/0	

	(Day 1), 10 mg (Days 2–8). Warfarin 25 mg (Day 4). Treatment B: Warfarin 25 mg (Day 1) Open-label, 2-way crossover		
AC-055-106 Evaluation of PK interactions between macitentan and sildenafil in healthy male subjects. Safety and tolerability. 12 healthy subjects	Treatment A: Once daily oral macitentan for 4 days. Treatment B: Oral sildenafil t.i.d. for 3 days with a single oral dose on Day 4. Treatment C: Once daily oral macitentan for 4 days. Oral sildenafil t.i.d. for 3 days with a single oral dose on Day 4. Treatment A: Macitentan 30 mg (Day 1), 10 mg (Days 2–4). Treatment B: Sildenafil 20 mg t.i.d. (Days 1–3). Single 20 mg dose (Day 4). Treatment C: Macitentan 30 mg (Day 1), 10 mg Days 2–4. Concomitant sildenafil 20 mg t.i.d. (Days 1–3). Single 20 mg dose (Day 4). Open-label, 2-period crossover	0/0	
AC-055-107 Investigation of the	Treatment A: Single oral	0/1 serious/	Subject 10 experienced

<p>effect of ketoconazole on the PK of macitentan in healthy male subjects. Safety and tolerability. 11 healthy subjects</p>	<p>macitentan dose. Treatment B: Once daily oral ketoconazole for 24 days. Concomitant single oral macitentan. Treatment A: Macitentan 10 mg. Treatment B: Ketoconazole 400 mg (Days 1–24). Macitentan 10 mg (Day 5). Open-label, 2-period crossover</p>	<p>1 dropout</p>	<p>on the morning of Day 3 of ketoconazole treatment abdominal pain of moderate intensity which was diagnosed as appendicitis.</p> <p>Subject 12 discontinued study drug treatment due to a clinically significant increase in AST, ALT, and GGT. The subject received 400 mg ketoconazole daily for 18 days and received concomitantly a single dose of 10 mg ACT-064992 on Day 5 of Treatment Period B before he was withdrawn on Day 19. The increases in AST, ALT, and GGT reached 1.6, 4.0, and 2.7 times the upper limit of normal (ULN), respectively. Alkaline phosphatase remained within normal ranges. The increases in liver enzymes were asymptomatic, not associated with any AE, and resolved without sequelae.</p>
<p>AC-055-108 Biocomparison of tablet and (b) (4) formulations of macitentan in healthy male subjects. Safety and tolerability. 12 healthy subjects</p>	<p>Treatment A: Single oral macitentan dose. Treatment B: Single oral macitentan dose. Treatment A: Macitentan 10 mg</p>	<p>0/0</p>	

	tablet. Treatment B: Macitentan 10 mg (b) (4). Open-label, 2-way crossover		
AC-055-109 Investigation of the PK, safety and tolerability of macitentan in healthy Japanese and Caucasian subjects 10 healthy Japanese subjects (5 male, 5 female).	10 healthy Caucasian subjects (5 male, 5 female). Single oral macitentan dose Macitentan 10 mg Open-label, parallel group	0/0	
AC-055-110 Investigation of the PK, safety and tolerability of macitentan in subjects with mild, moderate, or severe hepatic impairment due to liver cirrhosis.	32 subjects (20 male, 12 female) 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment, 8 patients with severe hepatic impairment, 8 healthy subjects Single oral macitentan dose Macitentan 10 mg Open-label, parallel group	0/0	
AC-055-111 Investigation of the effects of cyclosporine and rifampicin on the PK of macitentan in healthy male subjects. Safety and tolerability	20 healthy subjects (10 subjects in Part A, 10 subjects in Part B). Part A: Once daily oral macitentan for 17 days. Cyclosporine b.i.d. for 11 days (Days 6–17) Part B: Once daily oral	0/0	

	<p>macitentan for 12 days. Once daily rifampicin for 7 days (Days 6–12)</p> <p>Part A: Macitentan 30 mg (Day 1), 10 mg (Days 2–17). Concomitant cyclosporine 100 mg b.i.d. (Days 6–17).</p> <p>Part B: Macitentan 30 mg (Day 1), 10 mg (Days 2–12). Concomitant rifampicin 600 mg (Days 6–12). Open-label, 2-part, 1-sequence crossover</p>		
<p>AC-055-112 [D-10.538] Investigation of the PK in patients with impaired renal function. Safety and tolerability.</p>	<p>8 patients with severe renal impairment, 8 healthy subjects Single oral macitentan dose Macitentan 10 mg Open-label,</p>	0/0	
<p>AC-055-113 Investigation of the effect of macitentan on spermatogenesis, sperm quality and serum hormone concentrations of the hypothalamus pituitary-adrenal and gonadal axes. PK, safety and tolerability.</p>	<p>84 healthy subjects Once daily oral macitentan or placebo for 12 weeks. Macitentan 10 mg tablet. Double-blind, Placebo controlled, parallel group</p>	0/1 (upper limb fracture/ clavicle fracture in 1 placebo subject)	<p>There was an error in treatment allocation so the number of subjects who received macitentan 10 mg or placebo for 12 weeks was much smaller than planned (14 and 11 subjects, respectively, rather than 42 per group as planned), and the study no longer had any reasonable power for testing the null</p>

			hypothesis.
AC-055-114 Investigation of the effect of repeated daily doses of 10 mg and 30 mg macitentan on the QT/QTc interval in healthy male and female subjects	64 healthy subjects (26 male and 38 female) Once daily oral macitentan or placebo for 8 days. Treatment A: Placebo with single (open-label) moxifloxacin 400 mg dose (Day 8) Treatment B: Macitentan 10 mg Treatment C: Macitentan 30 mg Treatment D: Placebo Double-blind, double-dummy, placebocontrolled, 4-way crossover.	0/0	
AC-055-115a,b Safety and tolerability of macitentan in combination with dose-dense temozolomide in patients with recurrent glioblastoma. Efficacy and PK.	Up to 48 patients planned. 28 days (Period 1) + 11 months (Period 2). Macitentan (3–6 subjects/group): 30, 60, 90 mg or higher in 30 mg dose increment (up to 5 levels anticipated). Open-label, uncontrolled.		ongoing
AC-055-116a Investigation of the PK, PD, safety and tolerability of macitentan in male Japanese subjects.	16 healthy subjects. Once daily oral dose for 10 days. Macitentan (6 subjects/group): 3, 10 mg Placebo (2 subjects/group). Multiple ascending		ongoing

	dose, placebo controlled, double-blind.		
AC-055-117a Investigation of the PK, PD, safety and tolerability of macitentan in male Korean subjects.	30 healthy subjects planned. Once daily oral dose for 10 days. Macitentan (8 subjects/group): 3, 10, 30 mg Placebo (2 subjects/group). Multiple ascending dose, placebo controlled, double-blind.		ongoing

Attachment B

Study Report

Study ID: AC-055-302 SERAPHIN

Title Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to improve cliNical outcome: A multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, phase 3 study to assess the effects of macitentan on morbidity and mortality in patients with symptomatic pulmonary arterial hypertension

Reviewer's efficacy summary

A total of 742 patients from 151 centers in 39 countries were randomized in a 1:1:1 ratio to the macitentan 3 mg (n = 250), macitentan 10 mg (n = 242) and placebo groups (n = 250). The subjects were predominantly female, white, living outside the US (mostly in Europe or Asia), and had a mean age of 45.6 years (3% of subjects were less than 18 years of age). The mean time from PAH diagnosis to randomization in the study population was 2.7 years and idiopathic PAH was the most common etiology (55%) followed by collagen vascular disease (30%), congenital shunts (8%), drugs and toxins (3%), and HIV infection (1%). The baseline mean 6MWD was approximately 360 m, the mean Borg dyspnea index was approximately 3.5 across the groups, and most patients were WHO FC II (52%) or WHO FC III (46%).

Around one third of subjects had at least one sign of heart failure with peripheral edema being the most common. The majority (approximately 64%) of patients were receiving concomitant PAH therapy with sildenafil being the most common (58%). The percentages of patients taking sildenafil were similar across treatment groups. The most frequently reported concomitant diseases were ventricular failure, hypertension, and scleroderma.

The treatment groups are fairly well balanced. The mean baseline walk distance was a little shorter for the placebo group. However, there is no other indication that the placebo group was sicker than the active treatment groups.

Regarding the primary endpoint, the incidence rate of patients with CEC confirmed events was lower for the macitentan 10 mg group (31%) compared to macitentan 3 mg (38%) and placebo (46%) groups. The reporting of death was slightly more frequent for macitentan 3 mg (8%) compared to placebo (7%) and macitentan 10 mg (7%). There were more IV/SC prostanoids initiations in the placebo group (2%) compared to the macitentan groups (0.4% each). The largest cause of a CEC confirmed endpoint for all groups was worsening of PAH. There was a higher incidence rate of placebo patients (37%) reporting this portion of the primary endpoint compared to macitentan 3 mg (29%) and macitentan 10 mg (24%).

Regarding subgroups, there are few differences in effect regarding gender and race (the "other" category was small). Those patients with no PAH therapies at baseline had a greater effect compared to the patients who were taking background therapy. Patients with idiopathic PAH etiology had a greater effect than those with an etiology of collagen vascular disease or congenital shunts (small sample size). It is of concern that there is no indication that macitentan 10 mg is better than placebo in the sites located in North America (although there is an effect in

Western Europe/Israel where medical care should be similar to care in the US). This could be a result of small sample size in North America.

The placebo-corrected mean change (\pm SD) from baseline at endpoint in 6MWD was 16.8 m (\pm 96.95) in the macitentan 3 mg group and 22.0 m (\pm 92.58) in the macitentan 10 mg group. These changes were statistically significant.

A higher percentage of patients in macitentan groups improved their WHO functional class compared to the placebo patients. There was some improvement in the Borg dyspnea index for the macitentan dose groups (-0.7 for 3 mg and -0.5 for 10 mg). The placebo group grew a little worse.

Background

Primary objective

The primary objective of the study was to demonstrate that either dose (3 mg or 10 mg) of macitentan reduces the risk of morbidity and mortality in patients with symptomatic PAH.

Secondary objective

To evaluate the effect of ACT-293987 on exercise capacity and other secondary and exploratory efficacy endpoints in patients with PAH.

Study design

This was a multicenter, double-blind, placebo-controlled, parallel-group, event-driven, Phase 3 study in which patients were randomized in a 1:1:1 ratio to three treatment groups (3 mg or 10 mg macitentan, or placebo). The study included a screening period (up to 28 days) followed by a treatment period from randomization to the end of treatment (EOT) visit. End of study (EOS) occurred when the target of 285 events confirmed by the Clinical Event Committee (CEC) was expected to have been achieved.

The EOT visit either coincided with the EOS visit for patients who were still on study treatment or occurred earlier in case of premature discontinuation of study drug.

Patients who prematurely discontinued study treatment (double-blind) due to clinical worsening of PAH and obtained written approval from Actelion, and patients who completed the study as scheduled, could enter the open-label extension study, SERAPHIN OL. Patients who had opted not to participate or who were not eligible to participate in the open-label extension study, SERAPHIN OL, were given a 28-day safety follow-up visit.

Number of subjects

A total of 699 subjects were planned and 742 subjects were actually randomized (1:1:1 ratio) to macitentan 3 mg (250 subjects), macitentan 10 mg (242 subjects) or placebo (250 subjects).

Study duration/centers

Study Dates: First patient, first visit: May 25, 2008

Last patient, last visit: March 15, 2012

A total of 158 centers in approximately 39 countries participated in the study. The demographic regions included North America (11% of patients), Asia (30%), Latin America (17%), Western Europe and Israel (19%), Eastern Europe and Turkey (25%).

Inclusion criteria

Eligible patients were required to have met all of the following inclusion criteria before treatment initiation:

- Signed informed consent prior to any study-mandated procedure
- Symptomatic PAH in modified WHO FC II to IV
- PAH belonging to Groups 1.1 to 1.3 of the Venice classification:
 - Idiopathic
 - Familial
 - Related to:
 - Collagen vascular disease
 - Simple (atrial septal defect, ventricular septal defect, patent ductus arteriosus) congenital systemic-to-pulmonary shunts at least 1 year post-surgical repair
 - HIV infection
 - Drugs and toxins
- PAH diagnosis confirmed by hemodynamic evaluation performed prior to randomization and showing all of the following:
 - Mean pulmonary artery pressure (mPAP) > 25 mmHg
 - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg
 - PVR at rest ≥ 320 dyn × sec/cm⁵

For patients who were to participate in the pharmacokinetic/pharmacodynamic (PK/PD) sub-study [Section 9.5.1.7.1], hemodynamic evaluation was required to have been performed within 3 months prior to randomization [Section 9.5.4]. For all other patients, hemodynamic evaluation was required to have been performed within 1 year prior to randomization.

Following Protocol Amendment 2, the inclusion criteria for mPAP, PCWP and PVR were modified from ≥ 25 mmHg, < 15 mmHg, and ≥ 240 dyn × sec/cm⁵, respectively, to < 25 mmHg, ≤ 15 mmHg, and ≥ 320 dyn × sec/cm⁵, respectively, as presented above

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- 6MWD \geq 50 m at screening and randomization

Following Protocol Amendment 2, the upper limit of the 6MWD (475 m) was taken out of the protocol [Appendix 16.1.1.2.4].

The 6MWTs performed at screening and randomization were required to satisfy the following criteria:

- 6MWD was required to be \geq 50 m or the patient was not to be included in the study
- The second 6MWD (6MWD#2 at randomization) was required to be \geq 50 m and within 10% of 6MWD#1 (at screening) or a third test was required (6MWD#3).
- 6MWD#3 (at randomization) was required to be \geq 50 m and within 10% of 6MWD#2 or the patient was not to be included in the study.

- Men or women \geq 12 years of age:

Women of childbearing potential* were allowed to participate in the study if they had a negative serum pre-treatment pregnancy test and consistently and correctly used (from screening and up to 28 days after discontinuation of study treatment) a reliable method of contraception with a Pearl Index of less than 1% (oral hormonal contraceptive, implant, vaginal hormone ring, intrauterine system, or tubal ligation only in combination with condom), were sexually abstinent, or had a vasectomized partner.

Following Protocol Amendment 3, the requirements for tubal ligation were clarified to include tubal ligation only in combination with a condom [Appendix 16.1.1.2.6] as presented above.

*A woman was considered to have childbearing potential unless she met at least one of the following criteria:

- previous bilateral salpingo-oophorectomy or hysterectomy
- premature ovarian failure confirmed by a specialist gynecologist
- pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
- age $>$ 50 years and not treated with any kind of hormone replacement therapy for at least 2 years prior to screening, with amenorrhea for at least 24 consecutive months prior to screening, and a serum follicle stimulating hormone level of $>$ 40 IU/L if the investigator had insufficient evidence that the woman was postmenopausal

Following Protocol Amendment 2, a clarification of the requirements for the measurement of serum follicle stimulating hormone was added (as presented above), which stated that the measurement was to be performed if the investigator had insufficient evidence to establish the postmenopausal status of a woman [Appendix 16.1.1.2.4].

Exclusion criteria

Eligible patients were required to have met none of the following exclusion criteria at treatment initiation:

- PAH associated with portal hypertension thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders or splenectomy
- PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and, combined and complex systemic-to-pulmonary shunts, corrected or non-corrected
- PAH associated with significant venous or capillary involvement (PCWP > 15 mmHg), known pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis
- Persistent pulmonary hypertension of the newborn
- Pulmonary hypertension belonging to Groups 2 to 5 of the Venice classification
- Moderate to severe obstructive lung disease: forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) < 70% and FEV₁ < 65% of predicted value after bronchodilator administration
- Moderate to severe restrictive lung disease: total lung capacity (TLC) < 60% of normal predicted value
- Moderate to severe hepatic impairment, e.g., Child-Pugh Class B or C
- Estimated creatinine clearance < 30 mL/min (*this criterion was added following Protocol Amendment 1, see Appendix 16.1.1.2.2*)
- Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal
- Hemoglobin < 75% of the lower limit of the normal range
- Systolic blood pressure < 100 mmHg
- Acute or chronic impairment (other than dyspnea), limiting the ability to comply with the study requirements
- Pregnant or breast-feeding
- Known concomitant life-threatening disease with a life expectancy < 12 months
- Body weight < 40 kg
- Any condition that prevented compliance with the protocol or adherence to therapy
- Recently started (< 8 weeks prior to randomization) or planned cardio-pulmonary rehabilitation program based on exercise
- Treatment with ERAs within 3 months prior to randomization
- Systemic treatment within 4 weeks prior to randomization with immunosuppressants: calcineurin or mTOR inhibitors (e.g., cyclosporine A and tacrolimus, everolimus, sirolimus)
- Treatment with CYP3A inducers within 4 weeks prior to randomization (*this criterion added following Protocol Amendment 1, see Appendix 16.1.1.2.2*)

- Known hypersensitivity to drugs of the same class as the study drug, or any of their excipients
- Planned treatment or treatment with another investigational drug within 1 month prior to randomization

Assigning treatment groups

Patients who satisfied the eligibility criteria were randomized in a 1:1:1 ratio to receive macitentan (3 mg or 10 mg) or placebo using a centralized randomization system via Interactive Voice Response (IVR) or Interactive Web Response (IWR). An independent service provider, [REDACTED]^{(b) (4)} was responsible for the central randomization services. The dose of study drug assigned at randomization was fixed.

Concomitant medications

Allowed

Treatment with oral diuretics was allowed if it had been ongoing at a stable dose for at least 1 month before randomization. Optimization of the dose of oral diuretics was allowed during the treatment period.

Following Protocol Amendment 2, the requirement for duration of the stable dose of oral diuretics was reduced from 3 months to 1 month. Optimization of the dose of oral diuretics was allowed during the treatment period.

Data on the dose of oral diuretics were not reported in the CRF and were not analyzed.

The following treatments for PAH were allowed if they had been taken by the patients at a stable dose for at least 3 months prior to randomization:

- Oral or inhaled prostanoids (e.g., beraprost, iloprost)
- Oral phosphodiesterase inhibitors (e.g., sildenafil)
- Calcium channel blockers
- L-arginine

Any introduction of a new treatment for PAH without documented worsening of PAH was strongly discouraged during the study period. If an additional PAH-specific therapy was started without a protocol-defined morbidity event, study drug was not to be discontinued (unless the additional therapy was an ERA), and patients were followed up to EOS according to the visit and assessment schedule.

Prohibited concomitant medications

- ERAs (e.g., bosentan and ambrisentan) unless they were initiated for clinical worsening of PAH and after study drug discontinuation
- Intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil) unless they were initiated for a morbidity event
- Specific immunosuppressants: calcineurin or mTOR inhibitors (e.g., cyclosporine A and tacrolimus, everolimus, sirolimus)
- CYP3A inducers (carbamazepine, rifampin, rifabutin and St John's wort)
- Any investigational drug other than the study drug

SERAPHIN open label (OL)

The following patients were given the option to continue into SERAPHIN OL and receive open-label macitentan 10 mg once daily treatment (if the SERAPHIN OL protocol was approved at the respective investigational center):

- Patients who prematurely discontinued study treatment (double-blind) due to a morbidity event and obtained written approval from Actelion.
- Patients who completed the SERAPHIN study (AC-055-302) as scheduled. Patients who permanently discontinued study treatment for reasons other than clinical worsening of PAH (e.g.,

AEs other than PAH worsening, withdrawal of consent, administrative reasons) were not allowed to enter the SERAPHIN OL extension study.

Advisory committees

- 1) Steering committee
- 2) Data safety and monitoring board
- 3) Liver safety board

Primary efficacy endpoint

Pre-IND communication / Response to proposed composite endpoint dated October 3, 2007: In response to a 27 August 2007 Pre-IND submission containing a description of the proposed composite endpoint for study AC-055-302, the Division, upon consultation and review with Dr Robert Temple, agreed that the proposed composite endpoint appeared to be acceptable.

The primary objective was assessed as the time from start of study treatment to the first morbidity or mortality event (primary endpoint) up to end of treatment plus 7 days and was a composite including the following components:

- death, or onset of a treatment-emergent AE with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or,
- atrial septostomy or hospitalization for atrial septostomy, or,
- lung transplantation or hospitalization for lung transplantation, or,
- initiation of i.v. or s.c. prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of i.v. or s.c. prostanoids, or,
- other worsening of PAH.

Other worsening of PAH was defined by the combined occurrence in a patient of all the following three events:

- at least 15% decrease in the 6MWD from baseline, confirmed by two 6MWTs, performed on separate days, within 2 weeks of each other.

AND,

- worsening of PAH symptoms that included at least one of the following:
 - o increase in WHO FC, or no change in patients in WHO FC IV at baseline,
 - o appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy,

AND,

- need for new treatment(s) for PAH that included the following:
 - o oral or inhaled prostanoids (e.g., iloprost),
 - o oral phosphodiesterase inhibitors (e.g., sildenafil),
 - o ERAs (e.g., bosentan, ambrisentan) only after discontinuation of the study treatment,
 - o intravenous diuretics.

Adjudication of all events by the independent Clinical Endpoints Committee (CEC) was done in a blinded manner. The CEC adjudicated the type of primary endpoint event and confirmed

whether a primary event of mortality up to EOT + 7 days was due to PAH. The CEC had the right to override strict protocol definitions to adjudicate an event.

Regarding the 6MWT (from minutes dated 12/01/2007):

3. An independent Clinical Event Committee (CEC) will review and confirm all mortality and morbidity events in a blinded fashion. In the situation where, despite all efforts to ensure protocol compliance having been undertaken, a second 6-MWT could not be performed as confirmation of clinical worsening of PAH, the CEC will adjudicate on the clinical worsening. If adjudicated as clinical worsening of PAH by the CEC, these events will be included in the primary analysis.

The primary objective of reduction in the risk of a morbidity or mortality event was assessed as the time from start of study treatment to the first morbidity or mortality event up to end of treatment (EOT), defined as follows:

- Death, or onset of a treatment-emergent AE with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or
- Atrial septostomy or hospitalization for atrial septostomy, or
- Lung transplantation or hospitalization for lung transplantation, or
- Initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of i.v. or s.c. prostanoids, or
- Other worsening of PAH

Other worsening of PAH was defined by the combined occurrence in a patient of all the following three events:

- At least 15% decrease in the 6MWD from baseline, confirmed by two 6MWTs, performed on separate days, within 2 weeks of each other. AND
- Worsening of PAH symptoms that included at least one of the following:
 - o Increase in WHO FC, or no change in patients in WHO Class IV at baseline
 - o Appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy

AND

- Need for new treatment(s) for PAH that included the following:
 - o Oral or inhaled prostanoids (e.g., iloprost)
 - o Oral phosphodiesterase inhibitors (e.g., sildenafil)
 - o ERAs (e.g., bosentan, ambrisentan) only after discontinuation of the study treatment
 - o Intravenous diuretics

Clinical worsening events were adjudicated in a blinded fashion by an independent clinical event committee (CEC). If the investigator determined that a subject had experienced an endpoint, the information was submitted to the CEC for either the committee's rejection that an event occurred or concurrence that an event occurred.

Secondary efficacy endpoints

- Change in 6MWD from baseline to Month 6
- Proportion of patients with improvement in modified WHO FC from baseline to Month 6
- Time to death due to PAH or hospitalization for PAH up to EOT that included:
 - Death due to PAH (as adjudicated by the CEC) up to EOT + 7 days, or onset of a treatment-emergent AE with a fatal outcome due to PAH occurring up to 4 weeks after EOT, or

- Hospitalization for PAH up to EOT + 7 days
- Time to death of all causes up to EOT + 7 days or occurrence of onset of a treatment emergent AE with a fatal outcome up to EOT + 4 weeks.

-Time to death of all causes up to EOS2

The protocol-defined endpoint was (clarified in the SAP).

This protocol-defined exploratory endpoint was changed to a secondary endpoint in the SAP

Exploratory efficacy endpoint(s)

- Change in 6MWD from baseline to all assessed time-points
- Change in modified WHO FC from baseline to all assessed time-points
- Change in Borg dyspnea index from baseline to all assessed time-points
- Achievement and/or maintenance of a 6MWD \geq 380 m at all assessed time-points
- Change in N-terminal pro-B type natriuretic peptide (NT-pro-BNP) from baseline to Month 6
- Change from baseline to all visits in the Quality of Life (QoL) assessed by the SF-36 questionnaire for patients \geq 14 years of age at randomization¹
- Time to death due to PAH up to EOS2

1 The time-points specified in the protocol were changed to include all visits.

2This endpoint was not described in the protocol, but was introduced in the SAP.

Imputation

Primary endpoint: no imputation method was used for the primary efficacy endpoint. If an assessment for the confirmation of the clinical worsening of PAH was missing (mostly there were missing confirmatory second 6MWT), the qualification of the event for inclusion in the analysis of the primary endpoint was left to the clinical judgment of the CEC.

Secondary endpoint: if 6MWT data were missing, the following imputation rules were applied: The last available post-baseline value obtained up to the last day of the Month 6 window (i.e., the earliest day between Study Day 270 and EOT + 7 days) was carried forward to impute the missing value unless one of the following was valid:

- If the patient had died before or on the last day of the Month 6 window, a distance of '0 m' was imputed for the missing values.
- If the patient had experienced a CEC-confirmed event and had been alive up to the last day of Month 6 window and had no 6MWD value between the occurrence of the event and the last day of the Month 6 window (inclusive), the worst case imputation was applied. The value to be imputed was the 25th percentile of the ordered distribution of available 6MWD values in the same analysis set. The available values were taken from Month 6 for the patients with 6MWD data in the Month 6 window.

Missing data of patients for whom no post-baseline values were available after applying the above imputation rules were imputed by carrying forward the baseline value.

Results

Disposition

A total of 742 patients from 151 centers in 39 countries were randomized in a 1:1:1 ratio to the macitentan 3 mg (n = 250), macitentan 10 mg (n = 242) and placebo groups (n = 250). One subject randomized to placebo (6001/11099) never received treatment so the all treated group included 741 patients.

Premature discontinuation of study

A total of 368 patients (49.7%) completed the study and 373 patients (50.3%) discontinued treatment prematurely. The breakdown of discontinuations by treatment groups was 47.2% in the macitentan 3 mg group, 44.2% in the macitentan 10 mg group, and 59.4% in the placebo group.

The reasons for discontinuation are shown below by treatment group.

Table 11 Summary of reasons for discontinuation of treatment, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of reasons for discontinuation from the treatment
 Analysis set: All treated

Preferred term *	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one reason	148	59.4%	118	47.2%	107	44.2%
DISEASE PROGRESSION LEADING TO OL*	80	32.1%	57	22.8%	50	20.7%
ADVERSE EVENT	31	12.4%	34	13.6%	26	10.7%
DISEASE PROGRESSION NOT LEADING TO OL**1	20	8.0%	17	6.8%	9	3.7%
DEATH	12	4.8%	10	4.0%	10	4.1%
WITHDRAWAL FROM TREATMENT	11	4.4%	7	2.8%	12	5.0%
ADMINISTRATIVE/OTHER	5	2.0%	2	0.8%	5	2.1%
WITHDRAWAL OF CONSENT	1	0.4%	3	1.2%	4	1.7%
LOST TO FOLLOW-UP	3	1.2%	2	0.8%	-	-
TREATMENT FAILURE	3	1.2%	2	0.8%	-	-
ADMINISTRATION OF FORBIDDEN DRUG	2	0.8%	1	0.4%	-	-

* Enrolment into the Open Label study following a morbidity event
 **Patients who terminated the treatment due to a mortality/morbidity event
 1 Disease progression not leading to OL is a component of adverse events leading to discontinuation
 Table FWTS_T - Produced by (b) (4) on 26APR12 - Data dump of 26APR12
 (Page 1/1)

A morbidity event followed by enrollment in the SERAPHIN open label was the most frequent reason for discontinuation of study treatment in all three groups (22.8% macitentan 3 mg, 20.7% macitentan 10 mg, 32.1% placebo). Placebo subjects were more likely and macitentan 10 mg subjects were less likely to discontinue the main study and go into the open label trial.

An adverse event leading to discontinuation of study treatment occurred in 13.6% macitentan 3 mg, 10.7% macitentan 10 mg, and 12.4% placebo. These events included morbidity events (without subsequent enrollment into the SERAPHIN open label study) in 6.8% of patients in the macitentan 3 mg group, 3.7% of patients in the macitentan 10 mg group, and 8.0% of patients in the placebo group. Again, placebo subjects were more likely and macitentan 10 mg subjects were less likely to discontinue the study (and not continue in the open label trial).

Death was reported nearly equally across treatment group (4.8% placebo, 4.0% macitentan 3 mg and 4.1% macitentan 10 mg) as were the drop outs for other reasons. This indicates that macitentan is well tolerated and patients are more likely to stay on the medication (they could be feeling better) compared to patients randomized to placebo.

Demographics

The demographic characteristics of the randomized subjects are shown below by treatment group.

Table 13 Summary of patient demographics, All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
SEX [n (%)]				
n	249	248	242	739
Males	65 26.1%	61 24.6%	48 19.8%	174 23.5%
Females	184 73.9%	187 75.4%	194 80.2%	565 76.5%
AGE (years)				
n	249	248	242	739
Mean	46.7	44.5	45.5	45.6
Standard deviation	17.03	16.26	14.99	16.13
Standard error	1.08	1.03	0.96	0.59
Median	46.0	43.0	45.0	45.0
Q1 , Q3	32.0 , 61.0	31.0 , 57.0	34.0 , 56.0	33.0 , 58.0
Min , Max	13.0 , 85.0	12.0 , 80.0	13.0 , 76.0	12.0 , 85.0
AGE [n (%)]				
n	249	248	242	739
< 18	7 2.8%	7 2.8%	6 2.5%	20 2.7%
18 - 64	199 79.9%	208 83.9%	209 86.4%	616 83.4%
>= 65	43 17.3%	33 13.3%	27 11.2%	103 13.9%
BMI (kg/m²)				
n	249	248	242	739
Mean	25.2	25.8	25.6	25.5
Standard deviation	5.11	6.36	6.06	5.86
Standard error	0.32	0.40	0.39	0.22
Median	24.6	24.8	24.4	24.6
Q1 , Q3	21.6 , 28.1	21.2 , 29.6	21.7 , 28.2	21.6 , 28.7
Min , Max	14.9 , 49.0	15.2 , 61.9	15.4 , 52.1	14.9 , 61.9
RACE [n (%)]				
n	249	248	242	739
Caucasian/white	131 52.6%	137 55.2%	135 55.8%	403 54.5%
Black	8 3.2%	5 2.0%	6 2.5%	19 2.6%
Asian	71 28.5%	69 27.8%	65 26.9%	205 27.7%
Hispanic	37 14.9%	37 14.9%	35 14.5%	109 14.7%
Other	2 0.8%	-	1 0.4%	3 0.4%
LOCATION [n (%)]				
n	249	248	242	739
US	23 9.2%	25 10.1%	19 7.9%	67 9.1%
Non-US	226 90.8%	223 89.9%	223 92.1%	672 90.9%
REGION [n (%)]				
n	249	248	242	739
North America	30 12.0%	30 12.1%	23 9.5%	83 11.2%
Western Europe/Israel	50 20.1%	41 16.5%	48 19.8%	139 18.8%
Eastern Europe/Turkey	59 23.7%	63 25.4%	62 25.6%	184 24.9%
Asia	68 27.3%	70 28.2%	68 28.1%	206 27.9%
Latin America	42 16.9%	44 17.7%	41 16.9%	127 17.2%

Overall, the subjects were predominantly female, white, living outside the US (mostly in Europe or Asia), and had a mean age of 45.6 years (3% of subjects were less than 18 years of age). Differences between treatment groups were small indicating that randomization was successful in patient distribution.

Disease characteristics at baseline

The disease characteristics of the randomized patients are shown below by treatment group.

Table 14 Summary of baseline characteristics, All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
Time from PAH diagnosis (days)				
n	247	247	241	735
Mean	942	1079	951	991
Standard deviation	1362.0	1659.1	1325.1	1456.9
Standard error	86.7	105.6	85.4	53.7
Median	460	425	476	462
Q1 , Q3	180 , 1279	178 , 1230	174 , 1090	178 , 1225
Min , Max	6 , 13267	1 , 11957	2 , 10199	1 , 13267
Etiology of PAH [n (%)]				
n	247	247	241	735
Idiopathic	126 51.0%	144 58.3%	134 55.6%	404 55.0%
Familial	3 1.2%	8 3.2%	2 0.8%	13 1.8%
Collagen vascular disease	81 32.8%	70 28.3%	73 30.3%	224 30.5%
Congenital shunts	26 10.5%	15 6.1%	21 8.7%	62 8.4%
HIV infection	3 1.2%	1 0.4%	6 2.5%	10 1.4%
Drugs and toxins	8 3.2%	9 3.6%	5 2.1%	22 3.0%
6mn Walk Test (m) (absolute)				
n	249	248	242	739
Mean	352.4	364.1	362.6	359.6
Standard deviation	110.62	95.52	93.21	100.15
Standard error	7.01	6.07	5.99	3.68
Median	360.0	378.0	378.0	372.0
Q1 , Q3	284.0 , 428.0	311.0 , 425.0	300.0 , 434.0	300.0 , 430.0
Min , Max	65.0 , 650.0	80.0 , 610.0	90.0 , 578.0	65.0 , 650.0
Signs of right heart failure [n (%)]				
n	249	248	242	739
Patients with at least one sign	78 31.3%	76 30.6%	76 31.4%	230 31.1%
Hepatomegaly	25 10.0%	29 11.7%	26 10.7%	80 10.8%
Ascites	6 2.4%	2 0.8%	3 1.2%	11 1.5%
Peripheral edema	34 13.7%	43 17.3%	43 17.8%	120 16.2%
S3 gallop	12 4.8%	7 2.8%	8 3.3%	27 3.7%
Hepato-jugular reflux	12 4.8%	16 6.5%	15 6.2%	43 5.8%
Central venous pressure >8 mmHg	23 9.2%	27 10.9%	23 9.5%	73 9.9%
Other	16 6.4%	14 5.6%	14 5.8%	44 6.0%
WHO functional class [n (%)]				
n	249	248	242	739
I	-	-	1 0.4%	1 0.1%
II	129 51.8%	138 55.6%	120 49.6%	387 52.4%
III	116 46.6%	105 42.3%	116 47.9%	337 45.6%
IV	4 1.6%	5 2.0%	5 2.1%	14 1.9%
Concomitant PAH therapy [n (%)]				
n	249	248	242	739
No	95 38.2%	85 34.3%	88 36.4%	268 36.3%
Yes	154 61.8%	163 65.7%	154 63.6%	471 63.7%
Sildenafil	140 56.2%	146 58.9%	140 57.9%	426 57.6%
Tadalafil	2 0.8%	3 1.2%	2 0.8%	7 0.9%
Vardenafil	8 3.2%	5 2.0%	8 3.3%	21 2.8%
Iloprost	3 1.2%	13 5.2%	10 4.1%	26 3.5%
Beraprost	4 1.6%	5 2.0%	6 2.5%	15 2.0%
Treprostinil	-	1 0.4%	-	1 0.1%

- mean time from PAH diagnosis to randomization in the study population was 2.7 years,
- idiopathic PAH was the most common etiology (55%) followed by collagen vascular disease (30%), congenital shunts (8%), drugs and toxins (3%), and HIV infection (1%)
- baseline mean 6MWD was approximately 360 m
- mean Borg dyspnea index was approximately 3.5 across the groups,

-most patients were WHO FC II (52%) or WHO FC III (46%).

Around one third of subjects had at least one sign of heart failure with peripheral edema being the most common.

The majority (approximately 64%) of patients were receiving concomitant PAH therapy with sildenafil being the most common (58%)⁵. The percentages of patients taking sildenafil were similar across treatment groups. Other commonly used drugs included furosemide and spironolactone.

The most frequently reported concomitant diseases were ventricular failure, hypertension, and scleroderma. The treatment groups were balanced.

The treatment groups are fairly well balanced. The mean baseline walk distance was a little shorter for the placebo group. However, there is no other indication that the placebo group was sicker than the active treatment groups.

Summary of baseline hemodynamics is shown below.

⁵ Endothelin receptor antagonists were prohibited as were IV or SQ prostanoids.

Table 15 Summary of hemodynamic baseline characteristics, All-randomize set

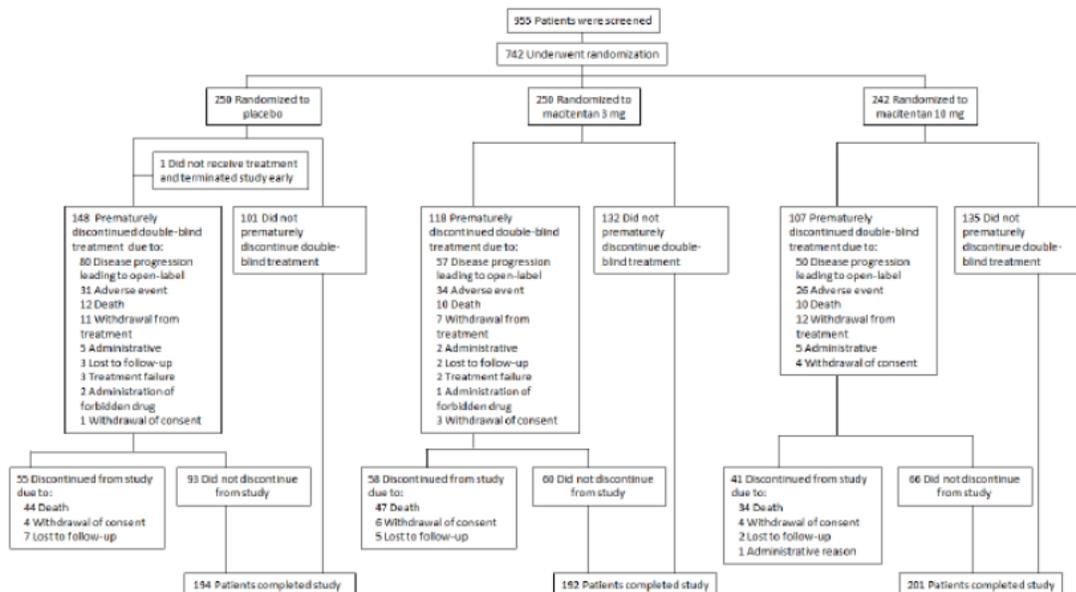
	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Mean Right Atrial Pressure (mmHg)			
n (missing)	242 (8)	247 (3)	238 (4)
Mean	8.8	9.2	9.2
Standard deviation	5.59	5.32	6.03
Median	8.0	8.5	8.0
Q1 , Q3	5.0 , 11.0	5.0 , 12.0	5.0 , 12.0
Min , Max	0.0 , 36.0	0.0 , 26.0	0.0 , 34.0
Mean Pulmonary Arterial Pressure (mmHg)			
n (missing)	248 (2)	248 (2)	242 (0)
Mean	53.1	55.1	53.5
Standard deviation	18.13	16.74	17.63
Median	51.5	54.5	52.0
Q1 , Q3	40.0 , 62.5	43.0 , 65.5	41.6 , 63.0
Min , Max	25.0 , 128.0	25.0 , 104.3	20.0 , 129.0
Pulmonary capillary wedge pressure (mmHg)			
n (missing)	244 (6)	243 (7)	235 (7)
Mean	9.5	9.8	9.5
Standard deviation	3.38	3.30	3.44
Median	10.0	10.0	10.0
Q1 , Q3	7.0 , 12.0	7.0 , 12.0	7.0 , 12.0
Min , Max	1.0 , 15.0	3.0 , 23.0	0.0 , 16.0
Cardiac Index (l/min/m²)			
n (missing)	248 (2)	248 (2)	240 (2)
Mean	2.44	2.36	2.36
Standard deviation	0.799	0.788	0.777
Median	2.42	2.21	2.38
Q1 , Q3	1.87 , 2.91	1.84 , 2.73	1.83 , 2.75
Min , Max	0.79 , 5.60	0.74 , 5.81	0.80 , 6.24
Pulmonary Vascular Resistance (dyn*sec/cm⁵)			
n (missing)	244 (6)	243 (7)	233 (9)
Mean	996	1044	1040
Standard deviation	784.3	624.2	672.5
Median	831	914	863
Q1 , Q3	511 , 1253	533 , 1371	520 , 1351
Min , Max	184 , 8436	200 , 3244	85 , 4615
Total Pulmonary Resistance (dyn*sec/cm⁵)			
n (missing)	248 (2)	248 (2)	240 (2)
Mean	1204	1265	1242
Standard deviation	853.0	690.5	731.2
Median	1046	1149	1054
Q1 , Q3	674 , 1429	708 , 1600	711 , 1600
Min , Max	286 , 9309	338 , 3911	188 , 5231
Mixed venous oxygen saturation (SvO₂) (%)			
n (missing)	223 (27)	221 (29)	222 (20)
Mean	64.9	64.0	64.5
Standard deviation	8.81	10.52	9.71
Median	65.0	65.0	66.0
Q1 , Q3	59.0 , 71.0	60.0 , 71.0	59.0 , 71.0
Min , Max	40.0 , 93.0	26.0 , 97.0	35.0 , 85.0

The groups were fairly well balanced regarding hemodynamics.

Disposition of patients

The figure below shows the disposition of patients.

Figure 2 Disposition of patients



A total of 742 patients from 151 centers in 39 countries were randomized in a 1:1:1 ratio to the macitentan 3 mg (n = 250), macitentan 10 mg (n = 242) and placebo groups (n = 250).

A total of 590 patients (80%) completed the study as planned and 22%, 17% and 22% of patients withdrew prematurely for macitentan 3 mg, macitentan 10 mg, and placebo groups, respectively. The reasons for withdrawal are shown below by treatment group.

Table 60 Summary of reasons for premature discontinuation from the study, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of reasons for premature discontinuation from the study
 Analysis set: All randomized

Reason for discontinuation	Placebo	Macitentan	Macitentan
	N=250	3 mg N=250	10 mg N=242
	No.	No.	No.
Total patients with at least one reason	55 22.0%	56 22.4%	41 16.9%
Death	44 17.6%	47 18.8%	34 14.0%
Withdrawal of subject's consent	3 1.2%	6 2.4%	4 1.7%
Lost to follow-up	7 2.8%	3 1.2%	2 0.8%
Administrative reason	1 0.4%	-	1 0.4%

Table FWDS_A - Produced by (b) (4) on 04MAY12 - Data dump of 26APR12
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A total of three patients (two in the macitentan 3 mg group -5702/15109, 1901/10606, 1 patient in the placebo group - 6002/11080) who did not follow appropriate ICF procedure are not included in this Table. These patients discontinued study due to administrative reasons (placebo) and loss to follow-up (macitentan 3 mg).

Death was the main reason for patient withdrawal (19% macitentan 3 mg, 14% macitentan 10 mg, 18% placebo). Other reasons for premature discontinuation from the study included withdrawal of consent (2% macitentan 3 mg, 2% macitentan 10 mg, 1% placebo) and loss to follow up (1% macitentan 3 mg, 1% macitentan 10 mg, 3% placebo).

EFFICACY RESULTS

The primary objective of reduction in the risk of a morbidity or mortality event was assessed as the time from start of treatment to the first morbidity or mortality event up to end of treatment (EOT), defined as follows:

- Death or onset of a treatment-emergent adverse event with a fatal outcome occurring within 4 weeks of study treatment discontinuation, or
- Atrial septostomy or hospitalization for atrial septostomy, or
- Lung transplantation or hospitalization for lung transplantation, or
- Initiation of intravenous or subcutaneous prostanoids (e.g., epoprostenol, treprostinil) or hospitalization for initiation of intravenous or subcutaneous prostanoids, or
- Other worsening of PAH

Other worsening of PAH was defined by the combined occurrence in a patient of all the following three events:

- At least 15% decrease in the 6MWD from baseline, confirmed by two 6-minute walk tests, performed on separate days, within 2 weeks of each other.

AND

- Worsening of PAH symptoms that included at least one of the following:
 - Increase in WHO FC, or no change in patients in WHO FC IV at baseline
 - Appearance or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy

AND

- Need for new treatment(s) for PAH that included the following:
 - Oral or inhaled prostanoids (e.g., iloprost)
 - Oral phosphodiesterase inhibitors (e.g., sildenafil)
 - Endothelin receptor antagonists (e.g., bosentan, ambrisentan) only after discontinuation of the study treatment
 - Intravenous diuretics

The function of the clinical endpoints committee (CEC) was to review all mortality and morbidity events in a blinded fashion and to qualify or disqualify events. The table below shows the number and percent of patients by treatment group with at least one CEC confirmed event⁶.

⁶ The numbers of unconfirmed events were 20 for placebo, 16 for macitentan 3 mg and 9 for macitentan 10 mg.

Table 20 Summary of causes of primary endpoint events (CEC-confirmed), All-randomized set

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
	No.	No.	No.
Total PATIENTS with at least one confirmed event	116 46.4%	95 38.0%	76 31.4%
First confirmed event			
WORSENING OF PAH*	93 37.2%	72 28.8%	59 24.4%
DEATH	17 6.8%	21 8.4%	16 6.6%
IV/SC PROSTANOID INITIATION	6 2.4%	1 0.4%	1 0.4%
LUNG TRANSPLANTATION	-	1 0.4%	-

* Corresponds to 'Other worsening of PAH'
 CEC = Clinical Event Committee, EOT = End of treatment.
 Events confirmed by Independent CEC.
 Source: Table 89

Overall, the incidence rate of patients with CEC confirmed events was lower for the macitentan 10 mg group (31%) compared to macitentan 3 mg (38%) and placebo (46%) groups.

The reporting of death was slightly more frequent for macitentan 3 mg (8%) compared to placebo (7%) and macitentan 10 mg (7%). There were more IV/SC prostanoids initiations in the placebo group (2%) compared to the macitentan groups (0.4% each).

The largest cause of a CEC confirmed endpoint for all groups was worsening of PAH. There was a higher incidence rate of placebo patients (37%) reporting this portion of the primary endpoint compared to macitentan 3 mg (29%) and macitentan 10 mg (24%).

NB: CEC review and adjudication

In all, there were 341 morbidity/mortality events in 313 patients reviewed by the CEC:

- 48 events had to be resubmitted to the committee at least once;
- 102 received inconsistent adjudication and were discussed;
- 69 of the 102 events had disagreements related to the presence of a valid event.

Many of the conflicts resulted from the lack or inappropriately timed confirmatory walk test in ill patients.

2. The table below provides the requested information for the 67 patients who experienced the 69 events that required consensus for a valid primary endpoint event.

		Placebo (N=250)	Macitentan 3 mg (N=250)	Macitentan 10 mg (N=242)	Total (N=742)
Number of patients with adjudicated events		130	104	79	313
Number (%) ^(a) of patients with disagreement ^(b)		30 (23.1%)	23 (22.1%)	14 (17.7%)	67 (21.4%)
Number of adjudicated events		141	113	87	341
Number of events with disagreement ^(b)		30	25	14	69
Consensus	EVENT=YES	20	18	11	49
	EVENT=NO	10	7	3	20
(a) percentages based on the total number of patients with at least one adjudicated event (b) disagreement with regards to the presence of a valid primary endpoint event Two patients (12474 and 10960) in the Macitentan 3mg group had both two adjudicated events and for each of these patients, a confirmed event was recorded following an unconfirmed one. Source: cecdbrev.xpt (raw data) and cec.xpt (nonCDISC analysis dataset)					

Overall, there were fewer events (14) in the macitentan 10 mg group that caused disagreement compared to macitentan 3 mg (25) and placebo (30). The committee eventually reached consensus for most of the disputed events.

The table below shows the Kaplan-Meier estimate of the first confirmed event up to end of treatment plus 7 days. This is for all randomized patients.

Table 19 Kaplan-Meier estimate of the first confirmed morbidity or mortality event up to EOT + 7 days (CEC), All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT + 7 days (CEC) (Kaplan-Meier estimate)
 Analysis set: All randomized

K-M estimate of event-free (%)	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Month 6			
Patients at risk	188	213	208
Patients censored	14	11	17
Patients with event	48	26	17
K-M estimate (%)	80.1	89.3	92.7
Month 12			
Patients at risk	160	188	187
Patients censored	22	18	22
Patients with event	68	44	33
K-M estimate (%)	71.4	81.6	85.5
Month 18			
Patients at risk	135	166	171
Patients censored	25	19	26
Patients with event	90	65	45
K-M estimate (%)	61.5	72.5	79.9
Month 24			
Patients at risk	122	147	155
Patients censored	29	22	30
Patients with event	99	81	57
K-M estimate (%)	57.3	65.5	74.3
Month 30			
Patients at risk	64	80	91
Patients censored	74	82	86
Patients with event	112	88	65
K-M estimate (%)	50.2	61.9	70.0
Month 36			
Patients at risk	23	32	41
Patients censored	112	124	129
Patients with event	115	94	72
K-M estimate (%)	47.0	55.0	63.2
Month 42			
Patients at risk	1	4	1
Patients censored	133	151	165
Patients with event	116	95	76
K-M estimate (%)	43.9	52.4	49.1
Treatment difference			
Hazard ratio		0.704	0.547
97.5% CL of hazard ratio		0.516, 0.960	0.392, 0.762
Logrank p-value		0.0108	<.0001

K-M= Kaplan-Meier, CL= 2-sided confidence limits.
 CEC = Clinical Event Committee, EOT = End of treatment.
 Events confirmed by Independent CEC.
 Table MMTS_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12
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The hazard ratio versus placebo for the occurrence of a morbidity or mortality event in the macitentan 3 mg group was 0.704 (97.5% CLs 0.516, 0.960, log rank p = 0.0108). In the macitentan 10 mg dose group, the effect versus placebo was highly statistically significant as measured by the hazard ratio of 0.547 (97.5% CLs 0.392, 0.762, log rank p < 0.0001).

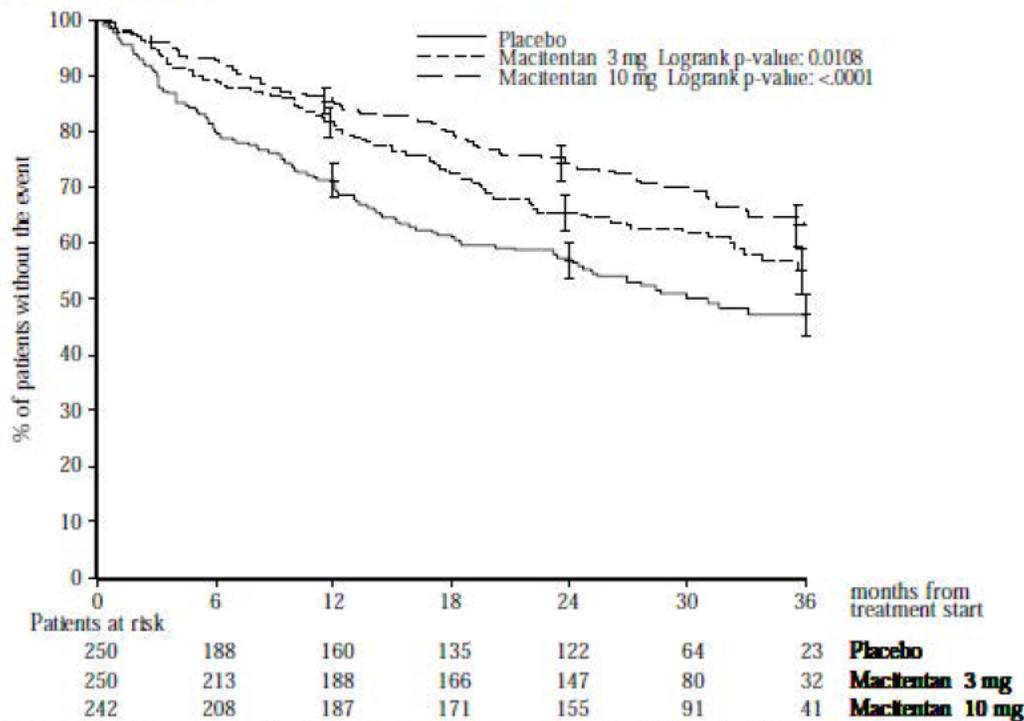
The Kaplan-Meier curves are shown below. The placebo separates from the macitentan groups about 12 months and all groups are separated from one another at 24 months. At 36 months the macitentan 10 mg is still distinct from placebo.

Figure 3 Kaplan-Meier curves of the first confirmed morbidity or mortality event up to EOT + 7 days, All-randomized set (Kaplan-Meier estimate)

ACT-064992, Protocol AC-055-302

Time to first confirmed morbidity/mortality event up to EOT+7 days (CEC) (Kaplan-Meier estimate with standard error bars)

Analysis set: All-randomized



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Statistical tests are performed including all data available during the follow-up period.
 Figure MMTBG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

A total of 94 (26 macitentan 3 mg, 34 macitentan 10 mg and 34 placebo) patients discontinued study treatment without experiencing events for the primary endpoint. Of these, 29 (7 macitentan 3 mg, 9 macitentan 10 mg and 13 placebo) did not experience a primary endpoint event even though they showed signs of PAH worsening.

The groups of patients discontinuing treatment showing or not showing signs of PAH worsening are displayed below.

Table 22 Summary of reasons for discontinuation from the treatment for patients without a primary endpoint event by signs of PAH worsening at the time of study drug discontinuation, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of reasons for discontinuation from the treatment for patients without a primary endpoint event by signs of PAH worsening at the time of study drug discontinuation
 Analysis set: All randomized

Preferred term	Placebo N=134		Macitentan 3 mg N=155		Macitentan 10 mg N=166		All patients N=455	
	No.	%	No.	%	No.	%	No.	%
Patients discontinuing treatment showing signs of PAH worsening	13	9.7%	7	4.5%	9	5.4%	29	6.4%
ADVERSE EVENT	6	4.5%	2	1.3%	8	4.8%	16	3.5%
DISEASE PROGRESSION NOT LEADING TO OL**	4	3.0%	-	-	1	0.6%	5	1.1%
WITHDRAWAL FROM TREATMENT	3	2.2%	4	2.6%	-	-	7	1.5%
TREATMENT FAILURE	2	1.5%	1	0.6%	-	-	3	0.7%
WITHDRAWAL OF CONSENT	1	0.7%	-	-	1	0.6%	2	0.4%
ADMINISTRATION OF FORBIDDEN DRUG	1	0.7%	-	-	-	-	1	0.2%
Patients discontinuing treatment showing NO sign of PAH worsening	21	15.7%	19	12.3%	25	15.1%	65	14.3%
WITHDRAWAL FROM TREATMENT	7	5.2%	3	1.9%	12	7.2%	22	4.8%
ADVERSE EVENT	6	4.5%	9	5.8%	6	3.6%	21	4.6%
ADMINISTRATIVE/OTHER	5	3.7%	2	1.3%	4	2.4%	11	2.4%
WITHDRAWAL OF CONSENT	-	-	3	1.9%	3	1.8%	6	1.3%
LOST TO FOLLOW-UP	3	2.2%	2	1.3%	-	-	5	1.1%

**Patients who terminated the treatment due to a mortality/morbidity event
 Table FWTENS_A - Produced by (b) (4) on 22JUN12 - Data dump of 26APR12
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The results are consistent with the primary analysis when the patients showing signs of PAH worsening are considered to have reached an endpoint and are included in the analysis.

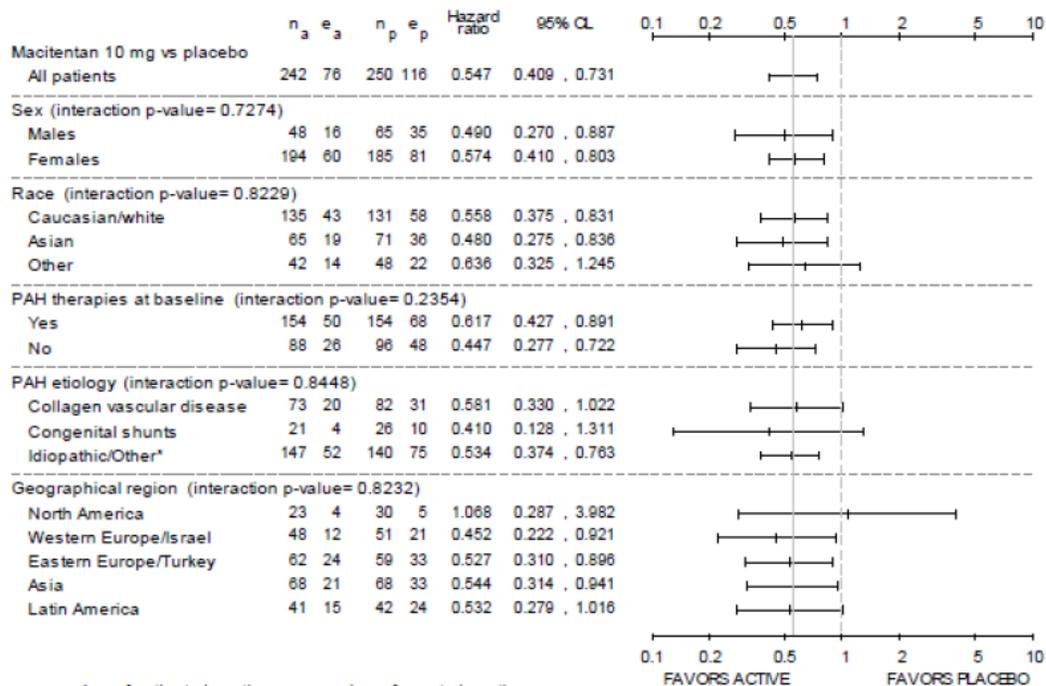
Table 21 Results of sensitivity analyses on the primary endpoint, All-randomized set

Sensitivity analyses	Treatment difference vs placebo	
	Hazard ratios (97.5% CLs, logrank p-value)	
	Macitentan 3 mg	Macitentan 10 mg
Analysis including events for patients who showed signs of worsening of PAH prior to premature discontinuation of study treatment	0.686 (0.509, 0.924, logrank p = 0.0044)	0.559 (0.408, 0.766, logrank p < 0.0001)

Subgroups

Subgroups examined for treatment effect (macitentan 10 mg vs. placebo) included sex, race, PAH therapies, PAH etiology and geographic regions. The figure below is a forest plot for time to first morbidity/mortality (hazard and 95% confidence limits).

ACT-064992, Protocol: AC-055-302
 Forest plot for time to first morbidity/mortality event (HR and 95% CL) - exploratory subgroup analysis
 Analysis set: All-randomized



n_a = number of patients in active; e_a = number of events in active
 n_p = number of patients in placebo; e_p = number of events in placebo

*Other etiology consists of idiopathic or familial PAH, or PAH related to HIV infection or drugs and toxins.

Figure MMT_HR_SG_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12

There is no difference in effect regarding gender and race (the “other” category was small). Those patients with no PAH therapies at baseline had a greater effect compared to the patients who were taking background therapy.

Patients with idiopathic PAH etiology had a greater effect than those with an etiology of collagen vascular disease or congenital shunts (small sample size).

It is of concern that there is no indication that macitentan 10 mg is better than placebo in the sites located in North America (although there is an effect in Western Europe/Israel where medical care should be similar to care in the US). This could be a result of small sample size in North America.

Concomitant PAH use

The table below shows the use of concomitant PAH at baseline.

Table 14 Summary of baseline characteristics, All-randomized set

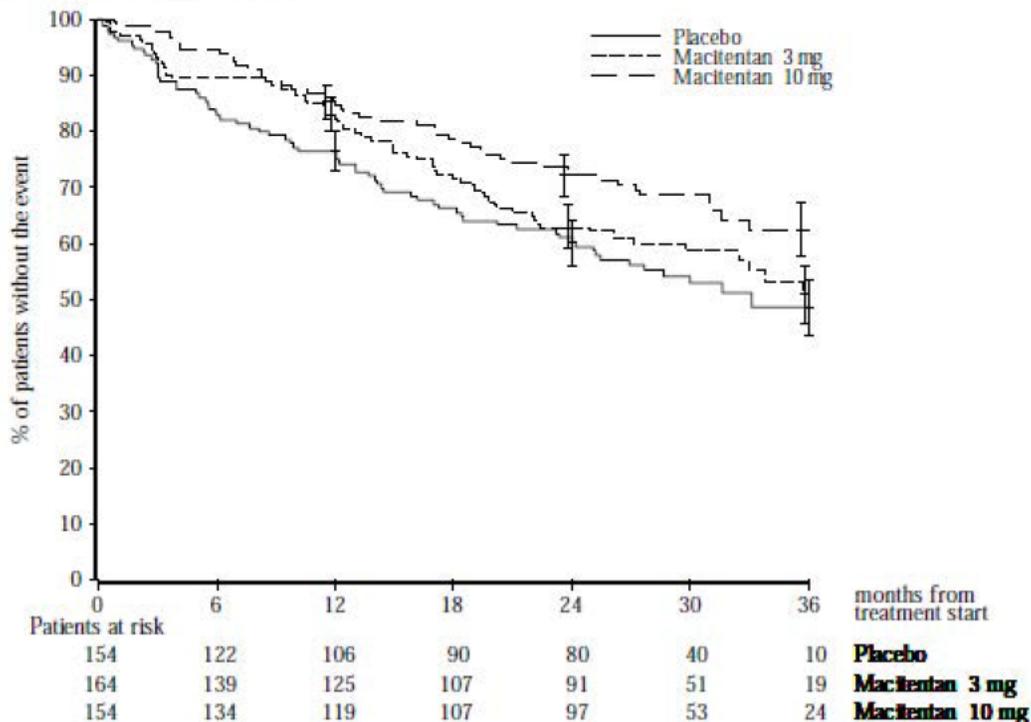
	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242	All patients N=742
Concomitant PAH therapy [n (%)]				
n	249	248	242	739
No	95 38.2%	85 34.3%	88 36.4%	268 36.3%
Yes	154 61.8%	163 65.7%	154 63.6%	471 63.7%
Sildenafil	140 56.2%	146 58.9%	140 57.9%	426 57.6%
Tadalafil	2 0.8%	3 1.2%	2 0.8%	7 0.9%
Vardenafil	8 3.2%	5 2.0%	8 3.3%	21 2.8%
Iloprost	3 1.2%	13 5.2%	10 4.1%	26 3.5%
Beraprost	4 1.6%	5 2.0%	6 2.5%	15 2.0%
Treprostinil	-	1 0.4%	-	1 0.1%

Sixty four percent of subjects (64%) were receiving PAH therapy at baseline and the incidence rates across treatment groups were similar. The most frequently used drug was sildenafil (58% of all randomized subjects were receiving sildenafil at baseline).

The figures below shows the Kaplan-Meier curves of the mortality or morbidity events for patients (figure 8) on concomitant PAH therapies followed by those not on concomitant PAH therapies (figure 7), for all treatment groups.

Figure 8 Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events for patients with concomitant PAH therapy at baseline, All-randomized set

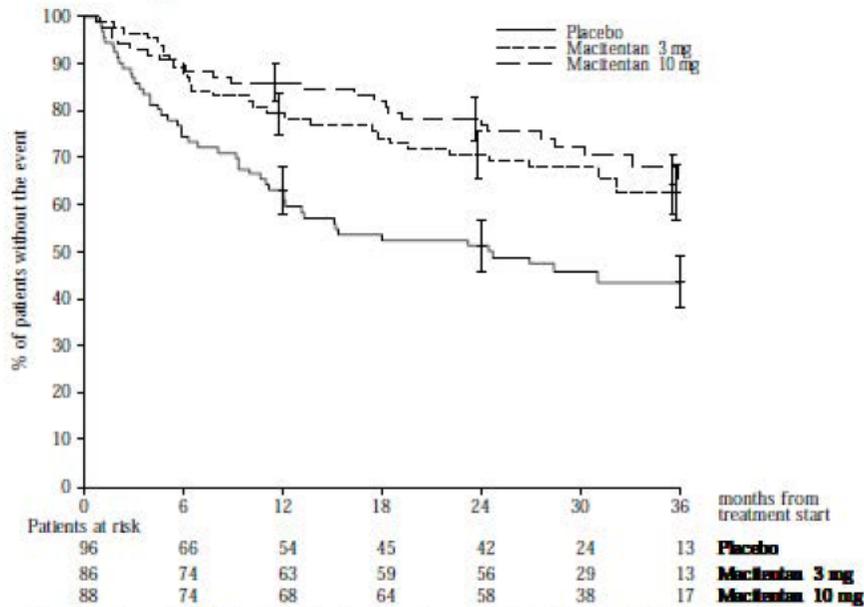
ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days (CEC) by concomitant PAH therapy at baseline (Kaplan-Meier estimate with standard error bars)
 Concomitant PAH therapy at baseline: Yes



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Figure MMT_PAHEG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

Figure 7 Kaplan-Meier curves of the CEC-confirmed morbidity or mortality events for patients without concomitant PAH therapy at baseline, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by concomitant PAH therapy at baseline
 (Kaplan-Meier estimate with standard error bars)
 Concomitant PAH therapy at baseline: No

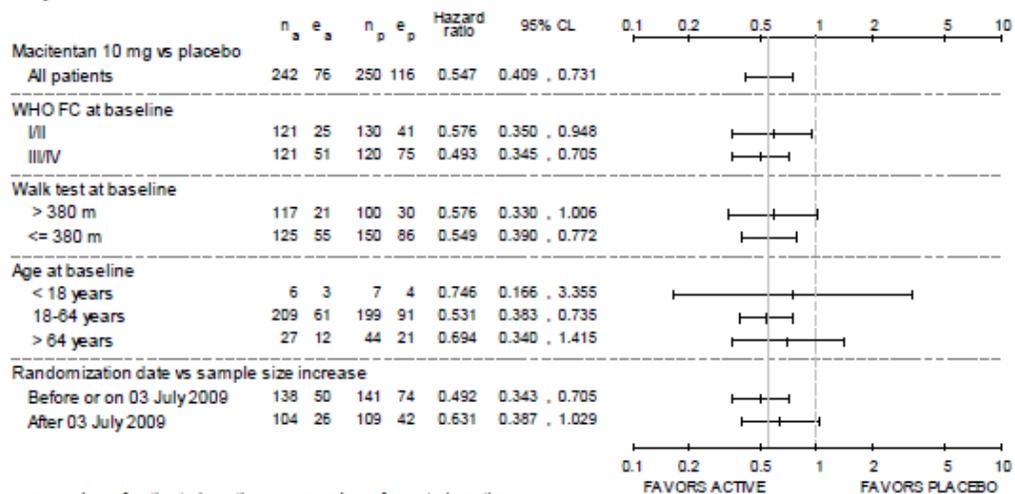


CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Figure MMT_PAHFG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

The primary endpoint for macitentan 10 mg compared to placebo by disease characteristics (WHO functional class, walk distance, age and randomization date vs. sample size increase) at baseline are shown below.

Figure 10 Primary endpoint (hazard ratio and 95% CLs) by baseline disease and demographic characteristics – robustness analysis, macitentan 10 mg vs placebo, All-randomized set

ACT-064992, Protocol: AC-055-302
 Graphical display for time to first confirmed morbidity/mortality event up to EOT+7 days (CEC)(HR and 95% CL) by baseline disease and demographic characteristics - Robustness of primary endpoint
 Analysis set: All-randomized



n_a = number of patients in active; e_a = number of events in active
 n_p = number of patients in placebo; e_p = number of events in placebo

CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.

Overall, the treatment effect was similar regardless of WHO FC, baseline walk distance, age (the group less than 18 years had few patients), and when the patients enrolled into the study.

Secondary endpoints

Secondary endpoints included change in 6MWD from baseline to Month 6, proportion of patients with improvement in modified WHO FC from baseline to Month 6, time to death due to PAH or hospitalization for PAH up to end of treatment (death due to PAH as identified by CEC up to end of treatment plus 7 days, or onset of a treatment-emergent adverse event with a fatal outcome due to PAH occurring up to 4 weeks after end of treatment, or hospitalization for PAH up to end of treatment plus 7 days), time to death of all causes up to end of treatment (death from all causes up to end of treatment plus 7 days, or onset of a treatment-emergent adverse event with a fatal outcome occurring up to 4 weeks after end of treatment, and time to death from all causes up to end of study).

Change in 6MWD from baseline to Month 6

The 6MWT was performed at screening, randomization (Day 1), Month 3, Month 6, and every 6 months thereafter, and at EOT/event visit.

The mean baseline walk distances were 352 m for placebo, 354 m for macitentan 3 mg, and 363 m for macitentan 10 mg. After 6 months of treatment, the placebo group had a mean decrease of 9.4 m compared to a mean increase of 7.4 m for the macitentan 3 mg group and 12.5 m for the macitentan 10 mg group in walk distance.

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Maryann Gordon, M.D.
NDA 204410, Opsumit® (macitentan)

The placebo-corrected mean change (\pm SD) from baseline in 6MWD was
16.8 m (\pm 96.95) in the macitentan 3 mg group and
22.0 m (\pm 92.58) in the macitentan 10 mg group.

The placebo-corrected median change from baseline in 6MWD was
14.0 m (97.5% CLs 2.0, 27.0, Wilcoxon rank sum $p = 0.0122$) in the macitentan 3 mg
group and
15.0 m (97.5% CLs 2.0, 28.0, Wilcoxon rank sum $p = 0.0078$) in the macitentan 10 mg
group.

Table 27 Change from baseline in walk distance to Month 6, All-randomized se

ACT-064992, Protocol: AC-055-302
 Change from baseline in walk distance to month 6
 Analysis set: All randomized

Walk distance (m)	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Use of supplemental oxygen during baseline walk test			
n	249	248	242
Yes	18 7.2%	21 8.5%	8 3.3%
No	231 92.8%	227 91.5%	234 96.7%
Baseline			
n	249	248	242
Mean	352	364	363
Standard deviation	110.6	95.5	93.2
Median	360	378	378
Q1 , Q3	284 , 428	311 , 425	300 , 434
Min , Max	65 , 650	80 , 610	90 , 578
Month 6			
n	249	248	242
Mean	343	371	375
Standard deviation	146.5	124.1	114.7
Median	365	394	390
Q1 , Q3	268 , 447	317 , 450	333 , 445
Min , Max	0 , 657	0 , 615	0 , 595
Imputations for missing values			
n	249	248	242
Total imputed at Month 6	52 20.9%	32 12.9%	30 12.4%
With an event (not death)			
Worst value	5 2.0%	2 0.8%	-
Carry-forward	23 9.2%	12 4.8%	10 4.1%
With an event (death only)			
Worst value	9 3.6%	6 2.4%	4 1.7%
Without an event			
Carry-forward (baseline)	7 2.8%	2 0.8%	10 4.1%
Carry-forward (not baseline)	8 3.2%	10 4.0%	6 2.5%
Change from baseline			
n	249	248	242
Mean	-9.4	7.4	12.5
Standard deviation	100.59	93.15	83.54
Median	1.0	17.0	15.5
Q1 , Q3	-42.0 , 44.0	-15.0 , 50.0	-14.0 , 51.0
Min , Max	-380.0 , 292.0	-465.0 , 258.0	-423.0 , 247.0
TREATMENT EFFECT			
Mean		16.8	22.0
Standard deviation		96.95	92.58
Standard error		8.70	8.36
97.5% CL of mean		-2.7 , 36.4	3.2 , 40.8
Median		14.0	15.0
97.5% CL of median		2.0 , 27.0	2.0 , 28.0
p-value Wilcoxon rank sum		0.0122	0.0078

Most study subjects did not use supplemental oxygen (>90%). However, supplemental oxygen was used less by macitentan 10 mg (3.3%) compared to placebo (7.2%) and macitentan (8.5%), indicating that subjects in the macitentan group were, perhaps, a little less sick.

Missing walk data

There were 52 (20.9%) placebo subjects, 32 (12.9%) macitentan 3 mg subjects and 30 (12.4%) macitentan 10 mg subjects who did not have 6 month walk data. Table 27 (above) shows how many subjects were assigned worst rank and how many were carried forward.

Overall, the mean change from baseline for 6MWD at month 6 was the longest for macitentan 10 mg group (12.5 m) compared to macitentan 3 mg (7.4 m) and placebo (-9.4 m). The mean treatment effect, therefore, was 16.8 m for macitentan 3 mg and 22.0 m for macitentan 10 mg. These increases in walk are statistically significant (0.0122 and 0.0078, respectively) but not clinically impressive.

6MWD at all assessed time points

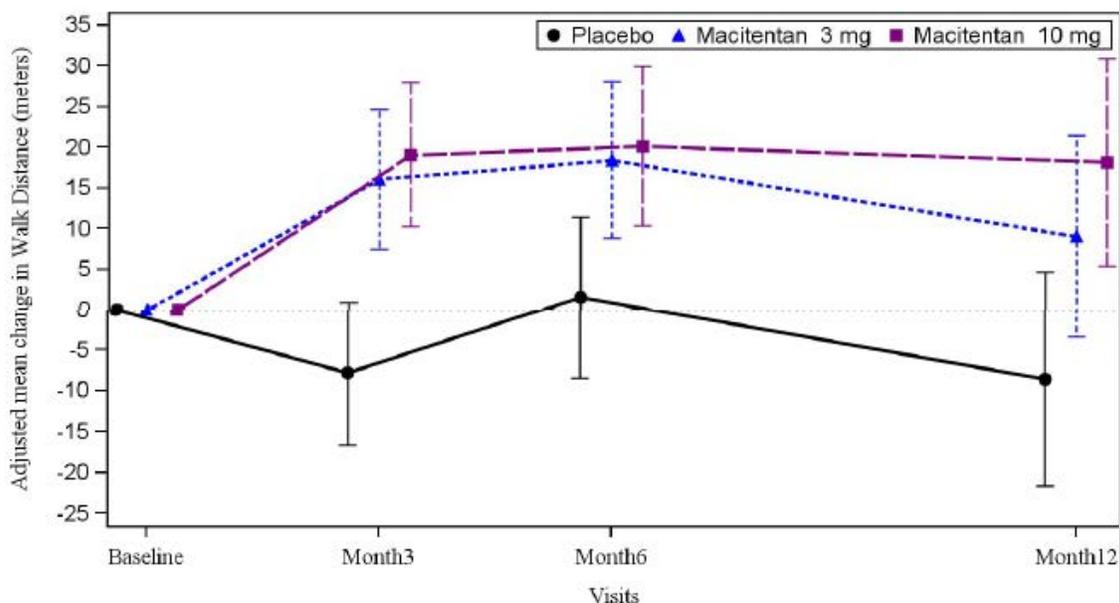
The figure below shows the change from baseline in the walk distance at months 3, 6 and 12.

Figure 17 Change from baseline in 6MWD at all visits up to Month 12, All-randomized set

ACT-064992, Protocol: AC-055-302

Plot of adjusted mean (95% CL) changes from baseline in Walk Distance values (meters) by visit up to Month 12

Analysis set: All-randomized



95% confidence limits of adjusted mean are displayed.

While the walk distance tended to drop below or stay near baseline level for the placebo group, both macitentan groups improved by month 3 and remained above baseline level at month 6 and month 12 as well.

Improvements in WHO functional class

At baseline, most patients were WHO class II or III. The table below shows the change in class at month 6 by treatment group.

Table 28 Improvements in WHO functional class: change from baseline to Month 6, All-randomized set

ACT-064992, Protocol: AC-055-302
 Improvements in WHO functional class: change from baseline to month 6
 Analysis set: All randomized

	n	Baseline	n	Month 6							
				I		II		III		IV	
				No.	%	No.	%	No.	%	No.	%
Placebo	249	I	-	-	-	-	-	-	-	-	-
		II	129	6	2.4%	101	40.6%	15	6.0%	7	2.8%
		III	116	1	0.4%	24	9.6%	60	24.1%	31	12.4%
		IV	4	-	-	1	0.4%	-	-	3	1.2%
Macitentan 3 mg	248	I	-	-	-	-	-	-	-	-	-
		II	138	13	5.2%	106	42.7%	11	4.4%	8	3.2%
		III	105	2	0.8%	30	12.1%	61	24.6%	12	4.8%
		IV	5	-	-	-	-	4	1.6%	1	0.4%
Macitentan 10 mg	242	I	1	1	0.4%	-	-	-	-	-	-
		II	120	18	7.4%	93	38.4%	8	3.3%	1	0.4%
		III	116	-	-	33	13.6%	75	31.0%	8	3.3%
		IV	5	-	-	-	-	3	1.2%	2	0.8%
		Placebo		Macitentan 3 mg		Macitentan 10 mg					
n		249		248		242					
Improved		32 12.9%		49 19.8%		54 22.3%					
Exact 97.5% CLs*		8.5%, 18.4%		14.4%, 26.1%		16.6%, 28.9%					
TREATMENT EFFECT:											
Risk Ratio				1.54				1.74			
97.5% CLs				0.96, 2.46				1.10, 2.74			
p-value Fisher's exact test				0.0395				0.0063			

* Clopper-Pearson formula
 Table WHOS_A - Produced by (b)(4) on 26APR12 - Data dump of 26APR12
 (Page 1/1)

At month 6, most patients did not change class. However, for those patients who improved in class, they were more likely to have been randomized to macitentan 3 mg and 10 mg (20% and 22%, respectively) compared to placebo (13%).

Regarding those patients that became worse by month,

- Placebo: 3% changed from class II at baseline to IV and 12% from class III at baseline to IV.
- Macitentan 3 mg: 3% changed from class II at baseline to IV and 5% from class III at baseline to IV.
- Macitentan 10 mg <1% changed from class II at baseline to IV and 3% from class III at baseline to IV.

Deaths caused by PAH or hospitalizations caused by PAH (end of treatment)

The table below shows the numbers and percentages of subjects whose CEC confirmed death or hospitalization was linked to PAH, by treatment group.

Table 116 Summary of all death due to PAH or hospitalization for PAH occurring up to EOT + 7 days, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of all death due to PAH or hospitalization for PAH occurring up to EOT + 7 days
 Analysis set: All randomized

	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one cause of death due to PAH or hospitalization for PAH	84	33.6%	65	26.0%	50	20.7%
Total patients with at least one cause of death due to PAH / Preferred term*	14	5.6%	14	5.6%	7	2.9%
RIGHT VENTRICULAR FAILURE	6	2.4%	5	2.0%	5	2.1%
PULMONARY ARTERIAL HYPERTENSION	3	1.2%	6	2.4%	2	0.8%
SUDDEN CARDIAC DEATH	2	0.8%	1	0.4%	-	-
RESPIRATORY FAILURE	-	-	2	0.8%	-	-
ACUTE RESPIRATORY FAILURE	1	0.4%	-	-	-	-
CARDIOPULMONARY FAILURE	1	0.4%	-	-	-	-
DEATH	1	0.4%	-	-	-	-
RENAL FAILURE	1	0.4%	-	-	-	-
PULMONARY EMBOLISM	-	-	-	-	1	0.4%
SUDDEN DEATH	-	-	1	0.4%	-	-
Total patients with at least one hospitalization for PAH	82	32.8%	58	23.2%	49	20.2%
Patients with confirmed worsening of PAH with a fatal outcome within 4 weeks of EOT (a)	1	0.4%	2	0.8%	-	-

EOT = End of treatment.

* Death due to PAH within EOT +7 confirmed by Clinical Event Committee (CEC). (a) Includes deaths within 4 weeks of EOT following a confirmed (CEC) worsening of PAH with a fatal outcome. Preferred terms from case report form (CRF) using MedDRA v.14.0, a patient may have more than one cause of death.

Table DPHCS_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12
 (page 1/1)

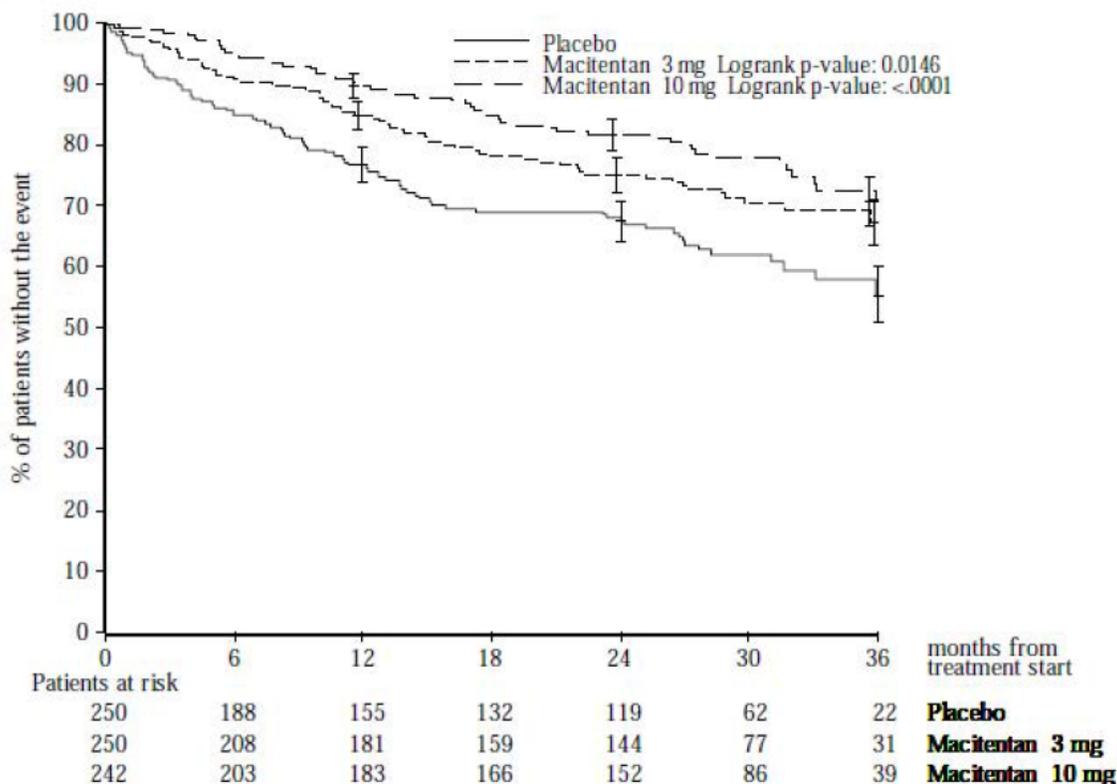
There was a lower incidence rate of subjects with a cause of death linked to PAH in the macitentan 10 mg group (3%) compared to macitentan 3 mg (6%) and placebo (6%).

There was a lower incidence rate of subjects with at least one hospitalization for PAH in the macitentan 10 mg group (20%) compared to macitentan 3 mg (23%) and placebo (33%).

The Kaplan-Meier curves of death or hospitalization because of PAH are shown below.

Figure 13 Kaplan-Meier curves of death due to PAH or hospitalization for PAH up to EOT + 7 days, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to death due to PAH or hospitalization for PAH up to EOT + 7 days (Kaplan-Meier estimate) with standard error bars)
 Analysis set: All-randomized



EOT = End of treatment. Death due to PAH confirmed by Clinical Event Committee (CEC), includes deaths within 4 weeks of EOT following a confirmed (CEC) worsening of PAH with a fatal outcome. Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up. Statistical tests are performed including all data available during the follow-up period.
 Figure DHPHGB_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

Hospitalizations

The table below shows the number per year of all-cause hospitalizations and number per year of in-patient hospital days by treatment group.

Table 151 **Number per year of all-cause hospitalizations and number per year of in-patient hospital days for all causes from baseline up to EOT + 28 days, All treated set**

ACT-064992, Protocol: AC-055-302
 Number per year of all-cause hospitalizations and number per year of in-patient hospital days
 for all causes from baseline up to EOT + 28 days
 Analysis set: All treated

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Number per year of all-cause hospitalizations			
n	249	250	242
Mean	1.0	0.6	0.5
Standard deviation	2.27	1.22	1.81
Standard error	0.14	0.08	0.12
Median	0.0	0.0	0.0
Q1 , Q3	0.0 , 1.0	0.0 , 0.8	0.0 , 0.4
Min , Max	0.0 , 24.4	0.0 , 10.0	0.0 , 24.4
Number per year of in-patient hospital days for all causes			
n	249	250	242
Mean	12.2	7.5	5.7
Standard deviation	37.57	21.12	19.38
Standard error	2.38	1.34	1.25
Median	0.0	0.0	0.0
Q1 , Q3	0.0 , 9.0	0.0 , 4.2	0.0 , 3.3
Min , Max	0.0 , 340.9	0.0 , 172.7	0.0 , 182.6

Table HOSAS_T - Produced by (b) (4) on 06JUN12 - Data dump of 26APR12
 (Page 1/1)

The numbers per year of all-cause hospitalizations were similar for all treatment groups.

The number of in-patient hospital days for all causes was lower for macitentan 10 mg (5.7 days) compared to macitentan 3 mg (7.5 days) and placebo (12.2 days).

Deaths from all causes (end of treatment)

All deaths are shown in the table below by treatment group.

Table 121 Summary of all death cases occurring up to EOT + 7 days (CRF)

ACT-064992, Protocol: AC-055-302
 Summary of all death cases occurring up to EOT + 7 days (CRF)
 Analysis set: All randomized

Cause of death (preferred term)	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one cause	19	7.6%	21	8.4%	14	5.8%
RIGHT VENTRICULAR FAILURE	6	2.4%	4	1.6%	6	2.5%
PULMONARY ARTERIAL HYPERTENSION	4	1.6%	6	2.4%	2	0.8%
SUDDEN DEATH	-	-	1	0.4%	2	0.8%
RESPIRATORY FAILURE	1	0.4%	2	0.8%	-	-
SUDDEN CARDIAC DEATH	2	0.8%	1	0.4%	-	-
ACUTE RESPIRATORY FAILURE	1	0.4%	1	0.4%	-	-
DEATH	1	0.4%	-	-	1	0.4%
ACUTE MYOCARDIAL INFARCTION	-	-	-	-	1	0.4%
ANGIOSARCOMA	-	-	1	0.4%	-	-
ARRHYTHMIA	-	-	-	-	1	0.4%
BACTERIAL SEPSIS	-	-	-	-	1	0.4%
CARDIAC ARREST	-	-	1	0.4%	-	-
CARDIO-RESPIRATORY ARREST	-	-	-	-	1	0.4%
DIARRHOEA INFECTIOUS	-	-	1	0.4%	-	-
HYPOVOLAEMIC SHOCK	-	-	1	0.4%	-	-
METASTATIC NEOPLASM	-	-	1	0.4%	-	-
MULTI-ORGAN DISORDER	-	-	1	0.4%	-	-
MULTI-ORGAN FAILURE	-	-	-	-	1	0.4%
OESOPHAGEAL VARICES HAEMORRHAGE	-	-	1	0.4%	-	-
PNEUMONIA INFLUENZAL	-	-	1	0.4%	-	-
ROAD TRAFFIC ACCIDENT	-	-	1	0.4%	-	-
SEPTIC SHOCK	-	-	1	0.4%	-	-
SYSTEMIC SCLEROSIS	-	-	-	-	1	0.4%
CARDIOGENIC SHOCK	2	0.8%	-	-	-	-
ACUTE LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
CARDIAC FAILURE CONGESTIVE	1	0.4%	-	-	-	-
CARDIOPULMONARY FAILURE	1	0.4%	-	-	-	-
LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
PANCREATIC MASS	1	0.4%	-	-	-	-
RENAL FAILURE	1	0.4%	-	-	-	-
SEPSIS	1	0.4%	-	-	-	-

CRF = Case report form , EOT = End of treatment: deaths reported on CRF up to EOT+7 days or occurring within four weeks of EOT following an adverse event with a fatal outcome that started up to EOT+7 days.
 Patients may have more than 1 cause of death. Preferred terms coded using MedDRA version 14.0.
 Table DCS_A - Produced by (b)(4) on 26APR12 - Data dump of 26APR12
 (Page 1/1)

There was a lower incidence rate of death resulting from any cause in the macitentan 10 mg group (6%) compared to macitentan 3 mg (8%) and placebo (8%).

Deaths from all causes (end of study)

The table below shows the number and percentages for deaths from all causes up to the end of study by treatment group.

**Table 126 Summary of all death cases occurring up to EOS (CRF),
 All-randomized set**

ACT-064992, Protocol: AC-055-302

Summary of all death cases occurring up to EOS (CRF), Analysis set: All randomized

Cause of death (preferred term)	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one cause	44	17.6%	47	18.8%	34	14.0%
RIGHT VENTRICULAR FAILURE	12	4.8%	10	4.0%	11	4.5%
PULMONARY ARTERIAL HYPERTENSION	8	3.2%	11	4.4%	7	2.9%
SUDDEN DEATH	-	-	2	0.8%	5	2.1%
CARDIAC ARREST	1	0.4%	2	0.8%	2	0.8%
SUDDEN CARDIAC DEATH	2	0.8%	2	0.8%	1	0.4%
DEATH	1	0.4%	2	0.8%	1	0.4%
RESPIRATORY FAILURE	1	0.4%	3	1.2%	-	-
MULTI-ORGAN FAILURE	-	-	2	0.8%	1	0.4%
CARDIOGENIC SHOCK	3	1.2%	1	0.4%	1	0.4%
PULMONARY EMBOLISM	2	0.8%	1	0.4%	1	0.4%
ACUTE MYOCARDIAL INFARCTION	-	-	1	0.4%	1	0.4%
CARDIOPULMONARY FAILURE	2	0.8%	-	-	1	0.4%
LEFT VENTRICULAR FAILURE	2	0.8%	-	-	1	0.4%
ACUTE RESPIRATORY FAILURE	1	0.4%	1	0.4%	-	-
CARDIO-RESPIRATORY ARREST	1	0.4%	-	-	1	0.4%
SEPTIC SHOCK	1	0.4%	1	0.4%	-	-
ACUTE RIGHT VENTRICULAR FAILURE	-	-	-	-	1	0.4%
ADVERSE DRUG REACTION	-	-	1	0.4%	-	-
ANGIOSARCOMA	-	-	1	0.4%	-	-
ARRHYTHMIA	-	-	-	-	1	0.4%
BACTERIAL SEPSIS	-	-	-	-	1	0.4%
CARDIAC FAILURE	-	-	-	-	1	0.4%
CARDIAC FAILURE CHRONIC	-	-	1	0.4%	-	-
CHRONIC RESPIRATORY FAILURE	-	-	1	0.4%	-	-
CIRCULATORY COLLAPSE	-	-	-	-	1	0.4%
COLON CANCER	-	-	1	0.4%	-	-
DIARRHOEA INFECTIOUS	-	-	1	0.4%	-	-
ENTEROCOCCAL SEPSIS	-	-	1	0.4%	-	-
GASTROINTESTINAL HAEMORRHAGE	-	-	1	0.4%	-	-
HAEMATEMESIS	-	-	-	-	1	0.4%
HYPONATRAEMIA	-	-	1	0.4%	-	-
HYPOTENSION	-	-	-	-	1	0.4%
HYPOVOLAEMIC SHOCK	-	-	1	0.4%	-	-
LIVER INJURY	-	-	1	0.4%	-	-
METABOLIC ACIDOSIS	-	-	1	0.4%	-	-
METASTATIC NEOPLASM	-	-	1	0.4%	-	-
MULTI-ORGAN DISORDER	-	-	1	0.4%	-	-
OESOPHAGEAL VARICES HAEMORRHAGE	-	-	1	0.4%	-	-
PNEUMONIA INFLUENZAL	-	-	1	0.4%	-	-
PULMONARY HYPERTENSION	-	-	-	-	1	0.4%
ROAD TRAFFIC ACCIDENT	-	-	1	0.4%	-	-
SYSTEMIC SCLEROSIS	-	-	-	-	1	0.4%
TOXICITY TO VARIOUS AGENTS	-	-	-	-	1	0.4%
RENAL FAILURE	2	0.8%	-	-	-	-
ACUTE LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
AORTIC ANEURYSM RUPTURE	1	0.4%	-	-	-	-
BRAIN CONTUSION	1	0.4%	-	-	-	-
BRAIN OEDEMA	1	0.4%	-	-	-	-
CARDIAC FAILURE CONGESTIVE	1	0.4%	-	-	-	-
CEREBROVASCULAR ACCIDENT	1	0.4%	-	-	-	-
PANCREATIC MASS	1	0.4%	-	-	-	-
PULMONARY OEDEMA	1	0.4%	-	-	-	-

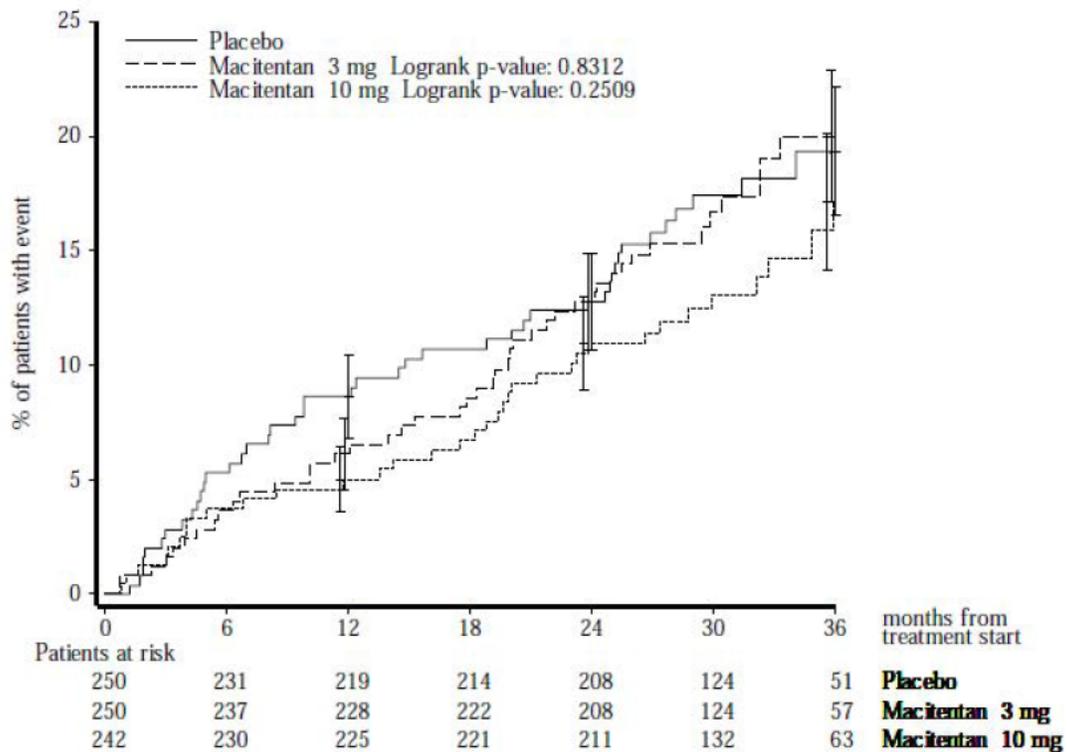
CRF = Case report form, EOS = End of study: deaths reported on CRF. Preferred terms coded using MedDRA version 14.0. Patients may have more than one cause of death.

Table DCEOS_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12, (Page 1/2)

There was a lower incidence rate of death resulting from any cause in the macitentan 10 mg group (14%) compared to macitentan 3 mg (19%) and placebo (18%). The Kaplan-Meier curves are shown below.

Figure 16 Kaplan-Meier curves of death of all causes up to EOS, All-randomized set

ACT-064992, Protocol: AC-055-302
 Time to death of all causes up to EOS (CRF) (Kaplan-Meier estimate with standard error bars)
 Analysis set: All-randomized



CRF = Case report form, EOS = End of study: deaths reported on CRF.
 Includes one patient who died after EOS following a confirmed (CEC) adverse event with a fatal outcome.
 Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
 Statistical tests are performed including all data available during the follow-up period.
 Figure DTEOBG_A - Produced by (b) (4) on 29MAY12 - Data dump of 26APR12

Borg dyspnea index

The table below shows the change from baseline at month 6 in the index by treatment group.

Table 35 Change from baseline in Borg dyspnea index to Month 6, All-randomized set

ACT-064992, Protocol: AC-055-302
 Change from baseline in Borg dyspnea index to month 6
 Analysis set: All randomized

Borg dyspnea index (Borg scale 0-10)

	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Baseline			
n	249	247	242
Mean	3.5	3.6	3.5
Standard deviation	2.11	2.27	2.27
Standard error	0.13	0.14	0.15
Median	3.0	3.0	3.0
Q1 , Q3	2.0 , 5.0	2.0 , 5.0	2.0 , 5.0
Min , Max	0.0 , 10.0	0.0 , 10.0	0.0 , 10.0
Month 6			
n	249	247	242
Mean	3.9	3.3	3.4
Standard deviation	2.76	2.43	2.47
Standard error	0.17	0.15	0.16
Median	3.0	3.0	3.0
Q1 , Q3	2.0 , 5.0	2.0 , 4.0	2.0 , 5.0
Min , Max	0.0 , 10.0	0.0 , 10.0	0.0 , 10.0
Imputations for missing values			
n	249	247	242
Total imputed at Month 6	52 20.9%	32 13.0%	30 12.4%
With an event			
Worst value	17 6.8%	9 3.6%	4 1.7%
Carry-forward	20 8.0%	11 4.5%	10 4.1%
Without an event			
Carry-forward (baseline)	7 2.8%	2 0.8%	10 4.1%
Carry-forward (not baseline)	8 3.2%	10 4.0%	6 2.5%
Change from baseline			
n	249	247	242
Mean	0.4	-0.3	-0.1
Standard deviation	2.10	2.40	2.02
Standard error	0.13	0.15	0.13
Median	0.0	0.0	0.0
Q1 , Q3	-1.0 , 1.0	-2.0 , 1.0	-1.0 , 0.0
Min , Max	-5.0 , 8.0	-8.0 , 9.0	-6.0 , 9.0
TREATMENT EFFECT			
Mean		-0.7	-0.5
Standard deviation		2.25	2.06
Standard error		0.20	0.19
97.5% CL of mean		-1.2 , -0.3	-1.0 , -0.1
Median		-0.5	-0.5
97.5% CL of median		-1.0 , 0.0	-1.0 , 0.0

Table BORGS_A - Produced by (b)(4) on 09MAY12 - Data dump of 26APR12
 Page (1/1)

There was some improvement in the index for the macitentan dose groups (-0.7 for 3 mg and -0.5 for 10 mg). The placebo group grew a little worse. These changes for the treatment groups were consistent at all clinic visits as shown in the table below.

Table 138 Repeated measures analysis of the change from baseline in Borg dyspnea index (Borg scale 0–10), All-randomized set

ACT-064992, Protocol: AC-055-302
 Repeated Measures Analysis of the Change from Baseline in Borg Dyspnea Index (Borg scale 0-10)
 Analysis set: All randomized

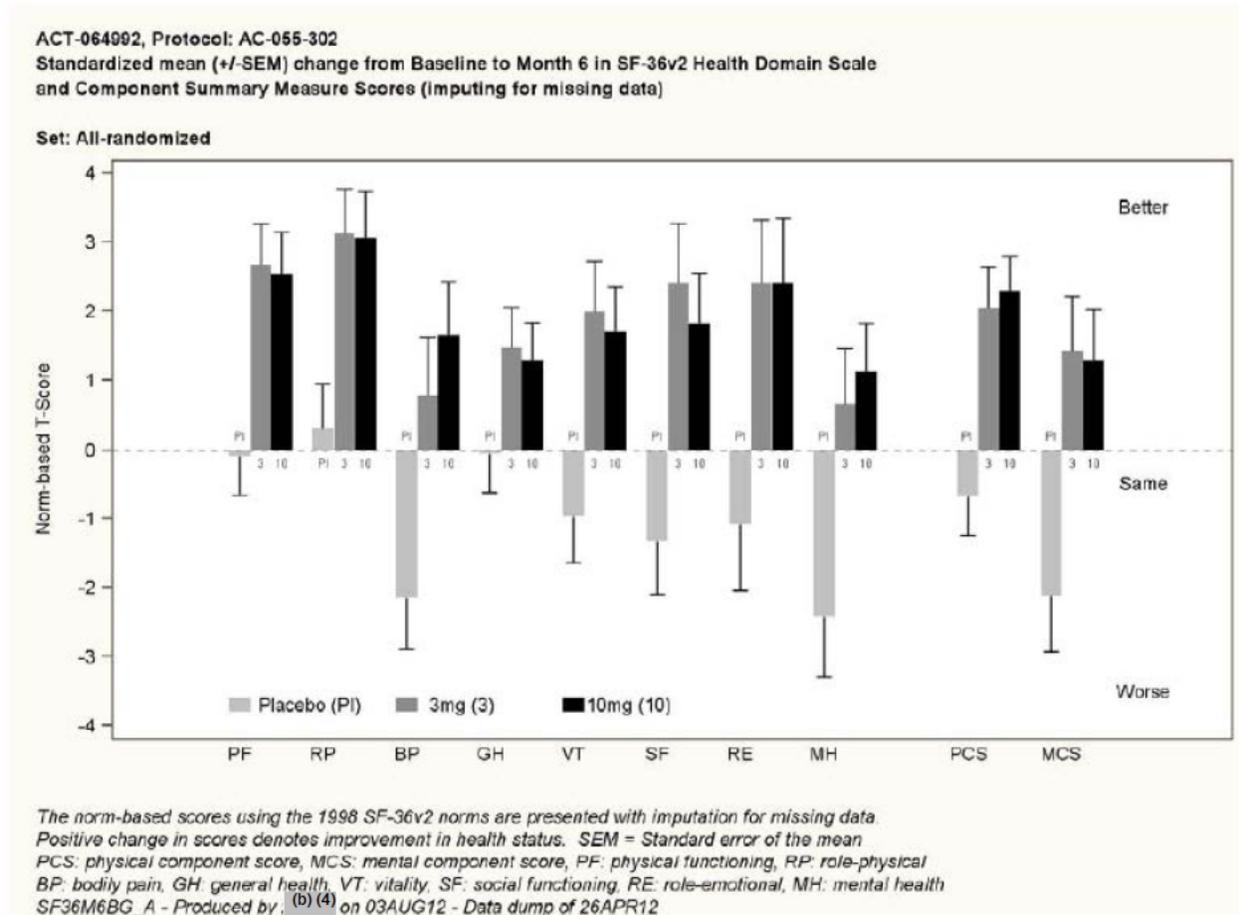
Test on Interaction term Interaction Treatment by Visit	p-value	Placebo N=250	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Adjusted Mean at Month 3 (95% CL) Difference to Placebo (95% CL) p-value*		0.13 (-0.09, 0.34)	-0.32 (-0.53, -0.11) -0.44 (-0.74, -0.14) 0.0038	-0.30 (-0.51, -0.09) -0.43 (-0.73, -0.12) 0.0057
Adjusted Mean at Month 6 (95% CL) Difference to Placebo (95% CL) p-value*		-0.02 (-0.24, 0.20)	-0.57 (-0.78, -0.36) -0.55 (-0.86, -0.25) 0.0004	-0.29 (-0.51, -0.07) -0.27 (-0.58, 0.04) 0.0834
Adjusted Mean at Month 12 (95% CL) Difference to Placebo (95% CL) p-value*		0.04 (-0.21, 0.29)	-0.39 (-0.63, -0.15) -0.43 (-0.78, -0.08) 0.0152	-0.37 (-0.61, -0.12) -0.41 (-0.76, -0.05) 0.0236
Adjusted# Treatment effect (95% CL) Difference to Placebo (95% CL) p-value*		0.05 (-0.13, 0.23)	-0.42 (-0.59, -0.24) -0.47 (-0.72, -0.22) 0.0002	-0.33 (-0.51, -0.15) -0.38 (-0.63, -0.13) 0.0029

Adjusted on visit and baseline value.

Quality of life questionnaire

The SF-36 questionnaire was used to assess quality of life. A higher score for the individual domains and summary component scores indicated a better condition of the patient.

Figure 18 Change from baseline to Month 6 in SF-36 health domains and component summary scores, All-randomized set (normalized)



The above figure indicates that the patients in the macitentan groups showed improvement compared to the patients in placebo.

Hemodynamic variables

A subgroup of subjects underwent hemodynamic measurements. The results are shown below.

Table 37 Treatment effect of macitentan (median changes vs placebo) on hemodynamic variables from baseline to Month 6, All-randomized set, patients participating in the PK/PD sub-study

	Placebo	Macitentan 3 mg	Macitentan 10 mg
PVR (dyn × sec/cm⁵)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 504 (±919)	Mean: -122 (±308)	Mean: -25 (±688)
Median [Range]	Median: 58 (-279, 3623)	Median: -61 (-1223, 587)	Median: -168 (-1690, 2668)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean percent change*: 62.2 (52.8, 73.3) Median percent change: 70.0 (56.0, 82.1)	Mean percent change*: 61.8 (49.9, 76.5) Median percent change: 63.5 (50.8, 78.3)
mRAP (mmHg)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 7.4 (±18.68)	Mean: 11.1 (±38.53)	Mean: 7.8 (±27.62)
Median [Range]	Median: 0 (-8, 75)	Median: 0 (-16, 182)	Median: 0 (-11, 119)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: 3.7 (-8.3, 15.6) Median: -0.6 (-3.0, 1.0)	Mean: 0.4 (-9.1, 9.9) Median: -1.0 (-3.0, 1.0)
mPAP (mmHg)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: 6.6 (±14.37)	Mean: -0.4 (±10.17)	Mean: 3.9 (±28.39)
Median [Range]	Median: 2.0 (-15, 57)	Median: 0 (-19.3, 2802)	Median: -2.0 (-33.0, 116.1)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: -6.9 (-12.0, -1.9) Median: -5.0 (-9.0, -1.0)	Mean: -2.7 (-11.7, 6.3) Median: -7.0 (-12.0, -2.0)
CI (L/min/m²)	n=67	n=62	n=57
Change from baseline (Mean [± SD])	Mean: -0.48 (±0.701)	Mean: 0.20 (±0.598)	Mean: 0.13 (±0.887)
Median [Range]	Median: -0.21 (-2.53, 0.44)	Median: 0.10 (-0.89, 1.76)	Median: 0.23 (-2.97, 1.99)
Treatment effect (macitentan vs placebo [97.5% CLs])		Mean: 0.68 (0.41, 0.94) Median: 0.53 (0.27, 0.86)	Mean: 0.61 (0.28, 0.93) Median: 0.58 (0.28, 0.93)

* Mean percent change over placebo = ratio of geometric means × 100

SAFETY REVIEW

Reviewer's safety summary

The mean durations of exposure in both macitentan groups (99.5 weeks and 103.9 weeks in the macitentan 3 mg group and 10 mg groups, respectively) were much longer than the exposure in the placebo group (85.3 weeks).

The maximum treatment duration was 188.0 weeks in both the macitentan 3 mg and 10 mg groups, and 184.9 weeks in the placebo group. This suggests that patients can tolerate the macitentan and, perhaps, believe that their disease is stable or has improved.

A somewhat higher percentage of macitentan patients (86% macitentan 3 mg and 88% macitentan 10 mg) added at least one concomitant medication during the study compared to placebo patients (84.8%). This may be the result of reported anemia in the macitentan groups and the prescribing of iron (10.8% macitentan 3 mg, 11.2% macitentan 10 mg and 3.6% placebo) as a result.

The use of antibiotics including amoxicillin/amoxicillin with clavulanate potassium, azithromycin, and ciprofloxacin were also higher in the macitentan groups compared to placebo. This raises the question of whether there is a greater chance of infection with use of macitentan.

Adverse events reported at higher rates in the 10 mg macitentan group compared to the placebo group (for events reported by at least 10% of macitentan 10 mg) are shown in the table below.

Percent of subjects (%)

Adverse events	Placebo N=249	Macitentan 10 mg N=242	Macitentan minus placebo
Anemia	3.2	13.2	10
Bronchitis	5.6	11.6	6
Headache	8.8	13.6	4.8
Nasopharyngitis	10.4	14.0	3.6
URTI	13.3	15.3	2

Anemia, headache, and respiratory tract infections were reported by more macitentan subjects than placebo subjects.

The observed risk of occurrences of adverse events associated with liver disorders and abnormal liver function were lower in the macitentan groups (for doses of 10 mg and less) compared to the placebo group. This could mean less liver congestion (i.e., less heart failure) with macitentan use.

The percentages of all reported deaths up to the end of study (EOS) were 17.6% for placebo, 18.8% macitentan 3 mg, and 14.0% macitentan 10 mg. There is no indication that macitentan up to 10 mg alters long term survival in subjects with PAH.

Reports of serious anemia were more frequent in the macitentan groups (2.0% macitentan 3 mg and 2.5% macitentan 10 mg) compared to placebo (0.4%). There were two discontinuations because of anemia (one each macitentan 3 mg and 10 mg) and one report of megaloblastic anemia (placebo). By month 3, there was a mean drop of about 1 g/dL in hemoglobin level from baseline in the macitentan 10 mg group which remained constant through month 16. No such decrease was seen in the placebo group. Drops in hemoglobin that were considered to be clinically relevant by the sponsor were more frequent in the macitentan 10 mg group (13.9%) compared to macitentan 3 mg (7.9%) and placebo (3.8%). There were 30 subjects (5 placebo, 9 macitentan 3 mg, 16 macitentan 10 mg) with reports of severe anemia and/or had a need for transfusion.

Markedly lower platelet counts were greatest in the macitentan 10 mg group (8.3%) compared to macitentan 3 mg (2.5%) and placebo (3.4%). Reports of serious thrombocytopenia included 1 each for macitentan 10 mg and placebo groups.

The percentages of drop out for the placebo and the macitentan 10 mg groups were similar (12% and 11%, respectively).

There were slightly higher incidence rates of reports of marked laboratory abnormalities for serum creatinine in the macitentan 10 mg (1.3%) and macitentan 3 mg (1.7%) compared to placebo (0.4%). There is no convincing evidence that the use of macitentan 10 mg or less has a harmful effect on the renal system.

Background

Extent of exposure

The table below shows the mean number of weeks that subjects were treated as well as the number (and percent) of subjects treated by selected months, by treatment group.

Table 38 Summary of treatment duration, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of treatment duration
 Analysis set: All treated

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Duration (weeks)			
n	249	250	242
Mean	85.3	99.5	103.9
Standard deviation	53.65	50.82	52.44
Standard error	3.40	3.21	3.37
Median	101.3	115.6	118.4
Q1 , Q3	30.0 , 128.9	52.6 , 136.3	60.0 , 144.0
Min , Max	0.3 , 184.9	0.7 , 188.0	0.3 , 188.0
Patients treated [n (%)]			
n	249	250	242
At least 3 months	223 89.6%	237 94.8%	226 93.4%
At least 6 months	197 79.1%	217 86.8%	208 86.0%
At least 12 months	163 65.5%	191 76.4%	188 77.7%
At least 18 months	139 55.8%	168 67.2%	171 70.7%
At least 24 months	124 49.8%	148 59.2%	157 64.9%
At least 30 months	67 26.9%	80 32.0%	91 37.6%
At least 36 months	24 9.6%	33 13.2%	41 16.9%
At least 42 months	1 0.4%	3 1.2%	2 0.8%

Table EXPOS_T - Produced by (b)(4) on 26APR12 - Data dump of 26APR12
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The mean durations of exposure in both macitentan groups (99.5 weeks and 103.9 weeks in the macitentan 3 mg group and 10 mg groups, respectively) were much longer than the exposure in the placebo group (85.3 weeks).

The maximum treatment duration was 188.0 weeks in both the macitentan 3 mg and 10 mg groups, and 184.9 weeks in the placebo group. This suggests that patients can tolerate the macitentan and, perhaps, believe that their disease is stable or has improved.

Concomitant medication

The table below shows the concomitant drugs taken after the start of the study by at least 10% of the patients in any treatment group.

Table 154 Summary of concomitant treatments that started on treatment, by frequency, All-randomized set

ACT-064992, Protocol: AC-055-302
 Summary of concomitant treatments that started on treatment, by frequency
 Analysis set: All randomized

Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	No.	%	No.	%	No.	%
ALL TREATMENT CLASSES						
Total patients with at least one concomitant treatment	212	84.8%	215	86.0%	213	88.0%
Total number of concomitant treatments	1524		2040		1680	
FUROSEMIDE	77	30.8%	81	32.4%	71	29.3%
PARACETAMOL	52	20.8%	64	25.6%	65	26.9%
SPIRONOLACTONE	28	11.2%	43	17.2%	28	11.6%
AMOXICILLIN	24	9.6%	31	12.4%	29	12.0%
AMOXICILLIN W/CLAVULANATE POTASSIUM	16	6.4%	25	10.0%	30	12.4%
IRON	9	3.6%	27	10.8%	27	11.2%
HEPARIN	33	13.2%	27	10.8%	26	10.7%
AZITHROMYCIN	22	8.8%	25	10.0%	25	10.3%
OMEPRAZOLE	23	9.2%	26	10.4%	21	8.7%
CIPROFLOXACIN	12	4.8%	21	8.4%	22	9.1%
POTASSIUM	25	10.0%	20	8.0%	20	8.3%

A somewhat higher percentage of macitentan patients (86% macitentan 3 mg and 88% macitentan 10 mg) added at least one concomitant medication during the study compared to placebo patients (84.8%). This may be the result of reported anemia in the macitentan groups and the prescribing of iron (10.8% macitentan 3 mg, 11.2% macitentan 10 mg and 3.6% placebo).

The use of antibiotics including amoxicillin/amoxicillin with clavulanate potassium, azithromycin, and ciprofloxacin were also higher in the macitentan groups compared to placebo. This raises the question of whether there is a greater chance of infection with use of macitentan.

Treatment emergent adverse events

The table below shows the number and percent of adverse events reported by at least 3% in any treatment group in order of frequency.

Table 40 Summary of adverse events during treatment period and up to 28 days after treatment discontinuation with incidence of at least 3% in any macitentan group, displayed by frequency, All-treated set

System Organ Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	N=249		N=250		N=242	
	No.	%	No.	%	No.	%
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one AE	240	96.4%	240	96.0%	229	94.6%
Total number of AEs	1365		1614		1446	
PULMONARY ARTERIAL HYPERTENSION	87	34.9%	75	30.0%	53	21.9%
UPPER RESPIRATORY TRACT INFECTION	33	13.3%	50	20.0%	37	15.3%
OEDEMA PERIPHERAL	45	18.1%	40	16.0%	44	18.2%
NASOPHARYNGITIS	26	10.4%	37	14.8%	34	14.0%
RIGHT VENTRICULAR FAILURE	56	22.5%	37	14.8%	32	13.2%
HEADACHE	22	8.8%	33	13.2%	33	13.6%
ANAEMIA	8	3.2%	22	8.8%	32	13.2%
DIZZINESS	27	10.8%	24	9.6%	26	10.7%
BRONCHITIS	14	5.6%	20	8.0%	28	11.6%
DYSPNOEA	22	8.8%	26	10.4%	18	7.4%
COUGH	30	12.0%	20	8.0%	21	8.7%
CHEST PAIN	20	8.0%	20	8.0%	19	7.9%
URINARY TRACT INFECTION	14	5.6%	16	6.4%	21	8.7%
DIARRHOEA	17	6.8%	14	5.6%	22	9.1%
INSOMNIA	10	4.0%	17	6.8%	17	7.0%
SYNCOPE	21	8.4%	21	8.4%	11	4.5%
HYPOTENSION	11	4.4%	14	5.6%	15	6.2%
HYPOKALAEMIA	14	5.6%	13	5.2%	14	5.8%
PALPITATIONS	13	5.2%	14	5.6%	12	5.0%
ARTHRALGIA	10	4.0%	15	6.0%	11	4.5%
PHARYNGITIS	7	2.8%	11	4.4%	15	6.2%
BACK PAIN	21	8.4%	16	6.4%	9	3.7%
NAUSEA	13	5.2%	13	5.2%	12	5.0%
INFLUENZA	4	1.6%	11	4.4%	14	5.8%
RESPIRATORY TRACT INFECTION VIRAL	9	3.6%	9	3.6%	15	6.2%
SINUSITIS	6	2.4%	11	4.4%	11	4.5%
FATIGUE	15	6.0%	11	4.4%	9	3.7%
PNEUMONIA	13	5.2%	10	4.0%	10	4.1%
GASTROENTERITIS	3	1.2%	12	4.8%	8	3.3%
EPISTAXIS	9	3.6%	11	4.4%	8	3.3%
VOMITING	17	6.8%	8	3.2%	10	4.1%
RESPIRATORY TRACT INFECTION	10	4.0%	9	3.6%	9	3.7%
PYREXIA	9	3.6%	9	3.6%	9	3.7%
THROMBOCYTOPENIA	7	2.8%	6	2.4%	12	5.0%
PAIN IN EXTREMITY	15	6.0%	10	4.0%	7	2.9%
DYSPEPSIA	14	5.6%	10	4.0%	7	2.9%
ABDOMINAL PAIN UPPER	11	4.4%	5	2.0%	11	4.5%
GASTRITIS	7	2.8%	10	4.0%	6	2.5%
CONSTIPATION	6	2.4%	9	3.6%	7	2.9%
ABDOMINAL PAIN	4	1.6%	8	3.2%	7	2.9%
MYALGIA	4	1.6%	7	2.8%	8	3.3%
SKIN ULCER	3	1.2%	7	2.8%	8	3.3%
RASH	7	2.8%	8	3.2%	6	2.5%
ASPARTATE AMINOTRANSFERASE INCREASED	10	4.0%	9	3.6%	4	1.7%
GASTROESOPHAGEAL REFLUX DISEASE	10	4.0%	8	3.2%	5	2.1%
DEPRESSION	8	3.2%	5	2.0%	8	3.3%
HYPERTENSION	4	1.6%	8	3.2%	3	1.2%
RHINITIS	2	0.8%	3	1.2%	8	3.3%

Events reported at higher rates in the macitentan groups compared to the placebo group (for events reported by at least 10% of any treatment group) are shown in the table below.

Percent of subjects (%)

Adverse events	Placebo N=249	Macitentan 3mg N=250	Macitentan10 mg N=242
URTI	13.3	20.0	15.3
Nasopharyngitis	10.4	14.8	14.0
Headache	8.8	13.2	13.6
Anemia	3.2	8.8	13.2
Bronchitis	5.6	8.0	11.6
UTI	5.6	6.4	8.7
Hypotension	4.4	5.6	6.2
Pharyngitis	2.8	4.4	6.2
Influenza	1.6	4.4	5.8
Viral respiratory tract infection	3.6	3.6	6.2
Sinusitis	2.4	4.4	4.5
Gastroenteritis	1.2	4.8	3.3
Thrombocytopenia	2.8	2.4	5.0
Rhinitis	0.8	1.2	3.3

Symptoms associated with infections were reported by more by macitentan subjects than placebo subjects. Also, anemia, headache and thrombocytopenia reportings were higher in the macitentan groups compared to placebo.

On the other hand, adverse events including PAH, right heart failure, and cough were reported by more placebo subjects compared to macitentan subjects.

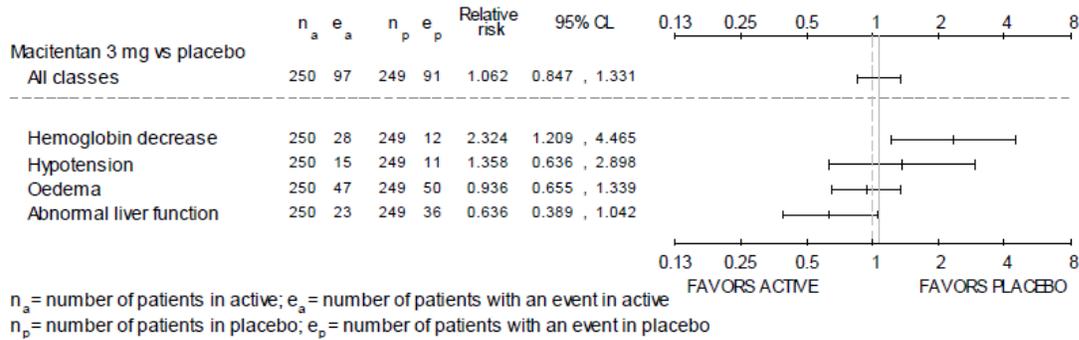
Percent of subjects (%)

Adverse events	Placebo N=249	Macitentan 3mg N=250	Macitentan10 mg N=242
PAH	34.9	30.0	21.9
Right ventricular failure	22.5	14.8	13.2
Cough	12.0	8.0	8.7

The figure below shows the relative risk of occurrence of the sponsor-selected adverse events of special interest.

Figure 56 Graphical display for incidence of AEs of special interest – relative risk and 95% CLs, All-treated set

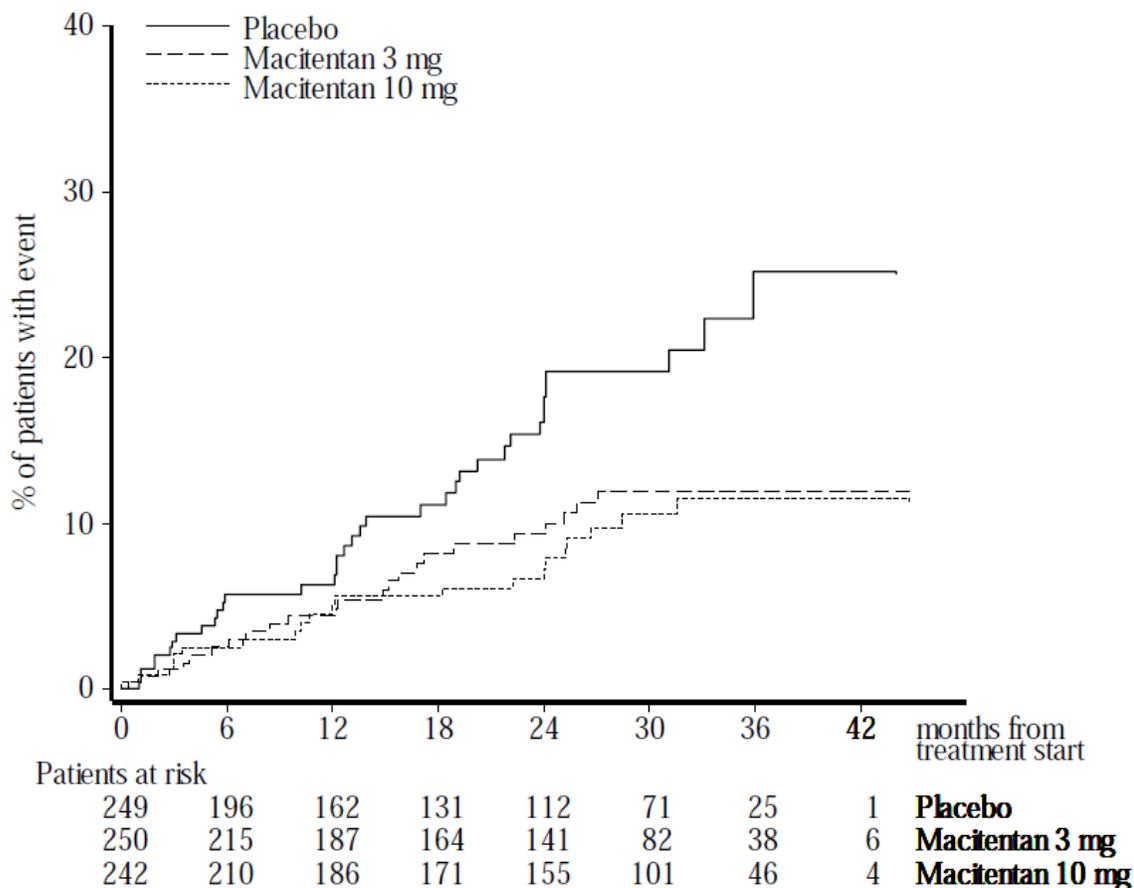
ACT-064992, Protocol: AC-055-302
 Graphical display for incidence of AEs of special interest – Relative Risk and 95% CL
 Analysis set: All-treated



Of these events, the results for hemoglobin decrease is the most likely to be related to macitentan use. On the other hand, hypotension, edema, and, especially, abnormal liver function are probably unrelated. See the figure below showing the Kaplan-Meier curves of liver disorders and abnormal liver function related adverse events.

Figure 19 Kaplan-Meier curves of liver disorders and abnormal liver function-related adverse events up to 28 days after treatment discontinuation, All-treated set

ACT-064992, Protocol: AC-055-302
 Time to first abnormal liver function related adverse event up to 28 days after treatment discontinuation
 Analysis set: All-treated



The observed risk of occurrence of adverse events associated with liver disorders and abnormal liver function was lower in the macitentan groups compared to the placebo group. This could mean less liver congestion (i.e., less heart failure) with macitentan use.

Serious Safety

Deaths

The numbers (and percentages) of patients who died after the start of study treatment up to end of treatment (EOT) plus 28 days were 22 (8.8%) in the macitentan 3 mg group, 16 (6.6%) in the macitentan 10 mg group, and 21 (8.4%) in the placebo group.

The table below is a summary of all reported deaths within the above stated time frame.

Table 42 Summary of all death cases occurring during treatment period and up to 28 days after treatment discontinuation, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of all death cases occurring during treatment period and up to 28 days after treatment discontinuation
 Analysis set: All treated

Cause of death	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one cause	21	8.4%	22	8.8%	16	6.6%
RIGHT VENTRICULAR FAILURE	6	2.4%	4	1.6%	6	2.5%
PULMONARY ARTERIAL HYPERTENSION	3	1.2%	6	2.4%	2	0.8%
SUDDEN DEATH	-	-	1	0.4%	2	0.8%
SUDDEN CARDIAC DEATH	2	0.8%	1	0.4%	1	0.4%
RESPIRATORY FAILURE	1	0.4%	2	0.8%	-	-
ACUTE RESPIRATORY FAILURE	1	0.4%	1	0.4%	-	-
DEATH	1	0.4%	-	-	1	0.4%
PULMONARY EMBOLISM	1	0.4%	-	-	1	0.4%
ACUTE MYOCARDIAL INFARCTION	-	-	-	-	1	0.4%
ANGIOSARCOMA	-	-	1	0.4%	-	-
ARRHYTHMIA	-	-	-	-	1	0.4%
BACTERIAL SEPSIS	-	-	-	-	1	0.4%
CARDIAC ARREST	-	-	1	0.4%	-	-
CARDIO-RESPIRATORY ARREST	-	-	-	-	1	0.4%
DIARRHOEA INFECTIOUS	-	-	1	0.4%	-	-
GASTROINTESTINAL HAEMORRHAGE	-	-	1	0.4%	-	-
HAEMATEMESIS	-	-	-	-	1	0.4%
HYPVOLEAEMIC SHOCK	-	-	1	0.4%	-	-
METABOLIC ACIDOSIS	-	-	1	0.4%	-	-
METASTATIC NEOPLASM	-	-	1	0.4%	-	-
MULTI-ORGAN DISORDER	-	-	1	0.4%	-	-
MULTI-ORGAN FAILURE	-	-	-	-	1	0.4%
OESOPHAGEAL VARICES HAEMORRHAGE	-	-	1	0.4%	-	-
PNEUMONIA INFLUENZAL	-	-	1	0.4%	-	-
ROAD TRAFFIC ACCIDENT	-	-	1	0.4%	-	-
SEPTIC SHOCK	-	-	1	0.4%	-	-
SYSTEMIC SCLEROSIS	-	-	-	-	1	0.4%
CARDIOGENIC SHOCK	2	0.8%	-	-	-	-
ACUTE LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
CARDIAC FAILURE CONGESTIVE	1	0.4%	-	-	-	-
CARDIOPULMONARY FAILURE	1	0.4%	-	-	-	-
LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
PANCREATIC MASS	1	0.4%	-	-	-	-
RENAL FAILURE	1	0.4%	-	-	-	-
SEPSIS	1	0.4%	-	-	-	-
SYSTEMIC LUPUS ERYTHEMATOSUS	1	0.4%	-	-	-	-

Table DEAS_T - Produced by (b) (4) on 07MAY12 - Data dump of 26APR12
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The most common causes of death were reported as right ventricular failure and PAH.

During the period of EOT plus 28 days and end of study (EOS), there were a total of 25, 18 and 23 patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively.

The table below shows all reported deaths up to EOS.

Table 126 Summary of all death cases occurring up to EOS (CRF), All-randomized set

ACT-064992, Protocol: AC-055-302

Summary of all death cases occurring up to EOS (CRF), Analysis set: All randomized

Cause of death (preferred term)	Placebo N=250		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
Total patients with at least one cause	44	17.6%	47	18.8%	34	14.0%
RIGHT VENTRICULAR FAILURE	12	4.8%	10	4.0%	11	4.5%
PULMONARY ARTERIAL HYPERTENSION	8	3.2%	11	4.4%	7	2.9%
SUDDEN DEATH	-	-	2	0.8%	5	2.1%
CARDIAC ARREST	1	0.4%	2	0.8%	2	0.8%
SUDDEN CARDIAC DEATH	2	0.8%	2	0.8%	1	0.4%
DEATH	1	0.4%	2	0.8%	1	0.4%
RESPIRATORY FAILURE	1	0.4%	3	1.2%	-	-
MULTI-ORGAN FAILURE	-	-	2	0.8%	1	0.4%
CARDIOGENIC SHOCK	3	1.2%	1	0.4%	1	0.4%
PULMONARY EMBOLISM	2	0.8%	1	0.4%	1	0.4%
ACUTE MYOCARDIAL INFARCTION	-	-	1	0.4%	1	0.4%
CARDIOPULMONARY FAILURE	2	0.8%	-	-	1	0.4%
LEFT VENTRICULAR FAILURE	2	0.8%	-	-	1	0.4%
ACUTE RESPIRATORY FAILURE	1	0.4%	1	0.4%	-	-
CARDIO-RESPIRATORY ARREST	1	0.4%	-	-	1	0.4%
SEPTIC SHOCK	1	0.4%	1	0.4%	-	-
ACUTE RIGHT VENTRICULAR FAILURE	-	-	-	-	1	0.4%
ADVERSE DRUG REACTION	-	-	1	0.4%	-	-
ANGIOSARCOMA	-	-	1	0.4%	-	-
ARRHYTHMIA	-	-	-	-	1	0.4%
BACTERIAL SEPSIS	-	-	-	-	1	0.4%
CARDIAC FAILURE	-	-	-	-	1	0.4%
CARDIAC FAILURE CHRONIC	-	-	1	0.4%	-	-
CHRONIC RESPIRATORY FAILURE	-	-	1	0.4%	-	-
CIRCULATORY COLLAPSE	-	-	-	-	1	0.4%
COLON CANCER	-	-	1	0.4%	-	-
DIARRHOEA INFECTIOUS	-	-	1	0.4%	-	-
ENTEROCOCCAL SEPSIS	-	-	1	0.4%	-	-
GASTROINTESTINAL HAEMORRHAGE	-	-	1	0.4%	-	-
HAEMATEMESIS	-	-	-	-	1	0.4%
HYPONATRAEMIA	-	-	1	0.4%	-	-
HYPOTENSION	-	-	-	-	1	0.4%
HYPOVOLAEMIC SHOCK	-	-	1	0.4%	-	-
LIVER INJURY	-	-	1	0.4%	-	-
METABOLIC ACIDOSIS	-	-	1	0.4%	-	-
METASTATIC NEOPLASM	-	-	1	0.4%	-	-
MULTI-ORGAN DISORDER	-	-	1	0.4%	-	-
ESOPHAGEAL VARICES HAEMORRHAGE	-	-	1	0.4%	-	-
PNEUMONIA INFLUENZAL	-	-	1	0.4%	-	-
PULMONARY HYPERTENSION	-	-	-	-	1	0.4%
ROAD TRAFFIC ACCIDENT	-	-	1	0.4%	-	-
SYSTEMIC SCLEROSIS	-	-	-	-	1	0.4%
TOXICITY TO VARIOUS AGENTS	-	-	-	-	1	0.4%
RENAL FAILURE	2	0.8%	-	-	-	-
ACUTE LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
AORTIC ANEURYSM RUPTURE	1	0.4%	-	-	-	-
BRAIN CONTUSION	1	0.4%	-	-	-	-
BRAIN OEDEMA	1	0.4%	-	-	-	-
CARDIAC FAILURE CONGESTIVE	1	0.4%	-	-	-	-
CEREBROVASCULAR ACCIDENT	1	0.4%	-	-	-	-
PANCREATIC MASS	1	0.4%	-	-	-	-
PULMONARY OEDEMA	1	0.4%	-	-	-	-

CRF = Case report form, EOS = End of study; deaths reported on CRF. Preferred terms coded using MedDRA version 14.0. Patients may have more than one cause of death.
 Table DCEOS_A - Produced by (b) (4) on 26APR12 - Data dump of 26APR12, (Page 1/2)

The numbers and (percentages) of all reported deaths were 44 (17.6%) for placebo, 47 (18.8%) macitentan 3 mg, and 34 (14.0%) macitentan 10 mg. Even with the added deaths, the two main reasons for death remain unchanged (right ventricular failure and PAH).

There is no indication that macitentan up to 10 mg alters survival in subjects with PAH.

Other serious adverse events

The percentages of patients who reported serious adverse events were 55% for placebo, 52% for macitentan 3 mg and 45% macitentan 10 mg.

The table below shows the reported serious adverse events (EOT plus 28 days after treatment discontinuation) by frequency.

Table 43 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation (at least 2 patients in any macitentan group), displayed by frequency, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by frequency
 Analysis set: All treated

System Organ Class / Preferred Term	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one SAE	137	55.0%	130	52.0%	109	45.0%
Total number of SAEs	246		246		189	
PULMONARY ARTERIAL HYPERTENSION	56	22.5%	48	19.2%	32	13.2%
RIGHT VENTRICULAR FAILURE	40	16.1%	21	8.4%	23	9.5%
PNEUMONIA	8	3.2%	7	2.8%	4	1.7%
SYNCOPE	6	2.4%	7	2.8%	4	1.7%
ANAEMIA	1	0.4%	5	2.0%	6	2.5%
HAEMOPTYSIS	4	1.6%	4	1.6%	3	1.2%
CHEST PAIN	1	0.4%	4	1.6%	3	1.2%
ATRIAL FLUTTER	2	0.8%	2	0.8%	4	1.7%
RESPIRATORY FAILURE	2	0.8%	3	1.2%	3	1.2%
GASTROENTERITIS	2	0.8%	3	1.2%	2	0.8%
PREGNANCY	2	0.8%	5	2.0%	-	
RENAL FAILURE ACUTE	-		4	1.6%	1	0.4%
DYSPNOEA	1	0.4%	2	0.8%	2	0.8%
PANCREATITIS ACUTE	-		3	1.2%	1	0.4%
BRONCHITIS	1	0.4%	2	0.8%	1	0.4%
CARDIAC ARREST	1	0.4%	3	1.2%	-	
PULMONARY EMBOLISM	1	0.4%	1	0.4%	2	0.8%
UPPER RESPIRATORY TRACT INFECTION	1	0.4%	3	1.2%	-	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	-		3	1.2%	-	
MEMORRHAGIA	-		2	0.8%	1	0.4%
SKIN ULCER	-		2	0.8%	1	0.4%
SUDDEN DEATH	-		1	0.4%	2	0.8%
SUPRAVENTRICULAR TACHYCARDIA	-		1	0.4%	2	0.8%
URINARY TRACT INFECTION	3	1.2%	-		2	0.8%
RESPIRATORY TRACT INFECTION	2	0.8%	-		2	0.8%
UPPER GASTROINTESTINAL HAEMORRHAGE	2	0.8%	2	0.8%	-	
ACUTE RESPIRATORY FAILURE	1	0.4%	2	0.8%	-	
ALANINE AMINOTRANSFERASE INCREASED	1	0.4%	-		2	0.8%
ASPARTATE AMINOTRANSFERASE INCREASED	1	0.4%	-		2	0.8%
DIARRHOEA	1	0.4%	-		2	0.8%
LIVER FUNCTION TEST ABNORMAL	1	0.4%	-		2	0.8%
LOWER RESPIRATORY TRACT INFECTION	1	0.4%	2	0.8%	-	
COLON CANCER	-		2	0.8%	-	
DYSFUNCTIONAL UTERINE BLEEDING	-		2	0.8%	-	
ERYSIPELAS	-		2	0.8%	-	
PYREXIA	-		2	0.8%	-	
SYSTEMIC SCLEROSIS	-		-		2	0.8%

Source: Table 169

As with cause of death, the reasons, PAH and right ventricular failure, were reported most frequently (both events had higher incidence rates in the placebo group compared to the macitentan groups).

Reports of serious anemia were more frequent in the macitentan groups (2.0% macitentan 3 mg and 2.5% macitentan 10 mg) compared to placebo (0.4%).

There were 6 patients with reports of serious acute renal failure/renal failure: 4 macitentan 3 mg, 1 macitentan 10 mg, 1 placebo.

There were 4 patients with reports of acute pancreatitis/ relapsing pancreatitis: 3 macitentan 3 mg, 1 macitentan 10 mg).

Other events including respiratory disorders, malignant neoplasms, and elevations of AST/ALT were similar across treatment groups.

Adverse events resulting in discontinuation of study treatment

The table below shows the adverse events leading to study drug discontinuation by frequency and treatment group.

Table 45 Summary of adverse events (including unrelated) leading to permanent discontinuation of study drug, by frequency, All-treated set

ACT-064992, Protocol: AC-055-302

System Organ Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	N=249		N=250		N=242	
	No.	%	No.	%	No.	%
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one AE	31	12.4%	34	13.6%	26	10.7%
Total number of AEs		37		40		32
PULMONARY ARTERIAL HYPERTENSION	10	4.0%	6	2.4%	4	1.7%
RIGHT VENTRICULAR FAILURE	6	2.4%	3	1.2%	4	1.7%
ALANINE AMINOTRANSFERASE INCREASED	-	-	3	1.2%	2	0.8%
ASPARTATE AMINOTRANSFERASE INCREASED	-	-	3	1.2%	2	0.8%
LIVER FUNCTION TEST ABNORMAL	2	0.8%	-	-	3	1.2%
PREGNANCY	1	0.4%	3	1.2%	-	-
HEADACHE	-	-	-	-	3	1.2%
ANAEMIA	-	-	1	0.4%	1	0.4%
COLON CANCER	-	-	2	0.8%	-	-
CARDIOGENIC SHOCK	1	0.4%	-	-	1	0.4%
HEPATITIS	1	0.4%	-	-	1	0.4%
JAUNDICE	1	0.4%	1	0.4%	-	-
SYNCOPE	1	0.4%	-	-	1	0.4%
ACUTE RIGHT VENTRICULAR FAILURE	-	-	1	0.4%	-	-
ALCOHOLISM	-	-	1	0.4%	-	-
ANGIOSARCOMA	-	-	1	0.4%	-	-
CARDIAC ARREST	-	-	1	0.4%	-	-
CHEST PAIN	-	-	-	-	1	0.4%
COLITIS ISCHAEMIC	-	-	1	0.4%	-	-
DIARRHOEA INFECTIOUS	-	-	1	0.4%	-	-
DIZZINESS	-	-	1	0.4%	-	-
DRUG INTOLERANCE	-	-	-	-	1	0.4%
DYSPNOEA	-	-	-	-	1	0.4%
ECZEMA	-	-	1	0.4%	-	-
GASTRIC ULCER HAEMORRHAGE	-	-	-	-	1	0.4%
HEART AND LUNG TRANSPLANT	-	-	1	0.4%	-	-
HEPATIC ENZYME INCREASED	-	-	-	-	1	0.4%
HYPERBILIRUBINAEMIA	-	-	-	-	1	0.4%
HYPOTENSION	-	-	-	-	1	0.4%
HYPOVOLAEMIC SHOCK	-	-	1	0.4%	-	-
INTERSTITIAL LUNG DISEASE	-	-	1	0.4%	-	-
METASTATIC NEOPLASM	-	-	1	0.4%	-	-
MULTI-ORGAN DISORDER	-	-	1	0.4%	-	-
OESOPHAGEAL VARICES HAEMORRHAGE	-	-	1	0.4%	-	-
PNEUMONIA	-	-	1	0.4%	-	-
PNEUMONIA INFLUENZAL	-	-	1	0.4%	-	-
SEPTIC SHOCK	-	-	1	0.4%	-	-
SUBDURAL HAEMATOMA	-	-	-	-	1	0.4%
TRANSAMINASES INCREASED	-	-	1	0.4%	-	-
TREATMENT FAILURE	-	-	-	-	1	0.4%
VOMITING	-	-	-	-	1	0.4%
ANAEMIA MEGALOBlastic	1	0.4%	-	-	-	-
ASCITES	1	0.4%	-	-	-	-
CARDIAC FAILURE CONGESTIVE	1	0.4%	-	-	-	-
CARDIOPULMONARY FAILURE	1	0.4%	-	-	-	-
CEREBROVASCULAR ACCIDENT	1	0.4%	-	-	-	-
GASTROENTERITIS	1	0.4%	-	-	-	-
HAEMOPTYSIS	1	0.4%	-	-	-	-
LEFT VENTRICULAR FAILURE	1	0.4%	-	-	-	-
LEUKOCYTOCLASTIC VASCULITIS	1	0.4%	-	-	-	-

There were 34 (13.6%) patients in the macitentan 3 mg group, 26 (10.7%) patients in the macitentan 10 mg group, and 31 (12.4%) of patients in the placebo group who reported at least one adverse event that resulted in the permanent discontinuation of study treatment.

The most frequently reported events that led to discontinuation of study treatment across the three groups were PAH (2.4% macitentan 3 mg, 1.7% macitentan 10 mg, 4.0% placebo) and right ventricular failure (1.2% macitentan 3 mg, 1.7% macitentan 10 mg, 2.4% placebo).

Adverse events associated with liver abnormalities were uncommon (<2% in any treatment group).

There were two discontinuations because of anemia (one each macitentan 3 mg and 10 mg) and one report of megaloblastic anemia (placebo).

There were few discontinuations for pneumonia/influenza, interstitial lung disease or headache.

There were 4 reported pregnancies:

-5 patients in the macitentan 3 mg group, 1 therapeutic abortion, 1 spontaneous abortion, 1 death from PAH prior to a scheduled abortion, 2 continued pregnancy after stopping study drug with both resulting in premature births:

- one case the baby had hyaline membrane disease complicated by sepsis, a grade 4 intracranial hemorrhage, and poor skin condition and death occurred 3 days after birth with persistent hypotension because of extreme prematurity. No obvious dysmorphism was noted and the prenatal screening at Week 18 had shown no anomaly.
- the other case the baby had no neonatal abnormalities.

Both placebo patients had therapeutic abortions.

Clinical laboratory

Hematology

The incidence rates of anemia reported as an adverse event were higher in the macitentan groups compared to placebo: 8.8%, 13.2%, and 3.2% for macitentan 3 mg, macitentan 10 mg, and placebo, respectively. Incidence rates of reports of serious anemia were 2.0%, 2.5% and 0.4% for macitentan 3 mg, macitentan 10 mg and placebo, respectively. Treatment drop outs because of anemia were rare.

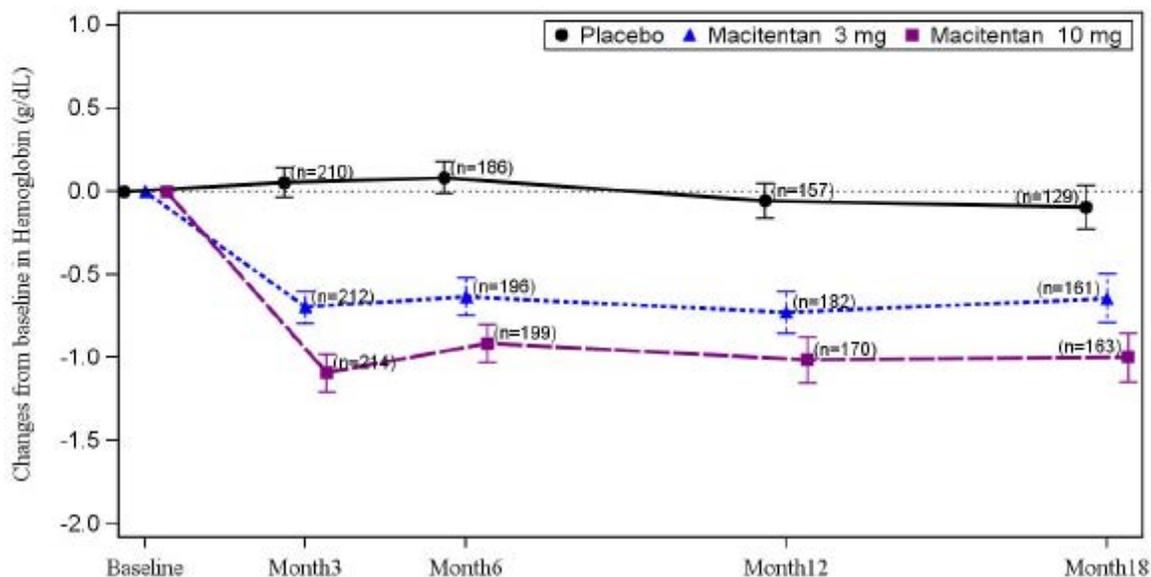
The mean change in hemoglobin values from baseline by visit is shown below.

Figure 20 Mean change in hemoglobin from baseline by visit (observed data), All-treated set

ACT-064992, Protocol: AC-055-302

Plot of mean changes from baseline in Hemoglobin values (g/dL) by visit (observed data)

Analysis set: All-treated



The majority of the decreases occurred early in the study (month 3) and then seemed to stabilize (no data after month 18).

The mean decreases (\pm SD) in hemoglobin (g/dl) were 0.7 ± 2.02 g/dL macitentan 3 mg, 1.1 ± 2.21 g/dL macitentan 10 mg, and placebo 0.1 ± 1.67 g/dL. (baseline hemoglobin values were similar).

Table 46 Incidence of marked hematology abnormalities up to 28 days after treatment discontinuation, All-treated set

Laboratory Abnormality	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
HEMATOLOGY						
Hemoglobin	HH	3 /237 1.3%	2 /241 0.8%	2 /230 0.9%		
	LL	9 /237 3.8%	19 /241 7.9%	32 /230 13.9%		
Hematocrit	HH	2 /237 0.8%	2 /241 0.8%	1 /230 0.4%		
	LL	5 /237 2.1%	15 /241 6.2%	15 /230 6.5%		
Leukocytes	HH	2 /236 0.8%	1 /241 0.4%	1 /229 0.4%		
	LL	0 /236 0.0%	2 /241 0.8%	12 /229 5.2%		
Platelets	HH	0 /235 0.0%	0 /240 0.0%	0 /230 0.0%		
	LL	8 /235 3.4%	6 /240 2.5%	19 /230 8.3%		
Incidence of pre-defined treatment-emergent laboratory abnormalities up to 28 days after treatment discontinuation						
Hemoglobin <= 8 g/dl	1 /237	0.4%	4 /241	1.7%	10 /230	4.3%
Hemoglobin > 8 g/dl and <= 10 g/dl	7 /237	3.0%	11 /241	4.6%	10 /230	4.3%

Values given are the number of patients with at least one abnormality/number of patients (%).
 HH and LL denote values above or below the Actelion marked reference range and having a clinically relevant change in the same direction.
 Source: Table 174 and Table 177

Drops in hemoglobin that were considered to be clinically relevant by the sponsor (labeled as LL in the table above) were more frequent in the macitentan 10 mg group (13.9%) compared to macitentan 3 mg (7.9%) and placebo (3.8%).

Transfusions

There were 30 subjects (5 placebo, 9 macitentan 3 mg, 16 macitentan 10 mg) with reports of severe anemia and/or need for transfusion.

Other hematology parameters

There were small decreases in mean leukocyte amounts (10e9/L) in the macitentan groups (-0.9 ± 2.78 macitentan 3 mg and -0.7 ± 2.27 macitentan 10 mg) compared to placebo 0 (±2.57). There is evidence of increased non-serious infections in subjects who received macitentan (see adverse events).

The table below shows the incidence of markedly abnormal hematology values by treatment group.

Table 174 Incidence of marked laboratory abnormalities during treatment period and up to 28 days after treatment discontinuation (combined central and local laboratory data), All-treated set

ACT-064992, Protocol: AC-055-302
 Incidence of marked laboratory abnormalities during treatment period and up to 28 days after treatment discontinuation (Combined central and local laboratory data)
 Analysis set: All treated

Laboratory Abnormality		Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
		No.	%	No.	%	No.	%
HEMATOLOGY							
Hemoglobin	HH	3 / 237	1.3%	2 / 241	0.8%	2 / 230	0.9%
	LL	9 / 237	3.8%	19 / 241	7.9%	32 / 230	13.9%
Hematocrit	HH	2 / 237	0.8%	2 / 241	0.8%	1 / 230	0.4%
	LL	5 / 237	2.1%	15 / 241	6.2%	15 / 230	6.5%
Leukocytes	HH	2 / 236	0.8%	1 / 241	0.4%	1 / 229	0.4%
	LL	0 / 236		2 / 241	0.8%	12 / 229	5.2%
Platelets	HH	0 / 235		0 / 240		0 / 230	
	LL	8 / 235	3.4%	6 / 240	2.5%	19 / 230	8.3%

Compared to no reports for the placebo groups, the incidence rates of markedly lower leukocyte count in the macitentan group (0.8% macitentan 3 mg and 5.2% macitentan 10 mg) are somewhat disconcerting.

Platelets

There are mild decreases in platelet counts in all treatment groups.

ACT-064992, Protocol: AC-055-302
 Change in laboratory parameters from baseline up to 28 days after treatment discontinuation
 Analysis set: All treated

HEMATOLOGY : Platelets (10e9/L)

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Baseline			
n (missing)	220 (29)	226 (24)	217 (25)
Mean	205	210	213
Standard deviation	74.2	65.5	72.1
Median	192	202	203
Q1 , Q3	156 , 246	165 , 248	156 , 260
Min , Max	41 , 524	54 , 415	66 , 422
Last up to 28 days after treatment discontinuation			
n (missing)	220 (29)	226 (24)	217 (25)
Mean	194	194	196
Standard deviation	69.9	60.4	68.9
Median	180	191	192
Q1 , Q3	144 , 231	150 , 225	146 , 243
Min , Max	41 , 499	62 , 389	32 , 491
Change from baseline			
n (missing)	220 (29)	226 (24)	217 (25)
Mean	-11	-16	-17
Standard deviation	52.2	50.7	57.4
Median	-9	-14	-16
Q1 , Q3	-36 , 16	-45 , 13	-41 , 11
Min , Max	-420 , 142	-194 , 178	-295 , 161

Table LABS T - Produced by (b)(4) on 23AUG12 - Data dump of 26APR12
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Markedly lower platelet counts (see table 174) were greatest in the macitentan 10 mg group (8.3%) compared to macitentan 3 mg (2.5%) and placebo (3.4%). Reports of serious thrombocytopenia included 1 each for macitentan 10 mg and placebo groups.

The table below shows the subjects whose thrombocytopenia was deemed to be severe by the investigator.

Patient number	Dose group	Likely/ possible cause of thrombocytopenia	Platelets values / Treatment	Resolved
5304/13115	10 mg	Single dose – acute renal failure – RHF – ischemic hepatitis – death	Platelets $69 \times 10^9/L$ / No specific treatment	NA
5502/13739	10 mg	Lung infection and sepsis, recurrent thrombocytopenia	Platelets $45 \times 10^9/L$ / Platelets transfusion	Yes
1201/14612	Placebo	Rectal hemorrhage	Platelets $10 \times 10^9/L$ / blood transfusion and thrombocytes	Yes
3104/13471	Placebo	Death due to PAH progression and cardiopulmonary failure	NA / No specific treatment	NA

* Intensity as assessed by the investigator

Chemistry

Liver tests

The table below shows the incidence rates of markedly abnormal liver function tests.

Table 49 Incidence of marked abnormalities in liver function test variables up to 28 days after treatment discontinuation (combined central and local laboratory data), All-treated set

Laboratory Abnormality	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
CLINICAL CHEMISTRY						
ALT	HH 14 /244	5.7%	12 /247	4.9%	14 /236	5.9%
AST	HH 17 /244	7.0%	12 /247	4.9%	12 /236	5.1%
Bilirubin	HH 25 /237	10.5%	7 /241	2.9%	9 /230	3.9%
Alkaline Phosphat.	HH 8 /237	3.4%	3 /241	1.2%	4 /230	1.7%

Values given are the number of patients with at least one abnormality/number of patients (%).
 HH and LL denote values above or below the Actelion marked reference range and having a clinically relevant change in the same direction.
 Source: Table 174

There is no evidence that abnormal liver function tests become elevated in subjects taking macitentan 10 mg or less.

The table below shows the incidence of pre-defined treatment emergent laboratory abnormalities.

Table 51 Incidence of pre-defined treatment-emergent laboratory abnormalities up to 28 days after treatment discontinuation (combined central and local laboratory data), All-treated set

Laboratory abnormality	Placebo(2) N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
ALT > 3*upper std	4 /244	1.6%	8 /247	3.2%	8 /236	3.4%
ALT or AST > 3*upper std	11 /244	4.5%	9 /247	3.6%	8 /236	3.4%
ALT or AST > 3*upper std and Bilirubin > 2*upper std(1)	4 /237	1.7%	5 /241	2.1%	4 /230	1.7%
ALT > 8*upper std	1 /244	0.4%	4 /247	1.6%	5 /236	2.1%
ALT or AST > 8*upper std	1 /244	0.4%	4 /247	1.6%	5 /236	2.1%
Bilirubin > 2*upper std	35 /237	14.8%	17 /241	7.1%	19 /230	8.3%

(1) Bilirubin > 2*upper std anytime

Values given are the number of patients with at least one abnormality/number of patients (%).

(2) Patient 1406/11104 (placebo) not included here, since TBIL > 2 * ULN reported from a local laboratory was not included in the clinical database

Patient 9103/12093 (macitentan 3 mg) included in this table did not have bilirubin values in the Hy's law range

Source: Table 178

There were higher incidence rates of reports of elevated ALT >8 times upper limit of normal in the macitentan patients (1.6 % macitentan 3 mg and 2.1% macitentan 10 mg) compared to placebo (0.4%).

There is no evidence, however, that macitentan 10 mg and lower doses provoke liver impairment.

Table 168 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by class, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by class
 Analysis set: All treated

System Organ Class / Preferred Term	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
INVESTIGATIONS						
Total patients with at least one SAE	2	0.8%	4	1.6%	5	2.1%
Total number of SAEs	4		4		9	
ALANINE AMINOTRANSFERASE INCREASED	1	0.4%	-		2	0.8%
ASPARTATE AMINOTRANSFERASE INCREASED	1	0.4%	-		2	0.8%
LIVER FUNCTION TEST ABNORMAL	1	0.4%	-		2	0.8%
HEPATIC ENZYME INCREASED	-		1	0.4%	1	0.4%
HAEMOGLOBIN DECREASED	-		1	0.4%	-	
HEPATITIS B VIRUS TEST POSITIVE	-		-		1	0.4%
HIV TEST POSITIVE	-		-		1	0.4%
INTERNATIONAL NORMALISED RATIO DECREASED	-		1	0.4%	-	
TRANSAMINASES INCREASED	-		1	0.4%	-	
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	0.4%	-		-	

Again, there is no convincing evidence that macitentan 10 mg or less has a deleterious effect on the liver.

The table below shows the summary of adverse events leading to permanent study drug discontinuations.

Table 170 Summary of adverse events (including unrelated) leading to permanent discontinuation of study drug by class, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of adverse events (including unrelated) leading to permanent discontinuation of study drug by class
 Analysis set: All treated

System Organ Class / Preferred Term	Placebo N=249		Macitentan 3 mg N=250		Macitentan 10 mg N=242	
	No.	%	No.	%	No.	%
INVESTIGATIONS						
Total patients with at least one AE	2	0.8%	4	1.6%	6	2.5%
Total number of AEs	2		7		8	
ALANINE AMINOTRANSFERASE INCREASED	-		3	1.2%	2	0.8%
ASPARTATE AMINOTRANSFERASE INCREASED	-		3	1.2%	2	0.8%
LIVER FUNCTION TEST ABNORMAL	2	0.8%	-		3	1.2%
HEPATIC ENZYME INCREASED	-		-		1	0.4%
TRANSAMINASES INCREASED	-		1	0.4%	-	
HEPATOBIILIARY DISORDERS						
Total patients with at least one AE	2	0.8%	1	0.4%	2	0.8%
Total number of AEs	2		1		2	
HEPATITIS	1	0.4%	-		1	0.4%
JAUNDICE	1	0.4%	1	0.4%	-	
HYPERBILIRUBINAEMIA	-		-		1	0.4%

In summary, macitentan effect on the liver appears to be negligible.

Renal parameters

There were slightly higher incidence rates of reports of marked laboratory abnormalities for serum creatinine in the macitentan 10 mg (1.3%) and macitentan 3 mg (1.7%) compared to placebo (0.4%).

The table below shows the reports of serious adverse events for renal and urinary disorders.

Table 168 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by class, All-treated set

ACT-064992, Protocol: AC-055-302
 Summary of serious adverse events during treatment period and up to 28 days after treatment discontinuation by class
 Analysis set: All treated

System Organ Class / Preferred Term	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	N=249		N=250		N=242	
	No.	%	No.	%	No.	%
RENAL AND URINARY DISORDERS						
Total patients with at least one SAE	4	1.6%	6	2.4%	2	0.8%
Total number of SAEs	4		7		3	
RENAL FAILURE ACUTE	-		4	1.6%	1	0.4%
GLOMERULONEPHRITIS	-		-		1	0.4%
LUPUS NEPHRITIS	-		-		1	0.4%
NEPHROLITHIASIS	-		1	0.4%	-	
RENAL IMPAIRMENT	-		1	0.4%	-	
TUBULOINTERSTITIAL NEPHRITIS	-		1	0.4%	-	
CALCULUS URINARY	1	0.4%	-		-	
PROTEINURIA	1	0.4%	-		-	
RENAL COLIC	1	0.4%	-		-	
RENAL FAILURE	1	0.4%	-		-	

There is no convincing evidence that the use of macitentan 10 mg or less has a harmful effect on the renal system.

Vital signs

The table below shows the mean changes at endpoint to systolic/diastolic blood pressure, pulse rate, and weight.

Blood pressure, pulse, weight

Table 54 Systolic and diastolic blood pressures, pulse rate and body weight: change from baseline up to 28 days after treatment discontinuation, condensed version, All-treated set

ACT-064992, Protocol: AC-055-302
 Systolic and diastolic blood pressures, pulse rate and body weight: change from baseline up to 28 days after treatment discontinuation. Condensed version
 Analysis set: All treated

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Systolic BP (mmHg)			
n (missing)	242 (7)	245 (5)	235 (7)
Baseline	115.3 ± 13.32	118.4 ± 13.42	116.4 ± 14.26
Last up to end of observation period	112.6 ± 16.00	113.5 ± 15.87	114.0 ± 16.47
Change from baseline	-2.7 ± 14.51	-1.9 ± 14.35	-2.4 ± 14.28
Diastolic BP (mmHg)			
n (missing)	242 (7)	245 (5)	235 (7)
Baseline	73.9 ± 9.39	73.7 ± 10.50	74.5 ± 9.19
Last up to end of observation period	71.1 ± 10.61	71.2 ± 10.51	70.3 ± 10.35
Change from baseline	-2.8 ± 12.21	-2.5 ± 11.24	-4.2 ± 10.16
Pulse Rate (bpm)			
n (missing)	242 (7)	245 (5)	235 (7)
Baseline	79.2 ± 11.86	80.1 ± 11.97	77.8 ± 12.06
Last up to end of observation period	81.2 ± 13.42	79.6 ± 13.81	79.2 ± 13.79
Change from baseline	2.0 ± 15.84	-0.5 ± 14.57	1.4 ± 13.10
Weight (Kg)			
n (missing)	240 (9)	245 (5)	235 (7)
Baseline	67.1 ± 15.31	67.6 ± 17.32	67.8 ± 18.48
Last up to end of observation period	67.5 ± 16.20	68.0 ± 16.59	68.9 ± 19.31
Change from baseline	0.4 ± 5.15	0.4 ± 5.25	1.1 ± 5.62

Note: reported values are mean ± standard deviation.
 Table VITPS_T - Produced by (b) (4) on 07MAY12 - Data dump of 26APR12
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There is no obvious effect of macitentan 10 mg or below on these parameters.

ECG

The table below shows the mean changes from baseline at endpoint for 12-lead ECG parameters.

Table 55 ECG variables: change from baseline up to 28 days after treatment discontinuation, All-treated set.

ACT-064992, Protocol: AC-055-302
 ECG parameters: change from baseline up to 28 days after treatment discontinuation. Condensed version
 Analysis set: All treated

	Placebo N=249	Macitentan 3 mg N=250	Macitentan 10 mg N=242
Heart Rate (bpm)			
n (missing)	231 (18)	235 (15)	226 (16)
Baseline	76.2 ± 12.99	78.7 ± 13.92	76.2 ± 12.93
Last up to end of observation period	79.6 ± 15.60	79.6 ± 15.04	77.8 ± 16.97
Change from baseline	3.4 ± 16.42	0.9 ± 15.61	1.6 ± 15.47
PQ (PR) Interval (ms)			
n (missing)	222 (27)	226 (24)	213 (29)
Baseline	166.8 ± 24.79	169.8 ± 27.24	171.9 ± 29.03
Last up to end of observation period	167.6 ± 31.86	172.7 ± 28.66	172.8 ± 32.10
Change from baseline	0.7 ± 27.43	2.9 ± 25.58	0.9 ± 27.25
QT Interval (ms)			
n (missing)	231 (18)	235 (15)	224 (18)
Baseline	395.8 ± 47.74	387.9 ± 46.30	395.6 ± 43.91
Last up to end of observation period	391.4 ± 42.02	389.1 ± 43.97	389.6 ± 49.20
Change from baseline	-4.3 ± 48.24	1.2 ± 50.68	-6.0 ± 49.68
QTc Interval (ms)			
n (missing)	231 (18)	235 (15)	224 (18)
Baseline	425.5 ± 42.26	421.6 ± 44.13	425.6 ± 40.95
Last up to end of observation period	426.6 ± 37.16	423.9 ± 38.43	420.7 ± 45.11
Change from baseline	1.2 ± 44.06	2.3 ± 47.76	-4.9 ± 50.38
QRS Interval (ms)			
n (missing)	231 (18)	235 (15)	224 (18)
Baseline	97.9 ± 24.25	96.3 ± 20.40	95.1 ± 20.01
Last up to end of observation period	100.3 ± 23.46	99.6 ± 20.46	97.6 ± 23.62
Change from baseline	2.4 ± 20.64	3.3 ± 17.14	2.5 ± 15.94

QTc Interval Fridericia formula (ms).

Note: reported values are mean ± standard deviation.

Table ECGPS_T - Produced by (b) (4) on 07MAY12 - Data dump of 26APR12

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There is no obvious effect of macitentan 10 mg or below on these parameters.

The most common treatment emergent ECG abnormalities are shown in the table below.

Table 57 Summary of treatment-emergent ECG abnormalities by frequency, All-treated set

ACT-064992, Protocol: AC-055-302, Summary of treatment-emergent ECG abnormalities by frequency
 Analysis set: All treated

ECG finding	Placebo		Macitentan 3 mg		Macitentan 10 mg	
	No.	%	No.	%	No.	%
Total patients with at least one ECG finding	194	53.8%	198	55.2%	109	45.0%
Total number of ECG findings	236		258		183	
NON SPECIFIC ST-T CHANGES	24	9.6%	27	10.8%	20	8.3%
INCOMPLETE RIGHT BUNDLE BRANCH BLOCK	21	8.4%	26	10.4%	21	8.7%
SINUS TACHYCARDIA	13	5.2%	22	8.8%	17	7.0%
RIGHT VENTRICULAR HYPERTROPHY	24	9.6%	23	9.2%	13	5.4%
RIGHT AXIS DEVIATION	22	8.8%	17	6.8%	12	5.0%
RIGHT ATRIAL ENLARGEMENT	23	9.2%	20	8.0%	7	2.9%
ST SEGMENT DEPRESSION	21	8.4%	15	6.0%	11	4.5%
VENTRICULAR EXTRASYSTOLES	9	3.6%	14	5.6%	9	3.7%
ATRIOVENTRICULAR BLOCK FIRST DEGREE	8	3.2%	6	2.4%	13	5.4%
SINUS BRADYCARDIA	8	3.2%	7	2.8%	10	4.1%
BUNDLE BRANCH BLOCK RIGHT	14	5.6%	7	2.8%	8	3.3%
LEFT ATRIAL ENLARGEMENT	6	2.4%	10	4.0%	5	2.1%
SUPRAVENTRICULAR EXTRASYSTOLES	3	1.2%	6	2.4%	5	2.1%
ATRIAL FLUTTER AND / OR FIBRILLATION	5	2.0%	7	2.8%	3	1.2%
SINUS ARRHYTHMIA	9	3.6%	6	2.4%	3	1.2%
ST-T CHANGES	2	0.8%	4	1.6%	3	1.2%
LEFT VENTRICULAR HYPERTROPHY	1	0.4%	5	2.0%	2	0.8%
OTHER FINDINGS	3	1.2%	3	1.2%	2	0.8%
LEFT AXIS DEVIATION	-	-	3	1.2%	2	0.8%
QT PROLONGED	-	-	4	1.6%	1	0.4%
INTRA-VENTRICULAR CONDUCTION DEFECT	2	0.8%	3	1.2%	1	0.4%
T WAVE ABNORMAL	2	0.8%	3	1.2%	1	0.4%
T WAVE INVERSION	2	0.8%	1	0.4%	3	1.2%
BILATERAL ATRIAL ENLARGEMENT	1	0.4%	4	1.6%	-	-
BUNDLE BRANCH BLOCK LEFT	3	1.2%	2	0.8%	-	-
LEFT POSTERIOR HEMI-BLOCK	1	0.4%	1	0.4%	1	0.4%
LOW VOLTAGE	1	0.4%	1	0.4%	1	0.4%
PULMONARY DISEASE PATTERN	1	0.4%	1	0.4%	1	0.4%
LEFT ANTERIOR HEMI-BLOCK	-	-	2	0.8%	-	-
MYOCARDIAL INFARCTION	-	-	2	0.8%	-	-
POOR R WAVE PROGRESSION	-	-	1	0.4%	1	0.4%
ST SEGMENT ELEVATION	-	-	1	0.4%	1	0.4%
PACEMAKER RHYTHM	1	0.4%	-	-	1	0.4%
PERSISTENT PRECORDIAL S WAVES	1	0.4%	1	0.4%	-	-
ATRIOVENTRICULAR BLOCK COMPLETE	-	-	1	0.4%	-	-
ATRIOVENTRICULAR BLOCK SECOND DEGREE	-	-	-	-	1	0.4%
MOBITE I	-	-	-	-	-	-
JUNCTIONAL TACHYCARDIA	-	-	-	-	1	0.4%
LATE R/S TRANSITION	-	-	-	-	1	0.4%
NODAL RHYTHM	-	-	1	0.4%	-	-
NON SPECIFIC T WAVE ABNORMALITIES	-	-	1	0.4%	-	-
SINOATRIAL BLOCK	-	-	-	-	1	0.4%
SUPRAVENTRICULAR TACHYCARDIA	-	-	-	-	1	0.4%
EARLY R/S TRANSITION	2	0.8%	-	-	-	-
DIGITALIS EFFECT	1	0.4%	-	-	-	-
HIGH VOLTAGE	1	0.4%	-	-	-	-
INCOMPLETE LEFT BUNDLE BRANCH BLOCK	1	0.4%	-	-	-	-

Note: only new ECG findings observed up to 28 calendar days after study treatment end are included.
 Table ECFS_T - Produced by (b) (4) on 07MAY12 - Data dump of 26APR12
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The incidence rates of these reported events are similar regardless of treatment groups.

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/s/

MARYANN GORDON
06/21/2013