Anemia

There was a decrease in mean hemoglobin and hematocrit in the ambrisentan groups compared to placebo. The table below shows the changes from baseline at week 12 for the combined studies 320 and 321.

Table 39 Hemoglobin and Hematocrit Change from Baseline to Week 12 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Hemoglobin (g/dL)						
Week 0	n	120	63	124	62	249
	Mean (SD)	14.4 (2.05)	14.8 (1.98)	14.7 (1.87)	14.4 (1.97)	14.6 (1.92)
Change from baseline to week 12[1]	n	106	55	116	59	230
	Mean (SD)	0.18 (1.04)	-0.87 (1.09)	-0.77 (1.19)	-0.93 (1.29)	-0.84 (1.19)
	Median	0.20	-0.70	-0.80	-1.1	-0.80
	Min, Max	-3.0, 3.4	-3.9, 1.6	-3.3, 3.7	-3.1, 5.1	-3.9, 5.1
Hematocrit (V/V)						
Week 0	n	118	60	121	60	241
	Mean	0.44 (0.062)	0.45 (0.061)	0.44 (0.06)	0.44 (0.06)	0.44 (0.06)
Change from baseline to week 12[1]	n	106	53	110	56	219
	Mean (SD)	0.01 (0.033)	-0.03 (0.034)	-0.02 (0.037)	-0.03 (0.043)	-0.03 (0.038)
	Median	0.0	-0.03	-0.02	-0.04	-0.03
	Min, Max	-0.09, 0.14	-0.12, 0.05	-0.11, 0.11	-0.10, 0.16	-0.12, 0.16

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 14.3.12

Overall there was a mean 0.84 g/dL decrease in the mean hemoglobin level in the combined ambrisentan group (n=230) compared to a mean 0.18 g/dL increase in the placebo group (n=106). Hematocrit had similar changes.

At week 12, there were decreases in mean hemoglobin/hematocrit levels in the ambrisentan group (all doses combined) compared to placebo (-0.84 g/dL/-0.03 V/V) compared to a mean increases in the placebo group (0.18 g/dL/ 0.01 V/V).

The number and percent of subjects in studies 320 and 321 who had a decrease in hemoglobin of $\geq$ 1g/dL as well as those with a decrease of > 15% and below the lower limit of normal are shown below by treatment group.

Table 40 Decreases in Hemoglobin from Baseline to Minimum Post-Baseline Values (AMB-320/321 Population: Safety)

Shift, n (%)	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined Ambrisentan (N = 261)
Decreases in Hemoglobin ≥1 g/dL					
Any decrease	23 (17.4)	39 (60.9)	83 (63.8)	49 (73.1)	171 (65.5)
Weeks 1-4	10 (7.6)	26 (40.6)	50 (38.4)	35 (5.2)	111 (42.5)
Weeks 4-12	13 (9.8)	13 (20.3)	33 (25.4)	14 (20.9)	60 (23.0)
Normal to low	6 (4.5)	5 (7.8)	9 (6.9)	8 (11.9)	28 (10.7)
Weeks 1-4	2 (1.5)	3 (4.7)	5 (3.8)	6 (8.9)	16 (6.1)
Weeks 4-12	4 (3.0)	2 (3.1)	4 (3.1)	2 (3.0)	12 (4.6)
High to normal	2 (1.5)	5 (7.8)	16 (12.3)	4 (6.0)	27 (10.3)
Weeks 1-4	1 (0.8)	5 (7.8)	11 (8.5)	4 (6.0)	21 (8.0)
Weeks 4-12	1 (0.8)	0 (0.0)	5 (3.8)	0 (0.0)	6 (2.3)
High to low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreases in Hemoglobin ≥15% and Below the Lower Limit of Normal					
Any decrease	5 (3.8)	3 (4.7)	7 (5.4)	7 (10.4)	17 (6.5)
Weeks 1-4	0 (0.0)	2 (3.1)	6 (4.6)	3 (4.5)	12 (4.6)
Weeks 4-12	5 (3.8)	1 (1.6)	1 (0.8)	4 (5.9)	5 (1.9)

Source: AMB320/321, Summary Table 14.3.19 and Summary Table 14.3.20

There were more decreases in hemoglobin ≥ 1 g/dL in the drug group (65.5% for the combined ambrisentan) compared to placebo (17. 4%) and there was an indication that it was dose dependent. This was also true for the sizable hemoglobin decrease defined as 15% from baseline and below lower limit of normal (6.5% versus 3.8%).

The same finding was observed in study 220 (at week 12).

Table 41 Hemoglobin and Hematocrit Change from Baseline at Week 12 (AMB-220 Population: Safety)

Treatment group		1 mg ambrisentan (N = 16)	2.5 mg ambrisentan (N = 19)	5 mg ambrisentan (N = 16)	10 mg ambrisentan (N = 13)	Combined ambrisentan (N = 64)
Hemoglobin (g/dL)						
Week 0	n	16	19	16	2	63
	Mean (SD)	14.5 (2.11)	13.3 (1.75)	14.9 (1.68)	15.2 (17.51)	14.4 (1.94)
Change from baseline to week 12	n	15	16	14	11	56
	Mean (SD)	-0.4 (1.21)	-0.7 (0.72)	-1.0 (0.85)	-1.4 (1.13)	-0.8 (1.03)
	Median	-0.5	-0.6	-0.9	-1.4	-0.8
	Min, Max	-2.4, 2.1	-2.2, 0.4	-2.7, 0.2	-3.0, 0.6	-3.0, 2.1
Hematocrit (V/V)						
Week 0	n	16	19	16	12	63
	Mean (SD)	0.43 (0.066)	0.40 (0.052)	0.44 (0.050)	0.46 (0.060)	0.43 (0.059)
Change from baseline to week 12	n	15	16	14	11	56
	Mean (SD)	-0.01 (0.038)	-0.02 (0.022)	-0.03 (0.03)	-0.04 (0.035)	-0.02 (0.033)
	Median	-0.02	-0.02	-0.03	-0.05	-0.02
	Min, Max	-0.1, 0.1	-0.1, 0.0	-0.1, 0.0	-0.1, 0.0	-0.1, 0.1

Source: AMB-220, Table 12.10

The table below shows the decreases from baseline over 24 weeks.

Table 42 Hemoglobin and Hematocrit Change from Baseline throughout the Study (AMB-220 Population: Safety)

Study week		Week 4	Week 8	Week 12	Week 16	Week 24
Hemoglobin (g/dL)						
Change from baseline	n	57	52	56	53	52
	Mean (SD)	-0.9 (0.82)	-0.8 (0.89)	-0.8 (1.02)	-0.9 (1.12)	-0.9 (1.24)
	Median	-0.9	-0.8	-0.8	-1.0	-1.0
	Min, Max	-2.9, 0.9	-2.5, 2.3	-3.0, 2.1	-3.0, 3.3	-3.0, 3.0
Hematocrit (V/V)						
Change from baseline	n	56	52	56	49	50
	Mean (SD)	-0.03 (0.026)	-0.02 (0.030)	-0.02 (0.033)	-0.03 (0.036)	-0.03 (0.038)
	Median	-0.03	-0.02	-0.02	-0.03	-0.03
	Min, Max	-0.1, 0.0	-0.1, 0.1	-0.1, 0.1	-0.1, 0.1	-0.1, 0.1

Source: AMB-220, Summary Table 14.4.11

Mild to moderate decreases in hemoglobin/hematocrit anemia appear linked to ambrisentan use (similar to bosentan). The effect seems to stabilize in the first several months of treatment.

Anemia was reported as an adverse event by 6% of the subjects in the AMB-320/321E combined analysis (24/383). One subject (AMB-222/143-003) was hospitalized twice (study days 10 and 112) because of anemia. She had a long history of frequent episodes of epistaxis. During both hospitalizations she was transfused and released. She remained on study drug (2.5 mg followed by 5 mg ambrisentan).

The mild decreases in hemoglobin and hematocrit are similar to those seen with other endothelin receptor antagonists.

Coagulation

Coagulation tests were obtained monthly for 50%-60% of subjects receiving an anticoagulant in the phase 3 studies AMB320 and 321.

The table below shows the changes in PT and INR values at week 4, by treatment group.

Table 44 Prothrombin Time and International Normalized Ratio Change from Baseline to Week 4 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N=132)	2.5 mg ambrisentan (N=64)	5 mg ambrisentan (N=130)	10 mg ambrisentan (N=67)	Combined ambrisentan (N=261)
PT (sec)						
Week 0	n	83	45	88	38	171
	Mean (SD)	18.8 (7.31)	19.1 (7.67)	18.5 (8.17)	19.6 (11.03)	18.9 (8.72)
Change from baseline to week 4[1]	n	76	37	80	37	154
	Mean (SD)	1.2 (7.53)	0.3 (6.14)	-0.4 (7.96)	-0.9 (16.30)	-0.4 (10.21)
	Median	0.50	-0.2	-0.2	-0.30	-0.2
	Min, Max	-28.0, 20.3	-20.1, 14.9	-50.0, 16.8	-47.0, 79.0	-50.0, 79.0
INR						
Week 0	n	84	45	89	42	171
	Mean	2.12 (1.042)	2.13 (1.491)	2.07 (1.105)	1.82 (0.843)	2.07 (1.23)
Change from baseline to week 4[1]	n	77	37	82	38	156
	Mean (SD)	0.28 (1.581)	-0.04 (1.649)	0.01 (1.143)	-0.23 (1.770)	-0.06 (1.43)
	Median	0.10	0.0	-0.04	-0.03	-0.02
	Min, Max	-5.22, 8.03	-8.58, 2.08	-4.04, 6.26	-6.72, 6.30	-8.58, 6.30

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 12.17

The changes to the doses of specific anticoagulants (sum of daily doses over 7 day period) were examined as well.

Table 12.18 Weekly Anticoagulant Dose, Prothrombin Time and International Normalized Ratio Percent Change from Week 0 at Week 12 (Population: Safety)

Treatment group		Placebo (N=132)	2.5 mg ambrisentan (N=64)	5 mg ambrisentan (N=130)	10 mg ambrisentan (N=67)	Combined ambrisentan (N=261)
Percent change in weekly anticoagulant dose	n	59	30	60	32	122
	Mean (SD)	32.3 (130.24)	18.5 (61.73)	15.2 (85.52)	16.9 (58.80)	16.4 (73.26)
	Median	0.00	0.00	0.00	0.00	0.00
Percent change in PT	n	69	36	74	29	139
	Mean (SD)	13.5 (42.80)	-1.9 (28.91)	8.9 (45.41)	-3.6 (28.93)	3.5 (38.82)
	Median	1.6	-1.2	3.6	0.00	0.83
	Min, Max	-57.1, 168.4	-61.9, 81.3	-76.1, 285.3	-65.0, 56.8	-76.1, 285.3
Percent change in INR	n	61	36	75	29	140
	Mean (SD)	23.24 (1.629)	1.18 (44.98)	11.84 (60.02)	1.46 (43.32)	6.95 (53.228)
	Median	0.02	2.09	3.26	0.00	1.77
	Min, Max	-60.83, 387.07	-77.10, 121.13	-77.46, 338.93	-84.18, 122.54	-84.18, 338.93

Source: Summary Table 14.5.13

The changes observed in the active treatment groups are not different from those observed in the placebo group.

In addition, there were no subjects in the ambrisentan arms of these 2 studies who reported a change in PT or INR that was considered to be an adverse event. There were scattered reports of changes in PT/INR as an adverse event in subjects participating in other studies.

Long term use of ambrisentan and coagulation values was evaluated in extension study AMB320-321E. The table below shows changes in INR values over 48 weeks, by treatment group.

Table 12.15 International Normalized Ratio Change from Baseline Over Time during the Preliminary Analysis Period (Population: Safety)

Treatment group		2.5 mg ambrisentan (N=78)	5 mg ambrisentan (N=171)	10 mg ambrisentan (N=134)	Combined ambrisentan (N=383)
INR					
Week 0	n	55	119	87	261
	Mean (SD)	2.33 (1.927)	2.12 (1.248)	2.01 (1.129)	2.13 (1.383)
Change from baseline Week 4	n	49	105	74	228
	Mean (SD)	-0.12 (1.091)	-0.16 (1.197)	-0.16 (1.394)	-0.15 (1.238)
	Median	-0.04	-0.03	-0.10	0.08
	Min, Max	-4.59, 2.28	-8.58, 1.92	-6.72, 6.30	-8.58, 6.30
Change from baseline Week 12	n	46	98	69	213
	Mean (SD)	-0.42 (1.864)	-0.01 (1.357)	-0.12 (1.261)	-0.13 (1.454)
	Median	0.01	0.04	0.00	0.02
	Min, Max	-8.30, 3.60	-7.71, 4.82	-6.92, 2.14	-8.30, 4.82
Change from baseline Week 24	n	40	68	47	155
	Mean (SD)	-0.07 (2.412)	0.11 (1.496)	-0.12 (0.946)	-0.01 (1.651)
	Median	-0.06	0.13	-0.12	0.01
	Min, Max	-8.10, 9.63	-7.58, 6.18	-1.77, 2.11	-8.10, 9.63
Change from baseline Week 36	n	35	46	42	123
	Mean (SD)	-0.29 (2.079)	0.09 (1.021)	0.25 (1.337)	0.03 (1.496)
	Median	-0.12	0.13	0.16	0.02
	Min, Max	-7.90, 4.40	-4.76, 1.98	-2.01, 5.85	-7.90, 5.85
Change from baseline Week 48	n	26	28	36	90
	Mean (SD)	-0.21 (1.879)	-0.018 (1.504)	-0.068 (1.221)	-0.094 (1.507)
	Median	0.35	0.21	-0.15	0.04
	Min, Max	-8.00, 1.87	-6.88, 1.44	-2.79, 5.16	-8.00, 5.16

Source: Summary Table 14.3.11

In summary, it is unlikely that there is a link between the use of ambrisentan and changes in coagulation.

Bleeding reports

The following subjects reported bleeding events that led to study drug discontinuation:

-subject 320/101-006 (10 mg) was hospitalized 14 days after the start of study drug because of hypoxic respiratory failure secondary to a rapidly recurring right pleural effusion. She complained of abdominal and flank pain with a marked increase in dyspnea. Her hematocrit had dropped from 30% to 19%, platelet count was 45 x10^3 U/L, and PTT was >150 s. Heparin was interrupted and the subject was started on lepirudin. She recovered and remained on study drug. On day 88, this subject was hospitalized because of an intracranial bleed. Her husband stated that the subject had fallen and hit her head. She died the next day (see death section)

Other reports of serious bleeding include:

-subject 321/242-005 reported anemia. Resolved.

-subject 321/207-009 reported severe epistaxis. Other medication change, resolved;

-subject 321/245-006 reported hemoptysis. Other medication change, resolved;

-subject 320/321/227-001 (2.5mg) had severe GI hemorrhage with drop in hematocrit, resolved;

-subject 320/321/155-003 (10mg) had severe hemoptysis;

-subject 320/321/214-002 (placebo) had severe epistaxis.

There were 30 subjects with reports of hemorrhagic events in 320/321E. Of these, 11 were serious with 3 of the 11 resulting in discontinuation/interruption of study drug.

-subject 320/321E/231-005 (2.5mg) with subacute subdural hematoma diagnosed day 91. Acenocoumarol was discontinued as was ambrisentan when subject withdrew her consent.

-subject 320/321E/116-008 (10mg) with subacute subdural hematoma diagnosed day 239 after traumatic event. Warfarin was discontinued; ambrisentan was interrupted for 6 days.

-subject 320/321E/104-003 (5mg) was discontinued because of hematochezia. Concomitant medication included warfarin.

7.1.8 Vital Signs

Mean heart rate decreased slightly more (1.4 bpm at week 12) for 244 subjects receiving ambrisentan (doses 2.5 mg-10 mg) compared to 113 subjects receiving placebo 90.2 bpm).

Mean blood pressure tended to decrease more in subjects receiving ambrisentan at week 12 compared to subjects receiving placebo.

Table 53 Blood Pressure Change from Baseline to Week 12 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Systolic Blood Pressure, mmHg						
Week 0	n	119	59	113	57	229
	Mean (SD)	118.6 (15.21)	117.6 (14.82)	116.2 (13.88)	115.9 (15.17)	116.5 (15.38)
Change from baseline to week 12[1]	n	113	58	122	64	244
	Mean (SD)	-0.6 (14.96)	-2.3 (14.64)	-2.1 (12.73)	-5.4 (15.32)	-3.0 (13.93)
	Median	0.0	-4.0	-0.5	-5.0	-3.5
	Min, Max	-36, 46	-38, 34	-34, 28	-50, 24	-50, 34
Diastolic Blood Pressure, mmHg						
Week 0	n	119	59	113	57	229
	Mean (SD)	74.5 (10.38)	74.7 (11.01)	74.1 (9.68)	72.5 (9.34)	73.8 (9.95)
Change from baseline to week 12[1]	n	113	58	122	64	244
	Mean (SD)	0.5 (9.57)	-4.1 (10.56)	-3.4 (10.57)	-6.0 (10.03)	-4.2 (10.44)
	Median	0.0	-1.5	-5.0	-5.5	-5.0
	Min, Max	-28, 20	-35, 20	-30, 41	-30, 20	-35, 41

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 12.21

There were sporadic reports of hypotension/syncope.

-subject 321/211-008 (2.5 mg) reported syncope day 50. Temporary discontinuation of study drug. Completed study

7.1.9 Electrocardiograms (ECGs)

QT study

For a detailed evaluation of the thorough QTc study, AMB-104, please see the review of it by the Division QTc team. The most succinct summary of it from that review is the following recommendation regarding a description of it for the label:

[redacted]

Abnormal ECGs

The number and percent of subjects with clinically significant abnormal ECG findings at screen, week 0, and week 12 for studies AMB 320 and 321 are shown below[8].

	AMB-320			AMB-321		
	placebo	5 mg	10 mg	placebo	2.5 mg	5 mg
N	67	67	67	65	64	63
CS abnormality, %						
Screening Visit	9.0	16.4	23.9	15.4	14.1	9.5
Week 0	10.4	14.9	19.4	12.3	10.9	4.8
Week 12	7.5	10.4	11.9	9.2	9.4	1.6

The vast majority of abnormalities were reported both at screen/baseline and week 12 and reflected the effects of PAH on the heart. There is no indication that ambrisentan causes cardiac abnormalities that can be detected by ECG changes after 12 weeks of treatment.

7.1.10 Immunogenicity

Allergic reaction

The following subjects reported events suggestive of allergic reaction:

-subject 320/321/211-009 (5 mg) reported dyspnea and erythematic swelling of face, hands, legs on day 15. She was discontinued 4 days after the event and the reaction resolved 28 days later.

-subject 320/321/211-010 (5mg) reported mild face edema and headache 3 days after start of drug. Study drug was stopped and the events resolved in one day. She was restarted on drug and the events reappeared. Study drug was then permanently discontinued.

8 ECG table dated March 5, 2007.

7.1.11 Human Carcinogenicity

Human carcinogenicity is impossible to evaluate in the small, short-term studies performed for this development program for PAH.

7.1.12 Special Safety Studies

Male fertility
Animal (rat studies) findings:

"Diffuse testicular atrophy (unilateral and bilateral) of massive severity was observed in one animal at 100 mg/kg/day and in two animals at 300 mg/kg/day. . . . During the recovery phase massive diffuse tubular atrophy was observed in one animal in each treatment group (10, 30, 100, and 300 mg/kg/day). The diffuse testicular tubular atrophy was not reversible during the 13-week recovery period at $\geq$ 10 mg/kg/day."

Semen specimens were collected during some of the studies:

Study AMB 320: few semen analyses were available for review (2 placebo subjects, 3 ambrisentan 5mg subjects, 7 ambrisentan 10 mg subjects). In the 10 mg group, there were 4 subjects with ejaculate volumes greater than 1.0mL in both week 0 and week 12 samples. Sperm densities decreased at week 12 compared to week 0 in all. One of the subjects also had decreasing motility from week 0 to week 12.

Study AMB 321: few complete semen samples were available for review (2 placebo subjects and 4 ambrisentan 5 mg subjects). One of the ambrisentan subjects was deemed to be azoospermic by the reviewer (expert consultant). There was little change for the remainder of the subjects. However, the data were very scant and it is not possible to rule out an effect of the drug on human male fertility.

Conclusion
While it is difficult to interpret these data, there is no indication that ambrisentan does not have an adverse effect on human male fertility. One of the expert reports recommended that the effect of drug on sperm concentration, motility, or morphology be examined after 24 weeks rather than at 12 weeks.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There were no signs or symptoms of withdrawal in patients discontinuing ambrisentan in the clinical trials, although withdrawal phenomena were not studied formally. There were no reports of abuse in the clinical trials and there are no pharmacologic actions of ambrisentan that would encourage abuse.

7.1.14 Human Reproduction and Pregnancy Data

In embryo-fetal toxicity studies in rats and rabbits abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of thymus and thyroid to form were observed. Ambrisentan was associated with an increased incidence of craniofacial abnormalities of the jaw and palate and other teratogenic findings at all doses administered

In the clinical trails four patients became pregnant while taking ambrisentan. All pregnancies were terminated by abortion.

7.1.15 Assessment of Effect on Growth

Children were not studied.

7.1.16 Overdose Experience

There were no reports of overdose with ambrisentan in the clinical trials.

7.1.17 Postmarketing Experience

Ambrisentan has not been marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

For descriptions of the trials and extent of exposure please see the first part of Section 7.1 above. The clinical development program for ambrisentan was not large, i.e., 483 subjects exposed, but typical of development programs for PAH, an orphan disease. We judge the exposure adequate for characterizing the major risks of this ERA, the third submitted for approval. Besides the usual problem of being able to detect rare events, the major limitation of exposure of this size is the inability to characterize adverse events in important subgroups, such as blacks and the elderly.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Phase 1 studies
The phase 1 studies are briefly described below.

Phase 1 Clinical Studies in Healthy Subjects

PK and Tolerability	**EE-001**	**M n = 63**	**Single ascending dose ambrisentan pharmacokinetics, pharmacodynamics and the effect of food on ambrisentan pharmacokinetics**
	EE-002	**M n = 30**	**Multiple ascending dose pharmacokinetics and pharmacodynamics of ambrisentan**
Bioequivalence	**AMB-103**	**M/F n = 65**	**Bioequivalence of clinical and commercial formulation ambrisentan tablets**
QT/QTc	**AMB-104**	**M/F n = 161**	**Correlation of ambrisentan pharmacokinetics and effect on QT/QTc interval**
Drug-Drug Interaction	**AMB-105**	**M/F n = 20**	**Pharmacokinetic drug-drug interaction with sildenafil**
	AMB-106	**M/F n = 22**	**Pharmacokinetic and pharmacodynamic drug-drug interaction with warfarin**

There were seven phase 1 studies (including AMB-107, a mass balance study not listed above). A total of 369 healthy volunteers participated in one of these seven studies.

The table below shows the numbers of subjects enrolled and the numbers withdrawn for adverse event for the phase 1 studies.

Study ID	Number enrolled	Number withdrawn for adverse event
EE-001	63	1 (50 mg: facial flush, shivering, sickness, nausea, vomiting, headache, vertigo, and dizziness)
EE-002	30	2 (10 mg: fever, diarrhea and 10 mg: headache)
AMB-103	65	1 (10 mg: strep infection)
AMB-104	161	1 (10 mg: palpitations)
AMB-105	20	0
AMB-106	22	0
AMB-107	8	0

The following table lists the number of subjects who reported adverse events in the phase 1 program, by drug dose.

Table 9.3.1.3 Number of subjects with adverse events (counted once per subject) by dose level

Type of event	Treatment administered (Placebo or BSF 208075)									
	Placebo N = 15	1 mg N = 7	5 mg N = 7	10 mg N = 7	15 mg N = 5	20 mg N = 14	50 mg N = 8	50 mg fed N = 7	100 mg N = 2	All N = 72
Conjunctival vascular disorder nos*						2	1			3
Constipation				1						1
Diarrhea	1									1
Dizziness						1	1		1	3
Feeling of warmth						1				1
Flatulence	1									1
Flushing					2		1	2	1	6
Flushing of face			2	1	2	5	3	5		18
Headache	2				1	6	1	3	2	15
Headache nos*				1	1	3	3	1	2	11
Headache temporal			1							1
Hypoesthesia		1								1
Malaise							1			1
Nasal congestion			1		1	1			1	4
Nausea		1				1			2	4
Nausea with vomiting							1			1
Neck rigidity			1							1
Shivering							1			1
Sweating attack			1							1
Unclassified			1							1
Vertigo							1			1
Vomiting						1	1			2
Total number of AEs (counted once per subject per treatment)	4	2	7	3	7	21	15	11	9	79

* nos = not otherwise specified

7.2.2.2 Postmarketing experience

Ambrisentan has not been marketed anywhere.

7.2.2.3 Literature

We found 27 citations in Pubmed searching on "ambrisentan". The majority of the articles were general discussions of ERAs; none provided source data not included in the NDA submission.

7.2.3 Adequacy of Overall Clinical Experience

From an efficacy viewpoint, the overall clinical experience was adequate for establishing the efficacy of ambrisentan in improving six minute walks. The clinical experience was marginal for demonstrating that ambrisentan improves clinical worsening and inadequate for confirming that ambrisentan improves symptoms or quality of life for PAH patients in general.

From a safety viewpoint, the overall clinical experience provides reasonable assurances about the safety of ambrisentan and reasonable characterization of its adverse event profile in the WHO group 1 PAH population as a whole. It is inadequate for characterizing adverse event profiles in important subgroups such as blacks and the elderly. It is also inadequate for characterizing effects upon male fertility as discussed in the Integrated Review of Safety. However, overall it is adequate for use in the general group 1 PAH population and adequate for approval.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The FDA pharmtox reviewer did not identify in his review any deficiencies in pre-clinical testing.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing, in particular the monitoring of liver function tests, was adequate in the study protocols and study conduct. Follow-up on serious adverse events was less than optimal in some cases, such as the suspicious death in a patient with liver function abnormalities. The semen analyses done were inadequate for ruling out an effect of the drug on human male fertility.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The FDA clinical pharmacology reviewer discusses in his review that whether ambrisentan is a substrate for OATP was not determined and with the limited mass balance information available clinically relevant metabolic interactions caused by metabolic inhibitors and inducers of ambrisentan or by pharmacogenetic polymorphisms cannot be ruled out.

Regarding interactions, the submission includes two studies that document that co-administration of sildenafil in healthy volunteers appears not to impact the PK of ambrisentan and ambrisentan does not affect the PK of sildenafil and N-desmethyl-sildenafil and that co-administered ambrisentan appears not to impact the PK of the warfarin enantiomers, and does not affect prothrombin time or International Normalization Ratio. These two drugs are ones commonly administered to PAH patients so demonstration of a lack of interaction with ambrisentan is important. However, the submission did not include an interaction study with cyclosporine, a drug that has been demonstrated to have a major interaction with the approved ERA bosentan.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Ambrisentan appears to share several toxicities with other ERAs: hepatotoxicity, anemia, teratogenicity, and interference with sperm production. The evaluation for potential adverse events in the ambrisentan development program is adequate for characterizing ambrisentan as a typical ERA. The program does not suggest that ambrisentan has any unusual toxicities but neither does it confirm that ambrisentan has any unique advantages. For the sponsor to establish the latter, studies directly comparing ambrisentan with the approved ERA bosentan would be needed. To eliminate any labeling cautions about testicular toxicity, much more extensive semen analyses are necessary. Finally, the FDA clinical pharmacology reviewer makes several recommendations in his review regarding better characterizations of metabolism and interactions—please see his review for those recommendations.

7.2.8 Assessment of Quality and Completeness of Data

Overall the quality and completeness of data were adequate. Please see Sections 4.4 and 7.2.5 for some specific comments.

7.2.9 Additional Submissions, Including Safety Update

Introduction

The 4-month safety update contains cumulative data through November 30, 2006 from the 3 ongoing trials (AMB-320/321-E, 220-E, and 222). Information about all subjects who were reported to have died or were discontinued because of an adverse event up to March 18, 2007 was submitted. There is one newly initiated open label trial (AMB-323) in subjects with pulmonary hypertension for which all reported deaths, serious adverse events and discontinuations for adverse events were submitted.

As of November 30, 2006, a total of 483 subjects[1] received ambrisentan in a phase 2 or 3 study. Mean exposure is about 1.5 years with maximum exposure more than 4 years. A total of 343 subjects received ambrisentan for at least 1 year and 120 subjects have received the drug for at least 2 years. Doses ranged from 2.5 to 10 mg once daily. The safety update added 32 weeks of exposure to ambrisentan since the close of the NDA data base.

The newly initiated study AMB-323 reported no deaths. There was one serious adverse event of worsening pulmonary hypertension. One subject discontinued study drug because of elevated liver enzymes. A total of 14 subjects have been enrolled into this open label study.

Deaths

Cumulative reported deaths through November 30, 2006 are shown below by study and treatment group.

Table 16 Cumulative Summary of Deaths in Subjects with Pulmonary Arterial Hypertension through 30 November 2006, All Phase 2 and 3 Studies

Treatment group[1]	Placebo	1 mg ambrisentan	2.5 mg ambrisentan	5 mg ambrisentan	10 mg ambrisentan
Phase 3, placebo-controlled studies					
AMB-320	2	NA	NA	1	1
AMB-321	4	NA	2	0	NA
Phase 2 Studies					
AMB-220	NA	1	0	0	1
AMB-222[2]	NA	0	0	1	2
Long-term Phase 2 and 3 studies					
AMB-320/321-E[2,3]	NA	1	5	18	10
AMB-220-E[2]	NA	0	1	0	4

[1]Deaths are attributed to the actual ambrisentan dose at the time of death.
[2]For ongoing studies deaths are reported through 30 November 2006. Of these, 21 occurred during the safety update period.
[3]Deaths that occurred during study AMB-320/321-E only (n = 34). Deaths that occurred while subjects received ambrisentan or placebo in AMB-320 and AMB-321 are counted for those studies only (n = 5).
NA = treatment not available in study

There were 21 additional deaths reported since the close of the NDA data base (February 17, 2006) and the close of the safety update data base. There were 3 additional reported deaths in AMB-222 at doses of 5 (1 subject) and 10 mg (2 subjects) and 18 additional reported deaths in AMB-320/321E at doses of 1 mg (1 subject), 2.5 mg (2 subjects), 5 mg (8 subjects), and 10 mg (7 subjects).

In addition, there were 6 subjects (5 from study AMB-320/321 and 1 from AMB-222) who died

Subject ID/age/sex	Dose/Duration	Comments
AMB-320/321-E		
255-001/44/f	2.5 mg for 336 days and 5 mg for 224 days	Sudden death. Subject was hospitalized because of asthma and during this time she experienced palpitations diagnosed as paroxysmal reciprocal AV node tachycardia and AV node dissociation. She stated that she experienced previous palpitations. Ablation was planned. Concurrently she reported muscle weakness that was diagnosed as polymyositis. Lab results showed mild to moderate elevated fibrinogen, C-reactive protein, leukocytes. The day before death, she developed nausea and vomiting. Prior LFTs were normal but on the day of death ALT and AST were 15xULN and total bilirubin was nearly 3xULN. Abdominal ultrasound was unremarkable. She had sudden collapse and

		could not be revived. Pathological findings included periarteritis nodosa and fresh and sclerotic infarction in the lungs. Cause of death was acute cardiovascular event secondary to paroyxmal tachycardia or pulmonary ebmbolism.
221-001/64/f	2.5 mg/675	Hospitalized on day 418 because of decompensated heart failure. Worsening pulmonary hypertension followed by sudden death about 6 months later.
242-002/31/m	2.5 mg for 682 days and 5 mg for 14 days	Hospitalized for anemia after bleeding from ruptured varicose vein. Was found to be anemic with elevated heart rate. Recovered after transfusion. Hospitalized about 2 weeks later for symptoms of worsening heart failure. ECHO showed dilated heart and he was placed on transplant list. Progressive renal failure and fluid retention. Developed cardiac arrest and died when CPR failed.
108-002/70/f	5 mg for 837 days	History of rectal cancer. Died respiratory failure while hospitalized for enteritis.
133-009/76/f	5 mg for 332 days	Death occurred 18 days after the last dose of ambrisentan because of anemia. She was hospitalized for low grade fever and night sweats. Blood cultures were postive for S. bovis. She developed a intracerebral hemorrhage and subsequently died. PT and INR were elevated. She had a history of mitral valve replacement and was presumed to have septic emboli from bacterial endocarditis.
155/005/63/f	5 mg for 97 days	Ambrisentan was discontinued on day 97 because of diarrhea and vomiting. She was hospitalized the next day, deteriorated, was sent home, attempted to be readmitted, was taken to the emergency room where she was found to be in a hypoglycemic coma (blood glucose 29 mg/dL). Abdomen was enlarged and painful on palpitation. Her LFTs were slightly elevated. She suffered a cardiac arrest and cause of death was listed as hypovolemic shock and dehydration secondary to gastroenteritis.
207-021/71/m	5 mg for 45 days	History of gastic carcinoma and gastric bleeding. Died suddenly at home. No autopsy.
211-002/62/f	5 mg for 638 days	Reported several serious adverse events (worsening heart failure, worsening PAF,

		diverticulosis, hypotysis, and large pericardial effusion) during study. Developed worsening dyspnea, peripheral edema, ascities. Blood and urine cultures were positive for staph and E. coli, respectively. Prior to dying, she was placed on a ventilator and developed multiorgan failure.
213-018/64/m	2.5 mg for 505 days and 5 mg for 91 days	Previous reports of progressive dyspnea, atrial fib/flutter, and syncope secondary to hypoxemia. While in the clinic he collapsed, was found to be in ventricular fib and could not be resuscitated.
227-002/70/f	5 mg for 406 days	Died of right heart failure.
241-002/69/f	2.5 mg for 338 days and 5 mg for 107 days	Sudden death. Prior to death subject developed increased dyspnea. She had reported a panic attack previously.
112-004/73/f	5 mg for 14 days and 10 mg for 219 days	Hospitalized for acute respiratory failure and died about 2 weeks later. Reported anemia.
116-009/68/f	5 mg for 14 days and 10 mg for 805 days	Hospitalized for severe dyspnea and died as a result of acute exacerbation of severe pulmonary hypertension.
117-002/22/f	5 mg for 14 day and 10 mg for 266 days	Sudden death secondary to intracranial hemorrhage. Previous events include bleeding post renal biopsy and pulmonary embolus. She was being treated with warfarin. Autopsy showed lupus nephritis, lung edema and congestion, bilateral pleral effusion, cardiomegaly, and a pulmonary embolus.
151-003/18/f	5 mg for 171 days and 10 mg for 4 days	Sudden death while hospitalized for worsening right heart failure.
155-002/48/m	5 mg for 14 days and 10 mg for 186 days	Died of respiratory failure after being hospitalized for worsening right heart failure
210-004/42/m	2.5 mg for 257 days, 5 mg for 86 days and 10 mg for 420 days.	Previous serious adverse events included leg ulcer, acute renal failure, right heart failure. He was hospitalized for worsening systemic hypotension. His heart failure progressed and he died of cardiovascular collapse.
213-001/71/m	2.5 mg for 251 days, 5 mg for 176 days and 10 mg for 239 days.	Previous serious adverse events included lung fibrosis, increased pulmonary hypertension, worsening right heart failure, and syncope. He was hospitalized for worsening right heart failure and respiratory infection. He continued to deteriorate and died of right heart failure.

AMB-222		
126-001/69/F	2.5 mg for 29 days and 5 mg for 225 days	Hospitalized and died because of right heart failure.
122-002/70/f	2.5 mg for 29 days, 5 mg for 14 days and 10 mg for 261 days.	Subject developed increased difficulty breathing. She refused to be hospitalized and died that day.
212/62/f	2.5 mg for 26 days, 5 mg for 255 days and 10 mg for 24 days.	Hospitalized and subsequently died of worsening pulmonary arterial hypertension.

Most deaths were related to heart failure, sudden death, and/or worsening respiratory condition, deaths similar to those associated with pulmonary hypertension and underlying diseases. No death appeared to be caused by liver failure or seemed unexpected.

Serious adverse events

The most commonly reported serious adverse events include right ventricular failure (7%), pulmonary hypertension (7%), pneumonia (2%), syncope (<2%), hypoxia (<2%), and pleural effusions (<2%) (table 14.3.6).

Discontinuations for adverse events

Discontinuations because of adverse events were reported for 52 subjects (14%) for all ambrisentan doses combined. Common events leading to discontinuation were cardiac disorders (5%) including right ventricular failure (3%), and respiratory disorders (4%) including pulmonary hypertension (3%). Other important events reported less often include postural dizziness/syncope (0.5%), cerebral/intracranial hemorrhage (0.5%), and renal failure /insufficiency (0.5%). There was one subject who discontinued because of face edema. (table 14.3.7).

Laboratory values

Liver function tests

The incidence rate of LFT > 3xULN for subjects on ambrisentan increased to 3.5% (compared to 2.7% in the original NDA). The cumulative incidence of LFTs >8x ULN was 0.8% (compared to 0.6% in the original NDA.

The additional subjects with elevated LFTs are shown below. The doses used ranged from 1 to 10 mg. The above incidence rates do not include all subjects listed below.

Dose	Subject ID	Sex/age	Time to >3xULN (wks)	Max ALT/AST (xULN)	Discontinued Study medication?
1 mg	01-007^	f/67	192	4/3	No
2.5 mg	252-001+	f/70	68	2/3	No
10 mg	104-004+	f/54	29	2/3	No
10mg	101-002+	f/29	99	10/2	No
1 mg	255-001+	f/44	80	15/15	Died#
10 mg	15-006^		182	4/4	Yes, temporary
5 mg	147-003*	f/44	21	7/6	yes

^study AMB 220-E
+study AMB 320/321-E
*study AMB 323
#see death section

Subject 101-002 was receiving dapsone (for lung infection) at the time of the ALT/AST increase. Dapsone was discontinued and both ALT/AST levels fell. The subject remained on ambrisentan for an additional 15 weeks without incident.

Subject 15-006 had periodic elevations of LFTs. Study drug was discontinued for 6 days and then restarted. LFTs started to increase and ambrisentan was down titrated to 5 mg. LFTs returned to normal 1 week later.

The Kaplan-Meier time to event analysis of time to ALT or AST > 3xULN and >5xULN has been updated to include the addition 32 weeks of data. This is shown below.

Subject 147-003 (study AMB-323, 5mg for 150 days) developed elevated liver enzymes (4-7xULN) and was discontinued. This subject is not included in the above figure.

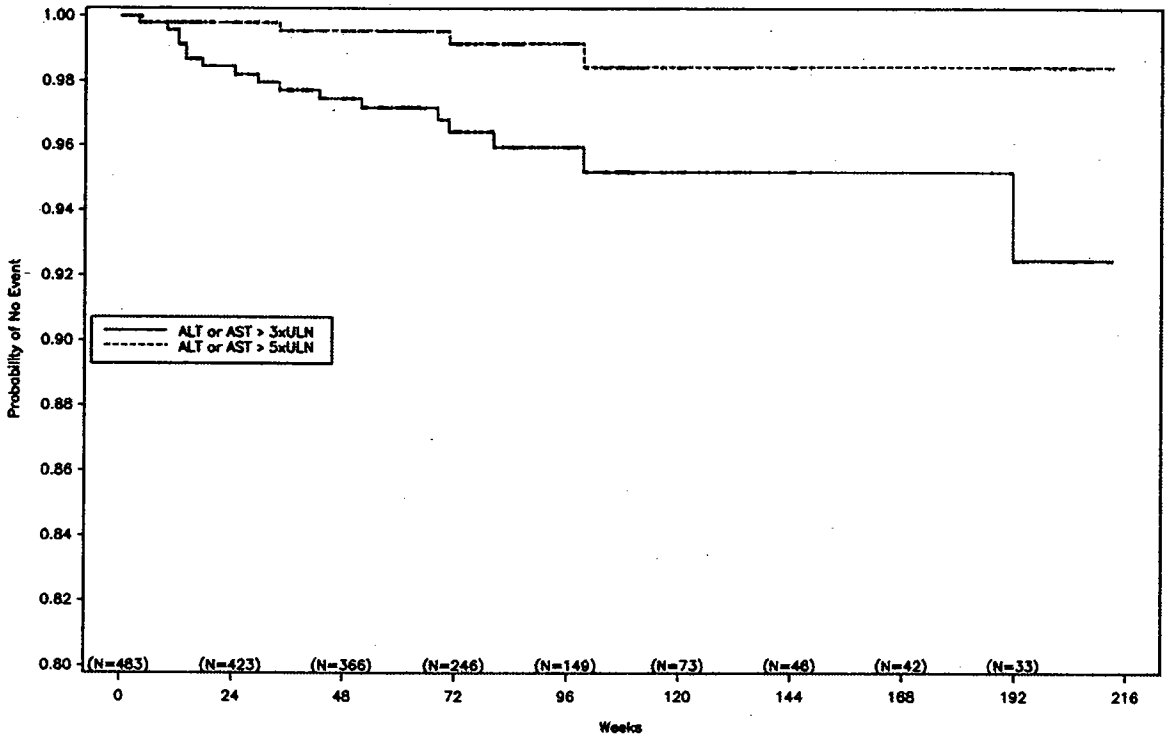
Anemia
There were 6 subjects with reports of serious anemia (including iron-deficient anemia). As previously shown in the NDA safety review, mean hemoglobin levels, hematocrit and red blood cell count decline by about week 4 in subjects taking ambrisetan and then remain stable.

Additional reports of deaths/withdrawals/serious adverse events received after November 30, 2006

Study AMB 320-321: 5 deaths included sudden death, pulmonary hypertension, cardiac arrest, cardiac failure/pneumonitis, right ventricular failure/thrombosis.

Study AMB 22: 1 death from worsening pulmonary hypertension.

Figure 1 Kaplan-Meier Curves for Time to ALT or AST Event for All PAH Subjects Who Received 1 or More Doses of Ambrisentan



Data for this analysis include subjects from the Phase I2 and Phase 3 studies (excluding AMB323) who received ambrisentan. AMB-320/321-E Subject 101-002 had an event of ALT >5xULN (10.24xULN) on 17Aug2006 (Week 99) that was recorded at a local laboratory and is included in this analysis.
Source: Figure 14.7.3

Study AMB 323 had 2 reports of elevated LFTs: 125-006 and 147-003. Subject 147-003 is discussed in the LFT section of this report.

Summary

The conclusions from the review of the original NDA submission remain unchanged. The additional data presented in the safety update are from uncontrolled trials.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were 483 subjects who received at least one dose of ambrisentan (dose range 1 mg to 10 mg qd) in one of the phase 2-3 studies. Most of the subjects (81%) received the 5 or 10 mg doses. A total of 161 subjects received ambrisentan for at least one year.

Safety problems

1) Elevated liver enzymes

As with bosentan, ambrisentan has been shown to be a hepatotoxin and capable of causing substantial damage to the liver. There were three ambrisentan subjects (0.6%), but no placebo subjects who reported LFTs > 8 x ULN. An additional 1.3%1 ambrisentan subjects had LFTs between 3 and 5 x ULN. It cannot be assumed that all LFT increases will resolve when ambrisentan is discontinued, although all appeared to do so in the clinical trials. Those patients with mild LFT elevations could be able to remain on drug. Close monitoring will be essential for all patients taking ambrisentan and all patients should be taking the lowest effective dose. There was one death for which drug induced liver failure cannot be ruled out (primarily for lack of follow up information). Box warning should be similar to the one for bosentan.

2) Pregnancy
Category X

3) Male fertility
Animal studies reported diffuse testicular atrophy. The attempts to determine the effect in adult male patients were inadequate.

[redacted]

5) Anemia
There were common, mostly mild, decreases in hemoglobin and hematocrit in the ambrisentan treated groups. This was rarely an adverse event of concern (which remains the case with bosentan).

6) Allergic reaction
There were two subjects with reports of allergic reaction (face edema). One subject had a positive re-challenge. Both subjects were permanently discontinued. This seems to be an uncommon and non serious adverse event.

Conclusions
The safety issues associated with the use of ambrisentan appear to be not unlike those associated with the use of bosentan. The safety labeling for ambrisentan, therefore, should be similar to the labeling for bosentan.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

For efficacy we evaluated the data from the two pivotal trials individually and did not pool because of the heterogeneity in the two studies, e.g., differences in magnitudes of placebo and drug-related walk changes.

7.4.1.2 Combining data

For safety we examined data primarily from the two pivotal trials combined and secondarily from the phase I studies combined. We examined special studies, such as the one in patients who experienced liver enzyme increases on another ERA, individually.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

We explored dose dependency for adverse findings as possible within the limitations of the safety data base size and the dose range tested. With those limitations it is impossible to demonstrate dose dependency for most adverse findings; the exception is hemoglobin reduction.

7.4.2.2 Explorations for time dependency for adverse findings

We and the sponsor explored time dependency for adverse findings particularly with regard to the changes in liver function tests. See Section 7.1.7.

7.4.2.3 Explorations for drug-demographic interactions

We explored drug-demographic interactions as possible within the limitations of the safety data base size. We did not identify any significant drug-demographic interactions with the exception that peripheral edema appears to occur more frequently with drug use in the elderly (age $\geq$ 65). However, the safety data base size is too small to provide assurance that other drug-demographic interactions do not exist.

7.4.2.4 Explorations for drug-disease interactions

The one drug-disease interaction we examined was comparative efficacy in patients with idiopathic PAH and secondary PAH. Ambrisentan appears to be less effective for improving walk distance in secondary PAH. See Section 6.1.4.4.2.

7.4.2.5 Explorations for drug-drug interactions

Because of the small size of the data base we did not try to explore drug-drug interactions.

7.4.3 Causality Determination

We did not perform any special analyses for causality determination but depended upon the usual presentations of adverse events by frequency.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The major outstanding issues regarding dosing regimen and administration are whether once daily dosing is optimal and whether dosing should be limited to a maximum of 10 mg daily. For a discussion of these issues see Section 6.1.6 and the FDA clinical pharmacologist's review.

8.2 Drug-Drug Interactions

Please see the FDA clinical pharmacologist's review for a complete discussion of drug-drug interactions. We present briefly below the most pertinent points made in that review.

The sponsor formally studied interactions of ambrisentan with sildenafil and with warfarin. Co-administration of sildenafil in healthy volunteers appears not to impact the PK of ambrisentan and ambrisentan does not affect the PK of sildenafil and N-desmethyl-sildenafil. Co-administered ambrisentan appears not to impact the pharmacokinetics of the warfarin enantiomers and does not affect prothrombin time or INR. The FDA clinical pharmacology reviewer concludes that the interaction liability of ambrisentan has not been adequately investigated because its metabolism has not been completely elucidated and recommends the following:

- Exploring the interaction potential of ambrisentan in humans when co-administered with drugs known to be strong inhibitors of OATP and P-gp such as cyclosporine A and rifampin. *In vitro* studies indicate that ambrisentan is a substrate of P-gp and a probable substrate of OATP.

- Exploring the interaction potential of ambrisentan in humans when co-administered with strong inhibitors of CYP3A (ketoconazole) and CYP 2C19 (omeprazole). The CYP 450 catalyzed metabolism of ambrisentan is likely to exceed 20% of the administered dose in humans.

8.3 Special Populations

Subgroups for Safety

There were no studies specifically designed to evaluate safety of ambrisentan in any subgroup including age, gender, race, etiology of PAH, and baseline WHO functional class. Overall, one cannot draw any conclusions about the safety in subgroups because of the small sample sizes.

There were no studies evaluating the safety of ambrisentan in subjects with either renal or liver impairment.

8.4 Pediatrics

As a drug indicated for an orphan population ambrisentan is exempt from the requirements of the Pediatric Research Equity Act. Because of its substantial reproductive toxicity it is debatable whether ambrisentan is suitable for use in children. However, PAH is a very serious, life-shortening disease so use in children may be considered.

8.5 Advisory Committee Meeting

We have not presented ambrisentan at an advisory committee meeting nor do we plan to present it.

8.6 Literature Review

We found 27 citations in Pubmed searching on "ambrisentan". The majority of the articles were general discussions of ERAs; none provided source data not included in the NDA submission.

8.7 Postmarketing Risk Management Plan

Because of the identified toxicities of ambrisentan, the sponsor submitted a postmarketing risk management plan. Please see the review by the Office of Surveillance and Epidemiology for a detailed analysis of this plan. We have the following comments:

- The sponsor identifies four risks to be addressed: teratogenicity, the potential risk of hepatotoxicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. To address these risks the sponsor is proposing the risk management plan summarized in Table 34.

- Planned distribution of ambrisentan is through a closed distribution system using specialty pharmacies. Prescribers and patients must be enrolled in the program. This approach is similar to that used for the approved ERA bosentan.

- The largest deviation from the bosentan riskmap is a relaxed frequency of liver function test (LFT) monitoring—monthly for bosentan and [redacted]

- Recommendations from the Office of Surveillance and Epidemiology are being communicated to the sponsor in a discipline review letter. Those recommendations and the issue of frequency of LFT monitoring will be discussed with the sponsor during labeling negotiations.

Table 34: Sponsor's Risk Management Plan Summary

8.8 Other Relevant Materials

We are unaware of any other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Regarding efficacy, the results of the two adequate and well-controlled studies, AMB-320 and AMB-321, for the common primary endpoint, change from baseline in six minute walk, provide substantial evidence that ambrisentan is effective in improving exercise capacity, at least at peak drug levels, from both clinical and statistical perspectives. The results are reasonably and clinically convincing that ambrisentan also improves time to clinical worsening but are less compelling for the other secondary endpoints. Regarding safety, ambrisentan has an adverse event profile similar to that of the approved ERA bosentan. The major concerns are hepatoxicity

and the potential for teratogenicity and testicular toxicity. Ambrisentan also shows other effects typical of ERAs including a slight reduction in hemoglobin, reduction in blood pressure, and peripheral edema.

The major unanswered question regarding ambrisentan is whether the once daily dosing regimen is optimal. The PK data do not support once daily dosing and walks were not performed at the interdosing interval to provide data on exercise effects at trough drug levels. On the other hand, the beneficial impact upon clinical worsening and the continued improvements in walks over 12 weeks suggest a more sustained effect. There is another unanswered question regarding whether higher doses would provide more benefit and there are also deficiencies in metabolic characterization that are described well in the FDA clinical pharmacologist's review.

9.2 Recommendation on Regulatory Action

From clinical and statistical perspectives we recommend approval of ambrisentan for the treatment of WHO group 1 PAH to improve exercise capacity. From a clinical perspective we also recommend approval to improve time to clinical worsening.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Because of the substantial potential toxicity (hepatoxicity, teratogenicity, and testicular toxicity), ambrisentan needs and the sponsor has proposed a risk management program.

9.3.2 Required Phase 4 Commitments

The sponsor must conduct a study to evaluate effects upon exercise capacity at a time remote from peak drug levels, e.g., in the late afternoon or evening or at the interdosing interval prior to taking the next dose. [redacted]

9.3.3 Other Phase 4 Requests

Regardless of the effects upon exercise capacity throughout the interdosing interval, the sponsor should study the effects upon efficacy and safety of a BID dosing regimen. The sponsor should also study dosages higher than 10 mg per day. The sponsor should also delineate better the metabolism and potential for interaction of ambrisentan as detailed in the FDA clinical pharmacologist's review.

9.4 Labeling Review

We have many specific comments regarding the proposed label that we will communicate to the sponsor during labeling negotiations.

9.5 Comments to Applicant

We will communicate our comments to the applicant in conjunction with the labeling negotiations.

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/s/

Thomas Marciniak
5/16/2007 01:03:22 PM
MEDICAL OFFICER

Maryann Gordon
5/18/2007 10:59:40 AM
MEDICAL OFFICER

Ququan Liu
5/18/2007 11:21:15 AM
BIOMETRICS

James Hung
5/18/2007 11:38:14 AM
BIOMETRICS

NDA#22081
Maryann Gordon, MD

Conclusions

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Summary

There were 483 subjects who received at least one dose of ambrisentan (dose range 1 mg to 10 mg qd) in one of the phase 2-3 studies. Most of the subjects (81%) received the 5 or 10 mg doses. A total of 161 subjects received ambrisentan for at least one year.

Safety problems

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As with bosentan, ambrisentan has been shown to be a hepatotoxin and capable of causing substantial damage to the liver. There were three ambrisentan subjects (0.6%), but no placebo subjects who reported LFTs > 8 x ULN. An additional 1.3%[1] ambrisentan subjects had LFTs between 3 and 5 x ULN. It cannot be assumed that all LFT increases will resolve when ambrisentan is discontinued, although all appeared to do so in the clinical trials. Those patients with mild LFT elevations could be able to remain on drug. Close monitoring will be essential for all patients taking ambrisentan and all patients should be taking the lowest effective dose. There was one death for which drug induced liver failure cannot be ruled out (primarily for lack of follow up information). Box warning should be similar to the one for bosentan.

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Category X

3) Male fertility
Animal studies reported diffuse testicular atrophy. The attempts to determine the effect in adult male patients were inadequate.

[redacted]

5) Anemia
There were common, mostly mild, decreases in hemoglobin and hematocrit in the ambrisentan treated groups. This was rarely an adverse event of concern (which remains the case with bosentan).

6) Allergic reaction

[1] Placebo subtracted

There were two subjects with reports of allergic reaction (face edema). One subject had a positive re-challenge. Both subjects were permanently discontinued. This seems to be an uncommon and non serious adverse event.

7.1 Methods and findings

Description of phase 2-3 clinical trials

There were six phase 2-3 trials. Two were large, randomized, double blind, placebo controlled efficacy trials (AMB-320 and AMB 321), one was a blinded dose ranging efficacy trial (AMB-220), one was an open label, uncontrolled trial with subjects who could not tolerate taking an endothelin receptor antagonist because of elevated LFTs, and two were open label extension trials that are ongoing (AMB-320/321E and AMB-220).

Table 2 Description of Ambrisentan Clinical Safety Studies

Study Identifier and Location of Study Report	Design	No. of Study Centers (Location)	Total No. Subjects Enrolled/ Completed	Gender M/F (%) Mean Age (y) (Range) Race C/NC (%)	Treatment Dose Route Regimen	Duration of Drug Treatment
PHASE 3 PLACEBO-CONTROLLED STUDIES IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION						
AMB-320[1,2,4] (ARIES-1) 5.3.5.1.1	Randomized, double-blind efficacy and safety study	46 investigative sites 8 countries	202/183	16/84 M/F 50.1 y (17–82 y) 69/31 C/NC	AMB 5 or 10 mg qd Pbo qd Orally	12 wks
AMB-321[1,2,4] (ARIES-2) 5.3.5.1.2	Randomized, double-blind efficacy and safety study	41 investigative sites 13 countries	192/170	26/75 M/F 50.9 y (20–81 y) 85/15 C/NC	AMB 2.5 or 5 mg qd Pbo qd Orally	12 wks
PHASE 2 STUDIES IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION						
AMB-220 5.3.5.2.1	Randomized, double-blind, dose-controlled, dose-ranging evaluation of exercise capacity for 12 wks, followed by 12-wk open-label extension	21 investigative sites 6 countries	64/58	16/84 M/F 51.4 y (22–78 y) 70/30 C/NC	AMB 1, 2.5, 5, or 10 mg qd Orally	Up to 28 wks 12 wks double-blind, 12 wks open-label
AMB-222 5.3.5.2.3	Open-label safety and efficacy study in subjects who previously discontinued ERA therapy due to serum aminotransferase abnormalities	17 investigative sites 4 countries	36 enrolled 2 withdrawn 34 ongoing Study ongoing	14/86 M/F 57.2 y (31–76 y) 78/22 C/NC	AMB 2.5, 5, or 10 mg qd Orally Titrated to balance efficacy/safety	Ongoing. As of 16 February 2006, mean exposure was 19.2 wks and maximum exposure was 36 wks
LONG-TERM PHASE 2 & 3 STUDIES IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION						
AMB-320/321-E[4] 5.3.5.3.2	Blinded, dose-controlled evaluation of safety and efficacy	85 investigative sites 18 countries	383 enrolled 3 did not enter extension study 64 withdrawn 316 ongoing	For combined analysis (n=383) 21/79 M/F 51.1 y (17.5-82.7 y) 77/23 C/NC	AMB 2.5, 5, or 10 mg po qd	Ongoing. Interim data cutoff 16Feb2006 mean exposure: 38.6 wks (0.74 y) maximum exposure: 109 wks (2.1 y)
AMB-220-E 5.3.5.2.2	Open-label, continuation from AMB-220	16 investigative sites 5 countries	54 enrolled 11 withdrawn 43 ongoing Study ongoing	15/85 M/F 51.1 y (22–79 y) 72/28 C/NC	AMB 1, 2.5, 5, or 10 mg po qd	Ongoing. Interim data cutoff 16Feb2006 mean exposure: 115 wks (2.2 y) and maximum exposure: 159 wks (3.1 y)

The numbers of subjects in these six studies are shown below, by maximum dose of ambrisentan.

Table 1 Ambrisentan Exposure for Subjects with Pulmonary Arterial Hypertension (Population: All Phase 2 and 3 Studies)

	1 mg ambrisentan (N = 3)	2.5 mg ambrisentan (N = 91)	5 mg ambrisentan (N = 217)	10 mg ambrisentan (N = 172)	Combined ambrisentan (N = 483)
Mean (SD), weeks	46.9 (68.61)	48.2 (38.29)	38.7 (37.26)	57.9 (48.49)	47.4 (42.69)
Median, weeks	13.0	42.3	27.9	47.7	36.1
Min, Max, weeks	1.9, 125.9	0.4, 167.3	0.1, 168.0	0.1, 184.3	0.1, 184.3
Duration, n					
≥12 weeks	2	79	184	152	417
≥6 months	1	68	109	109	287
≥1 year	1	30	51	79	161
≥1.5 years	1	10	22	47	80
≥2 years	1	7	14	26	48
≥3 years	0	5	5	13	23

Note: Exposure summarized by maximum dose received (safety treatment assignment) as of the 16 February 2006 cut-off date for ongoing studies
Source: Appendix 3, Table 14.1.4a

At total of 483 subjects received at least one dose of ambrisentan. Most of these subjects received the 5 or 10 mg dose, and 161 subjects received drug for at least one year.

Disposition of subjects

Placebo studies
A total of 394 subjects were randomized to either placebo, ambrisentan 2.5 mg, ambrisentan 5 mg, or ambrisentan 10 mg in the placebo controlled efficacy trials AMB-320 and -321. Both trials followed subjects for 12 weeks. The table below shows the number of subjects who were randomized, completed the study, or were withdrawn prematurely (by reason).

Number and (percent) of subjects

	placebo	AMB 2.5 mg	AMB 5 mg	AMB 10 mg
randomized	132	64	130	68
completed	111	58	121	63
Withdrawn premature	21 (16)	6 (9)	9 (7)	5 (7)
Adverse event	4	1	4	1
Early escape^	8	2	1	2
Other+	6	3	4	2

^defined as a gradual deterioration in subjects' clinical symptoms.
+see table below.

The percent of placebo subjects who withdrew (for any reason) was about twice the percent for the active treatment groups.

The 15 subjects whose reason for withdrawal was classified as "other" are described in the table below.

Study	Subject number	Reason for Discontinuation
Placebo		
AMB-320	111-001	formal withdrawal of consent (declined to continue with study medication)
AMB-320	129-001	Other: protocol violation
AMB-320	132-001	Non-compliance to any of the procedures (patient requested to stop drug for 2 weeks)
AMB-320	139-001	Treatment with other PAH treatment (IV epoprostenol)
AMB-320	156-001	formal withdrawal of consent (clinical worsening)
AMB-321	201-008	Clinical status did not improve
2.5 mg		
AMB-321	225-002	formal withdrawal of consent (decision of the patient)
AMB-321	229-002	formal withdrawal of consent (patient stated that study drug made her illness worse)
AMB-321	247-004	formal withdrawal of consent (marked dyspnea)
5 mg		
AMB-320	101-009	Lost to follow-up (patient did not return for visit 4 or 5, site attempted several contacts)
AMB-320	107-006	Other: patient developed left heart failure. Diagnosis revised: pulmonary venous hypertension
AMB-320	149-004	formal withdrawal of consent (too complicated; personal (private) reasons)
AMB-321	247-003	formal withdrawal of consent (the patient has refused to participate in the study due to her family's circumstances)
10 mg		
AMB-320	101-015	Discretion of Myogen (Note: The investigator randomized the subject prior to receipt of central laboratory liver function test results. The ALT/AST results were >1.5 ULN which was a protocol violation. Subject discontinued prior to 1st dose of study drug and was not included in analysis dataset [or ITT] since the subject never received drug.)
AMB-320	126-006	formal withdrawal of consent (patient decided to withdraw)

Duration of exposure

The mean numbers of weeks subjects were receiving treatment were similar for all groups. However, the minimum duration of treatment for the ambrisentan groups tended to be somewhat less (1-1.1 weeks) compared to the placebo group (2.7 weeks).

Table 3 Summary of Treatment Exposure (AMB-320/321 Population: Safety)

Treatment group	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Total weeks subject received drug					
Mean (SD)	11.4 (2.22)	11.9 (1.56)	11.6 (2.09)	11.8 (1.93)	11.7 (1.93)
Median	12.0	12.1	12.1	12.1	12.1
Min, Max	2.7, 14.0	1.1, 13.9	1.1, 13.4	0.9, 14.3	0.9, 14.3

Source: AMB-320/321 Table 12.1

Demographics

The demographics of the 393 subjects in the 2 placebo controlled trials are shown below.

Table 8 Demographics: Combined Analysis of Phase 3 Placebo-Controlled Studies (AMB-320/321: Population: Safety)

Treatment group Characteristic	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)	Total population (N = 393)
Gender, n (%)						
Male	29 (22.0)	16 (25.0)	23 (17.7)	14 (20.9)	53 (20.3)	82 (20.9)
Female	103 (78.0)	48 (75.0)	107 (82.3)	53 (79.1)	208 (79.7)	311 (79.1)
Race, n (%)						
Caucasian	100 (75.8)	54 (84.4)	104 (80.0)	44 (65.7)	202 (77.4)	302 (76.8)
Black	4 (3.0)	0 (0.0)	4 (3.1)	3 (4.5)	7 (2.7)	11 (2.8)
Asian	4 (3.0)	1 (1.6)	3 (2.3)	1 (1.5)	5 (1.9)	9 (2.3)
Hispanic	24 (18.2)	9 (14.1)	17 (13.1)	17 (25.4)	43 (16.5)	67 (17.0)
Other	0 (0.0)	0 (0.0)	2 (1.5)	2 (3.0)	4 (1.5)	4 (1.0)
Age, years, mean (SD)	49.4 (15.22)	51.6 (15.17)	51.6 (14.99)	49.3 (15.64)	51.0 (15.17)	50.5 (15.19)
<65 years	104 (78.8)	50 (78.1)	100 (76.9)	55 (82.1)	205 (78.5)	309 (78.6)
≥65 and <75 years	22 (16.7)	11 (17.2)	25 (19.2)	7 (10.4)	43 (16.5)	65 (16.5)
≥75 years	6 (4.5)	3 (4.7)	5 (3.8)	5 (7.5)	13 (5.0)	19 (4.8)
Weight, kg, mean (SD)	74.2 (19.59)	70.0 (15.17)	70.3 (16.65)	73.2 (20.92)	71.0 (17.50)	72.1 (18.27)
BMI, kg/m^2, mean (SD)	27.8 (6.21)	26.3 (5.40)	26.7 (5.38)	27.9 (7.10)	26.9 (5.88)	27.2 (6.00)
Region, n (%)						
US/Australia[1]	52 (39.4)	0 (0.0)	49 (37.7)	47 (70.1)	96 (36.8)	148 (37.7)
Eastern Europe	11 (8.3)	20 (31.3)	18 (13.8)	0 (0.0)	38 (14.6)	49 (12.5)
Latin America	33 (25.0)	16 (25.0)	24 (18.5)	16 (23.9)	56 (21.5)	89 (22.6)
Western Europe/Israel	36 (27.3)	28 (43.8)	39 (30.0)	4 (6.0)	71 (27.2)	107 (27.2)

[1]Because no subjects from Canada were enrolled, the geographical region of US/Canada/Australia is referred to as US/Australia
Source: AMB-320/321, Table 10.2 and Listing 16.2.1

Subjects were more likely to be female, white, and less than 65 years of age. The majority of study subjects were living in US/Australia/Western Europe/Israel.

The treatment groups were fairly well balanced for these demographics.

Baseline disease characteristics

Disease characteristics are shown below by treatment group.

Table 8 Demographics: Combined Analysis of Phase 3 Placebo-Controlled Studies (AMB-320/321: Population: Safety)

Treatment group / Characteristic	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)	Total population (N = 393)
Gender, n (%)						
Male	29 (22.0)	16 (25.0)	23 (17.7)	14 (20.9)	53 (20.3)	82 (20.9)
Female	103 (78.0)	48 (75.0)	107 (82.3)	53 (79.1)	208 (79.7)	311 (79.1)
Race, n (%)						
Caucasian	100 (75.8)	54 (84.4)	104 (80.0)	44 (65.7)	202 (77.4)	302 (76.8)
Black	4 (3.0)	0 (0.0)	4 (3.1)	3 (4.5)	7 (2.7)	11 (2.8)
Asian	4 (3.0)	1 (1.6)	3 (2.3)	1 (1.5)	5 (1.9)	9 (2.3)
Hispanic	24 (18.2)	9 (14.1)	17 (13.1)	17 (25.4)	43 (16.5)	67 (17.0)
Other	0 (0.0)	0 (0.0)	2 (1.5)	2 (3.0)	4 (1.5)	4 (1.0)
Age, years, mean (SD)	49.4 (15.22)	51.6 (15.17)	51.6 (14.99)	49.3 (15.64)	51.0 (15.17)	50.5 (15.19)
<65 years	104 (78.8)	50 (78.1)	100 (76.9)	55 (82.1)	205 (78.5)	309 (78.6)
≥65 and <75 years	22 (16.7)	11 (17.2)	25 (19.2)	7 (10.4)	43 (16.5)	65 (16.5)
≥75 years	6 (4.5)	3 (4.7)	5 (3.8)	5 (7.5)	13 (5.0)	19 (4.8)
Weight, kg, mean (SD)	74.2 (19.59)	70.0 (15.17)	70.3 (16.65)	73.2 (20.92)	71.0 (17.50)	72.1 (18.27)
BMI, kg/m^2, mean (SD)	27.8 (6.21)	26.3 (5.40)	26.7 (5.38)	27.9 (7.10)	26.9 (5.88)	27.2 (6.00)
Region, n (%)						
US/Australia[1]	52 (39.4)	0 (0.0)	49 (37.7)	47 (70.1)	96 (36.8)	148 (37.7)
Eastern Europe	11 (8.3)	20 (31.3)	18 (13.8)	0 (0.0)	38 (14.6)	49 (12.5)
Latin America	33 (25.0)	16 (25.0)	24 (18.5)	16 (23.9)	56 (21.5)	89 (22.6)
Western Europe/Israel	36 (27.3)	28 (43.8)	39 (30.0)	4 (6.0)	71 (27.2)	107 (27.2)

[1]Because no subjects from Canada were enrolled, the geographical region of US/Canada/Australia is referred to as US/Australia
Source: AMB-320/321, Table 10.2 and Listing 16.2.1

Subjects were mostly likely to be diagnosed with idiopathic PAH, to have been diagnosed with the disease for about two years, to be in WHO functional class II or III, and to have a baseline walk distance of around 345 meters. The groups were fairly well balanced.

Concomitant medication

The three most common concomitant medications included spironolactone, paracetamol, and dilitazem.

Serious safety

7.1.1 Deaths (all Phase 2-3 clinical studies)

A total of 27 subjects were reported to have died while on or within four weeks of discontinuing ambrisentan. The majority of the deaths (78%) were reported during the longterm extension studies.

Table 25 Summary of Deaths in Subjects with Pulmonary Arterial Hypertension (Population: All Phase 2 and 3 Studies)

Treatment group[1]	Placebo	1 mg ambrisentan	2.5 mg ambrisentan	5 mg ambrisentan	10 mg ambrisentan
Phase 3, placebo-controlled studies					
AMB-320	2	0	NA	1	1
AMB-321	4	0	2	0	NA
Phase 2 Studies					
AMB-220	NA	1	0	0	1
AMB-222[2]	NA	0	0	0	0
Long-term Phase 2 and 3 studies					
AMB-320/321-E[3]	NA	0	3	10	3
AMB-220-E[2]	NA	0	1	0	4

[1]Deaths are attributed to the actual ambrisentan dose at the time of death
[2]For ongoing studies deaths are reported through 16 February 2006
[3]Deaths that occurred during study AMB-320/31-E only. Deaths that occurred while subjects received ambrisentan or placebo in AMB-320 and AMB-321 are counted for those studies only.
NA = treatment not available in study

N.B. Subject 321/235/003 had been randomized to placebo (and is listed in the placebo column in table 25) but was actually receiving ambrisentan 5 mg for 8 day at time of death. She is discussed under the 5 mg dose in the table below.

During the two placebo controlled trials, there were ten deaths: six deaths[2] were reported in the placebo group (4.5%) and four in the ambrisentan group (1.2%). The ten deaths are discussed below, by treatment group.

Deaths reported during the placebo controlled trials

Subject ID/age/sex	Duration	Comments
placebo		
320/126-008/50y/f	15d	Right heart failure
320/139-001/32y/f	62d	Right heart failure
321/207-014/65y/m	72d	Cardiorespiratory arrest
321/235-005/40y/f	23d	Pulmonary thromboembolism and right heart failure
321/245-006/44y/f	68d	Worsening PAH
Amb 2.5		
321/207-002/66y/m	80d	Discontinued because of worsening PAH. Hospitalized, experienced 3 cardiac arrests. Died one day after the last dose of study drug.
321/230-004/29y/m	66d	Sudden worsening of dyspnea followed by death. Could not rule out pulmonary embolism. History of SLE.
Amb 5 mg		
320/156-007/28y/f	8d	Gastroenteritis (N&V with elevated GGT, total bilirubin, LDH, mild leukocytosis, protein and bilirubin in urine), pneumonia (consolidation on x-ray), sepsis with hypovolemic shock and cardiac arrest.
321/235-003/31y/f	67d placebo followed by	Developed decompensated right heart failure while on placebo and discontinued as "early

[2] Includes subject 321/235/003

	8d amb 5mg	escape." Started ambrisentan. Condition did not improve, subject developed sepsis and multiorgan failure leading to death.
Amb 10 mg		
320/101-006/77y/f	89d	Intracranial hemorrhage after (witnessed) fall. Concomitant med included warfarin

These deaths seem linked to the underlying disease rather than to the use of ambrisentan.

The additional 21 deaths reported during the other phase 2-3 trials are shown below.

Subject ID/age/sex	Dose/Duration	Comments
220/16-004/75y/m	1mg/13d	Appeared cyanotic at screening visit, increased edema dyspnea, fatigue day 8. Sudden death.
220/13-005/52y/m	10mg/44d	Seen in clinic 2 days, doing well. Died suddenly 2 days later.
320/321E/207-015/70y/f	2.5mg/365d	Hospitalized for worsening right heart failure with frequent supraventricular extrasystoles and anuria. She developed progressive hypotension followed by cardiorespiratory arrest.
320/321E/221-003/54y/f	**2.5mg/24d (Randomized to placebo in base study)**	**History of SLE. Developed epigastric pain with dark urine, back pain, nausea, vomiting. Hospitalized at another hospital and details are sparse (no documentation of LFTs, serum amylase). There were discussions about ALT and ALT 10-20xULN (unconfirmed). Drug induced hepatitis versus bile duct cholelithiasis/biliary sepsis/pancreatitis.**
320/321E/244-004/72y/f	2.5mg/393d	Developed dyspnea, cyanosis, cardiac arrest. She was revived but developed asystole and died 2 days later. Had been hospitalized previously for worsening PAH day 309.
320/321E/104-003/35y/f	5mg/115d	Hospitalized for dizziness, increased dyspnea, chronic cough. Became febrile, WBC rose, blood pressure dropped, developed nausea and vomiting. Arrested and could not be revived. Blood and lung cultures were positive for microorganism associated with indwelling catheter.

		Previously hospitalized for chest pain.
320/321E/116-003/68y/f	5mg/206d	Hospitalized for respiratory failure. She died the following day. Autopsy reported cause of death as respiratory failure.
320/321E/121-001/71y/f	5mg/235d/	History of 3 day bout of gastroenteritis with diarrhea, nausea, vomiting. Cardiac arrest while being transported to hospital because of dyspnea and chest pain. Arrested again in the emergency room. On admission chest x ray showed pulmonary edema. Labs: potassium 6.8mmol/L and creatinine 6.3 mg/dl. DNR was implemented. Cause of death was listed as presumed sepsis.
320/321E/207-005/49y/f	5mg/196d	Continued with signs and symptoms of worsening right heart failure. Was hospitalized twice. Experienced severe bradycardia followed by cardiac arrest. Resuscitation was unsuccessful.
320/321E/207-007/72y/m	5mg/365d	Hospitalized on day 253 because of tuberculous meningitis with encephalitis. Medical treatment was ineffective and he was discharged to home. He died a short time later.
320/321E/207-011/67y/f	5mg/205d	Hospitalized day 78 because of right heart failure. Hospitalized day 194 because of heart failure and acute renal failure. She had fallen 3 days previously and blood pressure on admission was 95/60 mmHg with heart rate 120 bmp. She became febrile with rapid deterioration. Death was attributed to cardiorespiratory arrest.
320/321E/207-025/57y/f	5mg/114d	Hospitalized day 12 because of worsening right heart failure. Hospitalized again for pulmonitis and acute respiratory failure. She died from cardiac arrest about 1 week later. Anemia was reported without laboratory values reported.
320/321E/211-004/69y/f	5mg/181d	Hospitalized because of right heart failure. She was found to be anemic. She died day 182 as a result of acute respiratory failure after having been transferred to a nursing home.

320/321E/235-004/32y/m	5mg/441d	Died of acute respiratory failure. Hospitalized for increased dyspnea and tachycardia on study day 441. Experienced cardiac arrest and could not be revived. HIV positive.
320/321E/132-008/24y/f	**5mg/12d**	**Discontinued from placebo day 37 because of worsening PAH (early escape). She was hospitalized for fluid overload and increased dyspnea. 8 days after starting ambrisentan (and 4 days after she had been discharged for the previous event) she was hospitalized for what was identified as exacerbation of SLE. Complaints included dyspnea at rest, chest pressure, nausea and vomiting. ECHO showed greatly enlarged right ventricle. LFTs were >7000 IU/L. Ambrisentan was discontinued, she was treated with epoprostenol and dobutamine and LFTs fell to ~100 IU/L. Thrombotic thrombocytopenia was diagnosed, plasma exchange was started and she developed asystole during the procedure. Autopsy showed diffuse alveolar hemorrhage, SLE, pulmonary hypertension, renal failure. Liver showed severe centrilobular congestion consistent with right heart failure. GGT at screen was mildly elevated as was ALT.**
320/321E/210-006/65y/f	10mg/523d[3]	Diagnosed with large, highly malignant nerve sheath sarcoma on day 444. Several months later she died of cardiac arrest and autopsy showed cardiac wall metastases.
320/321E/213-004/34y/f	2.5mg/364d 5mg/57d 10mg/3d	Subject died 422 days after start of study drug of multiorgan failure. On day of hospitalization she presented with severe cough and minor hemoptysis and was diagnosed with respiratory insufficiency and broncho-pneumonia. She developed right heart failure with persistent hypotension. LFTs were normal or mildly elevated initially, but became

[3] Includes 336 days on 5 mg and 187 days on 10 mg

		greatly elevated as did serum creatinine. She died after being denied a heart/lung transplant. Autopsy showed PAH with acute bronchitis and multi-organ failure. She had been hospitalized on day 361 for worsening PAH.
320/321E/213-008/65y/f	5mg/438d 10mg/221d	Died of acute heart failure. Had been hospitalized numerous times for pneumonia, worsening PAH, suspicion of malignant lymphadenopathy, repeated syncope with bronchopneumonia.
220E/13-007/68y/f	2.5mg/285 d 5mg/99d 2.5mg/29d 1mg/86d	Died of right heart failure on study day 490
220E/05-002/59y/f	1mg/86 d 2.5mg/24d 5mg/108d 10mg/54d	Hospitalized for psittacosis pneumonia on day 233. On study day 268 she was hospitalized for shortness of breath. After a lung biopsy she was found unresponsive. Autopsy showed bilateral organizing pneumonia.
220E/13-004/77y/m	2.5mg/17d 5mg/14d 10mg/252d	Hospitalized on day 282 for right heart failure with worsening dyspnea and decreased urine output. He died that day.
220E/15-005/66y/f	2.5mg/82d 5mg/30d 10mg/568d	Elevated LFTs on day 495 found when hospitalized for pneumonia. Drug discontinued and then restarted about 2 months later when LFTs normalized. She was hospitalized on day 672 because of pneumonia. ALT was within normal limits (bilirubin, GGT, Alk phos elevated). She died 7 days later of acute respiratory failure.
220E/21-009/54y/f	2.5mg/85d 5mg/30d 10mg/597d	Experienced dizziness and syncope day 672. Remained on drug. Again experienced syncope day 681. Study drug continued. Rehospitalized day 702 for increased shortness of breath, weight gain, peripheral edema, increased weakness and fatigue. Echo showed severe right ventricular dilatation and PAH. She collapsed and could not be resuscitated.

Drug induced hepatitis followed by death cannot be ruled out for subject 320/321E/221-003. Details about this case are unobtainable.

There was an extremely large rise in LFTs for subject 320/321E/132-008 which resolved in the drug was discontinued. Cause of death was probably SLE exacerbation.

The other deaths seemed linked to the underlying disease.

There were no reported deaths in the phase 1 studies.

7.1.2 Serious adverse events

Placebo controlled trials

Twice as many placebo subjects reported at least one SAE compared to the ambrisentan groups. The SAEs not leading to death and reported by at least two subjects in one or more groups are shown below.

Table 26 Serious Adverse Events (Other Than Death) Reported in >1 Subject in the Combined Ambrisentan Treatment Group (AMB-320/321 Population: Safety)

Treatment group Adverse event, n (%)	Placebo (N = 132)	Combined Ambrisentan (N = 261)
Any SAE	21 (15.9)	23 (8.8)
Right ventricular failure	8 (6.1)	5 (1.9)
Pneumonia	2 (1.5)	4 (1.5)
Worsening pulmonary hypertension	5 (3.8)	3 (1.1)
Dyspnea exacerbated	1 (0.8)	2 (0.8)
Peripheral edema	0 (0.0)	2 (0.8)

Source: AMB-320/321, Section 12.3.3.2 and Summary Table 14.3.9

Right heart failure was the most commonly reported event.

Extension trials

There were 97 subjects with at least one report of a SAE (excluding those who went on to die) during the long term extension studies (320/321E). Mean exposure of 38.6 weeks.

All events reported by at least two subjects are shown below.

Table 27 Serious Adverse Events with Outcomes Other Than Death in 2 or More Subjects Reported in the Combined Ambrisentan Treatment Group (AMB-320/321-E Population: Safety)

Treatment group Adverse event, n (%)	2.5 mg ambrisentan (N = 78)	5 mg ambrisentan (N = 171)	10 mg ambrisentan (N = 134)	Combined ambrisentan (N = 383)
No. of subjects with 1 or more SAE other than death[1]	20 (25.6)	37 (21.6)	40 (29.9)	97 (25.3)
Pulmonary hypertension	5 (6.4)	4 (2.3)	9 (6.7)	18 (4.7)
Right ventricular failure	2 (2.6)	10 (5.8)	6 (4.5)	18 (4.7)
Pneumonia	2 (2.6)	3 (1.8)	3 (2.2)	8 (2.1)
Syncope	3 (3.8)	1 (0.6)	2 (1.5)	6 (1.6)
Pregnancy	1 (1.3)	2 (1.2)	1 (0.7)	4 (1.0)
Hypoxia	1 (1.3)	1 (0.6)	2 (1.5)	4 (1.0)
Pleural effusion	0 (0.0)	1 (0.6)	3 (2.2)	4 (1.0)
Gastrointestinal hemorrhage	1 (1.3)	2 (1.2)	0 (0.0)	3 (0.8)
Anemia	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Atrial fibrillation	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Atrial flutter	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Retroperitoneal hemorrhage	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Peripheral edema	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Cholecystitis acute	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Cholelithiasis	1 (1.3)	0 (0.0)	1 (0.7)	2 (0.5)
Bronchopneumonia	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Subdural hematoma	1 (1.3)	0 (0.0)	1 (0.7)	2 (0.5)
Hepatic enzyme increased	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Fluid overload	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.5)
Hyperglycemia	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.5)
Localized osteoarthritis	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Renal failure acute	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Menorrhagia	0 (0.0)	1 (0.6)	1 (0.7)	2 (0.5)
Dyspnea exacerbated	1 (1.3)	0 (0.0)	1 (0.7)	2 (0.5)

[1]Preliminary analysis period includes the Week 1-120 interval with a mean exposure of 38.6 weeks and a maximum exposure of 109.0 weeks
Source: AMB-320/321-E, Table 12.9

Commonly reported SAEs were pulmonary hypertension and right ventricular failure. Two ambrisentan subjects reported increased hepatic enzymes as an SAE.

With the dose range so narrow, it is not possible to identify an event, other than elevated LFTs[4], that is possibly dose related.

[4] Based on the bosentan data.

7.1.3 Adverse events leading to study discontinuation (excluding early escape)

Placebo controlled trials[5]

A similar percent of subjects randomized to ambrisentan[6] (4%) discontinued because of an adverse event compared to placebo (5%). Only the event "right ventricular failure" was reported by more than one ambrisentan subject. Table 14.3.10

In the long term extension study 320/321E there were 34 (9%) withdrawals for adverse events[7]. Common events included right ventricular failure, infections, nervous system disorders, pulmonary hypertension.

Dose ranging trial (study 220)

There were three study drug discontinuations because of an adverse event during the double blind phase and one in the open label extension phase. These are shown below.

Table 12.8 List of Adverse Events Leading to Study Discontinuation (Population: ITT)

Treatment	Subject No.	Sex Age	Adverse Event verbatim / preferred term	Relation to study drug	SAE (Y/N)	Outcome
Blinded Treatment Period						
1 mg	16-004	M 75 yr	aggravated PAH / pulmonary hypertension NOS aggravated	unrelated	N	unresolved
			electromechanical dissociation/ electromechanical dissociation	unrelated	N	unresolved
			sudden death / sudden death	unrelated	Y	death
5 mg	24-001	F 57 yr	elevated AST ALT/ ALT increased	probably	Y	resolved
			elevated AST ALT/ AST increased	probably	Y	resolved
10 mg	13-005	M 52 yr	sudden death / sudden death	unrelated	Y	death
OLE Period						
5 mg	05-001[1]	F 62 yr	blood pressure low/ hypotension NOS	possibly	N	unresolved
			oxygen saturation low/ oxygen saturation decreased	possibly	N	unresolved

[1] In Listing 16.2.8, "Subject's medical status did not improve" was listed as the reason for discontinuation of study; however, Listing 16.2.25 indicated that the above AEs lead to discontinuation of the study.
Source: Listing 16.2.25

There was one discontinuation because of elevated ALT/AST. Subjects with elevated LFTs are discussed later in this section.

In the extension study there were 10 discontinuations: right heart failure (5), worsening pulmonary hypertension (2), exacerbated dyspnea (1), increased ALT/AST (1, noted above), acute respiratory failure/viral pneumonia (1). One subject reported recurrent cystitis and one reported intermittent headaches with nasal congestion.

Healthy volunteer Phase I studies

[5] Table 14.3.10
[6] All doses (2.5 mg-10 mg) combined
[7] Table 14.3.7 in AIRES-E

One healthy volunteer (#38) in study EE-001 discontinued after receiving the 50 mg dose because of facial flush, shivering, sickness, nausea, vomiting, headache, vertigo, and dizziness. The 100 mg dose was administered to 2 subjects without an obvious safety effect.

Other discontinuations in normal volunteer studies included subject 01-322 in study AMB-103 who dropped out because of streptococcal pharyngitis, subject 01-03 in study AMB-105 who dropped out because of headache and subject 01-147 in study AMB-104 who dropped out because of palpitations.

7.1.5 Routine adverse events

Placebo controlled trials

Adverse events reported by subjects randomized into study 320 or 321 are shown below.

Table 12 Adverse Events >3% Incidence in Placebo or Combined Ambrisentan Treatment Groups (AMB-320/321 Population: Safety)

Treatment group Adverse event, n (%)	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Subjects with at least 1 AE	108 (81.8)[1]	47 (73.4)	102 (78.5)	53 (79.1)	202 (77.4)
Peripheral edema	14 (10.6)	2 (3.1)	24 (18.5)	19 (28.4)	45 (17.2)
Headache	18 (13.6)	5 (7.8)	20 (15.4)	13 (19.4)	38 (14.6)
Dizziness	13 (9.8)	3 (4.7)	9 (6.9)	6 (9.0)	18 (6.9)
Nasal congestion	2 (1.5)	1 (1.6)	7 (5.4)	7 (10.4)	15 (5.7)
Cough	8 (6.1)	2 (3.1)	7 (5.4)	5 (7.5)	14 (5.4)
Dyspnea exacerbated	8 (6.1)	2 (3.1)	10 (7.7)	1 (1.5)	13 (5.0)
Upper respiratory tract infection	8 (6.1)	2 (3.1)	6 (4.6)	5 (7.5)	13 (5.0)
Palpitations	3 (2.3)	4 (6.3)	5 (3.8)	3 (4.5)	12 (4.6)
Dyspnea	4 (3.0)	1 (1.6)	7 (5.4)	3 (4.5)	11 (4.2)
Constipation	2 (1.5)	2 (3.1)	4 (3.1)	4 (6.0)	10 (3.8)
Fatigue	6 (4.5)	0 (0.0)	7 (5.4)	3 (4.5)	10 (3.8)
Nausea	12 (9.1)	2 (3.1)	5 (3.8)	3 (4.5)	10 (3.8)
Bronchitis	5 (3.8)	3 (4.7)	6 (4.6)	1 (1.5)	10 (3.8)
Flushing	1 (0.8)	4 (6.3)	5 (3.8)	1 (1.5)	10 (3.8)
Nasopharyngitis	1 (0.8)	0 (0.0)	7 (5.4)	2 (3.0)	9 (3.4)
Right ventricular failure	16 (12.1)	2 (3.1)	6 (4.6)	1 (1.5)	9 (3.4)
Abdominal pain	1 (0.8)	2 (3.1)	4 (3.1)	2 (3.0)	8 (3.1)
Chest pain	3 (2.3)	1 (1.6)	6 (4.6)	1 (1.5)	8 (3.1)
Insomnia	4 (3.0)	4 (6.3)	3 (2.3)	1 (1.5)	8 (3.1)
Epistaxis	5 (3.8)	2 (3.1)	2 (1.5)	4 (6.0)	8 (3.1)
Sinusitis	0 (0.0)	1 (1.6)	4 (3.1)	3 (4.5)	8 (3.1)
Arthralgia	5 (3.8)	3 (4.7)	1 (0.8)	2 (3.0)	6 (2.3)
Urinary tract infection	8 (6.1)	2 (3.1)	2 (1.5)	1 (1.5)	5 (1.9)
ALT increased	5 (3.8)	0 (0.0)	2 (1.5)	2 (3.0)	4 (1.5)
Pulmonary hypertension	7 (5.3)[1]	2 (3.1)	1 (0.8)	1 (1.5)	4 (1.5)

Note: Table reports AEs of >3% in the placebo group or combined ambrisentan group
[1]Subject 156-001 (placebo) had an event of clinical worsening of PAH that appeared to be nontreatment-emergent. Upon investigation, the event started after the first dose of study drug. This subject has been included in this summary table.
Source: AMB-320/321, Summary Table 12.3

The events from the above table and reported more often in the combined ambrisentan compared to the placebo group include peripheral edema 7%[8], headache 1%, nasal congestion 4%, palpitations 2%, dyspnea 1%, constipation 2%, flushing 3%, nasopharyngitis 3%, abdominal pain 2%, chest pain 1%, and sinusitis 3%.

Peripheral edema (in particular) and nasal congestion (less so) seem to suggest a positive relationship to dose.

Right ventricular failure, on the other hand, was reported almost 4 times more often by the placebo group than the combined ambrisentan group. However, this was more notable in the one study (321) than in the other.

A review of the nonplacebo controlled studies does not contradict the findings cited above.

Study 220 had both a double blind and an open label phase. The table below shows the adverse events reported both during the blinded phase (weeks 0-12) and during the entire study (weeks 0-24).

Table 18 Adverse Events ≥10% Incidence During Weeks 0-12 and 0-24 for the Combined Ambrisentan Group (AMB-220 Population: Safety)

Treatment period Adverse event, n (%)	Week 0-12 (N = 64)	Week 0-24 (N = 64)
Peripheral edema	16 (25.0)	17 (26.6)
Headache	10 (15.6)	14 (21.9)
Nasal congestion	12 (18.8)	13 (20.3)
Upper respiratory tract infection NOS	12 (18.8)	13 (20.3)
Cough	6 (9.4)	9 (14.1)
Nausea	8 (12.5)	9 (14.1)
Flushing	8 (12.5)	8 (12.5)
Dizziness	4 (6.3)	8 (12.5)
Nasopharyngitis	6 (9.4)	7 (10.9)
Sinusitis NOS	4 (6.3)	7 (10.9)
ALT increase	5 (7.8)	7 (10.9)
Palpitations	6 (9.4)	7 (10.9)

NOS = not otherwise specified, ALT = alanine aminotransferase
Source: AMB-220, Table 12.5

This suggests, but does not prove, that common events are more likely to be reported within the first 12 weeks rather than later.

Longterm uncontrolled studies

[8] All percents in this paragraph are "placebo subtracted"

7.1.7 Clinical laboratory evaluations

Liver enzymes

There was one death (320/321E/221-003) possibly linked to drug induced hepatotoxicity. See death section 7.1.1.

Number and percent of subjects with AST/ALT abnormalities for all 483 subjects are shown below by degree of severity.

Table 32 Serum Aminotransferase Abnormalities (ALT and/or AST) by Severity (Population: All Studies)

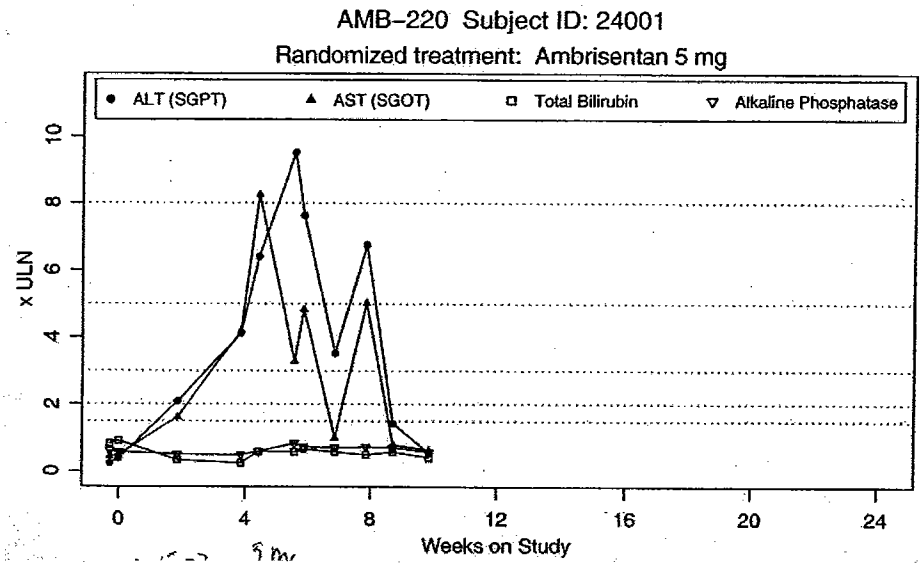
ALT and/or AST	≤12-week exposure (≤84 ± 4 days)		Cumulative incidence for all PAH studies (>1 day)[1]				
	Placebo (N = 132) n (%)	AMB (N = 483) n (%)	AMB (N = 483) n (%)	Distribution by dose at event, n			
				1 mg	2.5 mg	5 mg	10 mg
>3xULN and ≤5xULN	1 (0.8)	3 (0.6)	10 (2.1)	0	2	5	3
>5xULN and ≤8xULN	2 (1.5)	0 (0.0)	0 (0.0)	0	0	0	0
>8xULN	0 (0.0)	1 (0.2)	3 (0.6)	0	0	1	2
All >3xULN	3 (2.3)	4 (0.8)	13 (2.7)	0	2	6	5

[1]Incidence corresponds to an overall mean exposure for all PAH studies of 47.4 ± 42.69 weeks, and a maximum exposure of 184.3 weeks
Source: Table 33

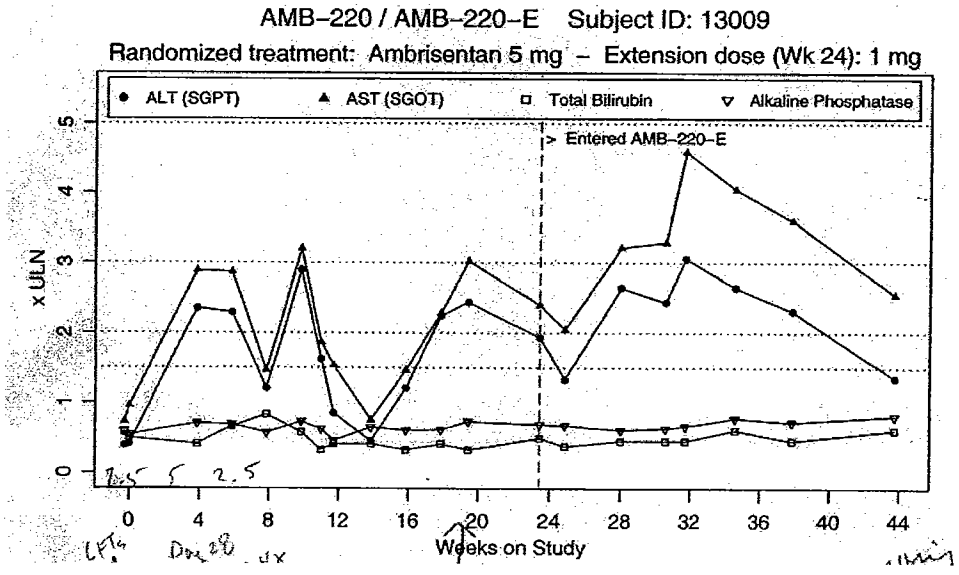
Cumulative incidence of AST/ALT > 3xULN was 3% for all subjects who received ambrisentan for up to 184 weeks. Of these 13 subjects with abnormalities, 3 were discontinued and 3 had dose reduction and/or dose interruption, 1 had a concomitant medication discontinued, and 6 were unchanged. There was one placebo subject who discontinued study medication. There was one subject (236-004) who had rising LFTs (3-5xULN). She was discontinued from sulfasalzine and remained on ambrisentan with a normalization of LFTs.

Discontinuations for abnormal LFTs

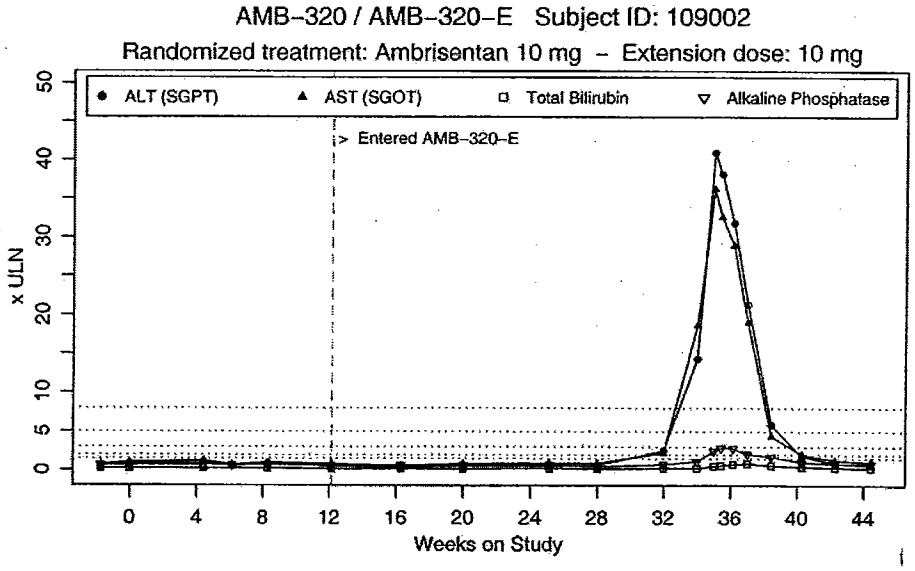
Patient ID/dose/age/sex	Abnormality/time on drug	comments
220 24-001/5mg/58y/f	ALT and AST 8-9 xULN/4 weeks	Elevated LFTs starting about 2 weeks after randomization. Subject was discontinued day 32 (2 weeks after drug was increased from 2.5mg). Enzymes were with normal range within 6 weeks after drug was stopped. (see figure below



Patient ID/dose/age/sex	Abnormality/time on drug	comments
220 13-009/5mg/45y/m	ALT and AST 3 xULN/ 9.9 weeks	Hepatic enzymes elevated on day 28. Dose was decreased to 2.5mg and then to 1mg. Enzymes remained elevated and subject was later discontinued. (see figure below)

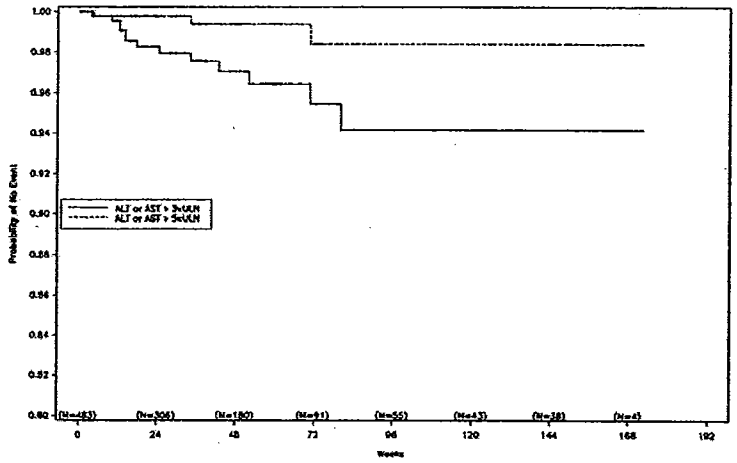


Patient ID/dose/age/sex	Abnormality/time on drug	comments
320/321E 109-002/10mg	ALT and AST 35-40 xULN/ 34 weeks	Study drug was discontinued on day 248 because of abnormal LFTs. Highest elevations were 35-30 x ULN. MI reported week 10. Subject remained asymptomatic. LFT elevation resolved about 1 month after drug was discontinued. (see figure below). Atorvastatin had been started on week 23.6 and was discontinued at the same time as ambrisentan.



The Kaplan Meier curves for time to ALT or AST >3xULN and >5xULN for the 483 subjects are shown below.

Figure 4 Kaplan-Meier Curves for Time to ALT or AST Event for All PAH Subjects Who Received 1 or More Doses of Ambrisentan



Source: Appendix 3, Figure 14.7.3

The risk of developing ALT/AST elevations >3 x ULN was 2.1% (95% CI: 0.6% to 3.5%) at 0.5 years of ambrisentan treatment and 3.6% (95% CI: 1.3% to 5.8%) after 1 year exposure.

The risk of developing ALT/AST elevations >5 x ULN was 0.2 % (95% CI: 0.0% to 0.7%) at 0.5 years of ambrisentan treatment and 0.6% (95% CI: 0.9% to 1.5%) after 1 year exposure.

Conclusion: While there were few subjects with substantial rises in LFTs, ambrisentan has been shown to be a hepatotoxin and capable of causing substantial damage to the liver. It cannot be assumed that all LFT increases will resolve when study drug is discontinued. There were subjects with mild LFT elevations who were able to remain on ambrisentan. Close monitoring is essential. There was one death for which drug induced liver failure cannot be ruled out (primarily for lack of follow up information).

Study 222

AMB-222 is an ongoing, single-arm, open-label study evaluating the incidence of increased serum aminotransferase concentrations after 12 weeks of ambrisentan therapy in subjects who previously discontinued bosentan or sitaxsentan treatment because of LFT abnormalities (AST and ALT >3xULN). Subjects received 2.5 mg ambrisentan daily for a period of 4 weeks before increasing the dose to 5 mg daily. After Week 24, investigators were allowed to adjust the dose of ambrisentan as clinically indicated. Subjects were monitored with clinical laboratory tests every 2 weeks and assessed for safety and efficacy every 4 weeks during the first 12 weeks of treatment. After Week 12, subjects who continued to receive ambrisentan were monitored with clinical laboratory tests every 4 weeks and were assessed for safety and efficacy every 12 weeks. After Week 48, subjects continued to be monitored with clinical laboratory tests every 4 weeks and were assessed for safety and efficacy every 24 weeks.

The previous LFT abnormalities for the 36 study subjects are in the table below. (N.B.: ERA=endothelin receptor antagonist.)

Table 10.4 Previous ERA Use and Associated LFT Elevations (Population: All Subjects)

LFT Elevations	Bosentan	Total N = 36 Sitaxsentan	First ERA Failure*
Subjects Who Discontinued ERA, n	34	5	36
Subjects With AST >3xULN, n (%)	32 (94.1)	4 (80.0)	33 (91.7)
Subjects With AST >5xULN, n (%)	21 (61.8)	4 (80.0)	24 (66.7)
Subjects With ALT >3xULN, n (%)	28 (82.4)	5 (100.0)	32 (88.9)
Subjects With ALT >5xULN, n (%)	10 (29.4)	3 (60.0)	13 (36.1)
Subjects With Total Bilirubin >2xULN, n (%)	1 (2.9)	0 (0.0)	1 (2.8)
Duration on ERA Before Discontinuation, weeks,			
Median	13.9	28.7	15.6
Min, Max	4, 141	17.6, 53.6	4, 141

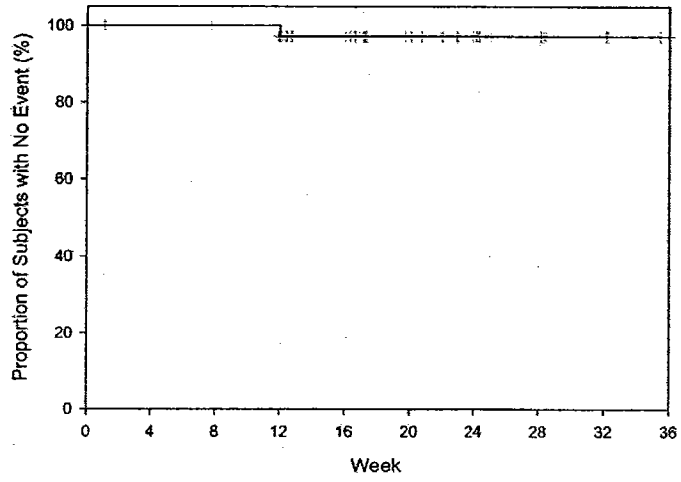
For each ERA, the first ERA discontinuation for each subject was counted.
*Subjects could have previously discontinued both bosentan and sitaxsentan.
Mean duration on prior ERA before discontinuation was calculated for the first episode of LFTs on each drug.
Source: Summary Table 14.1.3 and Listing 16.2.5

All subjects had to have normal LFTs at baseline.

There were 2 discontinuations (subject #104-001 for pain in extremity day 8 and subject #117-002 for palpitations day 22).

A Kaplan-Meier curve for the time to the first event of ALT/AST>3xULN up to 36 weeks (n=34 at 36 weeks) is shown below. There was one event reported of elevated LFTs (subject 133-002 with mild elevations of AST/ALT which returned to normal while subject remained on ambrisentan).

Figure 11.1 Time to First Event of ALT/AST Value >3xULN (Population: Safety)



Anemia

There was a decrease in mean hemoglobin and hematocrit in the ambrisentan groups compared to placebo. The table below shows the changes from baseline at week 12 for the combined studies 320 and 321.

Table 39 Hemoglobin and Hematocrit Change from Baseline to Week 12 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Hemoglobin (g/dL)						
Week 0	n	120	63	124	62	249
	Mean (SD)	14.4 (2.05)	14.8 (1.98)	14.7 (1.87)	14.4 (1.97)	14.6 (1.92)
Change from baseline to week 12[1]	n	106	55	116	59	230
	Mean (SD)	0.18 (1.04)	-0.87 (1.09)	-0.77 (1.19)	-0.93 (1.29)	-0.84 (1.19)
	Median	0.20	-0.70	-0.80	-1.1	-0.80
	Min, Max	-3.0, 3.4	-3.9, 1.6	-3.3, 3.7	-3.1, 5.1	-3.9, 5.1
Hematocrit (V/V)						
Week 0	n	118	60	121	60	241
	Mean	0.44 (0.062)	0.45 (0.061)	0.44 (0.06)	0.44 (0.06)	0.44 (0.06)
Change from baseline to week 12[1]	n	106	53	110	56	219
	Mean (SD)	0.01 (0.033)	-0.03 (0.034)	-0.02 (0.037)	-0.03 (0.043)	-0.03 (0.038)
	Median	0.0	-0.03	-0.02	-0.04	-0.03
	Min, Max	-0.09, 0.14	-0.12, 0.05	-0.11, 0.11	-0.10, 0.16	-0.12, 0.16

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 14.3.12

Overall there was a mean 0.84 g/dL decrease in the mean hemoglobin level in the combined ambrisentan group (n=230) compared to a mean 0.18 g/dL increase in the placebo group (n=106). Hematocrit had similar changes.

At week 12, there were decreases in mean hemoglobin/hematocrit levels in the ambrisentan group (all doses combined) compared to placebo (-0.84 g/dL/-0.03 V/V) compared to a mean increases in the placebo group (0.18 g/dL/ 0.01 V/V).

The number and percent of subjects in studies 320 and 321 who had a decrease in hemoglobin of $\geq$ 1g/dL as well as those with a decrease of > 15% and below the lower limit of normal are shown below by treatment group.

Table 40 Decreases in Hemoglobin from Baseline to Minimum Post-Baseline Values (AMB-320/321 Population: Safety)

Shift, n (%)	Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined Ambrisentan (N = 261)
Decreases in Hemoglobin ≥1 g/dL					
Any decrease	23 (17.4)	39 (60.9)	83 (63.8)	49 (73.1)	171 (65.5)
Weeks 1-4	10 (7.6)	26 (40.6)	50 (38.4)	35 (5.2)	111 (42.5)
Weeks 4-12	13 (9.8)	13 (20.3)	33 (25.4)	14 (20.9)	60 (23.0)
Normal to low	6 (4.5)	5 (7.8)	9 (6.9)	8 (11.9)	28 (10.7)
Weeks 1-4	2 (1.5)	3 (4.7)	5 (3.8)	6 (8.9)	16 (6.1)
Weeks 4-12	4 (3.0)	2 (3.1)	4 (3.1)	2 (3.0)	12 (4.6)
High to normal	2 (1.5)	5 (7.8)	16 (12.3)	4 (6.0)	27 (10.3)
Weeks 1-4	1 (0.8)	5 (7.8)	11 (8.5)	4 (6.0)	21 (8.0)
Weeks 4-12	1 (0.8)	0 (0.0)	5 (3.8)	0 (0.0)	6 (2.3)
High to low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreases in Hemoglobin ≥15% and Below the Lower Limit of Normal					
Any decrease	5 (3.8)	3 (4.7)	7 (5.4)	7 (10.4)	17 (6.5)
Weeks 1-4	0 (0.0)	2 (3.1)	6 (4.6)	3 (4.5)	12 (4.6)
Weeks 4-12	5 (3.8)	1 (1.6)	1 (0.8)	4 (5.9)	5 (1.9)

Source: AMB320/321, Summary Table 14.3.19 and Summary Table 14.3.20

There were more decreases in hemoglobin ≥ 1 g/dL in the drug group (65.5% for the combined ambrisentan) compared to placebo (17. 4%) and there was an indication that it was dose dependent. This was also true for the sizable hemoglobin decrease defined as 15% from baseline and below lower limit of normal (6.5% versus 3.8%).

The same finding was observed in study 220 (at week 12).

Table 41 Hemoglobin and Hematocrit Change from Baseline at Week 12 (AMB-220 Population: Safety)

Treatment group		1 mg ambrisentan (N = 16)	2.5 mg ambrisentan (N = 19)	5 mg ambrisentan (N = 16)	10 mg ambrisentan (N = 13)	Combined ambrisentan (N = 64)
Hemoglobin (g/dL)						
Week 0	n	16	19	16	2	63
	Mean (SD)	14.5 (2.11)	13.3 (1.75)	14.9 (1.68)	15.2 (17.51)	14.4 (1.94)
Change from baseline to week 12	n	15	16	14	11	56
	Mean (SD)	-0.4 (1.21)	-0.7 (0.72)	-1.0 (0.85)	-1.4 (1.13)	-0.8 (1.03)
	Median	-0.5	-0.6	-0.9	-1.4	-0.8
	Min, Max	-2.4, 2.1	-2.2, 0.4	-2.7, 0.2	-3.0, 0.6	-3.0, 2.1
Hematocrit (V/V)						
Week 0	n	16	19	16	12	63
	Mean (SD)	0.43 (0.066)	0.40 (0.052)	0.44 (0.050)	0.46 (0.060)	0.43 (0.059)
Change from baseline to week 12	n	15	16	14	11	56
	Mean (SD)	-0.01 (0.038)	-0.02 (0.022)	-0.03 (0.03)	-0.04 (0.035)	-0.02 (0.033)
	Median	-0.02	-0.02	-0.03	-0.05	-0.02
	Min, Max	-0.1, 0.1	-0.1, 0.0	-0.1, 0.0	-0.1, 0.0	-0.1, 0.1

Source: AMB-220, Table 12.10

The table below shows the decreases from baseline over 24 weeks.

Table 42 Hemoglobin and Hematocrit Change from Baseline throughout the Study (AMB-220 Population: Safety)

Study week		Week 4	Week 8	Week 12	Week 16	Week 24
Hemoglobin (g/dL)						
Change from baseline	n	57	52	56	53	52
	Mean (SD)	-0.9 (0.82)	-0.8 (0.89)	-0.8 (1.02)	-0.9 (1.12)	-0.9 (1.24)
	Median	-0.9	-0.8	-0.8	-1.0	-1.0
	Min, Max	-2.9, 0.9	-2.5, 2.3	-3.0, 2.1	-3.0, 3.3	-3.0, 3.0
Hematocrit (V/V)						
Change from baseline	n	56	52	56	49	50
	Mean (SD)	-0.03 (0.026)	-0.02 (0.030)	-0.02 (0.033)	-0.03 (0.036)	-0.03 (0.038)
	Median	-0.03	-0.02	-0.02	-0.03	-0.03
	Min, Max	-0.1, 0.0	-0.1, 0.1	-0.1, 0.1	-0.1, 0.1	-0.1, 0.1

Source: AMB-220, Summary Table 14.4.11

Mild to moderate decreases in hemoglobin/hematocrit anemia appear linked to ambrisentan use (similar to bosentan). The effect seems to stabilize in the first several months of treatment.

Anemia was reported as an adverse event by 6% of the subjects in the AMB-320/321E combined analysis (24/383). One subject (AMB-222/143-003) was hospitalized twice (study days 10 and 112) because of anemia. She had a long history of frequent episodes of epistaxis. During both hospitalizations she was transfused and released. She remained on study drug (2.5 mg followed by 5 mg ambrisentan).

The mild decreases in hemoglobin and hematocrit are similar to those seen with other endothelin receptor antagonists.

Coagulation

Coagulation tests were obtained monthly for 50%-60% of subjects receiving an anticoagulant in the phase 3 studies AMB320 and 321.

The table below shows the changes in PT and INR values at week 4, by treatment group.

Table 44 Prothrombin Time and International Normalized Ratio Change from Baseline to Week 4 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
PT (sec)						
Week 0	n	83	45	88	38	171
	Mean (SD)	18.8 (7.31)	19.1 (7.67)	18.5 (8.17)	19.6 (11.03)	18.9 (8.72)
Change from baseline to week 4[1]	n	76	37	80	37	154
	Mean (SD)	1.2 (7.53)	0.3 (6.14)	-0.4 (7.96)	-0.9 (16.30)	-0.4 (10.21)
	Median	0.50	-0.2	-0.2	-0.20	-0.2
	Min, Max	-28.0, 20.3	-20.1, 14.9	-50.0, 16.8	-47.0, 79.0	-50.0, 79.0
INR						
Week 0	n	84	45	89	42	171
	Mean	2.12 (1.042)	2.13 (1.491)	2.07 (1.105)	1.82 (0.843)	2.07 (1.23)
Change from baseline to week 4[1]	n	77	37	82	38	156
	Mean (SD)	0.28 (1.581)	-0.04 (1.649)	0.01 (1.143)	-0.23 (1.770)	-0.06 (1.43)
	Median	0.10	0.0	-0.04	-0.03	-0.02
	Min, Max	-5.22, 8.03	-8.58, 2.08	-4.04, 6.26	-6.72, 6.30	-8.58, 6.30

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 12.17

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The changes to the dose of specific anticoagulants (sum of daily doses over 7 day period) was examined as well.

Table 12.18 Weekly Anticoagulant Dose, Prothrombin Time and International Normalized Ratio Percent Change from Week 0 at Week 12 (Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Percent change in weekly anticoagulant dose	n	59	30	60	32	122
	Mean (SD)	32.3 (130.24)	18.5 (61.73)	15.2 (85.52)	16.9 (58.80)	16.4 (73.26)
	Median	0.00	0.00	0.00	0.00	0.00
Percent change in PT	n	60	36	74	29	139
	Mean (SD)	13.5 (42.80)	-1.9 (28.91)	8.9 (45.41)	-3.6 (28.93)	3.5 (38.82)
	Median	1.6	-1.2	3.6	0.00	0.83
	Min, Max	-57.1, 168.4	-61.9, 81.3	-76.1, 285.3	-65.0, 56.8	-76.1, 285.3
Percent change in INR	n	61	36	75	29	140
	Mean (SD)	23.24 (1.629)	1.18 (44.98)	11.84 (60.02)	1.46 (43.32)	6.95 (53.228)
	Median	0.02	2.09	3.26	0.00	1.77
	Min, Max	-60.83, 387.07	-77.10, 121.13	-77.46, 358.93	-84.18, 122.54	-84.18, 358.93

Source: Summary Table 14.3.13

The changes observed in the active treatment groups are not different from those observed in the placebo group.

In addition, there were no subjects in the ambrisentan arms of these 2 studies who reported a change in PT or INR that was considered to be an adverse event. There were scattered reports of changes in PT/INR as an adverse event in subjects participating in other studies.

Long term use of ambrisentan and coagulation values were evaluated in extension study AMB320-321E. The table below shows changes in INR values over 48 weeks, by treatment group.

Table 12.15 International Normalized Ratio Change from Baseline Over Time during the Preliminary Analysis Period (Population: Safety)

Treatment group		2.5 mg ambrisentan (N = 78)	5 mg ambrisentan (N=171)	10 mg ambrisentan (N = 134)	Combined ambrisentan (N = 383)
INR					
Week 0	n	55	119	87	261
	Mean (SD)	2.33 (1.927)	2.12 (1.248)	2.01 (1.129)	2.13 (1.385)
Change from baseline Week 4	n	49	105	74	228
	Mean (SD)	-0.12 (1.091)	-0.16 (1.197)	-0.16 (1.394)	-0.15 (1.238)
	Median	-0.04	-0.03	-0.10	0.08
	Min, Max	-4.59, 2.28	-8.58, 1.92	-6.72, 6.30	-8.58, 6.30
Change from baseline Week 12	n	46	98	69	213
	Mean (SD)	-0.43 (1.864)	-0.01 (1.357)	-0.12 (1.261)	-0.13 (1.454)
	Median	0.01	0.04	0.00	0.02
	Min, Max	-8.30, 3.60	-7.71, 4.82	-6.92, 2.14	-8.30, 4.82
Change from baseline Week 24	n	40	68	47	155
	Mean (SD)	-0.07 (2.412)	0.11 (1.496)	-0.12 (0.946)	-0.01 (1.651)
	Median	-0.06	0.13	-0.12	0.01
	Min, Max	-8.10, 9.63	-7.58, 6.18	-1.77, 2.11	-8.10, 9.63
Change from baseline Week 36	n	35	46	42	123
	Mean (SD)	-0.29 (2.079)	0.09 (1.021)	0.23 (1.337)	0.03 (1.496)
	Median	-0.12	0.13	0.16	0.02
	Min, Max	-7.90, 4.40	-4.76, 1.98	-2.01, 5.85	-7.90, 5.85
Change from baseline Week 48	n	26	28	36	90
	Mean (SD)	-0.21 (1.879)	-0.018 (1.304)	-0.068 (1.221)	-0.094 (1.307)
	Median	0.35	0.21	-0.15	0.04
	Min, Max	-8.00, 1.87	-6.88, 1.44	-2.79, 5.16	-8.00, 5.16

Source: Summary Table 14.3.1.1

In summary, it is unlikely that there is a link between the use of ambrisentan and changes in coagulation.

Bleeding reports

The following subjects reported bleeding events that led to study drug discontinuation:

-subject 320/101-006 (10 mg) was hospitalized 14 days after the start of study drug because of hypoxic respiratory failure secondary to a rapidly recurring right pleural effusion. She complained of abdominal and flank pain with a marked increase in dyspnea. Her hematocrit had dropped from 30% to 19%, platelet count was 45 $x10^3$ U/L, and PTT was >150 s. Heparin was interrupted and the subject was started on lepirudin. She recovered and remained on study drug. On day 88, this subject was hospitalized because of an intracranial bleed. Her husband stated that the subject had fallen and hit her head. She died the next day (see death section)

Other reports of serious bleeding include:

-subject 321/242-005 reported anemia. Resolved.

-subject 321/207-009 reported severe epistaxis. Other medication change, resolved;

-subject 321/245-006 reported hemoptysis. Other medication change, resolved;

-subject 320/321/227-001 (2.5mg) had severe GI hemorrhage with drop in hematocrit, resolved;

-subject 320/321/155-003 (10mg) had severe hemoptysis;

-subject 320/321/214-002 (placebo) had severe epistaxis.

There were 30 subjects with reports of hemorrhagic events in 320/321E. Of these, 11 were serious with 3 of the 11 resulting in discontinuation/interruption of study drug.

-subject 320/321E/231-005 (2.5mg) with subacute subdural hematoma diagnosed day 91. Acenocoumarol was discontinued as was ambrisentan when subject withdrew her consent.

-subject 320/321E/116-008 (10mg) with subacute subdural hematoma diagnosed day 239 after traumatic event. Warfarin was discontinued; ambrisentan was interrupted for 6 days.

-subject 320/321E/104-003 (5mg) was discontinued because of hematochezia. Concomitant medication included warfarin.

Allergic reaction
The following subjects reported events suggestive of allergic reaction:

-subject 320/321/211-009 (5 mg) reported dyspnea and erythematic swelling of face, hands, legs on day 15. She was discontinued 4 days after the event and the reaction resolved 28 days later.

-subject 320/321/211-010 (5mg) reported mild face edema and headache 3 days after start of drug. Study drug was stopped and the events resolved in one day. She was restarted on drug and the events reappeared. Study drug was then permanently discontinued.

Male fertility
Animal (rat studies) findings:

"Diffuse testicular atrophy (unilateral and bilateral) of massive severity was observed in one animal at 100 mg/kg/day and in two animals at 300 mg/kg/day. . . . During the recovery phase massive diffuse tubular atrophy was observed in one animal in each treatment group (10, 30, 100, and 300 mg/kg/day). The diffuse testicular tubular atrophy was not reversible during the 13-week recovery period at $\geq$ 10 mg/kg/day."

Semen specimens were collected during some of the studies:

Study AMB 320: few semen analyses were available for review (2 placebo subjects, 3 ambrisentan 5mg subjects, 7 ambrisentan 10 mg subjects). In the 10 mg group, there were 4 subjects with ejaculate volumes greater than 1.0mL in both week 0 and week 12 samples. Sperm densities decreased at week 12 compared to week 0 in all. One of the subjects also had decreasing motility from week 0 to week 12.

Study AMB 321: few complete semen samples were available for review (2 placebo subjects and 4 ambrisentan 5 mg subjects). One of the ambrisentan subjects was deemed to be azoospermic by the reviewer (expert consultant). There was little change for the remainder of the subjects. However, the data were very scant and it is not possible to rule out an effect of the drug on human male fertility.

Conclusion While it is difficult to interpret these data, there is no indication that ambrisentan does not have an adverse effect on human male fertility. One of the expert reports recommended that the effect of drug on sperm concentration, motility, or morphology be examined after 24 weeks rather than at 12 weeks.

ECG findings

QT study (see Christoffer Tornoe's review of QT study)

Abnormal ECGs

The number and percent of subjects with clinically significant abnormal ECG findings at screen, week 0, and week 12 for studies AMB 320 and 321 are shown below[9].

	AMB-320			AMB-321		
	placebo	5 mg	10 mg	placebo	2.5 mg	5 mg
N	67	67	67	65	64	63
CS abnormality, %						
Screening Visit	9.0	16.4	23.9	15.4	14.1	9.5
Week 0	10.4	14.9	19.4	12.3	10.9	4.8
Week 12	7.5	10.4	11.9	9.2	9.4	1.6

The vast majority of abnormalities were reported both at screen/baseline and week 12 and reflected the effects of PAH on the heart. There is no indication that ambrisentan causes cardiac abnormalities that can be detected by ECG changes after 12 weeks of treatment.

Vital signs

Mean heart rate decreased slightly more (1.4 bpm at week 12) for 244 subjects receiving ambrisentan (doses 2.5 mg-10 mg) compared to 113 subjects receiving placebo 90.2 bpm).

[9] ECG table dated March 5, 2007.

Mean blood pressure tended to decrease more in subjects receiving ambrisentan at week 12 compared to subjects receiving placebo.

Table 53 Blood Pressure Change from Baseline to Week 12 (AMB-320/321 Population: Safety)

Treatment group		Placebo (N = 132)	2.5 mg ambrisentan (N = 64)	5 mg ambrisentan (N = 130)	10 mg ambrisentan (N = 67)	Combined ambrisentan (N = 261)
Systolic Blood Pressure, mmHg						
Week 0	n	119	59	113	57	229
	Mean (SD)	118.6 (15.21)	117.6 (14.82)	116.2 (15.88)	115.9 (15.17)	116.5 (15.38)
Change from baseline to week 12[1]	n	113	58	122	64	244
	Mean (SD)	-0.6 (14.96)	-2.3 (14.64)	-2.1 (12.75)	-5.4 (15.32)	-3.0 (13.93)
	Median	0.0	-4.0	-0.5	-5.0	-3.5
	Min, Max	-56, 46	-38, 34	-34, 28	-50, 24	-50, 34
Diastolic Blood Pressure, mmHg						
Week 0	n	119	59	113	57	229
	Mean (SD)	74.5 (10.38)	74.7 (11.01)	74.1 (9.68)	72.5 (9.34)	73.8 (9.95)
Change from baseline to week 12[1]	n	113	58	122	64	244
	Mean (SD)	0.5 (9.57)	-4.1 (10.56)	-3.4 (10.57)	-6.0 (10.03)	-4.2 (10.44)
	Median	0.0	-1.5	-3.0	-3.5	-3.0
	Min, Max	-28, 20	-35, 20	-30, 41	-30, 20	-35, 41

[1]The baseline value was the most recent value prior to first dose
Source: AMB-320/321, Table 12.21

There were sporadic reports of hypotension/syncope.

-subject 321/211-008 (2.5 mg) reported syncope day 50. Temporary discontinuation of study drug. Completed study

Subgroups

There were no studies specifically designed to evaluate safety of ambrisentan in any subgroup including age, gender, race, etiology of PAH, and baseline WHO functional class. Overall, one cannot draw any conclusions about the safety in subgroups because of the small sample sizes.

There were no studies evaluating the safety of ambrisentan in subjects with either renal or liver impairment.

Phase 1 studies

The phase 1 studies are briefly described below.

Phase 1 Clinical Studies in Healthy Subjects

PK and Tolerability	EE-001	M n = 63	Single ascending dose ambrisentan pharmacokinetics, pharmacodynamics and the effect of food on ambrisentan pharmacokinetics
	EE-002	M n = 30	Multiple ascending dose pharmacokinetics and pharmacodynamics of ambrisentan
Bioequivalence	AMB-103	M/F n = 65	Bioequivalence of clinical and commercial formulation ambrisentan tablets
QT/QTc	AMB-104	M/F n = 161	Correlation of ambrisentan pharmacokinetics and effect on QT/QTc interval
Drug-Drug Interaction	AMB-105	M/F n = 20	Pharmacokinetic drug-drug interaction with sildenafil
	AMB-106	M/F n = 22	Pharmacokinetic and pharmacodynamic drug-drug interaction with warfarin

There were seven phase 1 studies (including AMB-107, a mass balance study not listed above). A total of 369 healthy volunteers participated in one of these seven studies.

The table below shows the numbers of subjects enrolled and the numbers withdrawn for adverse event for the phase 1 studies.

Study ID	Number enrolled	Number withdrawn for adverse event
EE-001	63	1 (50 mg: facial flush, shivering, sickness, nausea, vomiting, headache, vertigo, and dizziness)
EE-002	30	2 (10 mg: fever, diarrhea and 10 mg: headache)
AMB-103	65	1 (10 mg: strep infection)
AMB-104	161	1 (10 mg: palpitations)
AMB-105	20	0
AMB-106	22	0
AMB-107	8	0

The following table lists the number of subjects who reported adverse events in the phase 1 program, by drug dose.

Table 9.3.1.3 Number of subjects with adverse events (counted once per subject) by dose level

Type of event	Treatment administered (Placebo or BSF 208075)									
	Placebo N = 15	1 mg N = 7	5 mg N = 7	10 mg N = 7	15 mg N = 5	20 mg N = 14	50 mg N = 8	50 mg fed N = 7	100 mg N = 2	All N = 72
Conjunctival vascular disorder nos*						2	1			3
Constipation				1						1
Diarrhea	1									1
Dizziness						1	1		1	3
Feeling of warmth						1				1
Flatulence	1									1
Flushing					2		1	2	1	6
Flushing of face			2	1	2	6	3	5		18
Headache	2				1	6	1	3	2	15
Headache nos*				1	1	3	3	1	2	11
Headache temporal			1							1
Hypoesthesia		1								1
Malaise							1			1
Nasal congestion			1		1	1			1	4
Nausea		1				1			2	4
Nausea with vomiting							1			1
Neck rigidity			1							1
Shivering							1			1
Sweating attack			1							1
Unclassified			1							1
Vertigo							1			1
Vomiting						1	1			2
Total number of AEs (counted once per subject per treatment)	4	2	7	3	7	21	15	11	9	79

* nos = not otherwise specified

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/s/

Maryann Gordon
4/30/2007 11:39:15 AM
MEDICAL OFFICER

Safety update
NDA# 22081

Summary

The conclusions stated in the NDA safety review remain unchanged. The additional data presented in the safety update are from uncontrolled trials.

Introduction

The 4-month safety update contains cumulative data through November 30, 2006 from the 3 ongoing trials (AMB-320/321-E, 220-E, and 222). Information about all subjects who were reported to have died or were discontinued because of an adverse event up to March 18, 2007 was submitted. There is one newly initiated open label trial (AMB-323) in subjects with pulmonary hypertension for which all reported deaths, serious adverse events and discontinuations for adverse events were submitted.

As of November 30, 2006, a total of 483 subjects[1] received ambrisentan in a phase 2 or 3 study. Mean exposure is about 1.5 years with maximum exposure more than 4 years. A total of 343 subjects received ambrisentan for at least 1 year and 120 subjects have received the drug for at least 2 years. Doses ranged from 2.5 to 10 mg once daily. The safety update added 32 weeks of exposure to ambrisentan since the close of the NDA data base.

The newly initiated study[2] AMB-323 reported no deaths. There was one serious adverse event of worsening pulmonary hypertension. One subject discontinued study drug because of elevated liver enzymes. A total of 14 subjects have been enrolled into this open label study.

Deaths

Cumulative reported deaths through November 30, 2006 are shown below by study and treatment group.

[1] Excludes subjects enrolled into study AMB-323.
[2] As of September 5, 2006

Table 16 Cumulative Summary of Deaths in Subjects with Pulmonary Arterial Hypertension through 30 November 2006, All Phase 2 and 3 Studies

Treatment group[1]	Placebo	1 mg ambrisentan	2.5 mg ambrisentan	5 mg ambrisentan	10 mg ambrisentan
Phase 3, placebo-controlled studies					
AMB-320	2	NA	NA	1	1
AMB-321	4	NA	2	0	NA
Phase 2 Studies					
AMB-220	NA	1	0	0	1
AMB-222[2]	NA	0	0	1	2
Long-term Phase 2 and 3 studies					
AMB-320/321-E[2,3]	NA	1	5	18	10
AMB-220-E[2]	NA	0	1	0	4

[1]Deaths are attributed to the actual ambrisentan dose at the time of death.
[2]For ongoing studies deaths are reported through 30 November 2006. Of these, 21 occurred during the safety update period.
[3]Deaths that occurred during study AMB-320/321-E only (n = 34). Deaths that occurred while subjects received ambrisentan or placebo in AMB-320 and AMB-321 are counted for those studies only (n = 5).
NA = treatment not available in study

There were 21 additional deaths reported since the close of the NDA data base (February 17, 2006) and the close of the safety update data base. There were 3 additional reported deaths in AMB-222 at doses of 5 (1 subject) and 10 mg (2 subjects) and 18 additional reported deaths in AMB-320/321E at doses of 1 mg (1 subject), 2.5 mg (2 subjects), 5 mg (8 subjects), and 10 mg (7 subjects).

In addition, there were 6 subjects (5 from stud AMB 320/321 and 1 from AMB222) who died between December 1, 2006 and March 18, 2007.

Subject ID/age/sex	Dose/Duration	Comments
AMB-320/321-E		
255-001/44/f	2.5 mg for 336 days and 5 mg for 224 days	Sudden death. Subject was hospitalized because of asthma and during this time she experienced palpitations diagnosed as paroxysmal reciprocal AV node tachycardia and AV node dissociation. She stated that she experienced previous palpitations. Ablation was planned. Concurrently she reported muscle weakness that was diagnosed as polymyositis. Lab results showed mild to moderate elevated fibrinogen, C-reactive protein, leukocytes. The day before death, she developed nausea and vomiting. Prior LFTs were normal but on the day of death ALT and AST were 15xULN and total bilirubin was nearly 3xULN. Abdominal ultrasound was unremarkable. She had sudden collapse and

		could not be revived. Pathological findings included periarteritis nodosa and fresh and sclerotic infarction in the lungs. Cause of death was acute cardiovascular event secondary to paroyxmal tachycardia or pulmonary ebmbolism.
221-001/64/f	2.5 mg/675	Hospitalized on day 418 because of decompensated heart failure. Worsening pulmonary hypertension followed by sudden death about 6 months later.
242-002/31/m	2.5 mg for 682 days and 5 mg for 14 days	Hospitalized for anemia after bleeding from ruptured varicose vein. Was found to be anemic with elevated heart rate. Recovered after transfusion. Hospitalized about 2 weeks later for symptoms of worsening heart failure. ECHO showed dilated heart and he was placed on transplant list. Progressive renal failure and fluid retention. Developed cardiac arrest and died when CPR failed.
108-002/70/f	5 mg for 837 days	History of rectal cancer. Died respiratory failure while hospitalized for enteritis.
133-009/76/f	5 mg for 332 days	Death occurred 18 days after the last dose of ambrisentan because of anemia. She was hospitalized for low grade fever and night sweats. Blood cultures were postive for S. bovis. She developed a intracerebral hemorrhage and subsequently died. PT and INR were elevated. She had a history of mitral valve replacement and was presumed to have septic emboli from bacterial endocarditis.
155/005/63/f	5 mg for 97 days	Ambrisentan was discontinued on day 97 because of diarrhea and vomiting. She was hospitalized the next day, deteriorated, was sent home, attempted to be readmitted, was taken to the emergency room where she was found to be in a hypoglycemic coma (blood glucose 29 mg/dL). Abdomen was enlarged and painful on palpitation. Her LFTs were slightly elevated. She suffered a cardiac arrest and cause of death was listed as hypovolemic shock and dehydration secondary to gastroenteritis.
207-021/71/m	5 mg for 45 days	History of gastic carcinoma and gastric bleeding. Died suddenly at home. No autopsy.
211-002/62/f	5 mg for 638 days	Reported several serious adverse events (worsening heart failure, worsening PAF,

		diverticulosis, hypotysis, and large pericardial effusion) during study. Developed worsening dyspnea, peripheral edema, ascities. Blood and urine cultures were positive for staph and E. coli, respectively. Prior to dying, she was placed on a ventilator and developed multiorgan failure.
213-018/64/m	2.5 mg for 505 days and 5 mg for 91 days	Previous reports of progressive dyspnea, atrial fib/flutter, and syncope secondary to hypoxemia. While in the clinic he collapsed, was found to be in ventricular fib and could not be resuscitated.
227-002/70/f	5 mg for 406 days	Died of right heart failure.
241-002/69/f	2.5 mg for 338 days and 5 mg for 107 days	Sudden death. Prior to death subject developed increased dyspnea. She had reported a panic attack previously.
112-004/73/f	5 mg for 14 days and 10 mg for 219 days	Hospitalized for acute respiratory failure and died about 2 weeks later. Reported anemia.
116-009/68/f	5 mg for 14 days and 10 mg for 805 days	Hospitalized for severe dyspnea and died as a result of acute exacerbation of severe pulmonary hypertension.
117-002/22/f	5 mg for 14 day and 10 mg for 266 days	Sudden death secondary to intracranial hemorrhage. Previous events include bleeding post renal biopsy and pulmonary embolus. She was being treated with warfarin. Autopsy showed lupus nephritis, lung edema and congestion, bilateral pleral effusion, cardiomegaly, and a pulmonary embolus.
151-003/18/f	5 mg for 171 days and 10 mg for 4 days	Sudden death while hospitalized for worsening right heart failure.
155-002/48/m	5 mg for 14 days and 10 mg for 186 days	Died of respiratory failure after being hospitalized for worsening right heart failure
210-004/42/m	2.5 mg for 257 days, 5 mg for 86 days and 10 mg for 420 days.	Previous serious adverse events included leg ulcer, acute renal failure, right heart failure. He was hospitalized for worsening systemic hypotension. His heart failure progressed and he died of cardiovascular collapse.
213-001/71/m	2.5 mg for 251 days, 5 mg for 176 days and 10 mg for 239 days.	Previous serious adverse events included lung fibrosis, increased pulmonary hypertension, worsening right heart failure, and syncope. He was hospitalized for worsening right heart failure and respiratory infection. He continued to deteriorate and died of right heart failure.

AMB-222		
126-001/69/F	2.5 mg for 29 days and 5 mg for 225 days	Hospitalized and died because of right heart failure.
122-002/70/f	2.5 mg for 29 days, 5 mg for 14 days and 10 mg for 261 days.	Subject developed increased difficulty breathing. She refused to be hospitalized and died that day.
212/62/f	2.5 mg for 26 days, 5 mg for 255 days and 10 mg for 24 days.	Hospitalized and subsequently died of worsening pulmonary arterial hypertension.

Most deaths were related to heart failure, sudden death, and/or worsening respiratory condition, deaths similar to those associated with pulmonary hypertension and underlying diseases. No death appeared to be caused by liver failure or seemed unexpected.

Serious adverse events

The most commonly reported serious adverse events include right ventricular failure (7%), pulmonary hypertension (7%), pneumonia (2%), syncope (<2%), hypoxia (<2%), and pleural effusions (<2%) (table 14.3.6).

Discontinuations for adverse events

Discontinuations because of adverse events were reported for 52 subjects (14%) for all ambrisentan doses combined. Common events leading to discontinuation were cardiac disorders (5%) including right ventricular failure (3%), and respiratory disorders (4%) including pulmonary hypertension (3%). Other important events reported less often include postural dizziness/syncope (0.5%), cerebral/intracranial hemorrhage (0.5%), and renal failure/insufficiency (0.5%). There was one subject who discontinued because of face edema. (table 14.3.7).

Laboratory values

Liver function tests

The incidence rate of LFT > 3xULN for subjects on ambrisentan increased to 3.5% (compared to 2.7% in the original NDA). The cumulative incidence of LFTs >8xULN was 0.8% (compared to 0.6% in the original NDA.

The additional subjects with elevated LFTs are shown below. The doses used ranged from 1 to 10 mg. The above incidence rates do not include all subjects listed below.

Dose	Subject ID	Sex/age	Time to >3xULN (wks)	Max ALT/AST (xULN)	Discontinued Study medication?

1 mg	01-007^	f/67	192	4/3	No
2.5 mg	252-001+	f/70	68	2/3	No
10 mg	104-004+	f/54	29	2/3	No
10mg	101-002+	f/29	99	10/2	No
1 mg	255-001+	f/44	80	15/15	Died#
10 mg	15-006^		182	4/4	Yes, temporary
5 mg	147-003*	f/44	21	7/6	yes

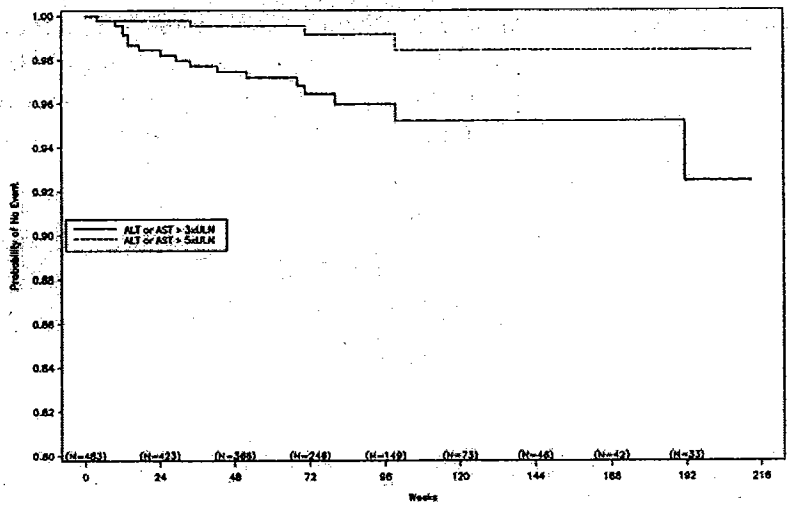
^study AMB 220-E
+study AMB 320/321-E
*study AMB 323
#see death section

Subject 101-002 was receiving dapsone (for lung infection) at the time of the ALT/AST increase. Dapsone was discontinued and both ALT/AST levels fell. The subject remained on ambrisentan for an additional 15 weeks without incident.

Subject 15-006 had periodic elevations of LFTs. Study drug was discontinued for 6 days and then restarted. LFTs started to increase and ambrisentan was down titrated to 5 mg. LFTs returned to normal 1 week later.

The Kaplan-Meier time to event analysis of time to ALT or AST > 3xULN and >5xULN has been updated to include the addition 32 weeks of data. This is shown below.

Figure 1 Kaplan-Meier Curves for Time to ALT or AST Event for All PAH Subjects Who Received 1 or More Doses of Ambrisentan



Data for this analysis include subjects from the Phase I2 and Phase 3 studies (excluding AMB323) who received ambrisentan.
AMB-320/321-E Subject 101-002 had an event of ALT >5xULN (10.24xULN) on 17Aug2006 (Week 99) that was recorded at a local laboratory and is included in this analysis.
Source: Figure 14.7.3

Subject 147-003 (study AMB-323, 5mg for 150 days) developed elevated liver enzymes (4-7xULN) and was discontinued. This subject is not included in the above figure.

Anemia

There were 6 subjects with reports of serious anemia (including iron-deficient anemia).

As previously shown in the NDA safety review, mean hemoglobin levels, hematocrit and red blood cell count decline by about week 4 in subjects taking ambrisetan and then remain stable.

Additional reports of deaths/withdrawals/serious adverse events received after November 30, 2006.

Study AMB 320-321: 5 deaths included sudden death, pulmonary hypertension, cardiac arrest, cardiac failure/pneumonitis, right ventricular failure/thrombosis.

Study AMB 22: 1 death from worsening pulmonary hypertension.

Study AMB 323 had 2 reports of elevated LFTs: 125-006 and 147-003. Subject 147-003 is discussed in the LFT section of this report.

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/s/

Maryann Gordon
4/30/2007 11:45:38 AM
MEDICAL OFFICER