Table 11.8 Mean Single-Dose and Steady-State Pharmacokinetic Parameters of Ambrisentan (Population: PK)

Single Dose				
	[redacted] (N = 4)		[redacted] (N = 16)	
Parameter	Mean	SD	Mean	SD
C_{max} (ng/mL)	102.5	42.73	270.7	76.97
t_{max} (hr)	2.03	0.82	2.63	1.20
λz (1/hr)[1]	0.075	0.019	0.083	0.027
$t_{1/2}$ (hr)[1]	9.70	2.33	9.40	3.89
$AUC_{(0\text{-}last)}$ (ng*hr/mL)	1002	403	2216	1018
$AUC_{(0\text{-}24)}$ (ng*hr/mL)[1]	1002	403	2453	983
$AUC_{(0\text{-}\infty)}$ (ng*hr/mL)[1]	1213	476	3066	1695

Steady-State								
	[redacted] (N = 4)		[redacted] (N = 5)		5 mg (N = 5)		10 mg (N = 3)	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
$C_{max,ss}$ (ng/mL)	111.0	43.31	405.4	199.17	603.8	220.85	1223.3	337.10
$C_{min,ss}$ (ng/mL)	25.8	25.89	88.1	43.05	70.9	45.23	198.2	149.54
$C_{avg,ss}$ (ng/mL)[2]	32.5	14.10	197.2	95.47	214.1	94.02	618.3	186.82
$t_{max,ss}$ (hr)	1.78	0.52	1.66	0.61	1.94	0.93	3.33	0.58
$\lambda z,ss$ (1/hr)[3]	0.073	0.008	0.047	0.003	0.071	0.014	0.097	0.061
$t_{1/2,ss}$ (hr)[3]	9.59	1.03	14.92	0.89	10.03	1.87	8.92	4.15
$AUC_{ss(0\text{-}last)}$ (ng*hr/mL)	777	276	3710	2208	5138	2257	14840	4484
$AUC_{ss(0\text{-}\tau)}$ (ng*hr/mL)[2]	781	339	4734	2291	5138	2257	14840	4484
nR_{Cmax}	1.16	0.40	1.66	0.83	1.01	0.29	1.34	0.21
nR_{AUC}[4]	0.96	0.45	1.62	0.13	1.16	0.55	1.94	0.42

[1] N = 13 for the 2.5 mg group
[2] N = 3 for the 1 and 2.5 mg groups
[3] N = 2 for the 1 mg group, N = 3 for the 2.5 mg group and N = 4 for the 5 mg group
[4] N = 3 for the 1 mg and 2.5 mg groups and N = 2 for the 10 mg group
Source: Summary Tables 14.3.3 and Summary Table 14.3.4

Steady-state data were available in 3 to 5 subject per dose group of [redacted] 5 mg and 10 mg. After a single dose, data from 4 and 16 subjects were available at the [redacted] mg dose levels, respectively. In the time interval between 6 h and 24 h no blood samples were collected. Therefore, the estimated AUC0-τ, AUC0-tlast, λz and t1/2 values may be biased. For these reasons the interpretation of the results is limited. The inter-subject variation about mean Cmax and AUC after single dose administration and at steady state ranges between 28% and 55%.

A comparison of AUC0-τ,ss in healthy subjects and patients are shown in the below table (arranged by Reviewer):

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Comparison of Steady-State Exposure of Ambrisentan in Healthy Subjects and PAH Patients

Study	Subjects	Sex	Age	BW	AUCo-τ,ss		Cmax,ss	
			years	kg	ng•h/mL		ng/mL	
					5 mg	10 mg	5 mg	10 mg
EE-002	16	M	29	76	2557	4689	378	731
AM-220	20	F>M	51	73	5138	14840	604	1223

The data indicate that both exposure parameters Cmax and AUC are greater in the patients than in the healthy volunteers suggesting that the oral clearance of ambrisentan in patients is significantly smaller than in healthy volunteers. However, it should be noted that the two populations not only differed in disease state, but also in gender, body weight and age. The patients with PAH were predominantly female and the healthy volunteers were male. The body weight of the patients was smaller and they were older than the volunteers. Because of the difference in several covariates between the two populations the discrepancy in CL/F may not be necessarily due to the difference in disease state alone.

PD

Endothelin-1 Plasma Concentrations

At baseline and week 12 the ET-1 plasma concentrations for the combined ambrisentan group showed significant intersubject variation (CV 145-183%). The median baseline and 12 week ET-1 concentrations in plasma were 0.24 fM/mLand 0.52 fM/mL, respectively. There was no correlation between ET-1 and ambrisentan plasma concentrations as shown in Figure 11.8:

BNP Plasma Concentrations

The BNP plasma concentrations at baseline and at 12 weeks showed considerable inter-subject variation (CV range 119%-152%). The median plasma concentrations at baseline and at week 12 were 111.15 ng/mL and 64.40 ng/mL, respectively.

cTnT Plasma Concentrations

At week 0 nearly all plasma concentrations of cTnT were below the level of quantification (0.01 ng/mL) and at week 12 no major changes were observed.

The impact of ambrisentan on the hemodynamic variables are shown in Table 11.6:

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Table 11.6 Cardiopulmonary Hemodynamics Baseline and Mean Changes from Week 0 to Week 12 (Population: Hemodynamics)

Treatment group	[redacted]	[redacted]	5 mg	10 mg	Total
n, at baseline	(n = 10)	(n = 9)	(n = 10)	(n = 5)	(n = 34)
n, change from baseline	(n = 9)	(n = 8)	(n = 9)	(n = 3)	(n = 29)
Cardiac index (L/min/m^2)					
Baseline, mean (SD)	2.52 (0.50)	2.40 (0.61)	2.31 (0.59)	2.47 (0.48)	2.42 (0.54)
Change at Week 12, mean (SD)	0.1 (0.31)	0.4* (0.48)	0.5 (0.62)	0.4 (0.16)	0.3* (0.47)
Mean PAP (mmHg)					
Baseline, mean (SD)	50.0 (17.77)	49.1 (13.40)	47.4 (10.25)	52.0 (11.47)	49.3 (13.29)
Change at Week 12, mean (SD)	-4.3* (4.00)	-4.3 (8.36)	-4.3* (4.82)	-13.3* (5.13)	-5.2* (6.20)
PVR (mmHg/L/min)					
Baseline, mean (SD)	10.5 (6.04)	10.0 (5.72)	11.0 (4.24)	10.3 (5.20)	10.5 (5.09)
Change at Week 12[1], mean (SD)	-2.2* (1.22)	-2.2* (2.49)	-3.5* (3.27)	-4.3 (2.82)	-2.8* (2.52)
RAP (mmHg)					
Baseline, mean (SD)	7.30 (4.06)	9.11 (6.09)	5.20 (3.55)	8.20 (2.86)	7.29 (4.50)
Change at Week 12, mean (SD)	0.9 (3.44)	-1.1 (6.08)	-0.4 (4.77)	-2.7 (5.51)	-0.5 (4.75)

[1]n = 8 for the [redacted] dose group, and n = 28 for all subjects.
*p-value <0.05, comparison to no mean change from Week 0 by paired t-test
Source: Summary Table 14.2.8

The results indicate that ambrisentan at week 12 increases cardiac index, and decreases mPAP and PVR relative to baseline.

Conclusions

Compared to healthy young male volunteers Cmax and AUC of ambrisentan at steady state in a group of predominantly female patients with moderate to severe PAH receiving 5 mg or 10 mg ambrisentan qd are significantly lower, suggesting a difference in oral clearance. A difference in the PK between healthy subjects and patients with PAH has been found with other endothelin receptor antagonists. Although it might be suspected that disease may be the most important covariate for ambrisentan it should be noted that gender, age and weight cannot be excluded as relevant covariates.
The median plasma concentrations of endothelin-1 and BNP concentrations in plasma tended to increase at 12 weeks compared to baseline. The cTnT plasma concentration data did not show a trend. There was no correlation between plasma concentrations of endothelin-1 and ambrisentan.

Ambrisentan at week 12 increases cardiac index, and decreases mPAP and PVR relative to baseline.

Comments

1. The relation of time of drug intake to time of the performance of the 6MWD and BDI in weeks 0, 4, 8 and 12 was not pre-specified. Therefore, there is no evidence form the study in support of the qd regimen. 6MWD and BDI should have been measured pre-dose to establish efficacy during the entire 24 h dose interval.

2. With a 2-stage approach more blood samples should have been collected in the time interval between 6 h and 24 h post dose to get unbiased AUC parameters. The determination of t1/2 from 2 points measured at 6 h and 24 h post-dose is problematic.

3. Methods and laboratories performing the cTnT and BNP assays and information on the validation of the methods should have been indicated in the report.

4. Evidence for the validation of the methods used for the determination of endothelin-1, BNP and cTnT should have been provided.

Study Report AMB 320/321-E (Aries-E): "A Long Term Study of Ambrisentan in Pulmonary Arterial Hypertension Subjects Having Completed AMB-320 or AMB 321"

Study Investigator and Site: 85 principal Investigators and 85 International Sites in 18 countries

Objectives

The primary objective of the study was to investigate the long-term safety of ambrisentan in subjects with PAH

The secondary objectives were to:

- Continue the efficacy assessments of studies AMB-320 and AMB 321
- Examine the lon-term treatment success with ambrisentan
- Compare long term survival of subjects treated with ambrisentan to the NIH registry of patients with PAH
- Explore the long term safety of the initiation of prostacycline therapy in PAH subjects receiving ambrisentan

Measures of interest included but were not limited to Population PK of ambrisentan in subjects with PAH and single dose and steady-state PK on a subset of patients. the latter subset is the focus of this review.

Methods

For the purpose of traditional PK single dose PK was perfomed in a subset of patients who had previously received placebo in studies AMB-320 or AMB 321. The PK at steady-state was performed in a subset of patients who had previously obtained ambrisentan in AMB-3210 or 321.

Pharmacokinetic Profiling

Bloood samples were drawn at predose, 0.5, 1, 2, 3, 4, 6, 9, 24 and 48 h after administration Subjects were given their morning dose of ambrisentanm while in the clinic and were required to withhold additional study drug until the 48 h blood draw had been performed.

Bioanalysis

A LC-MS/MS assay was used to measure the plasma concentrations of ambrisentan. The laboratory perfoming the assay was ,

PK Data Analaysis

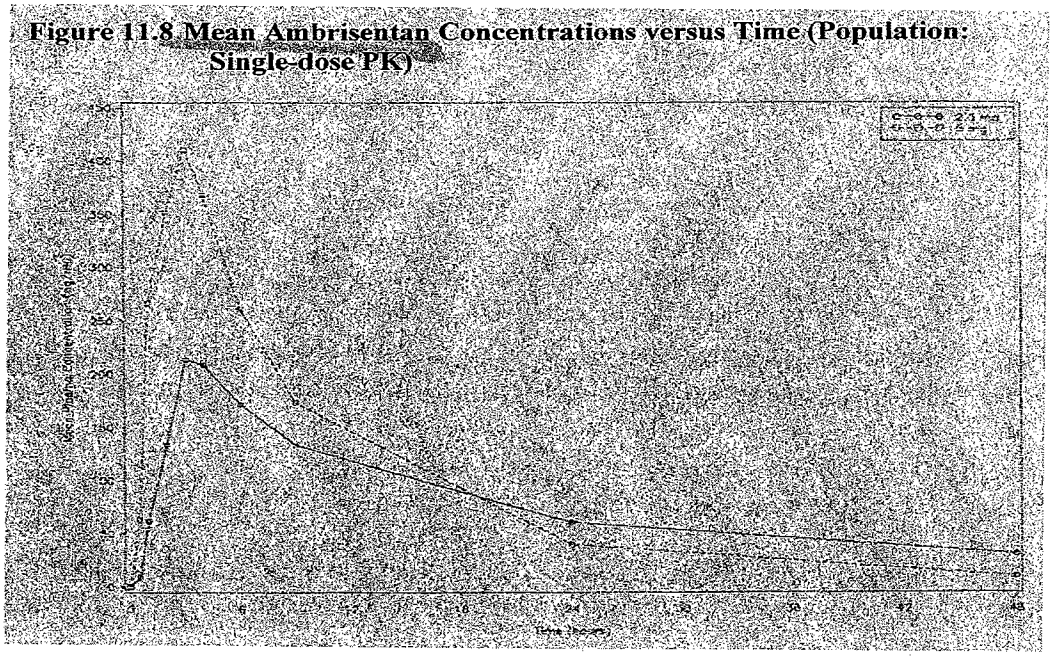
The single dose PK parameters to be determined were: Cmax, tmax AUC0-tlast, AUC0-00, λz and t1/2. The steady-state PK parameters to be determined included: Cmax,ss, Cmin,ss , tmax,ss, AUC0-τ,ss, Cave,ss, λz,ss

Results

Single dose data were available in 8 subjects, with 4 subjects receiving a single dose of 2.5 mg and 4 subjects a single dose of 5 mg ambrsisentan.

A plot of the mean plasma concentration are shown in the below figure

Figure 11.8 Mean Ambrisentan Concentrations versus Time (Population: Single-dose PK)



The geometric mean PK parameters in the 8 spatients are shown in the below table:

Table 11.18 Geometric Mean Pharmacokinetic Parameters in Subjects Receiving Single Doses of Ambrisentan

Treatment	2.5 mg (N = 4)	5 mg (N = 4)
Parameter	Mean (%CV)	Mean (%CV)
C_{max} (ng/mL)	237.0 (29.1)	472.2 (21.8)
t_{max} (hr)[1]	3.0 (3.0, 4.8)	2.0 (1.0, 4.0)
λ_z (1/hr)	0.047 (71.9)[3]	0.086 (45.9)
$t_{1/2}$ (hr)[1]	19.7 (8.1, 27)[3]	9.10 (4.8, 11.3)
$AUC_{(0-24)}$ (ng*hr/mL)	2712.2 (17.5)[2]	4003.0 (18.2)
$AUC_{(0-last)}$ (ng*hr/mL)	2969.3 (45.5)	4499.9 (24.5)
$AUC_{(0-\infty)}$ (ng*hr/mL)	4671.3 (40.0)[3]	4680.2 (24.8)

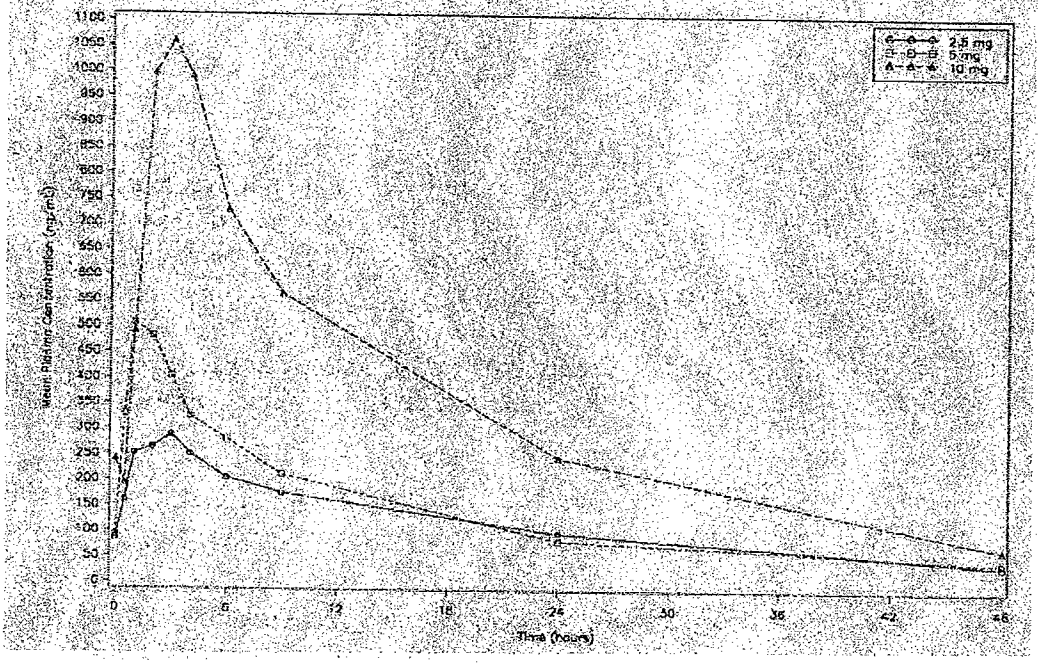
[1]For t_{max}, median (minimum, maximum) values are reported. For $t_{1/2}$, the arithmetic mean (minimum, maximum) values are reported. For λ_z, the arithmetic mean (%CV) is reported.
[2]N = 3
[3]N = 3. One Subject (242-002) was excluded from the calculation of $AUC_{0-\infty}$, $t_{1/2}$, and λ_z due to missing data at 24 and 48 hours post-dose
Source: Summary Table 14.4.5

The schedule for the blood draws was not optimal and data were from only 4 patients. Therefore, the data after single dose must be interpreted with caution.

The plasma concentrations of ambrisentan at steady state were available for 13 subjects receiving 2.5 mg qd, 10 patients receiving 5 mg qd and 3 patients receiving 10 mg qd.

A plot of the mean plasma concentrations of ambrisentan at the three dose levels are shown in the below plot:

Figure 11.9 Mean Ambrisentan Concentration versus Time (Population: Steady-state PK)



The geometric mean PK parameters are listed in the below table:

Table 11.19 Geometric Mean Pharmacokinetic Parameters in Subjects Receiving Steady-state Doses of Ambrisentan

Treatment	2.5 mg (N = 13)	5 mg (N = 10)	10 mg (N = 3)
Parameter	Mean (%CV)	Mean (%CV)	Mean (%CV)
$C_{max,ss}$ (ng/mL)	326.2 (21.8)	538.7 (36.6)	1146.8 (9.2)
$C_{min,ss}$ (ng/mL)	65.4 (52.0)	63.1 (66.3)	163.0 (31.5)
$C_{avg,ss}$ (ng/mL)	161.6 (29.3)	200.1 (37.4)	543.1 (11.2)
$t_{max,ss}$ (hr)[1]	2.0 (0.8, 3.1)	2.0 (1.0, 3.1)	2.0 (2.0, 4.0)
$\lambda_{z,ss}$ (1/hr)	0.042 (27.2)[2]	0.052 (35.0)	0.056 (25.5)
$t_{1/2,ss}$ (hr)[1]	17.94 (11.9, 33.6)[2]	15.23 (7.9, 31.0)	12.90 (9.7, 16.2)
$AUC_{ss(0\text{-}last)}$ (ng*hr/mL)	5321.4 (37.4)	5945.6 (44.4)	17183.8 (15.4)
$AUC_{ss(0\text{-}24)}$ (ng*hr/mL)	3876.1 (29.3)	4804.2 (37.4)	12591.3 (14.0)[3]

[1]For $t_{max,ss}$, median (minimum, maximum) values are reported. For $t_{1/2,ss}$ the arithmetic mean (minimum, maximum) values are reported. For λ_z, the arithmetic mean (%CV) is reported.
[2]N = 12
[3]N = 2
Source: Summary Table 14.4.5

The PK parameters obtained in the patients at steady are not incompatible with dose proportionate pharmacokinetics. The values for tmax and t1/2z are similar to those obtained in healthy subjects. The oral clearance ranges between 11 mL/min and 17 mL/min. The ratio of Cmin,ss to Cmax,ss ranges between 0.12-0.20.

Conclusion

The estimates for oral clearance of ambrisentan at steady-state in the PAH patients obtained by the traditional 2 stage PK method and POPPK approach are compatible. The values for tmax and apparent terminal half-life in the PAH patients are similar to those in heaslthy subjects.

Assay Validation Reports

5 Page(s) Withheld

5 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Given the uninterpretable results from the in vivo bioequivalence study and the identical composition of the commercial and clinical service formulations of the 5 mg and 10 mg tablets and the similarity among the formulations of the 2 strengths, the in vitro dissolution data submitted were reviewed. The goal was to investigate whether bioequivalence of the commercial and clinical service formulations could be demonstrated based on in vitro data possibly granting a biowaiver for the in vivo bioequivalence study.

The composition of the commercial and clinical service forms of the 5 mg and 10 mg tablets of ambrisentan are listed in the below table:

Table 3 Quantitative Compositions of Ambrisentan Tablet Clinical and Proposed Commercial Formulations

Formulation:	Phase 1		Clinical		Commercial	
Use:	Phase 1 Studies		Myogen Phase 1, 2, and 3 Studies		Registration, and Proposed Commercial	
Manufacturer:	[redacted]		[redacted]			
Tablet Strength	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg
Core Tablet (mg/tablet)						
Ambrisentan	5	10	5	10	5	10
Croscarmellose Sodium	[redacted]		[redacted]			
Lactose Monohydrate	[redacted]		[redacted]			
Magnesium Stearate	[redacted]		[redacted]			
Microcrystalline Cellulose	[redacted]		[redacted]			
Core Tablet Weight (mg):	[redacted]		[redacted]			
Film Coating (mg/tablet)	[redacted]		[redacted]			
[redacted]	–	–	[redacted]		–	–
[redacted]	–	–	–	–	[redacted]	
Total Tablet Weight (mg)	170	170	147	147	147	147

[redacted] made of [redacted] 5, and 10 mg tablets with the clinical formulation
'100 mg [redacted] Phase 1 coated tablets used [redacted]
'The 100 mg tablets were manufactured using [redacted]

The dissolution profiles in the media 0.1 N HCl, pH 3.0, pH 5.0 and pH 6.8 for the 5 mg and 10 mg commercial and clinical service formulations used in the bioequivalence study are shown in the figures below:

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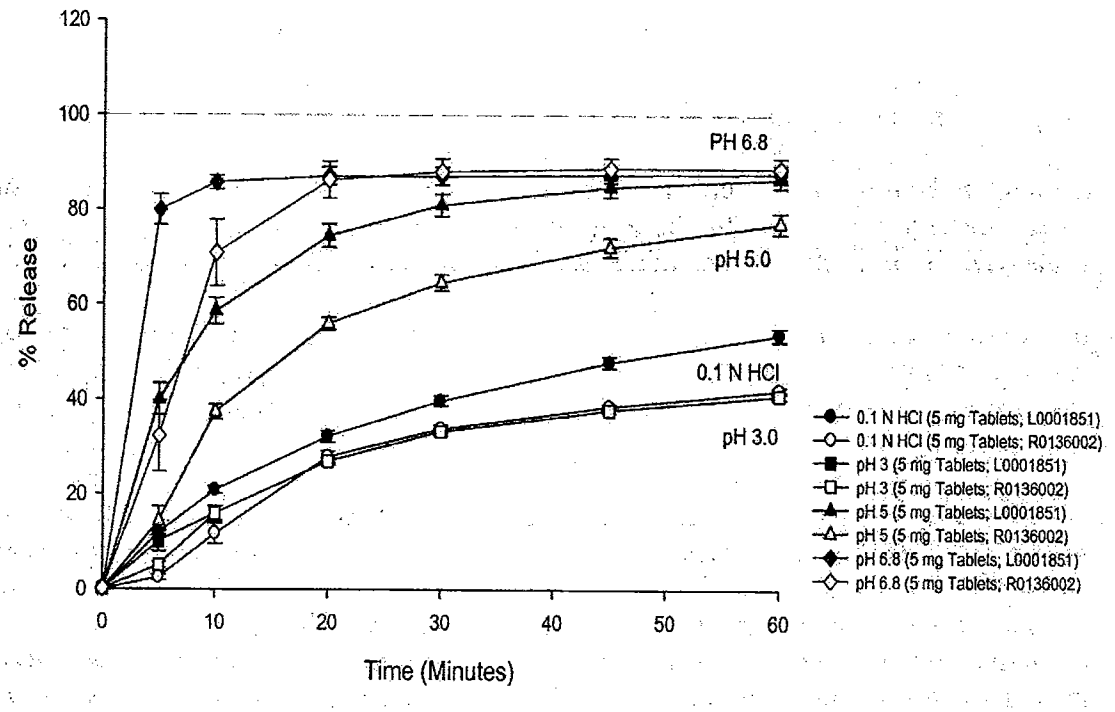
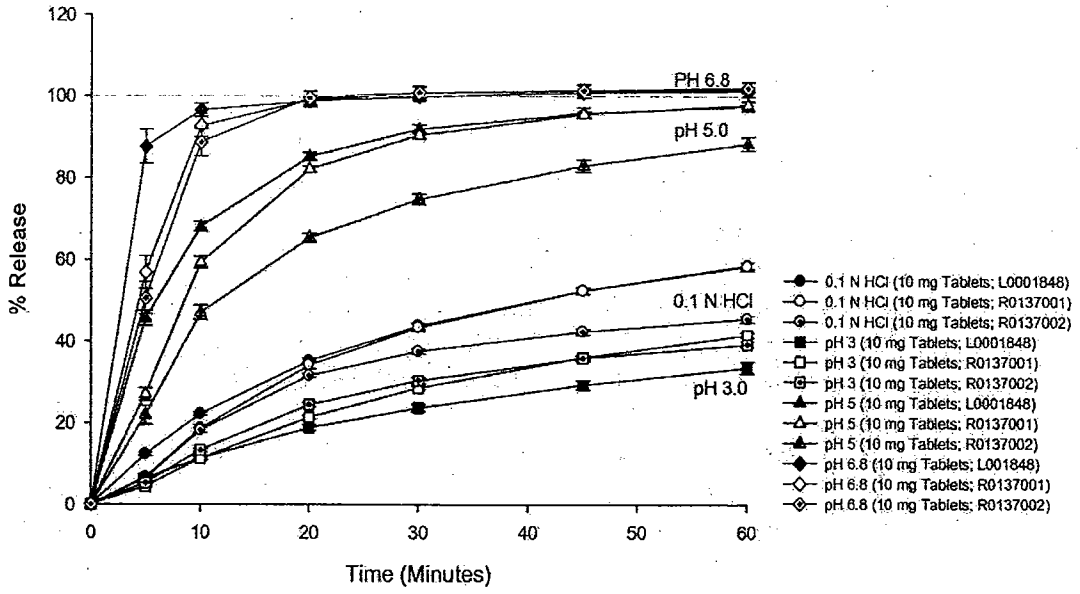
Figure 1 Dissolution Profiles from Clinical and Proposed Commercial (Registration) Formulation Lots Used in AMB-103 BE Study

5 mg



Drug Product Lot L0001851 = Clinical Formulation (closed symbols)
Drug Product Lot R0136002 = Commercial Formulation (drug substance batch 3109.F.04.4; open symbols)

10 mg



Drug Product Lot L0001848 = Clinical Formulation (closed symbols)
Drug Product Lot R0137001 = Commercial Formulation (drug substance batch 3109.F.04.2; open symbols)
Drug Product Lot R0137002 = Commercial Formulation (drug substance batch 3109.F.04.4; dotted symbols)

The results of the F2 tests performed with the data obtained in the four media for the commercial and clinical service formulations are listed in the below table:

Table 1 Comparability Testing (f_2 Analysis) for Multimedia Dissolution: Ambrisentan Tablets, 5 mg, Used in AMB-103 Bioequivalence Study

	f_2 Analysis[1] Phase 2/3 Clinical Formulation Drug Product Lot L0001851[3]			
	0.1 N HCl	pH 3.0	pH 5.0	pH 6.8
Commercial Formulation Drug Product Lot R0136002[2]	56 (Pass)	76 (Pass)	38[4] (Fail)	56 (Pass)

[1] f_2 comparability testing performed using 10, 20, 30, and 45 minute time point data. f_2 values of 50 or above between two lots indicate that the dissolution characteristics of each lot can be considered similar (Pass); f_2 values below 50 between two lots indicate that the dissolution characteristics of each lot are dissimilar (Fail).

[2] Registration lot manufactured with [redacted] drug substance batch 3109.F.04.4

[3] Clinical lot manufactured with [redacted] drug substance batch L0003139

[4] f_2 test result differs from the value (41) provided in original NDA. f_2 data included in Tables 1 and 2 used dissolution profiles (n = 6) obtained during the multimedia dissolution testing; additional dissolution profiles (n = 6-12) obtained during development of the pH 5.0 dissolution method were included in calculation of f_2 for pH 5.0 dissolution in the original NDA.

Table 2 Comparability Testing (f_2 Analysis) for Multimedia Dissolution: Ambrisentan Tablets, 10 mg, Used in AMB-103 Bioequivalence Study

	f_2 Analysis[1] Phase 2/3 Clinical Formulation Drug Product Lot L0001848[4]			
	0.1 N HCl	pH 3.0	pH 5.0	pH 6.8
Commercial Formulation Drug Product Lot R0137001[2]	90 (Pass)	71 (Pass)	70[5] (Pass)	78 (Pass)
Commercial Formualtion Drug Product Lot R0137002[3]	60 (Pass)	64 (Pass)	38[5] (Fail)	65 (Pass)

[1] f_2 comparability testing performed using 10, 20, 30, and 45 minute time point data. $f2$ values of 50 or above between two lots indicate that the dissolution characteristics of each lot can be considered similar (Pass); f_2 values below 50 between two lots indicate that the dissolution characteristics of each lot are dissimilar (Fail).

[2] Registration lot manufactured with [redacted] drug substance batch 3109.F.04.2

[3] Registration lot manufactured with [redacted] drug substance batch 3109.F.04.4

[4] Clinical lot manufactured with [redacted] drug substance batch L0003139

[5] f_2 test results differ from the values (66 and 37) provided in original NDA. f_2 data included in Tables 1 and 2 used dissolution profiles (n = 6) obtained during multimedia dissolution testing; additional dissolution profiles (n = 6-12) obtained during development of the pH 5.0 dissolution method were included in calculation of f_2 for pH 5.0 dissolution in the original NDA.

The results indicate a similar dissolution performance of the 5 mg and 10 mg commercial and clinical service formulations in the media 0.1 N HCl, pH 3.0 and pH 6.8. However, at pH 5.0 the 5 mg commercial tablet the 10 mg commercial tablet of Product Lot R 0137002 failed, whereas the 10 mg commercial tablets of Product lot R 0137001 passed. This result indicated that pH 5.0 medium is the most discriminatory for evaluating the in vitro dissolution performance of the tablets and is the medium proposed by the sponsor. However, given the compositional identity of the commercial and clinical service forms at the 5 mg and 10 mg levels and the proportional composition of the 5 mg and 10 mg tablets the discrepancy and inconsistency of the results were surprising. Indeed, there exist differences in [redacted] between the drug substances used in the commercial and clinical service formulations.The table below lists the differences in [redacted] and summarizes the in vitro perfomance of the 5 mg and 10 mg commercial and clinical service formulations:

Dose	Commercial			Service	
mg	Drug Substance Lot #	Drug Product Lot #		Drug Product	F2-Test pH 5
5	3109F.04.2	R0136002		L0001851	fails
10	3109F.04.4	R0137002		L0001848	fails
10	3109F.04.2	R0137001		L0001848	pass

[a]Drug substance lot L0003139 [b] Measured by % sieve retention: minimal: < 17%, slight: 17%, moderate: 45%, high: 48%

Green signifies that a formulation passes the F2 test and red signifies that a formulation fails the F2 test.The results indicates that the commecial 5 mg tablet ([redacted]) and the commercial 10 mg tablet ([redacted]) fail the F2 test in medium pH 5.0. In contrast the commercial 10 mg tablet [redacted]) passes the the F2 test in medium pH 5.0.

It is possible that both [redacted] impact the in vitro perfomance of the commercial formulations. Systematic studies are needed to determine the relative contributions of [redacted] to the in vitro dissolution behavior. In conclusion, the available in vitro evidence does not support granting a biowaiver. The sponsor did not submit in vitro dissolution data on the [redacted] commercial and clinical service formulations.

6. QTcIRT Report

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

IND or NDA	NDA 22-081
Brand Name	Letairis
Generic Name	Ambrisentan
Sponsor	Gilead
Indication	Treatment of pulmonary arterial hypertension (WHO Group 1)
Dosage Form	Tablets
Therapeutic Dose	5-10 mg qd
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Application Submission Date	12/13/2006
Review Classification	Priority NDA
Date Consult Received	02/06/2007
Date Consult Due	03/23/2007
Clinical Division	DCRP
PDUFA Date	06/18/2007

1. SUMMARY

1.1. OVERALL SUMMARY OF FINDINGS

The prespecified primary endpoint was the comparison of time-matched, baseline-adjusted QTcS (QTc calculated using Framingham/Sagie correction formula) for the group receiving high dose (4-fold maximum therapeutic dose) ambrisentan (at day 6) versus placebo (at day 6). One-sided 95% upper confidence intervals for the largest time-matched difference between ambrisentan and placebo (the baseline-adjusted QTcS) at day 6 (Hour 2) was higher than 10 ms (14.2 ms) and the mean estimate was higher than 5 ms (10.2 ms), i.e. above the levels recommended as the threshold for regulatory concern in the ICH E14 guideline. Similar results were reported for QTcF (QTc calculated using Fredericia correction formula). The largest time-matched mean difference of the drug and placebo after baseline adjustment for the high dose for QTcF was 8.9 msec and the one-sided 95% upper bound is 13.0 msec.

However, administration of ambrisentan resulted in an increase in heart rate, which had not been previously noted. The sponsor presents data suggesting that both the Framingham/Sagie and the Fredericia correction formulas appear to overcorrect the QT interval for heart rate. The sponsor performed a post hoc analysis correcting the QT using an individualized correction formula (QTcIb). The sponsor does not present any rationale for the use of this method. In this analysis, administration of ambrisentan was associated with an increase in mean time-matched and placebo-adjusted QTcIb that was below the levels recommended as the threshold for regulatory concern in the ICH E14 guideline (4.9 msec; upper bound of the 90% CI = 8.9 msec).

The agency performed its own analysis to find the best method for correcting the QT interval for the unanticipated increase in heart rate and found that the individualized correction formula (QTcIb) appeared to undercorrect the QT interval. A non-linear mixed-model correction (QTcM) appeared to best correct the QT interval. Using this model, the largest time-matched mean difference of the drug and placebo after baseline adjustment for the high dose for QTcM was 8 msec and the one-sided 95% upper bound is 12.3 msec at the t_{max} of the supratherapeutic dose of 40 mg. The study is considered a positive QT study since this is above the threshold of regulatory concern of 10 msec.

The exposure-response analysis was consistent with the primary endpoint analysis and a significant concentration-QT relationship was estimated. The predicted mean ddQTcM at mean C_{max} of the therapeutic and supratherapeutic doses were 1.7 and 6.2 msec, respectively, and the upper bounds of the 90% CI were 2.5 and 9.1 msec.

The highest expected clinical exposure is unknown since the sponsor did not perform any in vivo drug-drug interaction studies with P-gp inhibitors such as cyclosporine. Results from a drug-drug interaction study for bosentan (another endothelin receptor antagonist) showed substantial increase in bosentan exposure (about 30-fold increase in trough concentrations) when administered with cyclosporine, a P-gp, MRP2, OATP and CYP3A4 inhibitor. The exposure after administration of ambrisentan at 4-fold the therapeutic dose of 10 mg is therefore not expected to cover the highest expected clinical exposure.

1.2. RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

None

1.3. REVIEWER'S COMMENTS

In the pre-specified Statistical Analysis Plan the sponsor stipulated correction of the QT interval to account for heart rate by the Framingham/Sagie method. A substantial increase in heart rate observed after administration of ambrisentan in the study although a heart rate effect had not previously been noted. The sponsor states a post hoc analysis was developed to use individualized QT corrections for each subject. Based on the post hoc analysis, the sponsor concluded that administration of the maximum therapeutic dose of ambrisentan increased QTcIb less than the threshold of regulatory concern.

2. PROPOSED LABEL

The sponsor did not describe study results in the label. The following recommendations are suggestions for labeling only and are open to modification pending further discussion with the review division. We defer all final labeling decisions to the review division.

3. BACKGROUND

3.1. INDICATION

Pulmonary arterial hypertension

3.2. DRUG CLASS

Endothelin receptor antagonist

3.3. MARKET APPROVAL STATUS

Not approved.

3.4. PRECLINICAL INFORMATION

According to the current Investigator's Brochure, administration of ambrisentan to dogs was associated with mild increases in heart rate and mild decreases in blood pressure. No change in ECG parameters was noted. No hERG assays are mentioned.

3.5. PREVIOUS CLINICAL EXPERIENCE

The current Investigator's Brochure states that unusual prolongation of the QTc has not been noted during clinical development. The IB also does not report any episodes of *torsades de pointes.*

3.6. CLINICAL PHARMACOLOGY

The following table summarizes the key features of ambrisentan's clinical pharmacology.

Table 2 Highlights of Clinical Pharmacology (Generated by Reviewer)

Therapeutic dose	5 mg and 10 mg po qd	
Maximum tolerated dose	Not established. Ambrisentan was generally tolerated at doses up to 50 mg (single dose) and 10 mg qd (multiple dose)	
Principal adverse events	Peripheral edema (6.6%), nasal congestion (4.2%), and sinusitis (3.1%)	
Maximum dose tested	Single Dose	Healthy subjects: 100 mg PAH subjects: 5 mg
	Multiple Dose	Healthy subjects: 10 mg qd x 12 days PAH subjects: 10 mg qd (mean exposure: 57.9 weeks, max exposure 184.3 weeks)
Exposures Achieved at Maximum Tested Dose	Single Dose	Healthy subjects (100 mg EE-001): Cmax: 4521 (36.8) ng/mL $AUC_{0-\infty}$: 38066 (2.4) ng·hr/mL PAH subjects (5 mg AMB-320/321-E): Cmax: 472 (21.8) ng/mL $AUC_{0-\infty}$: 4680.2 (24.8) ng·hr/mL
	Multiple Dose	Healthy subjects (10 mg qd): EE-002: Cmax: 728 (9.8) ng/mL AUC_{0-t}: 4655 (12.5) ng·hr/mL AMB-104: C_{max}: 872 (25.5) ng/ml AUC_{0-t}: 6193 (23.0) ng·hr/mL AMB-106: Cmax: 948 (28.2) ng/mL AUC_{0-t}: 6106 (31.3) ng·hr/mL PAH subjects (10 mg qd) AMB-220: C_{max}: 1193 (27.6) ng/mL AUC_{0-24}: 14357 (30.2) ng·hr/mL AMB-320/321-E): C_{max}: 1146.8 (9.2) ng/mL AUC_{0-24}: 12591.3 (14.0) ng·hr/mL
Range of linear PK	Dose proportional increases in AUC: 1 to 100 mg single doses in healthy	

	subjects.	
Accumulation at steady state	The C_{max} and AUC_{0-24} values on Day 10 were less than 2% and 5% higher than the respective C_{max} and AUC_{0-24} on Day 1, indicating negligible ambrisentan accumulation during once daily oral administration of ambrisentan for 10 days in healthy male subjects.	
Metabolites	Ambrisentan was the predominant ambrisentan-related species circulating in the plasma. Three plasma metabolites of ambrisentan were identified: - 4-hydroxymethyl ambrisentan glucuronide (<10% of systemic exposure), - Ambrisentan glucuronide (<10% of systemic exposure), and - 4-hydroxymethyl ambrisentan (21.3% of systemic exposure). The binding affinity of 4-hydroxymethyl ambrisentan for the human ETA receptor was assessed to be 64-fold less than ambrisentan. The binding affinity of 4-hydroxymethyl ambrisentan glucuronide and ambrisentan glucuronide are unknown.	
Absorption	Absolute/Relative Bioavailability	Not determined
	Tmax	• Parent: 2-3 hrs (range 0.5-4 hrs) • 4-hydroxymethyl ambrisentan glucuronide: 3.5 hrs (range 1.5-8.0 hrs) • Ambrisentan glucuronide: 2.75 hrs (range 2.0-10.0 hrs) • 4-hydroxymethyl ambrisentan: 15.00 hrs (8.0-60 hrs)
Distribution	Vd/F	Healthy subjects: 21.1 L (Pop PK) PAH patients: 14.9 L (Pop PK)
	% bound	98.8% protein binding in plasma
Elimination	Route	• Primary route; 88% excreted (65.4% in feces, 22.1% in urine) • Other routes: Less than 5% of unchanged ambrisentan was eliminated in urine
	Terminal t½	• Ambrisentan: 12.9-17.9 hrs • Metabolites: Not reported
	CL/F	Healthy subjects: 2.25 L/hr (Pop PK) PAH subjects: 1.11 L/hr (Pop PK)
Intrinsic Factors	Age	No apparent effects based on Pop PK.
	Sex	No apparent effects based on Pop PK.
	Race	No apparent effects based on Pop PK.
	Hepatic & Renal Impairment	No clinical pharmacokinetic studies were conducted in subjects with renal or hepatic impairment. Since ambrisentan is primarily metabolized in the liver and both parent compound and metabolites are predominantly excreted in the bile/feces, the PK profile should not be affected in patients with renal insufficiency; therefore, no dose adjustment is warranted. In contrast, the clearance of ambrisentan may be reduced in patients with clinically significant hepatic impairment, resulting in increased exposure. The magnitude of this effect on safety and efficacy has not been

		evaluated; therefore, ambrisentan should be used with caution in this patient population.
Extrinsic Factors	Drug interactions	No significant drug interaction was observed between ambrisentan and sildenalfil in healthy subjects. AMB-105 (Drug-drug interaction (DDI) with sildenafil) Ambrisentan: C_{max}: AMB (839.5 ng/mL) vs AMB/sildenafil (808.4 ng/mL) Geometric mean ratio (90%CI): 96.3 (86.0, 107.8) $AUC_{0-\infty}$: AMB (4414.9 ng·hr/mL) vs. AMB/sildenafil (4790.5 ng·hr/mL) Geometric mean ratio (90%CI): 108.5 (102.6, 114.8) Sildenafil: C_{max}: sildenafil (52.5 ng/mL) vs AMB/sildenafil (59.5 ng/mL) Geometric mean ratio (90%CI): 113.4 (99.6, 129.1) $AUC_{0-\infty}$: sildenafil (167.8 ng·hr/mL) vs. AMB/sildenafil (165.5 ng·hr/mL) Geometric mean ratio (90%CI): 98.7 (87.7, 111.0) n-desmethyl-sildenafil: C_{max}: sildenafil (31.2 ng/mL) vs AMB/sildenafil (31.1 ng/mL) Geometric mean ratio (90%CI): 99.6 (87.2, 113.8) $AUC_{0-\infty}$: sildenafil (107.9 ng·hr/mL) vs. AMB/sildenafil (108.4 ng·hr/mL) Geometric mean ratio (90%CI): 100.5 (91.2, 110.8)
	Food Effects	Not determined
Expected High Clinical Exposure Scenario	Not reported	

4. SPONSOR'S SUBMISSION

4.1. OVERVIEW

The sponsor submitted pharmacokinetic and ECG data and study report for thorough QT study AMB-104 together with the investigator's brochure for ambrisentan.

4.2. QT STUDY 1

4.2.1. Title

A Phase 1, Single-blind, Randomized, Placebo- and Positive-controlled, Parallel-design, Multiple-dose, 3-arm Study of the Effects of Oral Ambrisentan on QTc Interval Prolongation in Healthy Adult Volunteers

4.2.2. Protocol Number

AMB-104

4.2.3. Objectives

To assess the effects of oral ambrisentan on electrocardiogram (ECG) parameters in healthy male and female subjects.

4.2.4. Design

4.2.4.1. Description

This was a single-blind, randomized, placebo- and positive-controlled, parallel-design, multiple-dose, 3-arm study with a 6-day treatment period to evaluate the effects of oral ambrisentan on ECG parameters in healthy adult volunteers.

Electrocardiograms were recorded using a standard digital 12-lead ECG recorder (MAC1200, GE Medical Systems) with pre-specified sampling times. Electrocardiogram sampling was designed to capture those periods when the concentration of ambrisentan was predicted to be highest. Additional ECGs were sampled during and after dosing. The time points for study endpoint ECG sampling were as follows: on day 0 (baseline) at -0.25, 1, 1.5, 2, 6, and 12 hours (where timing was based on respective dosing times for day 1); on days 1, 5, and 6 at -0.25, 1, 1.5, 2, 6, and 12 hours postdose; and 24 hours following the last dose on day 6. ECG sampling was to be immediately followed by PK sampling. Blood samples for PK analysis were obtained for measurements of plasma concentrations of ambrisentan at the following time points: on days 1, 5, and 6 at -0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours postdose; on day 4 at -0.25 hours (predose).

4.2.4.2. Sponsor's Justification for Design

Sponsor did not provide justification for study design.

4.2.4.3. Controls

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

4.2.4.4. Blinding

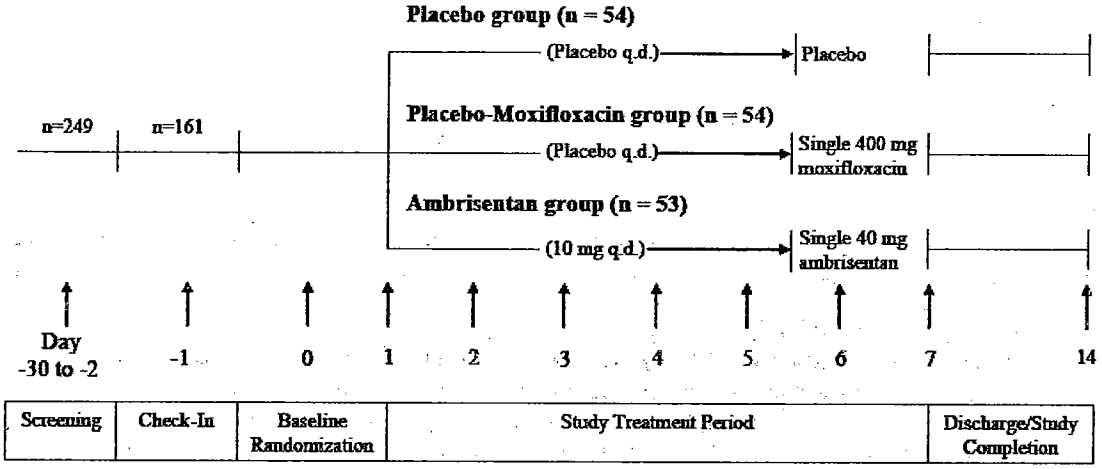
Subjects, and staff not administering study drug, were blinded to the treatments with the exception of moxifloxacin, which was not over-encapsulated.

4.2.5. Study Subjects

161 healthy male and female subjects, 18 to 55 years of age, with a body mass index between 18.5 and 29.9 kg/m^2 and body weight ≥ 50 kg with a normal 12-lead ECG were planned and randomized to ensure that at least 147 subjects provided QTc data near time to maximum plasma concentration (t_{max}) for ambrisentan.

4.2.6. Dosing Regimens

4.2.6.1. Treatment Arms



(Reproduced from sponsor's Figure 9.1 on page 26 in report AMB-104)

4.2.6.2. Sponsor's Justification for Doses

The selection of the 10 mg ambrisentan po qd dose was based on previous phase 1 and phase 2 clinical experience that demonstrated this dose is efficacious and well tolerated. Higher single doses (20, 50, and 100 mg) were associated with an increasing number of AEs, most particularly headache and flushing.

The selection of the 40 mg ambrisentan dose is consistent with the ICH E-14 guidance, which specifies using 4-10 times the anticipated therapeutic dose for QTc evaluations. The 400 mg moxifloxacin dose was selected as a positive control since this dose has demonstrated a significant change in QTc duration in prior studies.

4.2.6.3. Instructions with regard to meals

Each orally administered tablet was dosed individually and the total water consumed was 240 mL. The subject must have fasted for at least 8 hours. No more than 1 tablet was swallowed at a time.

While confined at the clinical site, subjects received a standardized bulk diet at scheduled times that did not conflict with other study-related activities. Dosing was preceded by an overnight fast (i.e., for at least 8 hours) from food (not including water) and was followed by a fast from food (not including water) for at least 4 hours postdose. Subjects were required to abstain from consuming foods or beverages known to induce or inhibit liver cytochrome p450 metabolic enzymes for 72 hours prior to Check-in until 48 hours following the last dose.

4.2.6.4. Study Assessments

Table 3.Highlights of Schedule of Interventions

Study Day	0	1	5	6
Intervention	No treatment	Single dose	Steady-state dose	Single high dose
12-Lead ECGs	Record ECGs### (Baseline)	Record ECGs###	Record ECGs###	Record ECGs###
PK Samples for drug	None collected	Collected***	Collected***	Collected***
Meal Instructions	None specified	To be dosed	To be dosed	To be dosed without

		without food	without food	food

###-0.25, 1, 1.5, 2, 6, and 12 hours postdose

***-0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 postdose on day 1, 5, and 6

4.2.6.5. Sponsor's justification for sampling schedule

4.2.6.6. Baseline

The Sponsor collected time-matched baseline QT values on the day prior to initiating dosing (Day 0) of the study for each treatment.

4.2.7. ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8. Sponsor's Results

4.2.8.1. Statistical Analyses

Table 3 lists the disposition of the subjects in the trial. A total of 161 subjects were randomized among the 3 treatment groups: 54 to placebo, 54 to moxifloxacin and 53 to ambrisentan. Although all subjects received at least 1 dose of study drug (ITT population), 11 subjects among the groups did not complete the study: 3 (5.6%) in the placebo group, 4 (7.4%) in the moxifloxacin group, and 4 (7.5%) in the ambrisentan group. One subject discontinued because of an adverse event, 4 subjects discontinued for non-compliance, 4 subjects withdrew consent, and 2 subjects were lost to follow-up. There was no significant difference between the groups in the number of subjects who completed the study, or in the reasons for discontinuation.

Table 4.Disposition of Subjects

Number of Subjects (%)	Placebo (N = 54)	Moxifloxacin (N = 54)	Ambrisentan (N = 53)	Total (N = 161)
Screened				249
Randomized	54 (100.0)	54 (100.0)	53 (100.0)	161
Completed	51 (94.4)	50 (92.6)	49 (92.5)	150
Withdrew	3 (5.6)	4 (7.4)	4 (7.5)	11
Eligible for:				
ITT Population	54 (100.0)	54 (100.0)	53 (100.0)	161
ECG End Point Population	53 (98.1)	52 (96.3)	52 (98.1)	157

Source: Study Report

Table 4 shows the demographic characteristics of the subjects. The subject population was predominately male (74.5%). The proportion of males and females were generally similar among the 3 treatment groups, with a slightly higher percentage of females in the ambrisentan group (28.3%) than in the placebo group (22.2%). Nearly half (47.8%) of the subjects were Black or African. The racial distribution was generally similar between the placebo and ambrisentan groups; however, the moxifloxacin group had slightly more Caucasian and slightly fewer Hispanic subjects than either of the other groups. Age, height, weight and body mass index were similar among the 3 treatment groups.

Table 5.Demographics and baseline Characteristics

Treatment Group Characteristic	Placebo (N = 54)	Moxifloxacin (N = 54)	Ambrisentan (N = 53)
Gender, n (%)			
Male	42 (77.8)	40 (74.1)	38 (71.7)
Female	12 (22.2)	14 (25.9)	15 (28.3)
Race, n (%)			
Hispanic or Latino	16 (29.6)	10 (18.5)	17 (32.1)
Black or African	25 (46.3)	26 (48.1)	26 (49.1)
Asian	1 (1.9)	0 (0.0)	0 (0.0)
White or Caucasian	12 (22.2)	18 (33.3)	10 (18.9)
Mean Age, years (SD)	35.9 (10.84)	35.0 (9.33)	37.6 (9.84)
Mean Weight, kg (SD)	76.5 (10.66)	77.6 (10.03)	75.3 (12.57)
Mean Height, cm (SD)	173.5 (9.58)	173.7 (8.04)	172.2 (9.28)
Mean BMI, kg/m^2 (SD)	25.4 (2.58)	25.7 (2.74)	25.2 (2.79)

Source: Study Report

4.2.8.1.1. Primary Analysis

The Intent-to-Treat Population (ITT) consisted of all randomized subjects who received at least 1 dose of any treatment. The statistical analyses were performed on the ITT sample.

Table 5 shows that one-sided 95% upper confidence intervals for the Largest Time-Matched Difference between ambrisentan and Placebo. The one-sided 95% upper limit of the baseline-adjusted QTcS of ambrisentan at day 6 (Hour 2) was higher than 10 ms (14.22 ms) and the mean estimate was higher than 5 ms (10.19 ms).

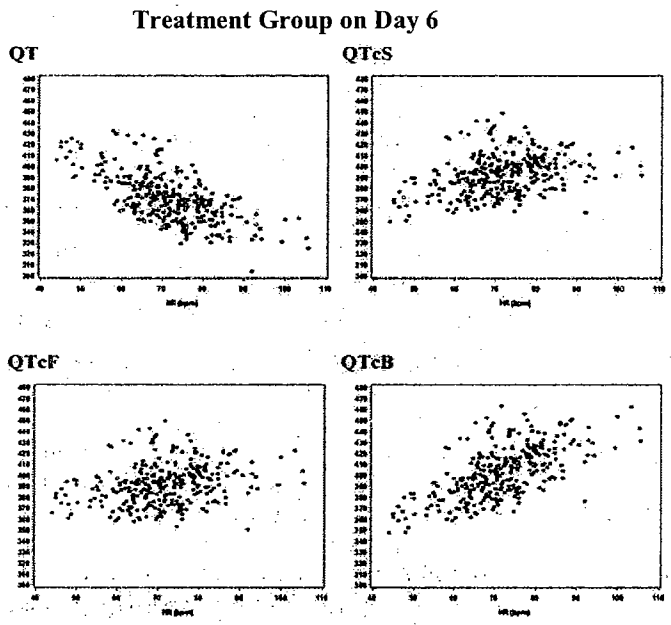
Table 6: Maximum Increase by Day in Mean Time-matched and Placebo-adjusted QT/QTc for the Ambrisentan Treatment Group

	Time point of maximum increase	Placebo time-matched change (msec)	AMB[1] time-matched change (msec)	AMB[1] Time-matched placebo-adjusted change (msec)		
		Mean (N = 53)	Mean (N = 52)[2]	Point estimate	90% CI[3]	All time points with upper bound of the 90% CI ≥10 msec (hr)
QT	Day 1 Predose	6.16	7.31	1.16	-3.78, 6.10	-
	Day 5 Hour 1	11.32	7.37	-3.95	-9.42, 1.53	-
	Day 6 Hour 1	7.66	2.53	-5.13	-10.99, 0.72	-
QTcIb	Day 1 Hour 1.5	4.40	6.33	1.93	-1.58, 5.45	-
	Day 5 Hour 1.5	2.05	4.53	2.48	-1.38, 6.34	-
	Day 6 Hour 2	-0.17	4.76	4.93	-0.92, 8.94	-
QTcS	Day 1 Hour 1.5	-2.72	2.15	4.87	0.96, 8.78	-
	Day 5 Hour 1.5	-3.67	4.00	7.67	3.50, 11.84	1.5, 2
	Day 6 Hour 2	-5.44	4.76	10.19	6.16, 14.22	1.5, 2, 6
QTcF	Day 1 Hour 1.5	-0.66	3.49	4.15	0.51, 7.79	-
	Day 5 Hour 1.5	-1.85	4.21	6.06	2.12, 10.00	-
	Day 6 Hour 2	-4.61	4.34	8.94	4.94, 12.95	2, 6
QTcB	Day 1 Hour 6	-3.79	2.92	6.71	2.35, 11.06	1.5, 2, 6
	Day 5 Hour 2	-6.20	5.90	12.10	7.60, 16.60	0, 1, 1.5, 2, 6, 12
	Day 6 Hour 2	-7.66	8.72	16.39	11.23, 21.54	0, 1, 1.5, 2, 6, 12

[1]AMB = ambrisentan; ambrisentan dose on days 1 and 5 was 10 mg; ambrisentan dose on day 6 was 40 mg
[2]N = 51 for all day 6 values and for day 1 hour 6 QTcB
[3]2-sided 90% confidence interval
Source: Summary Table 14.2.4

Figure 1 displays the relationships between heart rate and QT/QTc on day 6 for the ambrisentan treatment group. On day 6 for subjects receiving 40 mg ambrisentan, a strong inverse relationship was observed for heart rate and QT (i.e., QT values decreased with increased heart rate). QTcS appeared to overcorrect for heart rate in an apparent increase in QTcS with increased heart rate; this overcorrection was more apparent for QTcB. The sponsor chose in a post hoc analysis of QT to use QTcIb to correct the dependency of the QT interval on heart rate.

Figure 1: Relationship between Heart Rate and QT/QTc for Ambrisentan

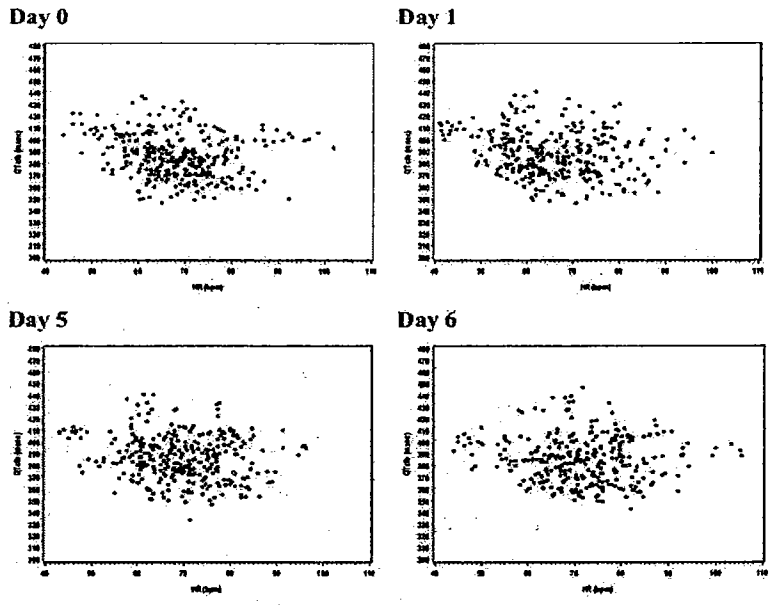


Source: Study Report

Figure 2 displays the relationships between heart rate and QTcIb for the ambrisentan treatment group. The QTcIb correction for heart rate substantially reduced the dependency of QTc on heart rate for all days of treatment; the sponsor concluded that QTcIb would provide a more accurate estimate of the potential effects of ambrisentan on QTc.

Figure 2: Relationship between Heart Rate and QTcIb for Ambrisentan Treatment

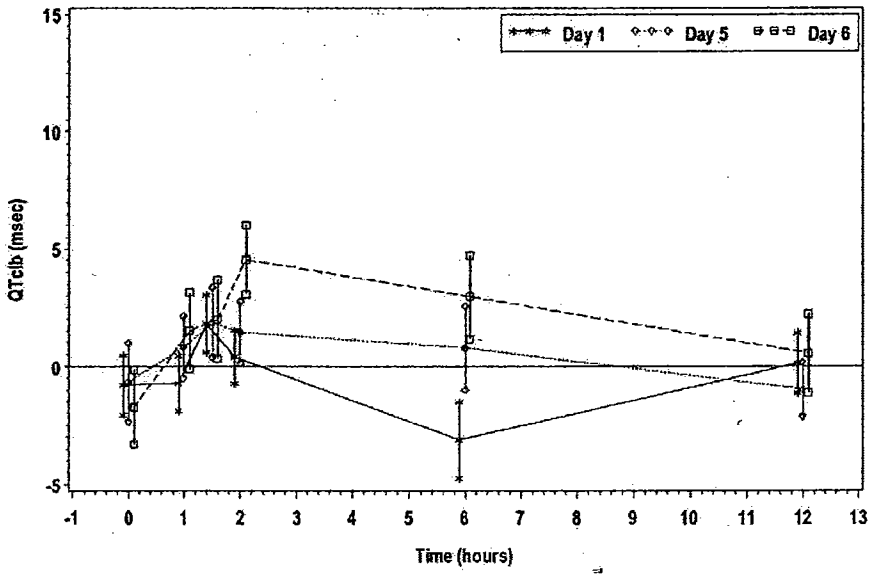
Over Time



Source: Study Report

Figure 3 displays the baseline-adjusted changes in QTcIb intervals relative to placebo for ambrisentan on days 1, 5, and 6. The pattern of increase and decrease in QTcIb values after administration of ambrisentan was similar on days 1, 5, and 6. At no time point did the mean QTcIb interval increase above 5 msec, and at no time point did the upper bound of the 90% CI exceed 10 msec.

Figure 3.Time-Matched and Placebo-Adjusted Change from Baseline in QTcIb over Time for the Ambrisentan Treatment Group



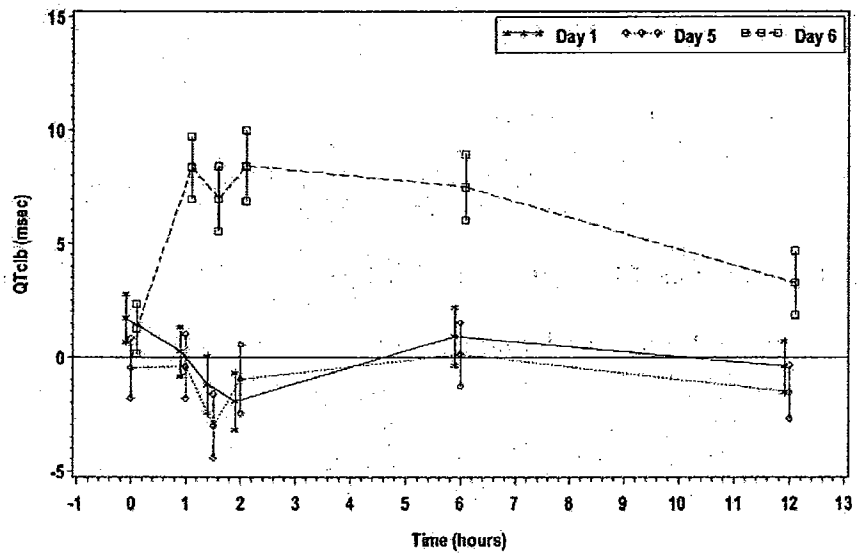
The administration of oral ambrisentan at 4-fold the therapeutic dose was associated with a slight increase in mean time-matched and placebo-adjusted QTcIb (4.93 msec; upper bound of the 90% CI = 8.94 msec). Multiple daily dosing with the maximum therapeutic dose of ambrisentan (10 mg qd) was also associated with a slight increase in

mean QTcIb (2.48 msec; upper bound of the 90% CI = 6.34 msec). Both the high dose and maximum therapeutic doses of ambrisentan had maximum increases in QTcIb that were less than the threshold stated in the E14 guidance.

A 4-fold increase in ambrisentan dose was associated with less than a 2-fold increase in the mean time-matched and placebo-adjusted QTc. Therefore, these data do not support a well-defined dose-response relationship on potential QT/QTc changes.

Figure 4 displays the baseline-adjusted changes in QTcIb intervals relative to placebo for moxifloxacin on days 1 and 5 (placebo) and on day 6 (moxifloxacin). With moxifloxacin, the mean change in QTcIb exceeded 5 msec for most time points (including the tmax time point, 1 hour) and all of the lower confidence bounds were >0 msec and most of the upper confidence bounds approached 10 msec.

Figure 4. Time-Matched and Placebo-Adjusted Change from Baseline in QTcIb over Time for the Moxifloxacin Treatment Group



Error bars = 2-sided 90% confidence intervals.
Source: Summary Figure 14.4.11.c

Table 6 lists the maximum increases in mean time-matched and placebo-adjusted QT/QTc for subjects receiving moxifloxacin. Moxifloxacin displayed the expected effect upon QTc interval, with both a lower bound of the 2-sided 90% CI >0 msec and an upper bound ≥10 msec at multiple time points. According to the sponsor, these treatment effects were consistent with the expected values for subjects treated with 400 mg moxifloxacin. Therefore, the study had sufficient sensitivity to provide data for the effects of ambrisentan on QTc.

Table 7: Maximum Increase on Day 6 in Mean Time-matched and Placebo-adjusted QT/QTc for the Moxifloxacin Treatment Group

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On Original

	Time point of maximum increase	Placebo time-matched change (msec)	Moxifloxacin time-matched change (msec)	Moxifloxacin time-matched placebo-adjusted change (msec)		
		Mean (N = 53)[2]	Mean (N = 53)	Point estimate (N = 53)	90% CI[2] (N = 53)	Time points with 90% CI >10msec (hr)
QT	Day 6 Hour 6	-6.71	-1.58	5.12	-0.75, 11.00	6
QTcIb	Day 6 Hour 2	-0.17	8.59	8.76	4.77, 12.75	1, 1.5, 2, 6
QTcS	Day 6 Hour 1	-6.42	6.54	12.96	8.41, 17.51	1, 1.5, 2, 6
QTcF	Day 6 Hour 1	-4.79	6.88	11.67	7.34, 16.00	1, 1.5, 2, 6
QTcB	Day 6 Hour 1	-11.25	5.99	17.24	11.79, 22.69	1, 1.5, 2, 6, 12

[1] PE = point estimate; [2]two-sided 90% confidence interval.
N = 52 for day 6 hour 2 QTcIb.
Source: Summary Table 14.2.4

Secondary Endpoint Analysis

Comparison of High Dose Ambrisentan (40 mg) to Maximum Therapeutic Dose (10 mg)

As shown in Table 5, the maximum increase in mean time-matched and placebo-adjusted QTc for the ambrisentan group on day 5 (10 mg ambrisentan) and day 6 (40 mg ambrisentan) were very similar. The day 6 to day 5 ratio of the maximum increase in mean time-matched and placebo-adjusted QTcIb was 2-fold. Similarly, the day 6 to day 5 ratios for the maximum increase in mean time-matched and placebo-adjusted QTcS, QTcF and QTcB changes were 1.33, 1.48, and 1.35 respectively. Therefore, a 4-fold increase in ambrisentan dose was associated with a 2-fold increase in the mean time-matched and placebo-adjusted QTcIb. This suggests a low risk of QTc prolongation at 4-times the maximum therapeutic dose.

Categorical Analysis

Table 7 lists a categorical summary of the incidence of subjects with potentially clinically significant absolute QT/QTc intervals and change from baseline on days 1, 5 and 6. After a single dose of ambrisentan (day 1), the percentage of subjects in the ambrisentan group with a change from baseline QTcIb or QTcS >30 msec or ≤60 msec was similar to the placebo group on days 1, 4, and 6. No subject, in any treatment group, had a shift in QTc (in all corrections) that exceeded 60 msec.

Table 8: Summary of the Change from Baseline QTc >30 msec and ≤ 60 msec

		Placebo (N = 53) n (%)	Moxifloxacin (N = 52) n (%)	Ambrisentan (N = 52) n (%)
QTcIb	Day 1	1 (1.9)	1 (1.9)	1 (1.9)
	Day 5	1 (1.9)	3 (5.8)	2 (3.8)
	Day 6	1 (1.9)	3 (5.8)	4 (7.7)
QTcS	Day 1	2 (3.8)	0 (0.0)	1 (1.9)
	Day 5	1 (1.9)	2 (3.8)	4 (7.7)
	Day 6	1 (1.9)	3 (5.8)	3 (5.8)

Source: Summary Table 14.2.8

4.2.8.1.2. Additional Analyses

Effects of Gender on the QT/QTc Analyses

On an average, higher QTc interval were observed for female subjects compared to male subjects, but these differences appeared to be primarily due to a greater increase in heart rate observed for female subjects. However, due to the small number of female subjects, no clear conclusions could be made for difference by gender on changes in QTc.

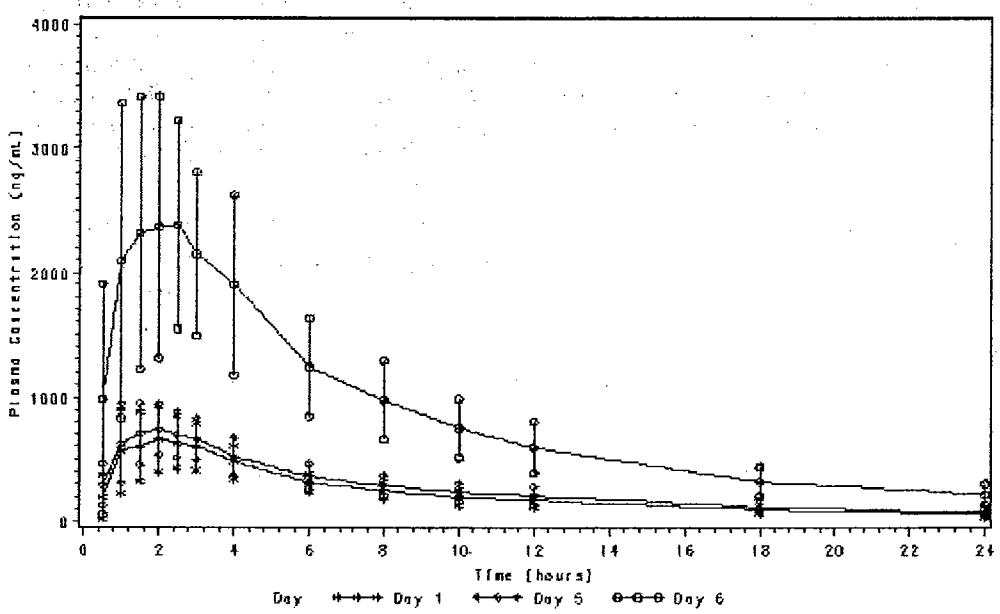
4.2.8.2. Safety Analysis

4.2.8.3. Clinical Pharmacology

4.2.8.3.1. Pharmacokinetic Analysis

Mean (SD) ambrisentan concentration-time profiles following oral administration of 10 mg qd on Day 1 and 5 and 40 mg single-dose on Day 6 are presented in the figure below. Mean (SD) peak concentrations of 829 (238) ng/ml and 898 (229) ng/ml on day 1 and 5, respectively, occurred approximately 2 h (range: 0.4 to 6.0 h) after dosing. Between-subject variability in Cmax was approximately 25%. The peak concentration on day 6 after a single 40 mg dose was 3273 (842) ng/mL with a t_{max} around 2 h (range 0.4 to 6.0 h).

Figure 5 Mean (SD) Plasma Concentration-Time Profile of Ambrisentan following Oral administration of 10 mg qd on Day 1 and 5 and 40 mg qd on Day 6



(Reproduced from sponsor's Figure 11.7 on page 59 in Report AMB-104)

4.2.8.3.2. Exposure-Response Analysis

Regression models for QTc were constructed to include PK parameters (t_{max}, C_{max}, and AUC). All three PK parameters were significantly associated with increased values for QTc at all three visit days.

Sponsor did not perform exposure-response analysis using plasma concentration and ddQTc measurements.

5. REVIEWERS' ASSESSMENT

5.1. STATISTICAL ASSESSMENTS

This reviewer reanalyzed the study data and the findings are consistent with the sponsors findings reported in Table 5.

5.2. CLINICAL PHARMACOLOGY ASSESSMENTS

QT Interval Correction

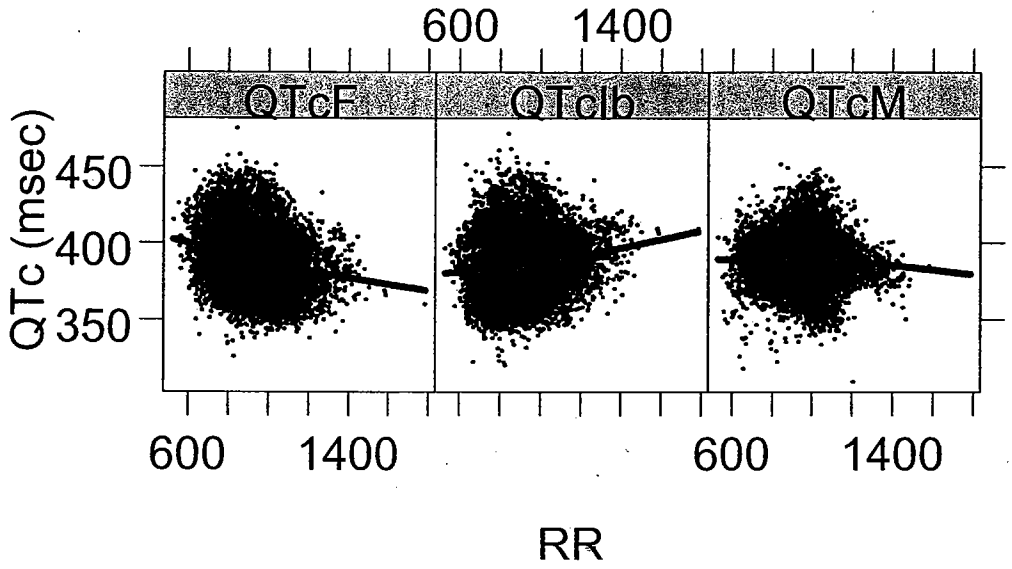
Three methods of heart-rate correction were performed:
(1) The Fridericia correction method,
(2) An individualized baseline corrected heart rate correction method, using the data from the baseline session, to calculate a corrected QT interval (QTcIb). The data from the placebo session was fit to the equation QTcIb = QT + slope*(1000 – RR) + error, and
(3) A non-linear mixed-model was used to derive the QTcM correction, i.e.

QTcM = QT/RR^b_i, b_i = b_pop * exp(eta_b)

where b_i is the individual exponent calculated using the population exponent b_pop and the inter-individual random-effects eta_b with mean 0 and variance ω^2. The model parameters were estimated using the relationship $\log_e(QT) = a + b * \log_e(RR) + \varepsilon$ using all values of QT and RR from baseline ECGs only. The population slope (b) estimate was 0.197 (IIV 89.1 CV%).

The different QT interval correction methods are shown in Figure 6 (and split by treatment and day in Figure 9 - Figure 11 in Appendix).

Figure 6 FDA Analysis: Scatter Plot of QTcF (Fridericia), QTcIb (Individual baseline), and QTcM (Mixed-Model) vs. RR Interval for ITT population. The Red Lines Are Local Regression Smooths.

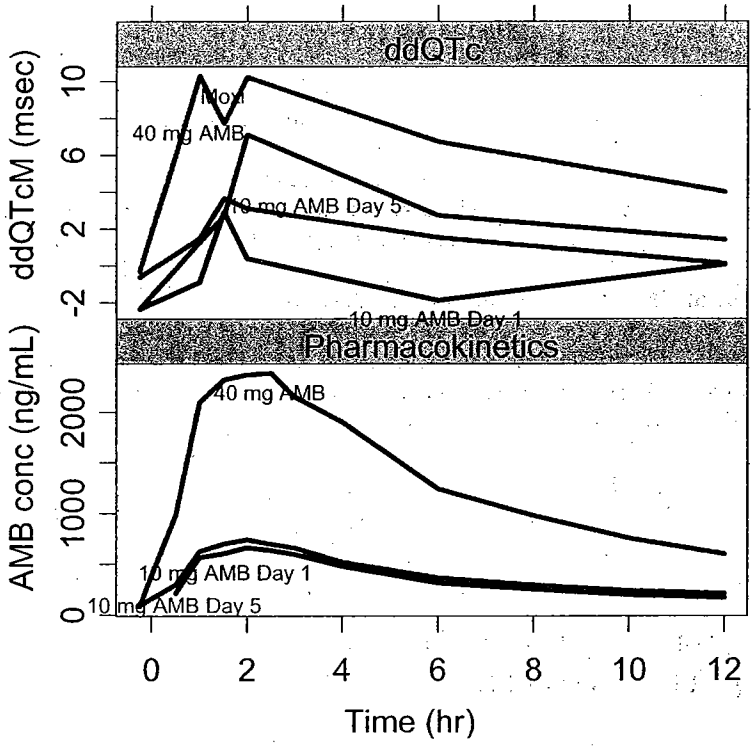


The Fridercia correction appears to overcorrects for the heart rate effect of ambrisentan while the individualized baseline correction of QT (QTcIb) suggested by the sponsor as primary correction method undercorrects for the heart rate effect. The mixed-model correction seems to best correct QT interval for the RR interval.

Exposure-Response Analysis

The plasma ambrisentan concentration and ddQTcM data were analyzed using a linear mixed-effects model. There was no evidence of a delay between the ddQTcM and plasma ambrisentan concentration (see Figure 7).

Figure 7 FDA Analysis: Mean ddQTcM and Ambrisentan Concentration Time Profiles



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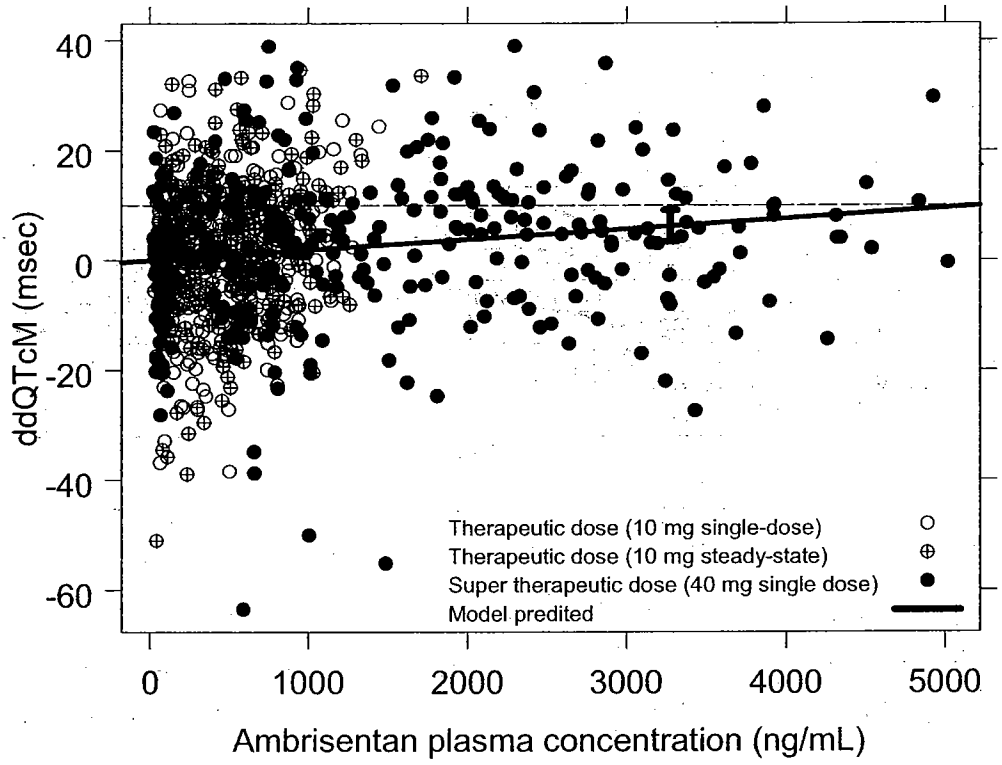
Three linear models were considered: model 1 is a linear model with an intercept, model 2 is a linear model with intercept fixed to zero, and model 3 is a linear model with no intercept. Table 9 summarizes the results of the models and the relationship is shown in Figure 8.

Table 9. FDA Analysis: Exposure Response Analysis of Ambrisentan

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcM = Intercept + slope*concentration		
Intercept, msec	-0.2342 (-1.58, 1.11); 0.7713	4.47
Slope, ms per mcg/ml	1.7758 (0.98,2.57); 0.0005	1.24
Residual Variability, msec	11.2	--
Model 2: Intercept (fixed) + slope*concentration		
Intercept, msec	0 (fixed);	4.47
Slope, ms per mcg/ml	1.9051 (1.03,2.78); 0.0011	1.24
Residual Variability, msec	11.6	--
Model 3: ddQTcM = slope*concentration		
Slope, ms per mcg/ml	1.6236 (0.38, 2.87); 0.0339	4.67
Residual Variability, msec	11.6	--

Figure 8 FDA Analysis: The Relationship between Ambrisentan Concentrations and ddQTcM was Described by a Linear Model with Intercept Fixed to Zero (Model 2)



The predicted change in ddQTcM at peak concentrations for each dose group was computed from the slope and 90% confidence interval of the slope as shown in Table 10. The predicted mean ddQTcM at mean C_{max} of the therapeutic and supratherapeutic doses were 1.71 and 6.24 msec, respectively, and the upper bounds of the 90% CI were 2.50 and 9.11 msec. These results are consistent with the primary endpoint using the E14 method where the largest time-matched mean difference of the drug and placebo after baseline adjustment for the high dose for QTcM was 7.98 msec and the one-sided 95% upper bound is 12.27 msec (see Table 12 and Figure 12).

Table 10. FDA Analysis: Predicted Change in ddQTcM Interval at Peak Concentrations

Dose Group	Predicted change in ddQTcM interval (msec)	
	Mean	90% Confidence Interval
10 mg qd (steady-state)		
Mean Cmax (898 ng/ml)	1.71	0.92, 2.50
40 mg qd (single dose)		
Mean Cmax (3273 ng/ml)	6.24	3.36, 9.11

5.3. CLINICAL ASSESSMENTS

No deaths, serious adverse events, syncope or episodes of *torsades de pointes* were noted in this study.

1 subject in the ambrisentan group withdrew due to palpitations prior to being dosed on day 6. The sponsor states that the cause of the palpitations could not be determined.

There was a slight decrease in mean systolic BP at hour 1.5 on day 5 (-4.4 mmHg and day 6 (-3.5 mmHg) in the ambrisentan treatment group. There were similar decreases in mean diastolic BP at hour 1.5 on day 5 (-5.7 mmHg) and day 6 (-5.7 mmHg). There was an increase in heart rate at hour 1.5 on day 5 (3.1 bpm) and day 6 (5.1 bpm) in the ambrisentan treatment group.

6. APPENDIX

6.1. TABLE OF STUDY ASSESSMENTS

Table 11 Schedule of Observations and Procedures

Procedure	Screening (4 weeks) day -30 to -2	Treatment groups 1, 2, and 3									
		Check-in day -1	Baseline day 0	day 1	day 3	day 3	day 4	day 5	day 6	Discharge day 7	Study F/U day 14
Informed Consent	X										
Clinic Confinement		X	X	X	X	X	X	X	X	X	
Demographics	X										
Medical History	X										
Interim Medical History and How Do You Feel? (HDYF)		X								HDYF? only	HDYF? only
Physical Examination	X										X
Abbreviated Physical Examination		X								X	
Randomization		X									
Drug/Alcohol Screen[1]	X	X									
HIV and Hepatitis Panel	X										
Pregnancy Test[2]	X	X									X
Standard Safety ECGs[3]	X	X		X	X	X	X	X	X	X	X
Database ECGs (in triplicate)[4]			X	X				X	X	X	
Study Drug Administration				X	X	X	X	X	X		
PK Blood Collections[5]				X	X		X	X	X	X	
Safety Labs[6]	X	X				X				X	X
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X

[1] Screening (day -30 to day -2) drug screen did not include alcohol test. Check-in drug screen included alcohol test.
[2] Female subjects only. Serum pregnancy test administered at Screening; urine pregnancy test administered at Check-in and Study Completion.
[3] Standard safety ECGs performed at the following time points: at Screening, at Check-in, on day 1 at -0.25 and 1.5 hours postdose, on days 2 through 5 at 1.5 hours postdose, on day 6 at -0.25, 1.5, and 24 hours postdose (day 7); and on day 14.
[4] Database ECGs were recorded at the following time points: on day 0 (baseline) at -0.25, 1, 1.5, 2, 6, and 12 hours (where timing was based on respective dosing times for day 1); on days 1, 5, and 6 at -0.25, 1, 1.5, 2, 6, and 12 hours postdose; and 24 hours (day 7) following the last dose on day 6.
[5] Blood samples for PK analysis obtained for measurements of plasma concentrations of ambrisentan at the following time points: on days 1, 5, and 6 at -0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours postdose; on day 4 at -0.25 hours (predose).
[6] Blood and urine samples for safety laboratory measurements (serum chemistry, hematology and urinalysis) at the following time points: at Screening, at Check-in, day 3, day 7 (Discharge), and at Study Completion (Follow-up day 14).
[7] Vital signs (oral temperature, respiratory rate, and supine blood pressure and pulse) obtained at Screening, at Check-in, on day 1 at -0.25 and 1.5 hours postdose, on days 2 through 5 at 1.5 hours postdose, and on day 6 at -0.25, 1.5 and 24 hours postdose (day 7), and at Study Completion (Follow-up day 14).

Source: Reproduced from sponsor's Table 9.3 on page 35 in Report AMB-104

6.2. QTc Corrections

Figure 9 FDA Analysis: QTcF vs. RR on Day 0, 1, 5, and 6 for Ambrisentan, Moxifloxacin, and Placebo Treatment

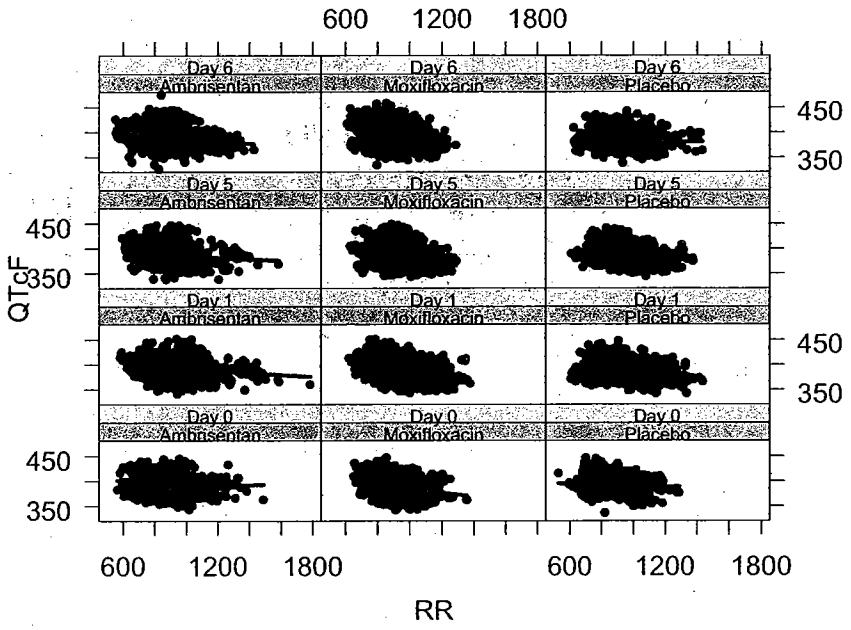


Figure 10 FDA Analysis: QTcIb vs. RR on Day 0, 1, 5, and 6 for Ambrisentan, Moxifloxacin, and Placebo Treatment

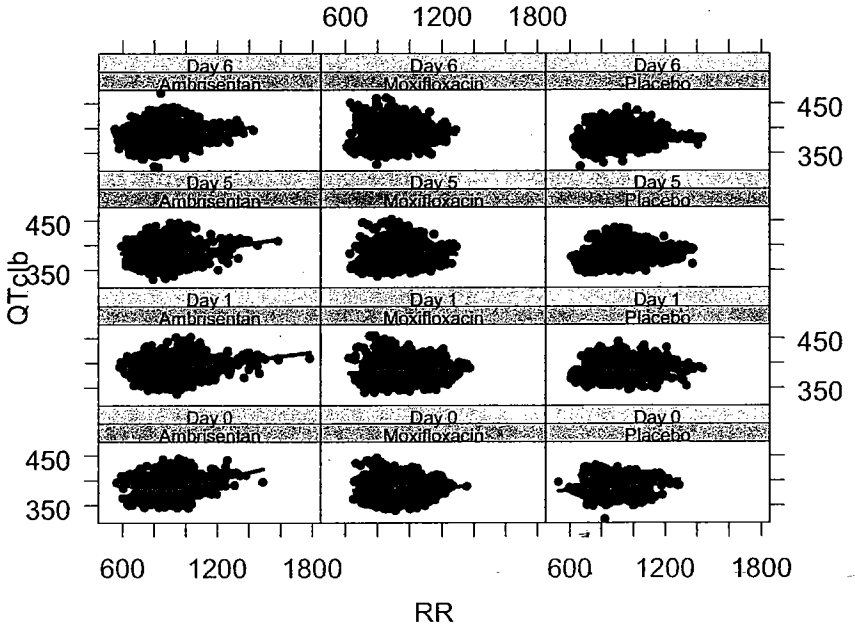
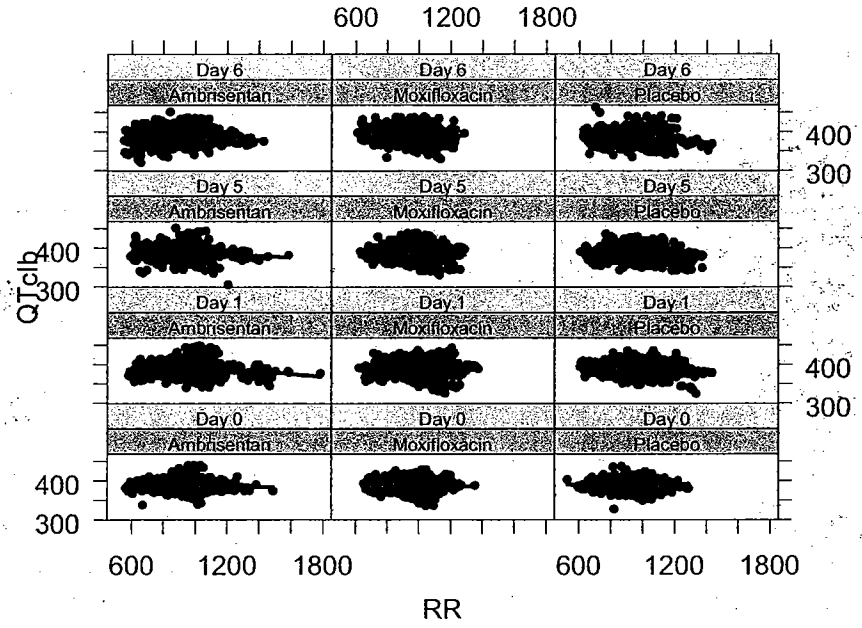


Figure 11 FDA Analysis: QTcM vs. RR on Day 0, 1, 5, and 6 for Ambrisentan, Moxifloxacin, and Placebo Treatment



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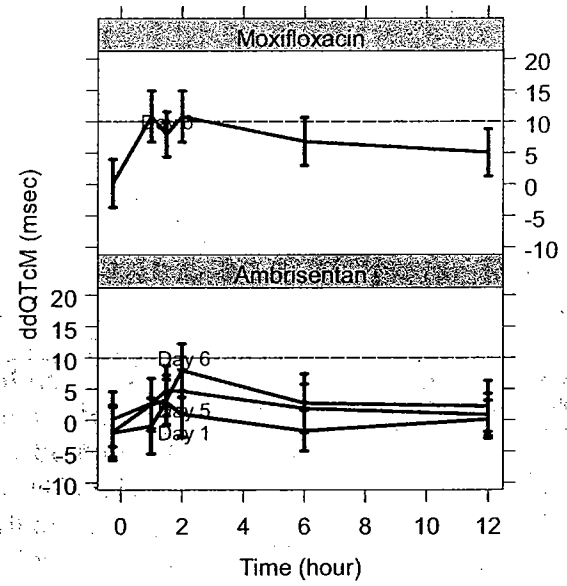
6.3. E14 ANALYSIS

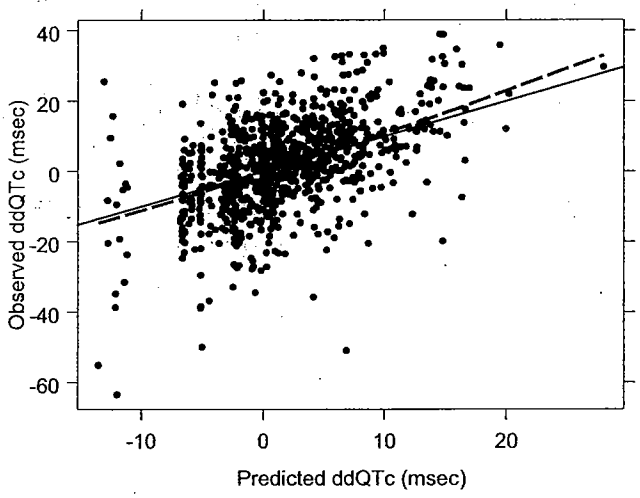
Table 12 FDA Analysis: E14 Time Matched Placebo-Adjusted Mean QTcM (90% CI) for Ambrisentan and Moxifloxacin

	Time point of maximum increase	Placebo time-matched change (msec)	AMB/Moxi time-matched change (msec)	Time-matched placebo-adjusted change (msec)		
QTcM		Mean	Mean	Point estimate	90% CI	All time points with upper bound of the 90% CI ≥ 10 msec (hr)
AMB	Day 1 Hour 1.5	2.70	5.60	2.90	-0.68, 6.48	-
AMB	Day 5 Hour 1.5	0.21	4.93	4.73	0.74, 8.72	-
AMB	Day 6 Hour 2	-1.95	6.03	7.98	3.69, 12.27	2
Moxi	Day 6 Hour 1	-2.71	8.09	10.80	6.71, 14.9	1, 1.5, 2, 6

Figure 12 FDA Analysis: E14 Time Matched Mean ddQTcM (90% CI) for Ambrisentan and Moxifloxacin



6.4. GOODNESS-OF-FIT PLOTS FOR LINEAR MODEL



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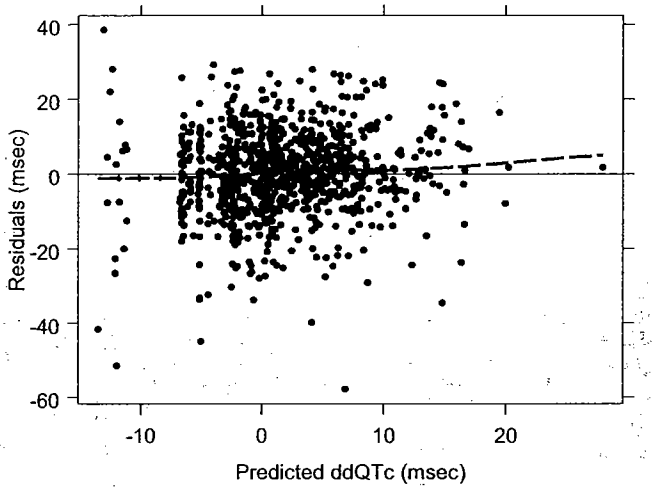
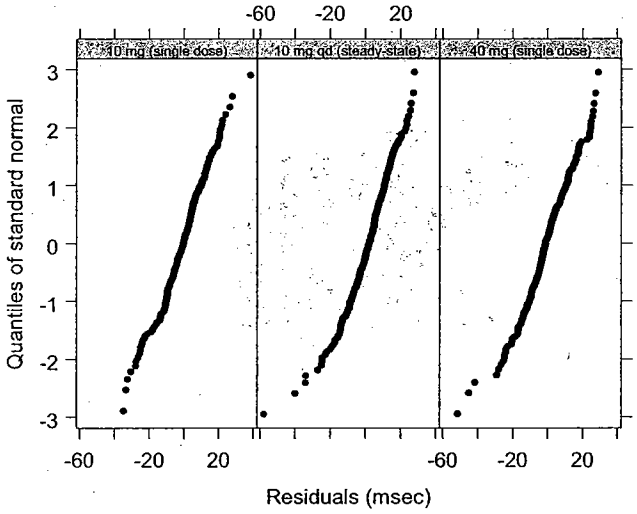
6.5. RESIDUALS VS. PREDITED DDQTCM



6.6. NORMAL PROBABILITY PLOT OF RESIDUALS STRATIFIED BY DOSE



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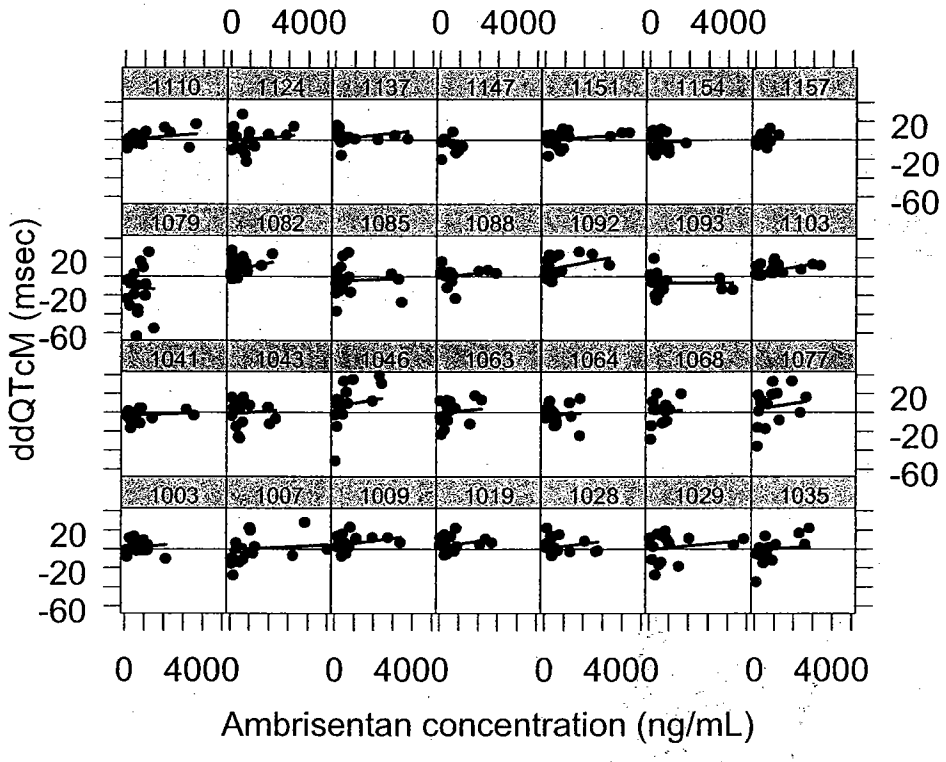
6.7. INDIVIDUAL DDQTCM VS. AMBRISENTAN PLOTS



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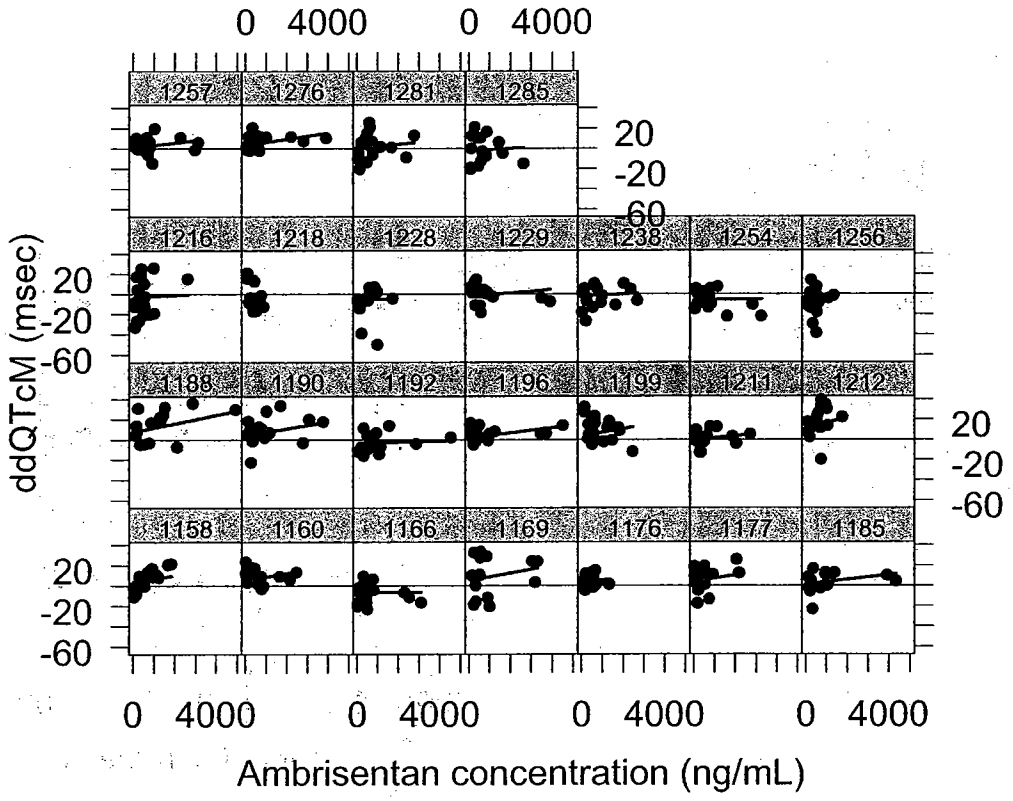

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22018**	**Brand Name**	**Letairis**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Ambrisentan**
Medical Division	**DCaRP**	**Drug Class**	**Endothelin-receptor antagonist**
OCPB Reviewer	**Peter Hinderling**	**Indication(s)**	**PAH**
OCPB Team Leader	**Patrick Marroum**	**Dosage Form**	**5 and 10 mg tablets**
		Dosing Regimen	**qd**
Date of Submission	**12-18-07**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review	**5-1-07**	**Sponsor**	**Gilead**
PDUFA Due Date	**6-18-07**	**Priority Classification**	**P**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X (Drug assay) PT and INR assay missing**			
I. Clinical Pharmacology				
Mass balance:	**X**			
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 1, 2:	x			
Phase 3:	x			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	19	19	19	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Provide information on PT and INR methods Study Report AMB-106 Provide readable Figures for Study Report EE-002
QBR questions (key issues to be considered)	**Interaction liability (impact of CYP inhibitors) Relevance of renal and hepatic function as covariates for exposure Activity of metabolites Rationale for QD dose regimen**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Peter Hinderling, 2-5-07**	
Secondary reviewer Signature and Date	**Patrick Marroum, 2-5-07**	

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

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Peter Hinderling
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Christoffer Tornoe
5/4/2007 04:45:23 PM
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Robert Kumi
5/7/2007 10:03:19 AM
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