CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION AMENDMENT

NDA #:	21-290
Related IND #:	[ ]
Applicant:	Actelion Ltd.
Name of Drug:	Tracleer™ (bosentan)
Indication:	Treatment for pulmonary arterial hypertension
Document reviewed:	Initial Study Report and electronic data set
Date of submission:	May 1, 2001
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Maryann Gordon, M.D. (HFD–110)

The purpose of this amendment is to review the results of the second pivotal study (AC-052-352). The results of this study were submitted by the sponsor after the initial NDA was filed. This study was designed to show that bosentan has an effect on change in walking distance in patients with primary arterial hypertension after 16 weeks of treatment.

Study AC-052-352 was conducted in fifteen centers in the US and twelve non-US centers including Israel, Australia and other countries in Europe and North America. Approximately half of all patients were from US centers. 214 patients with pulmonary arterial hypertension were randomized to one of three treatment groups (bosentan 125 mg b.i.d., bosentan 250 mg b.i.d., placebo) with equal probability. Patients in WHO functional Class III or IV were permitted to enroll in this study. Other baseline demographic characteristics are presented in Table 1. There does not appear to be any significant imbalance between the three groups with respect to these characteristics.

Table 1 Characteristics of all patients randomized in the three groups at baseline. For continuous variables, this table shows the group mean ± standard deviation. [*Source: Initial Report pp. 40,41, 45 Tables 5, 6, and 10 and reviewer's analysis*]

Characteristic	Bosentan 125 mg	Bosentan 250 mg	Placebo
N	75	70	69
Age (years)	50 ± 16	47 ± 16	47 ± 16
Gender (Male/Female)	18/ 57	13/ 57	15/ 54
Race (Caucasian/Black/Other)	58/ 5/ 12	54/ 7/ 9	59/ 1/ 9
Disease (Primary PH/ secondary PAH)	57/ 13	45/ 20	48/ 14
WHO Class (III/ IV)	69/ 6	62/ 8	65/ 4
Days from diagnosis to randomization	986 ± 1233	893 ± 1144	843 ± 1442
Distance walked at baseline (m) mean of last 2 measurements	327 ± 73	333 ± 75	344 ± 76

Patients who were randomized to either bosentan treatment group initially received 62.5 mg bid of the study drug. After 4 weeks, all patients were up-titrated to 125 mg or 250 mg b.i.d. of the study drug. This was the target dosage in the study, but could be down-titrated by half if drug-related adverse events were observed. Patients with body weight ≤ 40 kg were to receive half their target dose. Patients randomized to the placebo group were given the mathcing doses of placebo and titrated in the same way. Six-minute walking distances were measured twice before randomization as well as at four, eight, and sixteen weeks after randomization.

The primary efficacy variable is the change in distance walked from baseline to the end of the 16-week treatment period using a 6-minute walk test. The baseline distance is the average of the last two screening measurements where available. The last valid observation was carried forward for missing week-16 measurements. However, patients who died, underwent lung transplantation, or discontinued study medication due to worsening of pulmonary arterial hypertension and who did not have a valid assessment of 6-minute walk distance obtained at the time of premature withdrawal had a distance of zero meters assigned for the walk distance at the 16-week.

The primary analysis was the comparison of the two bosentan groups pooled together versus the placebo group using the Wilcoxon test. No adjustment was made for any covariates in this analysis.

After 16 weeks of double-blind treatment, patients in the bosentan groups showed a significant increase from baseline in distance walked. The results from the sponsor's analysis appear in Table 2. This analysis uses the ITT population. This population excluded one patient that was randomized in the bosentan 125 mg group who did not receive any study drug and had no post-randomization walking distances measured.

Table 2 Distance walked at baseline (average of 2 baseline measurements) and week 16 (mean ± standard deviation of distance measured in m). [*Source: Initial Report p. 45 Table 10*]

Characteristic	Bosentan 125 mg	Bosentan 250 mg	Placebo
Distance walked at baseline	326 ± 73	333 ± 75	344 ± 76
Distance walked at week 16	353 ± 115	380 ± 101	336 ± 130
Change from baseline to week 16	27 ± 75	46 ± 62	-8 ± 96
Difference between pooled bosentan groups and placebo group	mean=44	95% CI = (21, 67) p-value = 0.0002*	

The FDA reviewer verified the numbers in this table.

*Primary efficacy analysis using Wilcoxon test.

In the US centers alone, the results are consistent with the ITT analysis. The point estimate of the treatment effect is 36 m, the 95% confidence interval is (7, 64) and the p-value is 0.010.

Originally, the study was designed to have 80 patients in each of the three arms. However, based on the results of a separate study (Study 351), it was decided that the low dose was effective and that the two bosentan groups could be combined to gain power. Consequently, the planned target sample size was adjusted to 150. For reasons that were not made completely clear in the report, the investigators recruited more than this number at the end of the study. If only the first 150 patients randomized are analyzed, the results are consistent with the ITT analysis in Table 2. The point estimate of the treatment effect is 40 m, the 95% confidence interval is (14, 67) and the p-value is 0.006 [*Source: Initial Report Appendix 12*]

The summaries of the primary endpoint by race, age, and gender appear in Table 3. In each subgroup, the trend is in the direction of a positive treatment effect.

Table 3 95% confidence intervals for change in distance walked from baseline to week 16 (distance measured in m) among different subgroups. [*Source: FDA analysis*]

Subgroup	N	Bosentan (pooled) vs. Placebo	
		Mean difference	95% CI
Age <40	56	38.8	(2.6, 74.9)
Age between 40 and 59	102	58.3	(24.3, 92.3)
Age at least 60	55	22.1	(-18.7, 62.9)
Race: White	171	47	(20.5, 73.5)
Race: Black	13	27.5	(-102.8, 157.8)
Male	46	48.8	(-8.6, 106.1)
Female	168	43.1	(18.2, 68.0)

There were several pre-specified secondary endpoints analyzed by the sponsor. These results are reprinted here, but were not confirmed by the reviewer. The mean change in Borg dyspnea index for the pooled bosentan groups versus the placebo group showed an apparent treatment benefit [95% CI (-1.2 , -0.1), *Source: Table 10 of Initial Study Report*]. There was a numerical trend in favor of bosentan groups in the incidence of improvement in WHO functional class during the initial 16-week treatment period [95% CI (-2.9%, 25.2%), *Source: Table 10 of Initial Study Report*]. There appeared to be a significant benefit in the time to clincial worsening during the initial 16-week treatment period [p-value = 0.0038 from logrank test, *Source: Sec. 4.2.2.3 of Initial Study Report*].

According to the study report, the events that appeared to occur more frequently with bosentan than with placebo in the placebo-controlled studies include abnormal hepatic function (9.7% vs. 2.9%, respectively), syncope (9.0% vs. 5.8%) and flushing (9.0% vs. 4.3%). The incidence of abnormal hepatic function appearred to increase with

dose: 5.4% in the 125 mg group vs. 14.3% in the 250 mg group [*Source: Initial Report Table 18*]. Fourteen patients withdrew for clinical deterioration and the numbers were roughly equal in each group (3 in the 125 mg bosentan group, 6 in the 250 mg bosentan group, 5 in the placebo group) [*Source: Initial Report Table 22*]. There was one death during the 16-week treatment period in the 125 mg group, three deaths in the 250 mg group, and 2 deaths in the placebo group [*Source: Initial Report Table 19*].

Based on the two placebo controlled studies (AC-052-351 and AC-052-352), there appears to be persuasive evidence that 12 to 16 weeks of treatment of bosentan increases the change in walking distance relative to placebo ($p=0.020$ and $p=0.0002$). In the two studies combined, there were a total of 236 patients studied, and roughly 150 of these were assigned to bosentan treatment. Given this small amount of information, the incidence of abnormal hepatic function and flushing appeared to be greater in the bosentan groups in both studies. However, no other treatment related adverse events appeared to be associated with the use of bosentan 125 mg or 250 mg b.i.d. for 12 to 16 weeks.

/S/ 6/6/01

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This review consists of 5 pages of text, tables, and figures.

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STATISTICAL REVIEW AND EVALUATION

NDA #:	21-290
Related IND #:	[ ]
Applicant:	Actelion Ltd.
Name of Drug:	Tracleer™ (bosentan)
Indication:	Treatment for pulmonary arterial hypertension
Document reviewed:	Volumes 1-168
Date of submission:	November 17, 2000
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Maryann Gordon, M.D. (HFD–110)

1. Introduction

Bosentan is an endothelin receptor antagonist that has been studied in the United States and Europe for various indications, but has not been approved by the FDA. This NDA includes the results of one pivotal study (AC-052-351) that was designed to show that bosentan has an effect on change in walking distance in patients with primary arterial hypertension after 12 weeks of treatment. There are an additional two studies that provide information about the safety of bosentan in this population.

2.1 Study Design

Study AC-052-351 was conducted in five centers in the US and one in France. 32 patients with primary arterial hypertension (ambulatory adult patients with symptomatic, severe arterial hypertension) were randomized to bosentan or placebo in a 2:1 ratio. Although patients in WHO functional Class III or IV were permitted to enroll in this study, all patients who enrolled were class III at baseline. Other baseline demographic characteristics are presented in Table 2.1. There are differences in these characteristics that one would expect with such a small sample size.

Table 2.1 Characteristics of the patients in the two groups at baseline. For continuous variables, this table shows the group mean ± standard deviation. [*Source: Vol 1, p. 367 Table 4 and p. 369 Table 5 and verified by the reviewer*]

Characteristic	Bosentan	Placebo
N	21	11
Age (years)	52 ± 12	47 ± 14
Gender (Male/Female)	4/ 17	0/ 11
Race (Caucasian/Black/Other)	16/ 3/ 2	9/ 2/ 0
Disease (Primary PH/ PAH with scleroderma)	17/ 4	10/ 1
Time from diagnosis to randomization (days)	634 ± 528	1091 ± 1032
Distance walked at baseline (m) mean of 2 measurements	360 ± 86	355 ± 82

Patients who were randomized to the bosentan treatment group initially received 62.5 mg bid of the study drug. After 4 weeks, all patients were up-titrated to 125 mg bid of the study drug or placebo. This was the target dosage in the study, but could be down-titrated to 62.5 mg bid if drug-related adverse events were observed. Six-minute walking distances were measured twice before randomization as well as at four, eight, and twelve weeks after randomization.

3. Primary Efficacy Variable

The primary efficacy variable is the change in distance walked from baseline to the end of the 12-week treatment period using a 6-minute walk test. The baseline distance is the average of two screening measurements where available. The last valid observation was carried forward for missing 12-week measurements.

4. Secondary Efficacy Variables

Secondary efficacy variables included changes in distance walked at weeks 4 and 8, Borg dyspnea index, WHO functional class, clinical worsening (death, lung transplantation, discontinuation for clinical worsening), and various hemodynamic parameters.

5. Protocol Specified Planned Statistical Analysis

The primary analysis was the comparison of the two groups using Student's t-test. No adjustment was made for any covariates in this analysis. See Section 3 for details regarding the definition of the primary efficacy variable and how missing values were imputed.

6. Missing Observations

All 32 patients had two walking distances measured before randomization and the first post-randomization observation at Week 4. Two patients had no observation at week 8 (patients 10503 and 20101). These two patients were both in the placebo group. Six patients had no observation at Week 12 (patients 10105, 10110, 10404, 10503, 10505, and 20101). Of these six, only patient 10110 was in the bosentan group. Patients 10105, 10404, and 20101 withdrew from the study for clinical worsening. The last two walking distances for patient 10110 were 74 and 102 days after randomization. The first of these fell in the window for Week 8 and the latter did not fall in the window for Week 12. Similarly, patients 10503 and 10505 had their final walking distance measured after the window for the Week 12 visit expired. All patients with a missing Week 12 measurement had the last value carried forward with the exception of patient 20101.

According to the sponsor's study report, since patient 20101 had no valid post-randomization walk distance and the patient withdrew for clinical worsening, a week-12 distance of 0 m was imputed for this patient. The baseline walking distances for this

patient were 280 m and 255 m respectively taken 21 days and 1 day before randomization. The Week 4 distance for this patient was 250 m taken 30 days after randomization. Since this patient was in the placebo group, imputing a Week 12 distance of 0 in the analysis rather than carrying forward the last observed value will make the estimate of the treatment difference larger. The difference in the estimated treatment effect caused by the way that an individual missing observation is imputed is particularly pronounced because there are only 11 patients in the placebo group. The results of the analysis using the last value carried forward for this patient are contained in the next section.

7. Primary Analysis

After 12 weeks of double-blind treatment, patients in the bosentan group showed a significant increase from baseline in distance walked. The results from the sponsor's analysis appear in Table 7.1.

Table 7.1 Distance walked at baseline (average of 2 baseline measurements) and week 12 (mean ± standard deviation of distance measured in m). [*Source: Vol 1, p. 369 Table 5*]

Characteristic	Bosentan	Placebo
Distance walked at baseline	360 ± 86	355 ± 82
Distance walked at week 12	430 ± 66	350 ± 147
Change from baseline to week 12	70 ± 56	-6 ± 120
Difference between treatment groups	mean=76	95% CI = (12, 139) p-value = 0.020*

The FDA reviewer verified the numbers in this table.
*Primary efficacy analysis using Student's t-test.

Based on previous experience with similar data sets, baseline walking distance tends to be negatively correlated with change from baseline. The scatterplot of baseline walking distance versus change from baseline appears in Figure 7.1 (next page). In this scatterplot, only those 31 patients who had a valid post-randomization walking distance are included. The p-value for the slope is 0.005, which confirms that it might be useful to examine an exploratory analysis that adjusts for baseline distance. In addition, etiology of the disease has a significant impact on the primary efficacy variable. After adjusting for both baseline distance and etiology as well as the two-way interaction, the treatment effect remains significant (treatment effect= 72 m, p-value=0.011).

Although there appears to be a big difference in the two groups with respect to the number of days from diagnosis to randomization, this variable does not appear to be correlated with the primary efficacy variable (Spearman's rank correlation coefficient is –0.139). Therefore, no exploratory analysis was done that adjusted for this variable.

The primary analysis uses Student's t-test and the p-value is found under the assumption that the sample means are approximately normal. Because the sample sizes

are small, in hindsight it may have been better to use the non-parametric Wilcoxon test for the primary analysis or to use the permutation distribution to find the null distribution of the t-test statistic. There is very little difference in the p-values in this case, though (p=0.021 using the Wilcoxon test and p=0.017 using the permutation distribution of the t-test).

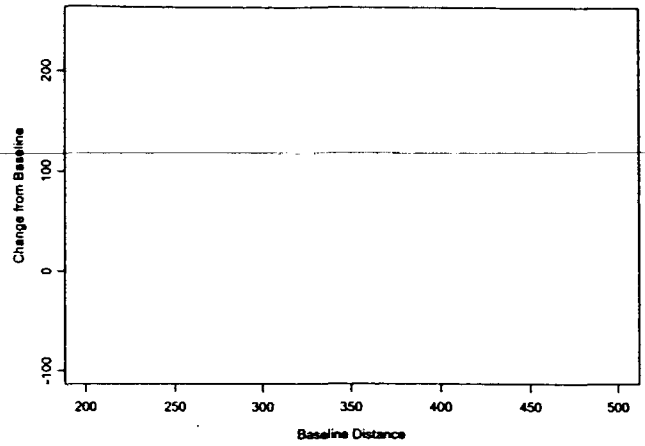

Figure 7.1 Scatterplot of baseline distance walked versus change from baseline.

Recall that patient 20101 discontinued from the study after the Week 4 visit for clinical deterioration and subsequently had a Week 12 walking distance of 0 m imputed. This patient's baseline walking distance was 267.5 m and their Week 4 distance was 250 m, a relatively minor decrease. If the last observed value is carried forward to Week 12 for this patient, then the mean change at Week 12 for the placebo patients is 16.9 with a standard deviation of 80. On the other hand, from Table 7.1, the mean change at Week 12 for the placebo patients is -6 when a value of 0 is imputed for this patient at Week 12. The p-value from the t-test remains significant (p=0.041) when the last observation is carried forward for patient 20101.

Each patient had two baseline walking distances measured. These two measurements were typically taken two or three days apart and the actual distances walked differed by about 7 m on average. Hence, it seems reasonable to average these two measurements to decrease the variance of the estimate of the change from baseline. However, it is also possible to analyze the data using only the last measurement before randomization. Table 7.2 contains the summary of the analysis using only the last distance walked before randomization. This has exactly the same information as table 6.1, except the analysis only uses the last baseline walking distance rather than averaging the two baseline measurements. There is almost no difference between the two tables; in particular, the p-value is 0.022 in Table 7.2 and 0.020 in Table 7.1.

Table 7.2 Distance walked at baseline (last measurement) and week 12 (mean ± standard deviation of distance measured in m). [*Source: FDA analysis*]

Characteristic	Bosentan	Placebo
Distance walked at baseline	365 ± 83	357 ± 85
Distance walked at week 12	430 ± 66	350 ± 147
Change from baseline to week 12	65 ± 55	-7.5 ± 118
Difference between treatment groups	mean=73	95% CI = (11, 135)
	p-value = 0.022 (Student's t-test)	

The treatment effect seemed to be consistent at each of the six centers. Figure 7.2 shows the mean change from baseline for each of the treatment groups at each of the six centers. The mean treatment difference was about 50 m in favor of the bosentan group at each center except center 102, where the difference was in favor of the placebo group. Clearly, with the very small number of patients involved here, it is not surprising to see some variation in the treatment effect at each center. However, it is reassuring to see that the apparent overall treatment effect is not driven by one or two particular centers.

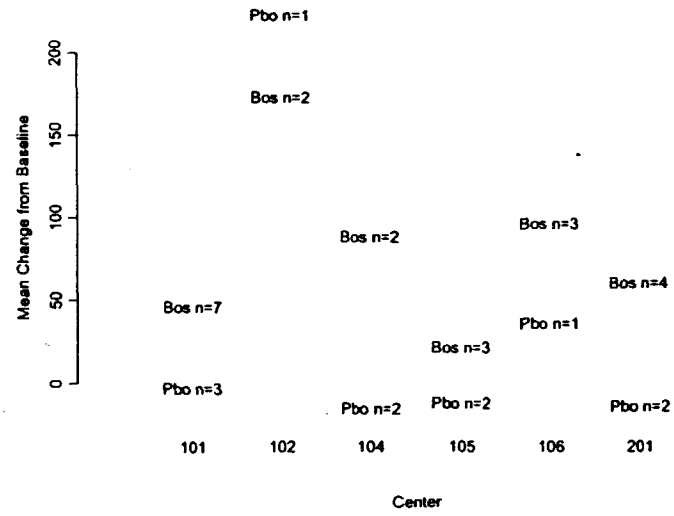

Figure 7.2 Mean change from baseline and number of patients at each center by treatment group. Note: the last observed walking distance (at week 4) was carried forward for patient 20101 to draw this figure.

8. Secondary Endpoints

The summaries for the secondary efficacy variables appear in Table 8.1. In all cases, these results show a trend toward a treatment benefit that supports the primary analysis.

Table 8.1 Secondary efficacy variables (count or mean ± standard error). [*Source: Vol 1, pp. 371-372 except first two rows*]

Characteristic	Bosentan	Placebo	p-value
Change in walking distance at Week 4	48 ± 8	30 ± 20	0.082[1]
Change in walking distance at Week 8	68 ± 14	-1.4 ± 36	0.026[1]
Change in Borg dyspnea index	-0.2 ± 0.4	1.4 ± 0.8	0.052[1]
# patients improving to WHO class II	9	1	0.106[2]
# patients with clinical worsening	0	3	0.033[2]
Change in PAP (mmHg)	-1.6 ± 1.2	5.1 ± 2.8	0.013[3]

The numbers in the first two rows were calculated and the remaining were verified by the FDA reviewer.
[1, 2, 3]P-values found from Student's t-test, Fisher's exact test, and nonparametric Wilcoxon test, respectively.

9. Adverse Events

According to the study report, the events that appeared to occur more frequently with bosentan than with placebo in the placebo-controlled studies include headache (14.3% vs. 10.5%), flushing (6.0% vs. 0.9%), abnormal hepatic function (4.9% vs. 1.8%), anemia (3.6% vs. 0.9%), and leg edema (3.8% vs. 0.0%). The incidences of flushing, headache, and leg edema appeared to be dose-related [*Source: Vol 1 p. 311*]. In Study AC-052-351, three patients withdrew for clinical deterioration- all three were in the placebo group. Moreover, there were no deaths during the 12-week treatment period of this study. Because of the small sample size, the information about clinical adverse events from this study alone is insufficient to make a meaningful assessment about safety.

10. Conclusions

Based on one placebo controlled study (Study AC-052-351) submitted with this NDA, there appears to be some evidence that 12-weeks of treatment with 125 mg bid of bosentan increases the change in walking distance relative to placebo (p=0.020 using the sponsor's imputation mthod). However, this is a small study with 32 patients and 19% missing values at Week 12. Depending on how the missing values are imputed, the nominal p-value will fluctuate. Since there is only one study with only 32 patients, this does not meet the FDA's usual standard of evidence for approval. Hence, the approval should depend on the results of the ongoing placebo controlled trial (Study AC-052-352)- that have not yet been submitted- and the medical officer's review of the overall safety database.

/S/ 3/23/01

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