CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-387
Drug Name:	Inhaled treprostinil sodium
Indication(s):	Treatment of pulmonary arterial hypertension
Applicant:	United Therapeutics Corporation
Date(s):	June 27, 2008
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
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Keywords: Nonparametric ANCOVA

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The primary endpoint of the study was change in exercise capacity at Week 12, as measured by the Peak 6MWD. A nonparametric analysis of covariance (ANCOVA), adjusted for baseline walk and disease etiology was performed for all patients. In the treated group, the median change from baseline was 22 m compared to a median improvement of 3 m in the placebo group (p=0.004, estimated difference of 20 m with a 95% confidence interval of (8, 33). According to the sponsor's study report, the treatment was well-tolerated and has an acceptable safety profile.

1.2 Brief Overview of Clinical Studies

This clinical program included 1 phase 3 safety and efficacy study. This was an international, double blind, multi-center, randomized, placebo controlled, parallel-group study in NYHA Class III and IV adult patients with severe PAH on a stable dose of 125 mg twice daily (BID) of bosentan or a stable dose of sildenafil for at least three months prior to study start. Patients were required to have a Baseline six-minute walk distance (6MWD) of 200-450 meters. This study consisted of a Baseline Visit and a Treatment Period, for a total of 12 weeks. The primary endpoint was the placebo corrected change in distance walked at 12 weeks compared to Baseline in the peak six-minute walk distance (6MWD). Peak 6MWT was assessed no less than ten minutes and no more than 60 minutes post study drug inhalation. All 6MWTs were scheduled to be performed 3-5 hours after the bosentan dose or 30 to 120 minutes after the sildenafil dose. These time periods correspond to the peak plasma concentrations for each of these concomitant therapies.

1.3 Statistical Issues and Findings

The primary endpoint, median change in 6MWD was analyzed using a nonparametric analysis of covariance (ANCOVA), with adjustment for etiology and baseline 6MWD. In the treated group, the median change from baseline was 22 m compared to a median improvement of 3 m in the placebo group (p=0.004, estimated difference of 20 m with a 95% confidence interval of (8, 33).

The secondary endpoints were analyzed in the following pre-specified hierarchy to control the Type I error rate: time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at Week 12, Peak 6MWD at Week 6, quality of life, signs and symptoms of PAH, and Peak 6MWD at Day 1. Four subjects in the treated group and 6 subjects in the placebo group experienced clinical worsening. There was no difference in the time to clinical worsening between treatment groups (p=0.5829).

2. INTRODUCTION

2.1 Overview

This clinical program included 1 phase 3 safety and efficacy study. This was an international, double blind, multi-center, randomized, placebo controlled, parallel-group study in NYHA Class III and IV adult patients with severe PAH on a stable dose of 125 mg twice daily (BID) of bosentan or a stable dose of sildenafil for at least three months prior to study start. Patients were required to have a Baseline six-minute walk distance (6MWD) of 200-450 meters. This study consisted of a Baseline Visit and a Treatment Period, for a total of 12 weeks. The primary endpoint was the placebo corrected change in distance walked at 12 weeks compared to Baseline in the peak six-minute walk distance (6MWD). Peak 6MWT was assessed no less than ten minutes and no more than 60 minutes post study drug inhalation. All 6MWTs were scheduled to be performed 3-5 hours after the bosentan dose or 30 to 120 minutes after the sildenafil dose. These time periods correspond to the peak plasma concentrations for each of these concomitant therapies.

The baseline demographics of the 235 patients studied are in Table 1. There do not appear to be any significant differences between the groups with respect to these variables. The mean age is about 55, the majority are female and NYHA Class III. About 2/3 were taking bosentan and the remainder were taking sildenafil as background therapy.

Table 1 Summary of demographics and other baseline data (ITT population).

Characteristic	Inhaled TRE (n = 115)	Placebo (n = 120)	Total (n = 235)
Age in Years: mean (range)	55 (20-75)	52 (18-75)	54 (18-75)
Gender: Male / Female (n)	22/93	22/98	44/191
PAH* Etiology: n (%)			
IPAH†	64 (56)	67 (56)	131 (56)
CVD‡	40 (35)	37 (31)	77 (33)
Other	11 (10)	16 (13)	27 (11)
Background PAH* Therapy: n (%)			
Bosentan	77 (67)	88 (73)	165 (70)
Sildenafil	38 (33)	32 (27)	70 (30)
Time on Background Therapy: Mean Weeks ± SD			
Bosentan	98 ± 79	90 ± 75	94 ± 77
Sildenafil	65 ± 60	77 ± 69	70 ± 64
Baseline NYHA§ Class: III / IV (n)	112 / 3	118 / 2	230 / 5
Baseline 6MWD¶: Mean ± SD (meters)	346 ± 63	351 ± 69	348 ± 66

* Pulmonary Arterial Hypertension

† Idiopathic Pulmonary Arterial Hypertension

‡ Collagen Vascular Disease

§ New York Heart Association

¶ 6-Minute Walk Distance

Source: p 53 of Study Report.

For the primary efficacy analysis of change in 6MWD at Week 12 in the ITT population, a non-parametric analysis of covariance (ANCOVA) was performed, with adjustment for baseline walk and disease etiology. An ordinary least squares regression was fit to the observed changes from baseline in distance walked at Week 1 Peak, Week 6 Peak, Week 12 Peak according to expanded windows and at Week 12 Peak according to the standard windows as a function of distance walked at baseline and disease etiology. Standardized ranks were calculated using the standardized residuals. Imputation was used for missing primary efficacy data. Lowest rank was assigned for death, discontinuation due to disease progression, and for patients in the study who initiated additional approved PAH therapy prior to the assessment. Last rank carried forward was assigned for adverse events or withdrawal of consent, and other reasons for missing assessments. The standardized ranks were re-calculated after imputation. Finally, the Cochran-Mantel-Haenszel mean score statistic and p-value were calculated to compare these standardized ranks between treatment groups. The median difference between treatment groups was determined by the Hodges-Lehmann estimate.

The secondary endpoints were analyzed in the following pre-specified hierarchy to control the Type I error rate: time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at Week 12, Peak 6MWD at Week 6, quality of life, signs and symptoms of PAH, and Peak 6MWD at Day 1. For clinical worsening, the p-value from the log-rank test was calculated. The changes in Borg dyspnea score would be compared using the Wilcoxon test. Changes in walking distance at other time points would be tested using similar methodology as the primary endpoint.

2.2 Data Sources

Electronic study reports (\\CDSESUB1\EVSPROD\NDA022387\0000) and data sets (\\cdsesub1\EVSPROD\NDA022387\0000\m5\datasets\lrx-triumph-001\analysis).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

For the primary efficacy analysis of change in 6MWD at Week 12 in the ITT population, a non-parametric analysis of covariance (ANCOVA) was performed, with adjustment for baseline walk and disease etiology. An ordinary least squares regression was fit to the observed changes from baseline in distance walked at Week 1 Peak, Week 6 Peak, Week 12 Peak according to expanded windows and at Week 12 Peak according to the standard windows as a function of distance walked at baseline and disease etiology. Standardized ranks were calculated using the standardized residuals. Imputation was used for missing

primary efficacy data. Lowest rank was assigned for death, discontinuation due to disease progression, and for patients in the study who initiated additional approved PAH therapy prior to the assessment. Last rank carried forward was assigned for adverse events or withdrawal of consent, and other reasons for missing assessments. The standardized ranks were re-calculated after imputation. Finally, the Cochran-Mantel-Haenszel mean score statistic and p-value were calculated to compare these standardized ranks between treatment groups. The median difference between treatment groups was determined by the Hodges-Lehmann estimate.

In both groups, about 90% of the subjects completed the study (see Table 2).

Table 2 Patient disposition

Study Disposition	Treatment		
	Inhaled Treprostinil n = 115	Placebo n = 120	Total n = 235
Completed Study n (%)	**102 (89)**	**110 (92)**	**212 (90)**
Did Not Complete Study n (%)	**13 (11)**	**10 (8)**	**23 (10)**
Death	0	1 (<1)	1 (<1)
Worsening PAH	3 (3)	0	3 (1)
Adverse Event	7 (6)	4 (3)	11 (5)
Withdrawal of Consent	3 (3)	5 (4)	8 (3)

Source: Study Report p. 48.

In the treated group, the median change from baseline was 22 m compared to a median improvement of 3 m in the placebo group (p=0.004, estimated difference of 20 m with a 95% confidence interval of (8, 33). Figure 1 shows a graph of the Observed Week 12 Peak values on the y-axis vs. the baseline values on the x-axis. Figure 2 shows the empirical cumulative distribution function for the observed changes from baseline to Week 12 Peak in both groups. I am not sure if this should really be called empirical distribution functions because missing values were excluded, but they are the observed values on the x-axis and the proportion of the observed values less than or equal to x on the y-axis; there is a jump of size 1/n at each observed value where n is the number of observed values in the group. Figure 3 shows boxplots of the standardized ranks of the residuals by treatment group, showing the active treatment group had a median larger than the placebo group.

Figure 1 Scatterplot of baseline values and observed Week 12 Peak distance walked (FDA analysis).

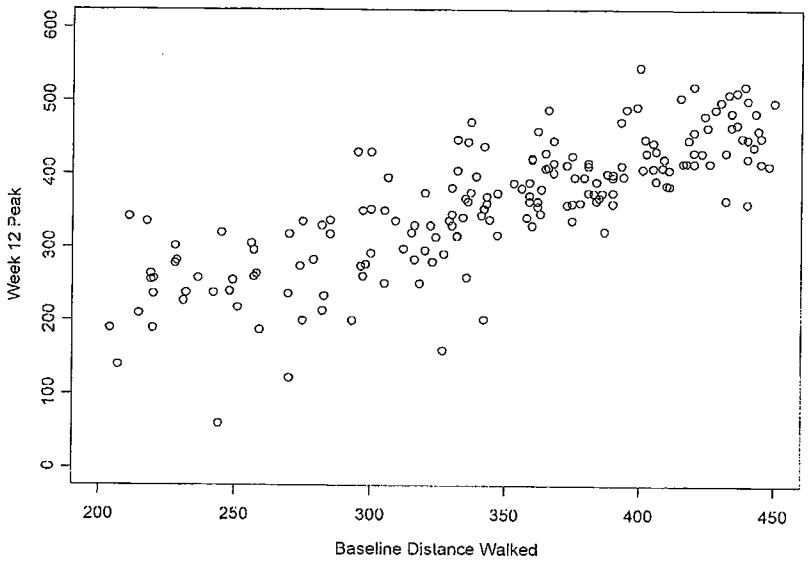


Figure 2 Empirical cumulative distribution function for both groups change in 6MWD from baseline at Week 12 Peak (FDA analysis).

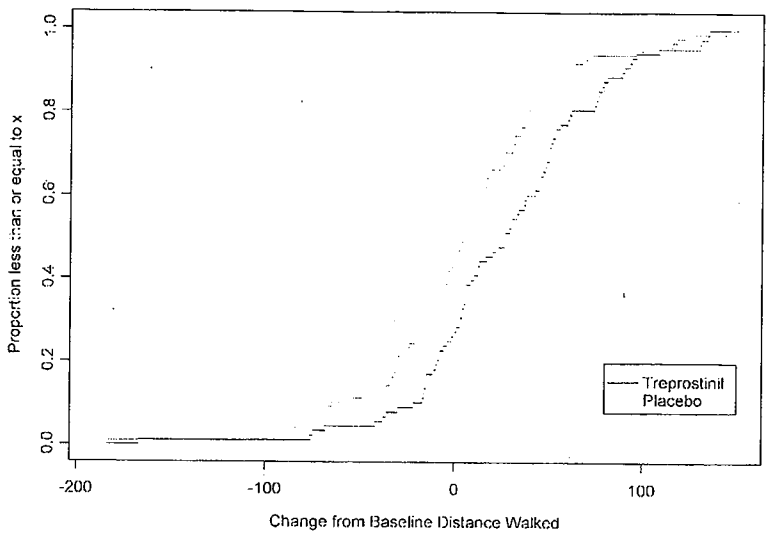
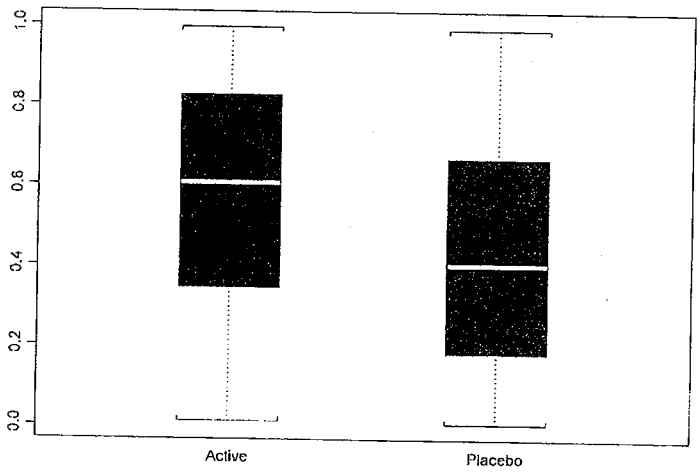


Figure 3 Boxplots of standardized ranks of residuals from regression at Week 12 Peak (FDA analysis).



There was no difference in the time to clinical worsening between treatment groups (p=0.5829). Therefore, none of the remaining secondary endpoints were tested or could be called statistically significant. No measurable median treatment effect on Borg dyspnea score (Hodges-Lehmann estimate of 0.0) was detected at any of the assessment periods (p=0.998 and p=0.623 at Weeks 6 and 12). Overall, there were no statistically significant difference in change in NYHA class between treatment groups (p= 0.807 at Week 12). There were no changes in signs and symptoms of PAH at Week 12. There was a small change in 6 minute walking distance at Week 12 trough and at Week 6 peak, but no change on Day 2 at peak.

3.2 Evaluation of Safety

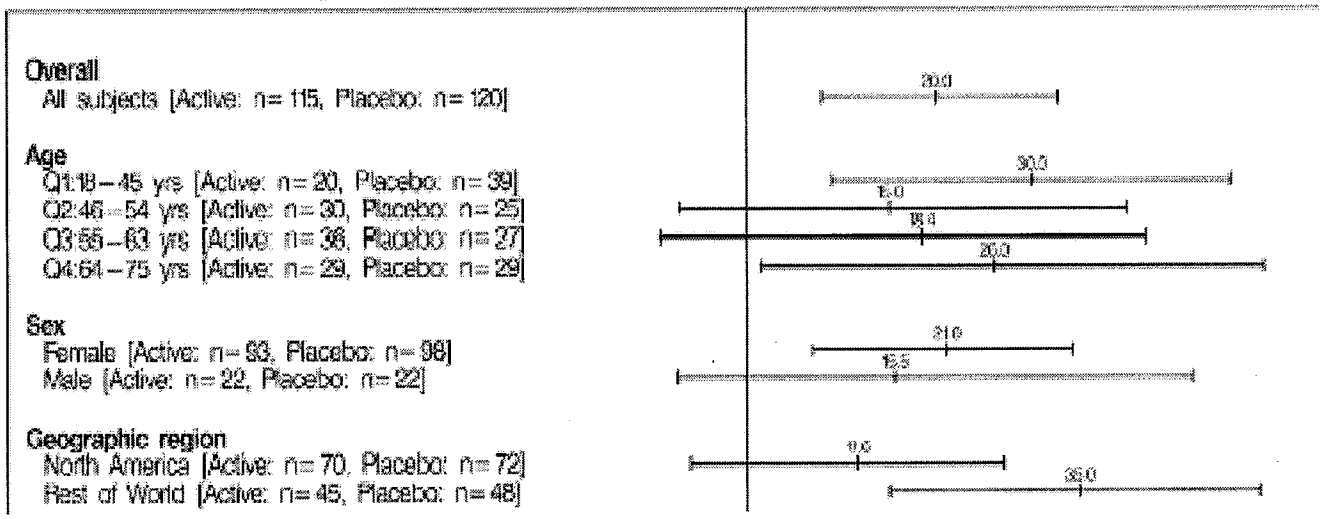
According to the sponsor's study report, the treatment was well-tolerated and has an acceptable safety profile. The most common adverse events in the treprostinil group were cough, headache, and nausea. Although less common, flushing and syncope also appeared to occur more often in the treprostinil group compared to placebo.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The difference in change in walking distance appeared to be consistent across age and gender subgroups (see Table 3). No analysis by racial subgroup was provided, possibly because almost all subjects were Caucasian.

Table 3 Patient disposition Sponsor's analysis of primary endpoint by subgroups.



Source: p 76 of Study Report.

4.2 Other Special/Subgroup Populations

The difference between treatment groups appeared to favor treprostinil in both North America and in the rest of the geographic regions combined (see Table 3).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary endpoint, median change in 6MWD was analyzed using a nonparametric analysis of covariance (ANCOVA), with adjustment for etiology and baseline 6MWD. In the treated group, the median change from baseline was 22 m compared to a median improvement of 3 m in the placebo group (p=0.004, estimated difference of 20 m with a 95% confidence interval of (8, 33).

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The primary endpoint of the study was change in exercise capacity at Week 12, as measured by the Peak 6MWD. A nonparametric analysis of covariance (ANCOVA), adjusted for baseline walk and disease etiology was performed for all patients. In the treated group, the median change from baseline was 22 m compared to a median improvement of 3 m in the placebo group (p=0.004, estimated difference of 20 m with a 95% confidence interval of (8, 33). According to the sponsor's study report, the treatment was well-tolerated and has an acceptable safety profile.

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