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
Office of Biostatistics

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)
Statistical Reviewer:	John Lawrence
Concurring Reviewers:	Jim Hung
Medical Division:	Division of Cariorenal Drug Products (HFD-110)
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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.

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