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APPLICATION NUMBER:

21-272

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #:	21-272
Applicant:	United Therapeutics Corporation
Name of Drug:	Uniprost™ (treprostinol sodium)
Indication:	Treatment for pulmonary arterial hypertension
Document reviewed:	Volumes 2.1, 2.24, and 2.27-2.50
Date of submission:	October 16, 2000
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Abraham Karkowsky, M.D. (HFD–110)

1. Introduction

Uniprost™, or UT-15, is a structural analog of epoprostenol (Flolan®) with a similar pharmacological profile. Flolan has been approved for the chronic treatment of patients with primary pulmonary hypertension and has been used to treat patients with pulmonary hypertension associated with other conditions. Unlike Flolan, Uniprost is chemically stable at room temperature and it has a longer half-life than Flolan. For these reasons, the sponsor believes that Uniprost would improve risks associated with treatment and should be considered as an alternative therapy for pulmonary arterial hypertension (PAH). There were two Phase III studies conducted by the sponsor to support the safety and efficacy of the treatment- Studies P01:04 and P01:05.

2. Study Design

The design of Studies P01:04 and P01:05 were identical. Each study was a multicenter, double-blind, parallel-group study. Patients between the ages of 8 and 75 were eligible for each study if they had a current documented diagnosis of PAH. On Day 1 of the Screening Period, routine baseline assessments were performed. On Day 2, the baseline Six-Minute Walk Test was administered. Patients whose baseline exercise capacity was less than 50 m or greater than 450 m were excluded from entering the Treatment Phase. Patients were randomized within strata determined by dichotomous levels of etiology of the disease (primary PH/ secondary PH) and baseline exercise capacity (low = 50-150 m/ high = 151-450 m). Randomization among patients with secondary PH was further stratified by use of vasodilators. The 12-Week Treatment Phase began immediately after baseline assessments and randomization on Day 2. Six-Minute Walk Tests were scheduled at Day 9, Day 44, and Day 87.

In order to select the sample size, an estimate of the expected treatment effect was made using data from a study using the active treatment Flolan. The treatment effect in

the Flolan study was an improvement of 45 m in change from baseline compared to placebo. Assuming a treatment effect for Uniprost of 55 m over placebo, it was expected that a sample size of 210 in a single study would provide a 95% chance of rejecting the null hypothesis at α=0.05. So, the actual sample sizes of 224 in Study P01:04 and 246 in P01:05 should have been adequate if the estimate of the treatment effect was reasonable.

Of the 470 patients randomized in both studies, 233 were assigned to receive the active treatment and 237 received the placebo. One patient assigned to the placebo group never received treatment. The remaining 469 patients constitute the modified Intent-To-Treat population (*mITT*). In the *mITT* population, the average age was 44.5, there were 382 females and 87 males, 396 Caucasians, 21 Blacks, 13 Asians, 33 Hispanics, 2 Native Americans, and 4 from a race other than those listed.

Patients received an initial dose of Uniprost or placebo of 1.25 ng/kg/min. This was the maximum allowable dose at the end of Week 1, but could be decreased to a tolerated dose. Following Week 1, patients were contacted weekly to assess whether changes in dosage were warranted. The dose was increased if symptoms did not improve and was reduced at the onset of any adverse experience that was judged to be related to study drug or there were changes in hemodynamics, vital signs, or clinical signs or symptoms that warranted reductions.

3. Primary Efficacy Variable

The primary endpoint of the two studies was change in exercise capacity at Week 12 as measured by distance walked in six minutes.

4. Secondary Efficacy Variables

Three principal reinforcing endpoints were prospectively identified: signs and symptoms of PAH, Dyspnea-Fatigue Rating, and an assessment of the occurrence of death, transplantation, or discontinuation from study drug due to clinical deterioration. Hemodynamics and Borg Dyspnea Score were defined as secondary endpoints.

5. Protocol Specified Planned Statistical Analysis

The primary analysis was a nonparametric analysis of covariance using the *mITT* population and the pooled data from the two studies. There is no provision for analyzing patients in the *mITT* population with no post-baseline walking distances. First, separate least squares regression models were fit to the Week 1, Week 6, and Week 12 distance walked as a function of baseline distance walked, center, etiology of PH (primary or secondary), and vasodilator use at baseline. On p. 30 of the Final Analysis Plan [Vol. 2.33] an additional covariate for use of steroids to treat PHT at baseline is included.

However, this covariate is not listed on p. 90 of the Study Report [Vol 2.27]. Standardized mid-ranks (also known as modified ridit scores), defined as rank/(# observations + 1), were determined from the residuals from the ordinary least squares regression. Missing values were imputed by carrying forward the standardized midrank from the last valid observation. The lowest standardized rank (0) was assigned to deaths, transplants, or clinical deterioration. Standardized mid-ranks were then recalculated and compared between treatment groups using the Cochran-Mantel-Haenzsel procedure mean score statistic with table scores stratified by the stratification factors used during randomization [*Source: Vol. 2.27 pages 88-92*].

According to a letter from the sponsor dated March 23, 2000, the analysis plan was modified slightly: if an exercise test is missing because "patient was too critically ill", the lowest standardized rank will be used for the nonparametric analysis.

The null hypothesis of no treatment difference was to be rejected if the two-sided p-value from the pooled analysis was less than 0.049 and both of the p-values from the individual studies were less than 0.049. This is the traditional standard for two confirmatory studies with an adjustment because the sponsor wanted to test the null hypothesis within the subgroup of PPH patients at α=0.001. If the global null hypothesis was not rejected, then the protocol states the null hypothesis would be rejected if the p-value from the pooled analysis was less than 0.01 and at least one of the analyses from a single study had a p-value less than 0.049. This gives the sponsor a second chance to reject the null hypothesis. This issue is discussed more thoroughly in Section 7.

6. Characteristics of Patients at Baseline and Dropouts

The baseline characteristics of the patients in the two treatment arms for the two studies are in Table 6.1. There was no significant difference between the two treatment arms with respect to any of these characteristics.

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Table 6.1 Characteristics of the patients in the two groups at baseline. For continuous variables, this table shows the group mean ± standard error of mean. [*Source: Vol. 2.27, Tables 11.2.1, 11.2.2.1, and 11.2.2.4*]

Characteristic	Uniprost Group	Placebo Group
N	233	237
Age (years)	44.6 ± 1	44.4 ± 1
Male (%)	15.5	21.6
Caucasian (%)	85	84
Years with PAH	4.3 ± 0.5	3.3 ± 0.4
NYHA Class II (%)	11	12
NYHA Class III (%)	82	82
NYHA Class IV (%)	8	7
Primary PH (%)	41	41
PAH associated with Scleroderma (%)	5	5
"" Limited Scleroderma (%)	6	3
"" Mixed Connective Tissue Disease (%)	3	4
"" Systemic Lupus Erythematosus (%)	3	8
"" Overlap Syndrome (%)	0.4	0.8
"" congenital systemic-to-pulmonary shunts (%)	25	22
Distance walked at baseline (m)	326 ± 5.5	327 ± 5.7

In the Uniprost group, 200 patients completed the 12 weeks of treatment. 6 patients discontinued due to clinical deterioration, 18 withdrew for adverse experiences, 7 died on study drug, and 2 withdrew consent. In addition to the 7 patients who died on Study Drug, 2 more patients died within 12 weeks from being randomized after they had withdrew from the study. A total of 13 patients withdrew for death, transplantation, or clinical deterioration [*Source: Vol. 2.27 Tables 10.1A, 11.4.1.2.3 and 12.5.5.*].

In the placebo group, 221 patients completed the 12 weeks of treatment, 6 patients deteriorated, 1 withdrew for adverse experiences, 7 died on study drug, 1 patient had a transplant, and 1 withdrew consent. In addition to the 7 patients who died on Study Drug, 3 more patients died within 12 weeks from being randomized after they had withdrew from the study. A total of 16 patients withdrew for death, transplantation, or clinical deterioration [*Source: Vol. 2.27 Tables 10.1A, 11.4.1.2.3 and 12.5.5.*].

In the *mITT* population, one patient did not have any exercise tolerance measurements post baseline, 455 patients had a Six-Minute Walk Test at Week 1, 468 patients had a Six-Minute Walk Test at Week 6, and 419 patients had a Six-Minute Walk Test at Week 12 [*Source: Vol. 2.27 Tables 11.4.1.1.2B, 11.4.1.1.4G, and 11.4.1.1.4H*].

7. Statistical Comments About the Analysis Plan

The decision to impute a worst possible score for those patients who died or discontinued for transplantation or clinical deterioration is reasonable. A nonparametric

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