

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-444/S003

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION --- NDA

NDA #: 20-444/S-003

Date: **MAY 24 1999**

Drug Class: 1P

Applicant: Glaxo Wellcome Inc.

Name of Drug: Flolan (epoprostenol sodium) for Injection

Indication: Treatment of Secondary Pulmonary Hypertension

Documents Reviewed: NDA Vol. 1, 3-10, 12-15 Dated December 11, 1998
SAS data sets Dated April 26, 1999
SAS data sets Dated May 6, 1999

User Fee Date: 6/11/99 (6 months)

Statistical Reviewer: Milton C. Fan, Ph.D.

Medical Reviewer: This review has been discussed with medical officer,
Kathy Robie-Suh, M.D.

Key Words: one study, nonparametric covariance analysis

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A. Background

Epoprostenol sodium injection has been approved for the long-term intravenous treatment of primary pulmonary hypertension (PPH) in NYHA Class III and Class IV patients. Due to the similar histopathology and clinical presentation of primary pulmonary hypertension and secondary pulmonary hypertension, the sponsor performed a 12-week open label multi-center clinical trial to assess the safety and efficacy of epoprostenol sodium injection in pulmonary hypertension (PH) secondary to the scleroderma spectrum disease (SSD).

In the current NDA, the sponsor seeks approval of epoprostenol sodium for injection for treatment of secondary pulmonary hypertension in patients refractory to conventional therapy.

The sponsor has submitted one controlled efficacy study (VA1A4001) in support of the proposed claim.

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B. Protocol VA1A4001

1. Description of Study

This study was a US and Canadian based multicenter (17 investigators), open-label, randomized, parallel trial to evaluate the efficacy and safety of epoprostenol sodium infusion plus conventional therapy (hereafter referred to as epoprostenol therapy) compared to conventional therapy alone (hereafter referred to as conventional therapy) in patients with pulmonary hypertension secondary (SPH) to SSD.

The primary objective of this study was to show epoprostenol therapy was superior to conventional therapy on exercise capacity.

Patients with moderate to severe SPH/SSD were enrolled into study. The study consisted of screening, baseline and treatment phase. Patients meeting all inclusion and exclusion criteria during the screening phase would enter the baseline phase during which exercise capacity, cardiopulmonary hemodynamic parameters, clinical signs and symptoms of pulmonary hypertension, Raynaud's severity, and presence of digital ulcers would be measured.

Following completion of the baseline phase assessments for each patient, study personnel contacted _____, an independent consultant in biomedical product development and received the randomization assignment. Randomization code was computer generated at _____. The code itself was known only to them and unblinding during the treatment phase could only be performed by _____ staff assigned to the study. Patients then would be randomized (1:1) to receive either epoprostenol sodium plus conventional therapy or conventional therapy alone for 12 weeks. The assignment of patients to study drug was based on a stratified randomized block design. Treatment assignments were stratified by vasodilator use (yes/no) at baseline, and exercise capacity at baseline (50 to 200 meters, > 200 meters), and randomized within blocks. Within each stratum, the block size was 4.

Since the study was open label, the treatment number and the actual treatment was disclosed to the site. As sponsor claimed, each site was instructed to blind the assessment of the primary endpoint, exercise capacity. A designated individual at each site was given information in the proper administration of the 6-minute walk test and was not aware of the patient's treatment assignment. All attempts were made to maintain the same tester with the same patient throughout the study. To further ensure that the tester remained blinded, all patients wore an ambulatory pump and a loose hospital gown over their clothes to mask the presence or absence of a chronic indwelling catheter during all 6-minute walk tests.

Each patient returned to the study center on Weeks 1, 6, and 12. Throughout the 12-Week treatment phase, all patients received conventional therapy at doses deemed appropriate by the investigator. Patients randomized to epoprostenol therapy were administered continuous infusion of epoprostenol sodium at doses based on clinical signs and

symptoms. During the 12-Week Treatment Phase, exercise capacity, Dyspnea-Fatigue Rating, Borg Dyspnea Score, NYHA Function Class, cardiopulmonary hemodynamic parameters, Raynaud's severity, and the formation of new digital ulcers were assessed at scheduled visits.

At the end of the treatment phase, all patients were dismissed from the study. Patients who completed the assessments at Week 12 were given the option to epoprostenol therapy through an open-label extension study (VA1A4002).

The primary measure of efficacy was exercise capacity as measured by the distance walked in meters during the 6-minute walk test after 12 weeks of study drug treatment. Data for the primary endpoint were analyzed using a nonparametric covariance analysis. In addition, a parametric analysis of covariance was also performed.

The secondary measures of efficacy were cardiopulmonary hemodynamic measures, clinical signs and symptoms of pulmonary hypertension (PH), clinical signs and symptoms of the scleroderma spectrum of disease (SSD), and survival. The difference between treatment groups in mean change in cardiopulmonary hemodynamic parameters from baseline to Week 12 was constructed with a two-sided, 95% confidence interval (C.I.) using Student's t distribution. Data from other endpoints (clinical signs and symptoms of PH, clinical signs and symptoms of SSD) were analyzed by determining the change from baseline to Week 12 between the two treatment groups and constructing a two-sided, 95% C.I. using a Wilcoxon Rank Sum Test statistic. Survival data were analyzed using a log-rank test.

In a previous sponsor study of the effects of 12 weeks infusion of epoprostenol sodium in patients with PPH, 6-minute walk test results indicated that conventional therapy patients decreased an average of 7.8 meters from baseline (standard deviation of 105.22), while epoprostenol therapy patients increased an average of 34.1 meters from baseline (standard deviation of 67.9 meters). Assuming standard deviation of 68 and 105 meters for the two treatment groups, 50 patients per treatment group would provide 80% power to detect a difference of 50 meters in the average change from baseline for the 6-minute walk test at the 0.05 level using a two-tailed t-test.

2. Sponsor's Analysis

One hundred and sixteen (116) patients were enrolled in the study. One hundred and eleven patients (111) were randomized in the study: 56 in epoprostenol therapy group and 55 in conventional therapy group.

Five patients (4 in epoprostenol therapy group and 1 in conventional therapy group) were placed in the wrong randomization strata because of incorrect information given to _____ at the time of randomization. Epoprostenol therapy patients (06306 and 01307) were randomized to the ≥ 200 meter baseline walk stratum, but only walked 187.5 and 192.0 meters, respectively, at baseline. Conventional therapy patient (06310) was randomized to the <200 meter baseline walk stratum, but walked exactly 200. Epoprostenol therapy patients (08301 and 15307) were randomized to the strata for no vasodilator use at baseline. Both of these patients were taking a vasodilator

at baseline. For the purpose of analysis, patients were assigned to the strata according to the actual data results.

There were four deaths in epoprostenol therapy group and five deaths in conventional therapy group. One patient in the epoprostenol therapy group withdrew prematurely from the study. Two patients in the conventional therapy group prematurely discontinued their participation in the study.

Efficacy analysis was based on the Intent-to-Treat (ITT) population. ITT population included all patients who received any amount of study drug, including conventional therapy.

2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline is given in attached Table 1. As seen from attached Table 1, the demographic and baseline characteristics were similar between two treatment groups with regard to age, sex, race, height, weight, vasodilator use, baseline walk category, SSD diagnosis, history of PH, and history of SSD at baseline except MYHA functional class.

2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary measure of efficacy was exercise capacity as measured by the distance walked in meters during the 6-minute walk test after 12 weeks of study drug treatment.

Treatment differences in exercise capacity were evaluated using a nonparametric covariance analysis. Specifically, a Cochran-Mantel-Haenszel correlation statistic was used on the residuals from an ordinary least squares regression of the ranks of the distance walked.

Using this methodology, an ordinary least squares regression was fit to the Week 12 distance walked using all available walk data. The following conditions were applied:

- a). For Week 12, the rank of the distance walked was used in the linear regression.
- b). For Week 12, patients who could not walk due to the severity of their disease or death, were assigned the lowest rank. This assumed that patients who could not walk due to the severity of their disease were worse than those patients who walked, regardless of the actual distance walked.
- c). For Week 12, other reasons for missing values for the distance walked (e.g., lost to follow-up, unable to walk due to leg amputation) were set to missing.
- d). Rank of baseline walk was included as covariates in the linear regression.

- e). The Cochran-Mantel-Haenszel correlation statistics was calculated on the actual residuals.

This analysis was repeated using 6-minute walk test data from Week 1 and Week 6. A parametric analysis of covariance was also performed on the 6-minute walk test scores. Additionally, if a patient could not walk at Week 12, either due to severity of disease or death, then the Week 12 value was assigned the distance at Week 1 or Week 6, whichever was the last walk data collected for that patient.

The results from the nonparametric analysis of covariance are shown below:

**Treatment Comparisons of the 6-Minute Walk Exercise Test (Meters)
(Nonparametric Analysis of Covariance)**

Week	n	Conventional Therapy		n	Epoprostenol Therapy		p-value*
		Baseline Median (m)	Median (m)		Baseline Median (m)	Median (m)	
1	55	240.0	238.0	55	270.0	265.0	0.4178
6	53	240.0	235.5	53	270.0	290.0	0.0028
12	53	240.0	192.0	55	270.0	316.0	<0.0001

Copied from Table 23, page 125, Vol. 3.

*Adjusted for baseline walk category and baseline vasodilator use category.

As seen from the table above, although at Week 1 there was no treatment difference in exercise capacity, at Weeks 6 and 12, the exercise capacity of patients in the epoprostenol therapy group was statistically significantly greater than those of patients in the conventional therapy group.

The results of parametric analysis of covariance on the 6-minute walk test scores are given in attached Table 2. As seen from attached Table 2, the parametric analysis yielded similar results at Weeks 6 and 12. In addition, at Week 1, there was also a statistical difference in exercise capacity between treatment groups.

2.3 Sponsor's Analysis of Secondary Efficacy Variable

2.3.1 Cardiopulmonary Hemodynamic Parameter

Cardiopulmonary parameters measured during this study (heart rate, SAP, RAP, PAP, CI, CO, PCWP, SvO₂, SaO₂, and PVR) are summarized in attached Table 3.

As seen from attached Table 3, statistically significant improvement in pulmonary-arterial pressure (PAP), pulmonary vascular resistance (PVR), right arterial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SvO₂) occurred in patients in

the epoprostenol treatment group compared to patients who received conventional therapy.

2.3.2 Clinical Signs and Symptoms of Pulmonary Hypertension (NYHA Class, Dyspnea-Fatigue Rating, and Borg Dyspnea Score)

Clinical signs and symptoms of PH were evaluated by measuring NYHA functional class, Dyspnea-Fatigue Rating, and Borg dyspnea score.

The results of analyses of NYHA functional class changes from baseline at Weeks 1, 6, and 12 are summarized in attached Table 4. As seen from attached Table 4, there was no significant difference in the median change in NYHA function class between treatment groups.

The results of analyses of the Dyspnea-Fatigue Rating changes from baseline to Weeks 1, 6, and 12 are summarized in attached Table 5. As seen from attached Table 5, the analysis of the median change from baseline to Weeks 1, 6, and 12 of the Dyspnea-Fatigue Rating showed a statistically significant improvement in the epoprostenol therapy group, compared to a decline in the conventional therapy group.

The results of analyses of Borg Dyspnea Scores changes from baseline at Weeks 1, 6, and 12 are summarized in attached Table 6. As seen from attached Table 6, analyses of the median change from baseline to Weeks 1, 6, and 12 of the Borg Dyspnea Scores showed significant statistical improvement for the epoprostenol therapy group over the conventional therapy group.

2.3.3 Clinical Signs and Symptoms of the Scleroderma Spectrum of Disease

Clinical signs and symptoms of SSD were determined by Raynaud's Severity Scores, as well as by evaluating digital ulcers and ischemic demarcations.

The results of analyses of Raynaud's Severity Scores changes from baseline at Weeks 6 and 12 are summarized in attached Table 7. As seen from attached Table 7, the Raynaud's Severity Score decreased in both treatment groups during the 12-week study. There was no significant difference in the median change from baseline to Weeks 6 and 12 of Raynaud's Severity Scores between treatment groups.

The results of analyses of digital ulcers and ischemic demarcations changes from baseline at Weeks 6 and 12 are summarized in attached Table 8. As seen from attached Table 8, there was no significant difference in the median change from baseline to Weeks 6 and 12 of digital ulcers and ischemic demarcations between treatment groups.

2.3.4 12-Week Survival

Four patients in the epoprostenol therapy group died during the course of the 12-week study, five patients in the conventional therapy group died during the same time period. There was no statistical significance in survival between treatment groups.

2.3.5 Safety

The incidence of adverse events occurred more frequently in the epoprostenol therapy group than in the conventional therapy group. Jaw pain, headache, and diarrhea occurred frequently in the epoprostenol therapy patients. General pain, flushing, vomiting, nausea, and rash occurred less frequently, but predominantly in the epoprostenol therapy patients. Anorexia and skin ulcers occurred in both treatment groups, but were reported in a greater percentage of epoprostenol patients.

3. Reviewer's Evaluation

3.1 Reviewer's Comments on Sponsor's Treatment Assignment

In this study, treatment assignments were based on a stratified randomized block design. Randomization was stratified by vasodilator use (yes/no) at baseline, and exercise capacity at baseline (50 to 200 meters, ≥ 200 meters). Randomization was not done within each study center. This caused imbalance problems on treatment assignment within some stratum and within some center. In stratum of vasodilator use (yes) at baseline and exercise capacity at baseline (≥ 200 meters), there were no patients assigned to epoprostenol therapy group and five (5) patients to conventional therapy group in site 13. Within center there were 5 of 17 (29%) centers with slight imbalance in treatment assignment with the difference of number of patients assigned treatments greater than 3 (see Attached Table 9). The imbalance in treatment assignment within center might cause the slightly imbalance in treatment group comparability in sex, age, weight, and NYHA function class.

Furthermore, this reviewer found that nine patients instead of five patients, as the sponsor claimed, were placed in the wrong strata. So, these nine patients were not randomized correctly. This led to assignment of 6 patients in epoprostenol therapy group and 3 patients in conventional therapy group. It seems the randomization was problematic.

3.2 Reviewer's Comments on Sponsor's Nonparametric Covariance Analysis

Nonparametric covariance analysis was discussed in detailed recently by Gary Koch in "Methodological Advances and Plans for Improving Regulatory Success for Confirmatory Studies" and "Issues for Covariance Analysis of Dichotomous and Ordered Categorical Data from Randomized Clinical Trials and Non-parametric Strategies for Addressing Them" which appeared in *Statistics in Medicine*, 17, 1675-1690 and 1863-1892, respectively, 1998.

The principal advantages of nonparametric methods are that their use does not involve any formal assumption (since randomization in the study is their basis), determination of exact p-value for their test statistics is possible (through corresponding permutation distributions), and their structure for adjusting for strata and/or covariables does not need any modification to address heterogeneity of treatment differences with strata of covariables.

3.3 Reviewer's Comments on Sponsor's Analysis of Primary Endpoint

3.3.1 Reviewer's Analysis of Exercise Capacities at Week 12

There were slightly disproportional number of patients who had exercise capacities data available at Week 12 (50 for epoprostenol therapy and 44 for conventional therapy, $p=0.174$).

In the sponsor's nonparametric analysis of covariance, patients who could not walk due to severity of their disease or death, were assigned the lowest rank. In the sponsor's parametric analysis of covariance, last observation carried forward (locf) method was used for imputing missing value at Week 12. These analyses were based on some kind of imputation for missing observation. Furthermore, all these analyses did not include all randomized patients.

To see whether there was bias in the sponsor's analyses, this reviewer performed alternative analysis of change from baseline based on available data using the t-test. The results are given below.

Reviewer's Analysis of Exercise Capacities at Week 12

		Change from Baseline				
Conventional Therapy		Epoprostenol Therapy				
n	Mean	Std. Error	n	Mean	Std. Error	p-value.
44	-40.7	12.31	50	42.9	15.12	0.00006

Copied from Table 25, page 127, Vol. 3.

P-value was obtained by the reviewer using t-test.

As seen from table above, epoprostenol therapy was significantly better than conventional therapy in terms of exercise capacities at Week 12 from the unadjusted analysis.

3.3.2 Reviewer's Analysis of Exercise Capacities at Week 12 Adjusting for Age

There was slightly imbalance in treatment group comparability in age ($p=0.055$). To see whether there was age effect on exercise capacities at Week 12, this reviewer performed parametric analysis of covariance based on available data on the change from baseline for 6-minute walked distance at Week 12. This model included age and interaction between age and treatment as factors in addition to treatment, walked distance at baseline and

vasodilator use at baseline. It was found that age had significant effect on exercise capacities at Week 12 ($p=0.0257$). The resulting p-value for between treatment groups was 0.0526 slighter greater than 0.05 significance level. The p-value for interaction between age and treatment was 0.2170 slighter greater than a 0.20 significance level often use for testing interaction. If the model did not include interaction term, the p-value for between treatment groups became 0.0003 highly significant.

After adjusting for age and interaction between treatment and age, the treatment effect became just borderline. So, the result of using alternative analyses of changes from baseline on exercise capacity at Week 12 might not be robust.

3.3.3 Exercise Capacities at Week 12 by Site

This reviewer tabulated the change of 6-minute walked distance at Week 12 from baseline by site based on available data. The table is given below.

Reviewer's Analysis of Exercise Capacities at Week 12 by Site

Site	Change from Baseline				p-value*
	Conventional Therapy		Epoprostenol Therapy		
n	Mean	n	Mean		
1	4	-47.75	3	-7.67	0.5959
2	4	51.75	2	86.00	0.4875
3	2	-10.00	8	68.49	0.2400
6	4	-89.75	5	86.40	0.0373
7	5	17.60	3	123.33	0.2330
9	2	-83.00	5	104.80	0.0814
10	2	15.25	1	-50.50	0.5403
13	6	-42.58	1	29.00	0.2113
14	3	-112.90	1	72.10	0.3711
15	1	-178.00	6	62.17	0.2113
17	1	-95.00	3	29.33	0.3711
21	4	-61.75	5	-50.70	0.3913
22	2	-102.85	1	-16.80	0.5403
23	3	1.00	2	-26.50	1.0000

Compiled by the reviewer.

*P-value was obtained by the reviewer using Wilcoxon test.

As seen from the table above, 6-minute walk test results in favor of epoprostenol therapy were not consistent across sites. The average of change from baseline for 6-minute walk distance for sites ranged from -178.0 to 51.75 meters for conventional therapy and from -50.50 to 123.33 for epoprostenol therapy. It also indicated that conventional therapy patients decreased their 6-minute walked distance at Week 12 in 10 of 14 sites, while epoprostenol therapy patients increased their 6-minute walked distance at Week 12 in 9 of 14 sites.

3.3.4 Exercise Capacities at Week 12 by Strata

This reviewer tabulated the change of walked distance at Week 12 from baseline by strata based on all available data. The table is given below.

Reviewer's Analysis of Exercise Capacities at Week 12 by Strata

Vasodilator Use	Strata Baseline walk distance	Change from Baseline				p-value [*]
		Conventional Therapy		Epoprostenol Therapy		
		n	Mean	n	Mean	
No	<200 meters	2	100.0	5	52.84	0.5613
No	≥ 200 meters	10	-76.38	10	65.41	0.0036
Yes	<200 meters	6	0.83	9	67.63	0.1116
Yes	≥ 200 meters	26	-47.33	26	23.86	0.0024

Complied by the reviewer.

*P-value was obtained by the reviewer using Wilcoxon test.

As seen from the table above, 6-minute walk test results in favor of epoprostenol therapy were not consistent across strata. The average of change from baseline for 6-minute walked distance for strata ranged from -76.38 to 100.0 meters for conventional therapy and from 23.86 to 67.63 for epoprostenol therapy. It also indicated that conventional therapy patients decreased their 6-minute walked distance at Week 12 in 2 of 4 strata, while epoprostenol therapy patients increased their 6-minute walked distance at Week 12 in all 4 strata. The superiority of epoprostenol therapy was only indicated in 3 strata. There might be numerical difference in favor of conventional therapy against epoprostenol therapy for the stratum of use of vasodilator (no) at baseline and baseline walk category (<200 meters). But, due to small sample size, the result would be inconclusive.

3.3.5 Exercise Capacities at Week 12 by Baseline Walk Category

This reviewer tabulated the change of walked distance at Week 12 from baseline by baseline walk category (<200 meters or ≥ 200 meters) based on all available data. The table is given below.

Reviewer's Analysis of Exercise Capacities at Week 12 Baseline Walk Category

Baseline walk category	Change from Baseline				p-value [*]
	Conventional Therapy		Epoprostenol Therapy		
	n	Mean	n	Mean	
<200 meters	8	25.63	14	62.35	0.2601
≥ 200 meters	36	-55.40	36	35.40	0.0001

Complied by the reviewer.

*P-value was obtained by the reviewer using Wilcoxon test.

As seen from the table above, 6-minute walk test results in favor of epoprostenol therapy were not consistent across baseline walk category. The average of change from baseline for 6-minute walked distance for strata ranged from -55.40 to 25.63 meters for conventional therapy and from 35.40 to 62.35 for epoprostenol therapy. It also indicated that conventional therapy patients decreased their 6-minute walked distance at Week 12 only in the baseline walk category (≥ 200 meters), while epoprostenol therapy patients increased their 6-minute walked distance at Week 12 in both baseline walk categories. The superiority of epoprostenol therapy reached statistical significance only in the baseline walk category (≥ 200 meters).

3.4 Subgroup Analyses

Per FDA's request, the sponsor provided results from the gender, race, and age subgroups analysis of exercise capacities at Week 12. The results are summarized below.

Exercise Capacities at Week 12 by Subgroup

Subgroup	Category	n	Change from Baseline		n	Change from Baseline		95% C.I.
			Conventional Therapy Mean	Std. Error		Epoprostenol Therapy Mean	Std. Error	
Gender	Male	9	-96.1	22.45	3	36.3	55.64	(-229.184, -35.616)
	Female	35	-26.4	13.46	47	43.4	15.82	(-112.359, -27.241)
Age	18-64	30	-38.0	15.97	40	59.3	14.12	(-139.207, -55.393)
	≥ 65	14	-46.5	18.80	10	-22.4	46.64	(-112.339, 64.139)
Race	White	36	-48.3	13.37	44	41.6	16.81	(-133.376, -46.424)
	Non-White	8	-6.4	29.87	6	53.2	28.53	(-142.938, 23.738)

Copied from Table 6, pages 14-19 NDA Suppl. Amendment Dated 4/26/99

95% C.I. was obtained by the reviewer.

A C.I. that does not contain 0 (zero) implies statistical significance

As seen from the table above, male patients in conventional therapy group showed the largest change whereas non-whites in conventional therapy group showed the smallest change from baseline of any of the subgroups. Patients greater 65 years old in epoprostenol therapy group had a negative mean change from baseline at Week 12.

Based on 95% confidence interval of the treatment difference, there was no treatment difference for subgroups of patients greater 65 and for non-White patients. But, note that due to the small sample sizes, the results might not be reliable.

This reviewer performed parametric analysis of covariance based on available data on the 6-minute walk test scores at Week 12. This model included age subgroup (18-64, ≥ 65) and interaction between age subgroup and treatment as a factor in addition to treatment, distance walked at base and vasodilator use at baseline. It was found that age subgroup

has significant effect ($p=0.0073$) on exercise capacities at Week. The interaction between age subgroup and treatment was statistically significant ($p=0.0546$) at 0.20 significance level. That reconfirmed the sponsor's finding on subgroup analysis for age.

C. Overall Summary and Recommendation

The sponsor has submitted one controlled efficacy study (VA1A4001) in support of the proposed claim.

For the primary endpoint of the 6-minute exercise capacity, patients in the epoprostenol therapy group had statistically significantly greater mean walk distance than those of patients in the conventional therapy group at Weeks 6 and 12 from both nonparametric and parametric analyses of covariance adjusting for baseline exercise capacity.

For cardiopulmonary hemodynamic parameters, statistically significant improvement in pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), right arterial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2) occurred in patients in the epoprostenol treatment group compared to patients who received conventional therapy.

For clinical signs and symptoms of pulmonary hypertension, statistically significant improvement was observed for the epoprostenol therapy group over the conventional therapy group for Dyspnea-Fatigue Rating and Borg Dyspnea Score but not for NYHA functional Class.

There was no treatment difference in survival or in clinical signs and symptoms of the scleroderma spectrum of disease at week 12.

In conclusion, the efficacy of the epoprostenol therapy is supported in one study (VA1A4001) but has not yet been duplicated in other studies. The efficacy of the epoprostenol therapy was shown in improvement of exercise capacity (primary endpoint) and some of the secondary endpoints including cardiopulmonary hemodynamic parameters and clinical signs and symptoms of pulmonary hypertension. But, there was no treatment difference in survival and clinical signs and symptoms of the scleroderma spectrum of disease. Moreover, the study was not well controlled with problems of treatment assignment. The efficacy is not consistent across investigators, strata, baseline walk category and age, as indicated in this reviewer's assessment. Furthermore, the efficacy results were not statistically persuasive.

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/S/
Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 13 pages of text and 10 pages of tables

Concur: Dr. Al-Osh
Dr. Welch

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- cc:
 - Archival NDA 20-444
 - HFD-180
 - HFD-180/Dr. Talarico
 - HFD-180/Dr. Robie-Suh
 - HFD-180/Mr. Strongin
 - HFD-715/Dr. Nevius
 - HFD-715/Dr. Welch
 - HFD-715/Dr. Al-Osh
 - HFD-715/Dr. Fan
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Table 1

Summary of Demographic and Baseline Characteristics --- Protocol VA1A400

Characteristics	Conventional Therapy (N=55)	Epoprostenol plus Conv. Therapy (N=56)	Between Treatment P-value
Sex			
Male	45 (82%)	51 (91%)	0.156
Female	10 (18%)	5 (9%)	
Race			
White	44 (80%)	49 (88%)	0.434
Black	5 (9%)	3 (5%)	
Asian	0 (0%)	1 (2%)	
Other	6 (11%)	3 (5%)	
Age (yr)			0.055
Mean	57.3	53.0	
S.D.	10.3	13.1	
Min-Max	32-78	23-77	
Height (cm)			0.277
Mean	165.0	163.2	
S.D.	8.9	8.4	
Min-Max	145-187	145-179	
Weight (kg)			0.153
Mean	74.7	70.2	
S.D.	16.7	16.4	
Min-Max	39-119	42-127	
NYHA Class			0.037
II	4 (7%)	1 (2%)	
III	45 (82%)	42 (75%)	
IV	6 (11%)	13 (23%)	
Vasodilator Use			0.889
No	17 (31%)	18 (32%)	
Yes	38 (69%)	38 (68%)	
Walk Category (meters)			0.293
< 200 meters	11 (20%)	16 (29%)	
≥ 200 meters	44 (80%)	40 (71%)	

Copied from Table 15, pages 104-106, Vol.3.

Anova is used to assess treatment differences in age, height, and weight and CMH test is used to assess treatment differences in gender and race.

P-value for NYHA class were obtained by the reviewer using CMH test.

P-values for vasodilator use, walk category, and SSD diagnosis were obtained by the reviewer using Chi-square test.

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Table 1 (continued)

Summary of Demographic and Baseline Characteristics --- Protocol VA1A400

Characteristics	Conventional Therapy (N=55)	Epoprostenol plus Conv. Therapy (N=56)	Between Treatment P-value
Walk Distance (meters)			0.997
Mean	269.88	269.97	
S.D.	100.18	111.17	
Min-Max	—	—	
SSD Diagnosis			0.962
Limited scleroderma	39 (71%)	38 (68%)	
Overlap Syndrome	6 (11%)	8 (14%)	
Feature of SSD	3 (5%)	3 (5%)	
Systematic sclerosis	7 (13%)	7 (13%)	
Pulmonary Hypertension History (months)			0.835
Mean	15.2	14.5	
S.D.	20.1	17.9	
Min-Max	—	—	
Scleroderma History (months)			0.634
Mean	94.8	85.9	
S.D.	102.8	93.0	
Min-Max	—	—	

Copied from Table 15, pages 104-106, Vol.3.

P-values for walk distance, pulmonary hypertension and scleroderma history were obtained by the reviewer using ANOVA.

P-values for vasodilator use, walk category, and SSD diagnosis were obtained by the reviewer using chi-square test.

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Table 2

Treatment Comparisons of the 6-Minute Walk Exercise Test (Meters)
(Parametric Analysis of Covariance)

Week	n	Conventional Therapy		Epoprostenol Therapy		p-value	
		Baseline Mean (m)	Mean (m)	Baseline Mean (m)	Mean (m)		
1	54	271.2	265.8	50	271.0	294.7	0.0252
6	52	271.9	257.9	51	265.6	299.3	0.0025
12	53	270.1	220.9	53	268.8	308.0	0.0001

Copied from Table 24, page 126, Vol. 3.

Adjusted for baseline walk and vasodilator use at baseline

Carrying forward results for missing values or results after transplant or deaths.

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Table 3

Treatment Comparisons of Cardiopulmonary Hemodynamic Measurements

Variable	Change from Baseline						95% C. I.*
	Conventional Therapy			Epoprostenol Therapy			
	n	Mean	Std. Error	n	Mean	Std. Error	
Heart Rate	48	-0.90	1.929	50	3.74	1.469	(-9.33, 0.056)
SAPs	48	-2.58	2.414	49	-8.99	2.610	(-.525, 13.35)
SAPd	48	0.35	1.373	49	-7.89	1.522	(4.247, 12.24)**
SAPm	48	-0.63	1.520	49	-8.26	1.689	(3.201, 12.07)**
RAPm	47	1.20	0.694	50	-1.26	0.818	(0.387, 4.537)**
PAPs	48	0.68	1.654	50	-7.42	1.516	(3.751, 12.45)**
PAPd	48	1.07	0.966	50	-3.83	1.060	(2.118, 7.687)**
PAPm	48	0.94	1.102	50	-5.03	1.089	(2.962, 8.975)**
Cardiac Index	48	-0.10	0.078	50	0.50	0.076	(-0.814, -0.391)**
Cardiac Output	48	-0.16	0.147	50	0.87	0.134	(-1.42, -.649)**
PCWP	44	0.79	0.879	47	0.45	0.809	(-1.96, 2.642)
SvO ₂	44	-1.07	1.243	45	3.55	1.420	(-8.30, -0.941)**
SaO ₂	48	-0.31	0.608	49	-0.33	1.087	(-2.42, 2.453)
PVR	44	0.92	0.557	47	-4.58	0.764	(3.665, 7.332)**

Copied from Table 27, page 130, Vol.3

* 95% confidence interval (C.I.) for the mean change from baseline between treatment groups.

** A C.I. that does not contain 0 (zero) implies statistical significance.

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Table 4 Summary of NYHA Class Change from Baseline

Week	Change from Baseline						H-L Estimate	95% C. I.*
	Conventional Therapy			Epoprostenol Therapy				
	n	Mean	Std. Error	n	Mean	Std. Error		
1	55	0.07	0.04	55	-0.05	0.05	0.0	(0.0, 0.0)
6	54	0.20	0.06	52	-0.27	0.08	0.0	(0.0, 1.0)
12	48	0.29	0.07	51	-0.43	0.09	1.0	(0.0, 1.0)

Copied from Table 30, page 133, Vol. 3

* 95% C. I. was obtained using nonparametric method.

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Table 5 Summary of Dyspnea-Fatigue Rating Change from Baseline

Week	Change from Baseline						H-L Estimate	95% C. I. [*]
	Conventional Therapy			Epoprostenol Therapy				
	n	Mean	Std. Error	n	Mean	Std. Error		
1	55	-0.47	0.15	55	0.22	0.16	0.0	(-1.0, 0.0)
6	54	-0.70	0.20	52	1.13	0.23	-2.0	(-2.0, -1.0) ⁻
12	47	-1.34	0.24	51	1.25	0.26	-2.0	(-3.0, -2.0) ⁻

Copied from Table 32, page 135, Vol. 3

^{*} 95% C.I. was obtained using nonparametric method.

⁻ A C.I. that does not contain 0 (zero) implies statistical significance.

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Table 6 Summary of Borg Dyspnea Score Change from Baseline

Week	Conventional Therapy		Change from Baseline		Epoprostenol Therapy		H-L Estimate	95% C. I. [†]
	n	Mean	Std. Error	n	Mean	Std. Error		
1	54	0.24	0.22	50	-0.97	0.31	1.0	(0.5, 2.0) ^{**}
6	51	0.25	0.28	48	-1.28	0.32	1.5	(1.0, 2.5) ^{**}
12	42	0.62	0.29	49	-1.79	0.37	2.5	(1.5, 3.5) ^{**}

Copied from Table 34, page 137, Vol. 3

[†] 95% C.I. was obtained using nonparametric method.

^{**} A C.I. that does not contain 0 (zero) implies statistical significance.

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Table 7 Summary of Raynaud's Severity Score Change from Baseline

Week	Change from Baseline				H-L Estimate	95% C. I.*	
	Conventional Therapy		Epoprostenol Therapy				
	n	Mean	Std. Error	n	Mean	Std. Error	
6	47	-0.34	0.44	48	-0.79	0.42	1.0 (0.0, 2.0)
12	40	-0.50	0.54	45	-1.69	0.42	1.0 (0.0, 3.0)

Copied from Table 36, page 139, Vol. 3

* 95% C.I. was obtained using nonparametric method.

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Table 8 Summary of Digital Ulcers and Ischemic Demarcations Change from Baseline

Week	Change from Baseline							
	Conventional Therapy			Epoprostenol Therapy			H-L Estimate	95% C. I.*
n	Mean	Std. Error	n	Mean	Std. Error			
6	53	-0.40	0.33	52	-2.13	1.03	0.0	(0.0, 0.0)
12	48	-0.50	0.61	51	-2.41	1.05	0.0	(0.0, 0.0)

Copied from Table 39, page 143, Vol. 3

* 95% C.I. was obtained using nonparametric method.

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Table 9 Actual Treatment Assignment by Strata

Site	Baseline Exercise Capacity \geq 200 M				Baseline Exercise Capacity 50 – 200 M			
	Vasodilator Use Yes		Vasodilator Use No		Vasodilator Use Yes		Vasodilator Use No	
	Conv.	Epop	Conv.	Epop	Conv.	Epop	Conv.	Epop
01	3	0	1	0	0	1	0	2
02	1	0	0	1	3	1	1	0
03	2	3	2	3	1	1	0	1
06	1	3	3	1	0	1	1	1
07	2	3	2	1	1	0		
08	1	3	0	0	0	0		
09	1	3			1	3		
10	2	1						
13	5	0	0	1	1	0	0	1
14	2	0	1	1			0	0
15	3	4			0	1	0	2
16	0	2						
17	1	3	2	0				
21	4	3	0	2			1	0
22	1	0	1	0	0	1		
23	1	1	1	1	1	0		
25			1	0				
Total	30	29	14	11	8	9	3	7

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