CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-845

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:	NDA 21-845
Drug Name:	Revatio (sildenafil) tablets
Indication(s):	Pulmonary Arterial Hypertension
Applicant:	Pfizer
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Review Priority:	Priority
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Keywords: sequential step-down closed testing procedure, sensitivity analysis, stratified t-test, stratification, missing data, survival analysis, Kaplan-Meier product limit, log-rank test, Wilcoxon test, ANOVA.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Reviewer's primary efficacy analysis of the single confirmatory Study A1481140 corroborated the sponsor conclusion that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p<0.001$) better than placebo relative to the change from baseline in the 6-minute walk distance at 12 weeks. Sensitivity analysis using a conservative imputation method supported the primary efficacy analysis.

The secondary efficacy analysis of Study A1481140 showed that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p\leq0.021$) better than placebo relative to the change from baseline at 12 weeks in pulmonary artery pressure (PAP). Relative to time to clinical worsening, comparison of sildenafil 80 mg to placebo showed no statistically significant reduction. Therefore, according to the pre-specified sequential step-down testing procedure, no further doses and secondary endpoints were evaluated.

Safety results showed that proportion of subjects with treatment related adverse events was higher in the sildenafil 80 mg group (66%) as compared to placebo (51%). All five subjects, who permanently discontinued from the study due to adverse events, were in the sildenafil 80 mg group, with one of the subjects having treatment related adverse events.

1.2 Brief Overview of Clinical Studies

This NDA contains one pivotal trial A1481140 as a basis for supporting the indication of PAH. This review pertains to this study.

1.3 Statistical Issues and Findings

In general, this reviewer agrees with the sponsor's analytical plan and statistical methods. To verify the sponsor's primary efficacy results based on the t-test stratified for etiology and baseline walking distance, this reviewer performed an alternative analysis of the primary endpoint using ANOVA with main effect for treatment group and factors for etiology and baseline walking distance. The reviewer's analysis supports the sponsor's results.

2. INTRODUCTION

2.1 Overview

This NDA contains one pivotal trial A1481140 as a basis for supporting the indication of PAH. This review pertains to this study.

2.2 Data Sources

Efficacy and safety data sets for Study A1481140 were provided by the sponsor on 12/02/2004 and are stored in the EDR: \\Cdsesub1\n21845\N_000\2004-12-02.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy of Study A1481140

Study Design

Study A1481140 was a multinational, multi-center, double-blind, double-dummy, parallel group study with three dose levels (20, 40 and 80 mg TID of sildenafil) and placebo. Two hundred and forty evaluable subjects (240) were required (60 per study arm). The study consisted of five visits, one telephone call to the subject and a follow-up visit for those subjects who did not enter extension Study A1481142.

Subjects were randomized to one of four treatment groups: placebo, sildenafil 20 mg, sildenafil 40 mg, or sildenafil 80 mg in a 1: 1: 1: 1 ratio. Subjects who were randomized to sildenafil 80 mg, received 40 mg for the first seven days and then underwent an up-titration to 80mg. Subjects randomized to placebo, sildenafil 20 mg or sildenafil 40 mg underwent a dummy up-titration after seven days. Study drug was taken three times a day, at least six hours apart. All subjects remained in the hospital at least eight hours after the first dose. Subjects were supplied with medication to last them until their next visit (a maximum of 35 days supplies).

Subjects were assigned to treatment groups using a central randomization scheme across all centers. Randomization to treatment arms was stratified according to baseline walking distance (< 325 m, ≥ 325 m) and etiology (primary pulmonary hypertension (PPH), PAH secondary to connective tissue disease (CTD), PAH with surgical repair), to ensure a balance in these factors across treatment groups. Eligible subjects were randomly assigned to treatment groups in a 1: 1: 1: 1 ratio (placebo: sildenafil 20 mg: sildenafil 40 mg: sildenafil 80 mg) according to a computer generated pseudo-random code using the method of random permuted blocks within strata.

Blinding

This was a double-blind, double dummy study using matching placebo tablets.

Efficacy variables

Primary efficacy variable

6-Minute Walk test
The distance a subject could walk in six minutes was measured at screening, baseline, Weeks 4, 8 and 12 at trough. The study personnel that performed the 6-Minute Walk test and the BORG dyspnea score were trained by the sponsor's personnel to perform these tests according to the study specific protocol in order to ensure standardization across centers and did not perform any of the other assessments. Where possible, subjects were assessed by the same person at each visit to ensure standardization.

Time to clinical worsening
Time from randomization to clinical worsening was assessed over the duration of the study and was based on data up to 12 weeks after randomization. Clinical worsening was defined as: death, lung transplantation, hospitalization due to PAH, initiation of prostacyclin therapy, or initiation of bosentan therapy.

BORG dyspnea score
The BORG dyspnea score was assessed by the subject at the end of the 6-Minute Walk test at screening, baseline, Weeks 4, 8 and 12, and if applicable at follow up.

Statistical Methods

Sample Size

The primary efficacy endpoint for this study was the change from baseline in the total distance walked during a 6-Minute Walk test at Week 12 of the study and was evaluated using a closed testing procedure. This consisted of a one-sided sequential step-down testing procedure in which the mean response in each sildenafil dose group was compared to the placebo group in a step-down fashion. This testing procedure protected the family-wise error rate at the pre-specified alpha level.

Assuming a treatment effect for sildenafil of 55 meters over placebo and a standard deviation of 75 meters, a sample size of 60 subjects per treatment group was required to detect this difference with 90% power at a one-sided significance level of 0.005 (i.e., a two-sided significance level of 0.01). Allowing for a withdrawal rate of 12.5%, 275 subjects (70 per group) were required to be randomized.

A blinded interim analysis was planned prior to the start of the study and was pre-specified in the protocol to allow a sample size re-estimation (SSR) to be performed during the study. This blinded interim analysis was performed when 50% (120) of the planned subjects had completed the study. The overall variability was obtained in a **blinded fashion**, i. e., without knowledge of a subject's treatment assignment, and then an adjustment factor was applied

based on the expected treatment difference (55 m) to get a revised estimate of the within-treatment standard deviation. This revised estimate of the standard deviation was used in conjunction with the expected treatment difference (55 m) to calculate a revised sample size.

A statistician independent of the sildenafil PAH project team performed the blinded interim analysis. Decision criteria for increasing the sample size or continuation of the trial according to the original sample size were pre-defined in the Interim Analysis Operational Plan (IAOP) prior to performing the SSR. The SSR indicated that the current study size had a power of at least 85% to detect the assumed treatment difference of 55 meters. Hence, in accordance with the decision criteria pre-specified in the IAOP, the sample size was not increased.

Statistical Analysis Plans

Subject Populations for Analysis

The following subject populations were defined for use in the efficacy and safety analyses:

1. ITT (full analysis set)
2. Per Protocol
3. Safety

The ITT population was used in the analysis of the efficacy endpoints. To be included in the ITT analysis for the primary endpoint, a subject must have received study drug, had a baseline measure and at least one post baseline measure.

The Per Protocol (PP) population was also used for the primary endpoint. The PP population included all subjects who satisfied the ITT criteria for the 6-minute walk test and who in addition had:

1. Taken 100± 20% of each tablet size;
2. Not violated any of the inclusion criteria;
3. Not deviated from the protocol with regard to concomitant medication use;
4. A Week 12 6-Minute Walk test performed at trough levels of sildenafil, i. e. at least three and a half hours after the previous dose.

Safety

All randomized subjects who took at least one dose of study medication were analyzed for safety.

Covariates

Randomization was performed using a stratified central randomization computer-generated list to assign subjects to treatment groups across all centers. Subjects were randomized to one of the 4 treatment groups (Placebo, sildenafil 20 mg, sildenafil 40 mg, and sildenafil 80 mg) in a 1: 1: 1: 1 ratio. The following 2 stratification factors were used:

1. Etiology of PAH (PPH, PAH secondary to connective tissue disease (CTD), and PAH with surgical repair);
2. Baseline exercise capacity (< 325 m, ≥ 325 m).

The analyses of the primary and secondary endpoints were therefore performed using the above two stratification factors as covariates. Center was not included as a covariate due to the small number of subjects anticipated at each center.

Sponsor's Statistical Analysis Methods

Primary Endpoint

The primary endpoint was evaluated using a one-sided sequential step-down testing procedure in which the mean response in each sildenafil dose group was compared to that in the placebo group in a step-down fashion. First, the highest dose group (80 mg TID) of sildenafil was compared to placebo. If no significant benefit was achieved, no further tests were to be carried out. If a significant benefit was achieved, then the next dose group (40 mg TID) was compared to placebo. Similarly, the 20 mg dose group was only compared to placebo if a significant benefit was achieved for the 40 mg group.

In each of these pair-wise comparisons the hypothesis:
Hoi: μ_0 (placebo) = μ_i,
where μ_i denotes the mean response at the i-th dose of sildenafil, is tested against the one-sided alternative:
Hai: $\mu_0 < \mu_i$.
The above procedure is a closed testing procedure and thus the family-wise error rate is protected at the pre-specified alpha level for the primary endpoint. Hence, all the pair-wise comparisons described above were carried out at the pre-specified one-sided alpha level of 0.005 (i.e., a two-sided alpha of 0.01).

The primary analysis was carried out using a two-sample t-statistic, stratified for baseline walking distance and etiology for the ITT and PP populations. The test statistic is a weighted combination of 6 t-test statistics with pre-specified weights. The test statistic is asymptotically distributed as a standard normal.

In the ITT analysis, subjects with a missing 6-Minute Walk test at Week 12 had an assessment imputed using the LOCF. A sensitivity analysis was carried out on all randomized and treated subjects, in which subjects who did not have any post-baseline 6-Minute Walk test assessment and subjects who died or underwent lung transplantation during the study had their 6-Minute Walk test distance at Week 12 set to the baseline result, whilst all other subjects used their 6-Minute Walk test at Week 12 or had their last observation carried forward.

Normality of the primary endpoint was investigated graphically for both the ITT and PP populations, by means of residual plots and normal probability plots after fitting a main effects analysis of variance model with factors for treatment and the two stratification variables.

If a significant treatment effect was observed, then potential heterogeneity of the treatment effect in the primary endpoint within different levels of each stratification factor was investigated graphically using:
1. Plots of mean level of response (and standard deviation) for each treatment group against each level of a specific stratification factor.
2. Scatter plots of each response for each treatment group against each level of a specific stratification factor.

Secondary Endpoints

The following testing strategy was pre-specified for the analysis of the secondary endpoints. If no statistically significant treatment effect was found for the primary endpoint then statistical tests would not be performed on the secondary endpoints. If a statistically significant treatment effect was observed in the primary endpoint, statistical tests on the three secondary endpoints listed above would be conducted in a hierarchical order as follows: First, mean PAP would be evaluated. If no significant treatment effect was found, then no further secondary endpoints would be evaluated. If a statistically significant treatment effect was observed in mean PAP, then the time to clinical worsening would be evaluated. If no significant treatment effect was found, then no further secondary endpoints would be evaluated. If a statistically significant treatment effect was observed in the time to clinical worsening, then the BORG dyspnea score would be evaluated. Using this closed testing procedure, the nominal type I error rate is conserved for the investigation of each secondary endpoint.

Each secondary endpoint undergoing statistical testing was evaluated using the same one-sided sequential step down testing procedure, as specified for the analysis of the primary endpoint, i. e. each sildenafil dose group was compared to the placebo group in a step-down fashion, starting with the highest dose (80 mg TID) and stopping when a specific comparison of a dose group against placebo showed no significant benefit. All pair-wise comparisons within each secondary endpoint were performed at the one-sided alpha level of 0.025 (which corresponds to a two-sided alpha of 0.05).

A statistically significant treatment effect in both the primary and secondary endpoints, as referred to above, was defined as obtaining at least one active dose, which had a significant benefit over placebo when applying the sequential step-down testing procedure.

Mean PAP was evaluated using a stratified t-test, time to clinical worsening was evaluated using a stratified log-rank test and BORG dyspnea score was evaluated using a stratified Wilcoxon test (Van-Elteren test). The stratification factors for each analysis were baseline walking distance and etiology (as specified for the primary endpoint). Event free subjects were included in the analysis of time to clinical worsening as censored observations at the time they discontinued from the study or at 84 days after randomization, whichever was the earlier. Kaplan-Meier curves and log-rank test are to be used for time to clinical worsening.

Reviewer's statistical methods for additional analyses

To verify the sponsor's primary efficacy results based on the t-test stratified for etiology and baseline walking distance, this reviewer performed an alternative analysis of the primary endpoint using ANOVA with main effect for treatment group and factors for etiology and baseline walking distance.

Results of Study

Subject Disposition

Sixty centers, USA (18), South America (2), Europe (25), Asia (4) and Rest of World, enrolled subjects into this study. The number of subjects recruited per center ranged from one to 22. There were three high recruiting centers, two (Germany and Poland) with 19 subjects and one (Italy) with 22 subjects. A total of 360 subjects were screened, 278 subjects were randomized to receive either placebo, sildenafil 20 mg, 40 mg or 80 mg TID. One subject randomized to receive sildenafil 40 mg did not receive treatment. All of 277 randomized subjects took at least one dose of study medication.

Table 1. Subject disposition in Study A1481140

		Sidenafil		
	Placebo	20 mg	40 mg	80 mg
Randomized	70	69	68	71
Received study drug	70	69	67	71
Completed study and entered extension study A148 1142	67	65	63	64
Included in the ITT analysis for 6-minute walk	66	67	64	69
Included in the PP population	38	39	38	46
Adverse events evaluation	70	69	67	71

Source: sponsor's Table 1.1.

Demographic characteristics

The 277 treated subjects included 68 (25%) men and 209 (75%) women. The treatment groups were balanced relative to baseline demographic and medical characteristics. The primary diagnosis for 175 subjects (63%) was PPH; 84 (30%) subjects had PAH secondary to CTD and 18 (6%) had PAH following surgical repair.

EFFICACY EVALUATION

Primary Endpoint: 6-Minute Walk Test

The primary efficacy endpoint of the study was the change from baseline in exercise capacity at Week 12 as measured by distance walked in six minutes. Of the 277 treated subjects, 7 subjects (Placebo: 4; 20 mg: 1; 40 mg: 2) had a missing baseline value, and 4 subjects (20 mg: 1; 40 mg: 1; 80 mg: 2) did not have any post baseline walk assessments. A total of 266 subjects were included in the ITT analysis for the primary endpoint. An increase in 6-Minute Walk distance was observed in all sildenafil dose groups compared to placebo at Week 4 and this effect was maintained at Weeks 8 and 12

The sponsor's primary analysis was carried out using a two-sample t-statistic, stratified for baseline walking distance and etiology. Subjects on all sildenafil doses were statistically significantly ($p<0.0001$) better than placebo relative to walk distance (Table 2). Mean placebo corrected treatment effects of 45 meters (99% CI: 21, 70), 46 meters (99% CI: 20, 72) and 50 meters (99% CI: 23, 77), were observed in favor of sildenafil 20 mg, sildenafil 40 mg, and sildenafil 80 mg, respectively.

Table 2. Sponsor's results for the treatment comparisons of the primary endpoint in the ITT population of Study A1481140

	Mean change from baseline			
	Placebo N=66	**Sildenafil 20 mg N=67**	**Sildenafil 40 mg N=64**	**Sildenafil 80 mg N=69**
Mean change (meters)	-3.7	41.3	44.1	46.8
P-value from stratified two-sample t-test* for comparison vs. placebo	-	<0.001	<0.001	<0.001

Source: sponsor's Table 5.2.1

**According to the step-down testing procedure, when a contrast of a specific dose level was found to be significant at the 0.005 level (one-sided), the contrast for the next lower dose level could be tested. Significance tests of six minute walking distance were performed using a stratified t-test (one-sided), with baseline walking distance and etiology as the stratification factors.*

To verify the sponsor's primary efficacy results based on the t-test stratified for etiology and baseline walking distance, this reviewer performed an alternative analysis of the primary endpoint using ANOVA with main effect for treatment group and class effects for etiology and baseline walking distance. The reviewer's analysis supports the sponsor's result that all three sildenafil doses were statistically significantly ($p<0.0001$) better than placebo at week

12 relative to 6-minute walk test. Reviewer's analysis also found that there was no statistically significant difference between the three sildenafil doses ($p \geq 0.74$). The reviewer's results are shown in Table 3.

Table 3. Reviewer's results for the treatment comparisons of the primary endpoint in the ITT population of Study A1481140

	Least Square Mean Change from Baseline			
	Placebo N=66	**Sildenafil 20 mg N=67**	**Sildenafil 40 mg N=64**	**Sildenafil 80 mg N=69**
LSM Change (meters)	0.2	38.8	42.1	50.6
P-value from ANOVA* for comparison vs. placebo	-	<0.001	<0.001	<0.001

** Source: reviewer's analysis using ANOVA with main effect for treatment group and class effects for etiology and baseline walking distance.*
According to the step-down testing procedure, when a contrast of a specific dose level was found to be significant at the 0.005 level (one-sided), the contrast for the next lower dose level could be tested.

A sensitivity analysis was carried out on all randomized and treated subjects in which subjects who did not have any post-baseline 6-Minute Walk test assessments and subjects who died during the study had their 6-Minute Walk test distance at Week 12 set to the baseline result, whilst all other subjects used their Week 12 6-Minute Walk test or had their last observation carried forward. The sensitivity analysis supported the primary analysis ($p<0.001$).

Subgroup analysis

Heterogeneity of the treatment effect in the primary endpoint was investigated within different levels of each stratification factor (etiology and baseline walking distance) and is summarized in Table 4. Of the 266 patients analyzed for the primary endpoint, 170 (64%) had PPH, 78 (29%) had PAH with CTD and 18 (7%) had PAH with surgical repair. As the number of subjects in the surgical repair subgroup was small (7%), this subgroup is not shown in this table. Of the 266 subjects analyzed for the primary endpoint, there were a total of 171 (64%) subjects with a baseline walking distance of $\geq$325 meters and 95 (36%) subjects with a baseline walking distance of $<$ 325 meters. Table 4 shows that the 80 mg dose was not significantly better than placebo in the CTD subgroup and for patients with baseline distance $\geq$ 325 m.

Table 4 Treatment comparisons of the primary endpoint by etiology and baseline walking distance in Study A1481140			
	Treatment comparisons versus placebo		
	Sildenafil 20 mg	Sildenafil 40 mg	Sildenafil 80 mg
PPH population (Placebo N=33)	N=43	N=42	N=46
Mean placebo corrected difference (SE)	40.0 (13.2)	46.9 (14.1)	61.6 (13.4)
99% CI	(6.0, 74.0)	(10.5, 83.4)	(27.0, 96.2)
CTD population (Placebo N=33)	N=20	N=18	N=19
Mean placebo corrected difference (SE)	55.1 (15.5)	47.5 (15.7)	31.7 (19.5)
99% CI	(15.2, 95.0)	(7.1, 87.9)	**(-18.6, 82.1)**
Baseline walk ≥325 (Placebo N=43)	N=44	N=41	N=43
Mean placebo corrected difference (SE)	39.0 (11.8)	36.3 (12.3)	29.2 (13.9)
99% CI	(8.6, 69.5)	(4.5, 68.0)	**(-6.7, 65.0)**
Baseline walk <325 (Placebo N=23)	N=23	N=23	N=26
Mean placebo corrected difference (SE)	57.6 (16.5)	65.4 (18.0)	86.5 (14.8)
99% CI	(15.0, 100.1)	(18.9, 111.8)	(48.2, 124.7)

Source: Sponsor's Table 5.2.2.2

PP Population

The analysis on the primary endpoint was also conducted for the subjects in the PP population. The PP population has only 161 subjects (61% of the ITT population). For this reason, the results of the PP population analysis should be interpreted with great caution in this case. In the PP population, subjects on all sildenafil doses achieved a statistically significant increase ($p<0.001$) in walk distance compared to those on placebo. Mean placebo-corrected treatment effects of 41 m, 42 m and 48 m, were observed in favor of sildenafil 20 mg, sildenafil 40mg, and sildenafil 80 mg, respectively.

Secondary Endpoints

Since a statistically significant treatment effect was observed in the primary endpoint, statistical tests were conducted on the three secondary endpoints in a hierarchical order as defined in the statistical analysis plan. Change from baseline in mean PAP was evaluated first, followed by time to clinical worsening and change from baseline in BORG Dyspnea score.

Mean PAP

Of the 277 treated subjects, 2 subjects (20 mg: 1; 40 mg: 1) had a missing baseline assessment, and 17 subjects (Placebo: 5; 20 mg: 3; 40mg: 3; 80 mg: 6) did not have any post baseline PAP assessments. Two subjects randomized to sildenafil 80 mg with no post baseline assessments died prior to their Week 4 assessment. A total of 258 subjects were therefore included in the ITT analysis for the secondary endpoint, mean PAP.

Subjects on all sildenafil doses achieved a statistically significant reduction in mean PAP compared to those on placebo (Table 5). A sensitivity analysis was carried out on all randomized and treated subjects, in which subjects who did not have any post-baseline mean PAP assessments and subjects who died during the study had their mean PAP at Week 12 set to the baseline result, whilst all other subjects used their Week 12 mean PAP or had their last observation carried forward. The results of this analysis support the main mean PAP analysis.

Table 5. Sponsor's results for the treatment comparisons of the change from baseline in mean PAP (mmHg) in the ITT population of Study A1481140

	Mean PAP change from baseline			
	Placebo N=65	**Sildenafil 20 mg N=65**	**Sildenafil 40 mg N=63**	**Sildenafil 80 mg N=65**
Mean PAP change (meters)	0.6	-2.1	-2.6	-4.7
P-value from stratified two-sample t-test* for comparison vs. placebo	-	<0.021	<0.006	<0.001

Source: Sponsor's Tables 5.3.1 and 5.3.2.

Time to clinical worsening and other secondary endpoints

Since a statistically significant treatment effect was observed in the mean PAP, statistical tests were conducted on the clinical worsening endpoint. The comparison of sildenafil 80mg with placebo showed no statistically significant reduction in time to clinical worsening and thus no further doses were statistically compared. Since no statistically significant treatment difference was observed in time to clinical worsening, statistical tests were not conducted on the BORG Dyspnea score and on tertiary endpoints.

3.2 Evaluation of Safety

Adverse Events

Discontinuations and Dose Reductions Due to Adverse Events

All five subjects who permanently discontinued from the study due to adverse events, were in the sildenafil 80 mg group. For one of the subjects, adverse events were classified as treatment related.

Incidence of Adverse Events

The proportion of subjects with treatment related adverse events was slightly higher in the sildenafil 80 mg group (placebo: 51%; sildenafil 20 mg: 55%; sildenafil 40 mg: 57%; and sildenafil 80 mg: 66%).
An overall summary of adverse event is presented in Table 6.

Table 6.
Overall Summary of Adverse Events

Number of subjects (%)	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Subjects evaluable for AEs	70	69	67	71
All Causality				
Number of AEs	367	351	348	362
Subjects with AEs	64 (91)	63 (91)	59 (88)	64 (90)
Subjects with serious AEs	12 (17)	10 (15)	10 (15)	9 (13)
Subjects with severe AEs	11 (16)	12 (17)	11 (16)	12 (17)
Subjects discontinued due to AEs	0	1 (1)	0	5 (7)
Subjects temporarily discontinued due to AE's	5 (7)	5 (7)	0	2 (3)
Treatment related				
Number of AEs	83	92	123	146
Subjects with AEs	36 (51)	38 (55)	38 (57)	47 (66)
Subjects with serious AEs	0	2 (3)	1 (2)	0
Subjects with severe AEs	1 (1)	2 (3)	2 (3)	5 (7)
Subjects discontinued due to AEs	0	0	0	1 (1)
Subjects temporarily discontinued due to AEs	0	2 (3)	0	0

Source: Sponsor's Table s 6.1.1.2.and 6.2.1.2.

Four subjects died during the study, one subject randomized to placebo TID, one subject randomized to sildenafil 20mg TID, and two subjects randomized to sildenafil 80mg TID. None of the deaths were judged as causally related to study drug by the investigators.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Six-minute Walk Test in pre-specified subgroups

Heterogeneity of the treatment effect in the primary endpoint was investigated within different levels of each stratification factor (etiology and baseline walking distance) and is summarized in Table 7. Of the 266 patients analyzed for the primary endpoint, 170 (64%) had PPH, 78 (29%) had PAH with CTD and 18 (7%) had PAH with surgical repair. The number of subjects in the surgical repair subgroup was small (7%). For this reason, this subgroup is not shown in this table. Of the 266 subjects analyzed for the primary endpoint, there were a total of 171 (64%) subjects with a baseline walking distance of ≥325 meters and 95 (36%) subjects with a baseline walking distance of < 325 meters.

Table 7. Treatment comparisons of the primary endpoint by etiology and baseline walking distance in Study A1481140

	Treatment comparisons versus placebo		
	Sildenafil 20 mg	Sildenafil 40 mg	Sildenafil 80 mg
PPH population (Placebo N=33)	N=43	N=42	N=46
Mean difference (SE)	40.0 (13.2)	46.9 (14.1)	61.6 (13.4)
99% CI	(6.0, 74.0)	(10.5, 83.4)	27.0, 96.2)
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Baseline walk ≥325 (Placebo N=43)	N=44	N=41	N=43
Mean difference (SE)	39.0 (11.8)	36.3 (12.3)	29.2 (13.9)
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Baseline walk <325 (Placebo N=23)	N=23	N=23	N=26
Mean difference (SE)	57.6 (16.5)	65.4 (18.0)	86.5 (14.8)
99% CI	(15.0, 100.1)	(18.9, 111.8)	(48.2, 124.7)

Source: Sponsor's Table 5.2.2.2

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical and analytical issues

In general, this reviewer agrees with the sponsor's analytical plan and statistical methods. To verify the sponsor's primary efficacy results using t-test stratified for etiology and baseline walking distance, this reviewer performed an alternative analysis of the primary endpoint using ANOVA with main effect for treatment group and class effects for etiology and baseline walking distance. The reviewer's analysis supports the sponsor's results.

5.2 Conclusions and Recommendations

Reviewer's analysis of the primary efficacy endpoint of the single pivotal Phase 3 Study A1481140 showed that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p<0.0001$) better than placebo relative to 6-minute walk test at 12 weeks.

The secondary efficacy analysis showed that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p\leq 0.021$) better than placebo relative to mean pulmonary artery pressure (PAP) at 12 weeks. Relative to time to clinical worsening, the comparison of sildenafil 80 mg to placebo showed no statistically significant reduction. Therefore, according to the pre-specified sequential step-down testing procedure, no further secondary endpoints and doses were evaluated. Safety results showed that proportion of subjects with treatment related adverse events was higher in the sildenafil 80 mg group. All five subjects who permanently discontinued from the study due to adverse events were in the sildenafil 80 mg group. For one of the subjects, adverse events were classified as treatment related.

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