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Long-Term Treatment with Sildenafil Citrate in Pulmonary Arterial Hypertension: SUPER-2

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Lewis J Rubin, MD, has been a consultant and investigator for Pfizer, Gilead, Actelion, and United Therapeutics.

David B. Badesch, MD, has received honoraria for service on steering committees or advisory boards for GlaxoSmithKline, Actelion/CoTherix, Gilead/Myogen, Pfizer/Encysive, United Therapeutics/Lung Rx, Lilly/ICOS, Mondo-Biotech/mondoGEN, Biogen IDEC, and Bayer. He has received grant support for clinical studies from GlaxoSmithKline, Actelion/CoTHerix, Gilead/Myogen, Pfizer/Encysive, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, and Novartis.

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How does this advance the field? Randomized clinical trials in pulmonary arterial hypertension are typically of relatively short duration. Long-term effects of drug therapy are important to assess because efficacy may wane as the disease progresses. While longer periods of treatment randomization would be ideal, such study is impractical for a life-threatening condition. Accordingly, open-label extension studies provide useful data regarding long-term outcomes with therapy.

What are the clinical implications? This report presents long-term data from a large, international open-label study following patients from the SUPER-1 randomized study of sildenafil in pulmonary arterial hypertension. In this long-term (up to 3 years) study, sildenafil appeared to sustain improvements and be well tolerated in most study patients, providing clinicians with critical findings on the chronic use of sildenafil in pulmonary arterial hypertension.

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Abstract

Background: The long-term safety and tolerability of sildenafil treatment for pulmonary arterial hypertension (PAH) were assessed.

Methods: 259 of 277 randomized and treated patients completed a 12-week, double-blind, placebo-controlled trial (SUPER-1) of oral sildenafil in treatment-naïve patients with PAH (96% functional class II/III) and entered an open-label uncontrolled extension study (SUPER-2) that continued until the last patient completed 3 years of sildenafil treatment. Patients were titrated to sildenafil 80 mg thrice daily (TID); 1 dose reduction for tolerability was allowed during the titration phase.

Results: The median duration of sildenafil treatment across SUPER-1 and 2 was 1242 days (range, 1-1523 days); 170 (61%) patients completed both studies, and 89 patients discontinued from SUPER-2. After 3 years, 87% of 183 patients on treatment were receiving sildenafil 80 mg TID. Of patients remaining under follow-up, 3%, 10%, and 18% were receiving a second approved PAH therapy at 1, 2, and 3 years, respectively. At 3 years post-SUPER-1 baseline, 127 patients had an increased six-minute-walk distance (6MWD); 81 improved and 86 maintained functional class. Most adverse events were of mild or moderate severity. At 3 years, 53 patients had died (censored, n=37). Three-year estimated survival was 79%; if all censored patients were assumed to have died, 3-year survival was 68%. No deaths were considered to be treatment related.

Conclusions: Long-term treatment of PAH initiated as sildenafil monotherapy was generally well tolerated. After 3 years, the majority of patients (60%) who entered the SUPER-1 trial improved or maintained their functional status, and 46% maintained or improved 6MWD.

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List of abbreviations:

APAH: associated pulmonary arterial hypertension

6MWD: 6-minute walk distance

cGMP: cyclic guanosine monophosphate

FC: functional class

HPAH: heritable pulmonary arterial hypertension

IPAH: idiopathic pulmonary arterial hypertension

PAH: pulmonary arterial hypertension

PDE5: phosphodiesterase type 5

SUPER: Sildenafil Use in Pulmonary Arterial Hypertension

TID: three times daily

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Pulmonary arterial hypertension (PAH) is a progressive disease leading to changes in pulmonary hemodynamics that eventually cause right ventricular enlargement and hypertrophy, and ultimately right heart failure.[1] Drugs from 3 classes, prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type-5 (PDE5) inhibitors, are currently approved to treat PAH.[2,3] Because treatments are not curative, patients require long-term therapy. The initial efficacy of PAH-targeted treatments has not always been maintained[4,5]; therefore, long-term efficacy and safety data are required to assess which treatment options optimally balance efficacy and safety in PAH patients.

Following several published reports suggesting that sildenafil is a beneficial treatment for PAH,[6-13] sildenafil was shown to be safe and efficacious over a 12-week interval in PAH in an international, multicenter, double-blind, placebo-controlled study (**S**ildenafil **U**se in **P**ulmonary Art**e**rial Hype**r**tension [SUPER]-1), in which patients were randomized to placebo or one of 3 doses of sildenafil citrate (20 mg, 40 mg, or 80 mg three times daily [TID]).[14] Patients who completed the SUPER-1 study were eligible for its open-label uncontrolled extension study (SUPER-2), the results of which are reported herein. The primary objectives of SUPER-2 were to describe the long-term safety and tolerability of sildenafil in PAH patients. Changes in 6-minute walk distance (6MWD) and World Health Organization (WHO) functional class (FC) status were documented, and survival was estimated.

Methods and Materials

Study design

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The extension study was conducted from December 2002 to February 2007; the study ended when the last patient enrolled in the extension study completed 3 years of sildenafil treatment. All patients entering the extension trial were titrated up to sildenafil 80 mg TID, unless the dose was not tolerated. Patients assigned to placebo or sildenafil 20 or 40 mg TID in SUPER-1 initially received sildenafil 40 mg TID; after 6 weeks, they were titrated to sildenafil 80 mg TID as tolerated. Patients in the sildenafil 80 mg TID group were maintained at this dose and underwent a dummy up-titration. Patients could down-titrate once during the initial 12 weeks of SUPER-2 for intolerable adverse events. Patients remained blinded to their SUPER-1 treatment assignment until all patients had completed 12 weeks of the SUPER-2 study. Assessments were conducted at scheduled visits: baseline (week 12 of SUPER-1), 6 and 12 weeks after beginning SUPER-2 treatment, and every 3 months thereafter.

Written informed consent was obtained from all patients; local institutional review boards or independent ethics committees approved the study protocol. The authors had full access to all study data and take responsibility for the integrity of the data and the accuracy of the analysis.

Patients

To enter SUPER-2, patients must have completed the SUPER-1 trial, and given informed consent to participate in the extension study. Patients were not permitted to take nitrates or nitric oxide donors of any kind, ritonavir, or alpha blockers. Conventional PAH therapies (warfarin, calcium channel blockers, digoxin, oxygen, and diuretics) were

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allowed. If (per the clinical investigator) a patient deteriorated, additional approved PAH therapy (including endothelin receptor antagonists and prostacyclin analogues, with dose adjustments as clinically indicated) could be started during SUPER-2. The protocol was amended in January 2005 to allow commercially available bosentan to be used concomitantly with sildenafil during SUPER-2.

Efficacy Measures

At all scheduled visits, 6MWD and WHO FC were assessed. If 6MWD or WHO FC data were missing at a visit, the worse score of non-missing neighbor values was used. If a patient was enrolled on the visit day but had a missing assessment and no subsequent assessment, then the data were classified as 'missing.' The survival status of all patients who discontinued (including patients who underwent lung or heart-lung transplantation) was followed on a yearly basis and at study end. Survival rates at 1, 2, and 3 years were calculated for all patients and by subgroups using Kaplan-Meier estimates.

Safety

Baseline for the safety data in the SUPER-2 study was considered to be week 12 of the SUPER-1 study. All observed or volunteered adverse events (AEs) in patients entering the extension study were recorded using Medical Dictionary for Regulatory Activities, with severity and the investigator's opinion of the relationship to the study treatment noted. Laboratory results were considered AEs if they were associated with accompanying symptoms; required additional testing or intervention; precipitated a

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change in study drug dose, discontinuation, or significant additional therapy; or if test results were considered to be an AE by the investigator.

Statistical Analyses

Statistical methods for the analysis of efficacy data mainly comprised simple descriptive summaries for each parameter assessed at the specified time points during the study. 6MWD categories were established *post hoc*. Unless otherwise stated, changes in measures are described relative to the SUPER-1 baseline, including all patients randomized (N=277) in the SUPER-1 study. Only patients who entered SUPER-2 were included for the percentage of patients on each dose of sildenafil during the extension study and the percentage of patients taking a second PAH therapy.

A Cox regression model was used to analyze the relationship between the initial change in 6MWD (change between week 0 and week 12 for sildenafil-treated SUPER-1 patients and change between week 12 and week 24 for placebo-treated SUPER-1 patients) and survival after the initial 12-week sildenafil treatment (from week 12 onward for sildenafil-treated SUPER-1 patients and from week 24 onward for placebo-treated SUPER-1 patients). The analysis was performed by baseline 6MWD, which was dichotomized as <325 m or ≥325 m, and also used for stratification during SUPER-1 randomization[14].

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The association of time since diagnosis (initiation of sildenafil treatment within versus beyond 0.3 years of diagnosis) with survival from SUPER-1 baseline was evaluated in a *post hoc* analysis.

Results

Patients

Of the 277 patients enrolled and treated in the SUPER-1 study, 259 entered the SUPER-2 extension (**Table 1**); 4 died and 8 withdrew before completing the SUPER-1 study; 6 elected not to enter SUPER-2 (**Figure 1**). At week 24 (after 12 weeks of SUPER-2), 95%, 3%, and 2% of patients who entered the extension study and remained on treatment (n=256) were receiving sildenafil 80, 40, and 20 mg TID, respectively. At 3 years, of the 183 patients who remained on sildenafil treatment, 87%, 8%, and 5% were receiving sildenafil 80, 40, and 20 mg TID, respectively. The median total duration of sildenafil treatment was 1242 days; the majority of patients (71%) received sildenafil monotherapy throughout the study. Of patients remaining under follow-up, 3%, 10%, and 18% were receiving additional PAH therapy at 1, 2, and 3 years, respectively; in almost all such cases, patients were receiving 1 additional therapy (33 subjects were taking 36 additional therapies at year 3), which was bosentan for 25 of these 33 patients.

6MWD and WHO Functional Class

At 3 years post SUPER-1 baseline, 127 (46%) of 277 patients increased 6MWD relative to SUPER-1 baseline, 49 (18%) patients decreased 6MWD from baseline, 53 (19%) had died, and 48 (17%) discontinued or were missing **(Table 2**). FC status was improved (n=

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81, 29%) or maintained (n=86, 31%) in 167 of 277 patients relative to SUPER-1 baseline; 15 (5%) patients had FC status decline, and 95 (34%) had died, discontinued, or had missing data (**Table 3**).

Survival

At 3 years from SUPER-1 baseline, 187 patients were alive, 53 had died, and 37 had been censored. The overall Kaplan-Meier survival estimate, based on data from all 277 SUPER-1 patients, was 79% (**Table 4**). The Kaplan-Meier estimate is upwardly biased; however, the most conservative figure for 3-year survival (*i.e.*, assuming that all censored patients had died) is 68%. Patients with idiopathic PAH had higher Kaplan-Meier 3-year survival than patients with PAH associated with connective tissue disease (81% vs 72%); patients walking ≥325 m at SUPER-1 baseline had better 3-year survival compared with those walking <325 m at SUPER-1 baseline (84% and 70%, respectively)

Kaplan-Meier estimates of survival by the 4 treatments (placebo and 3 sildenafil groups in the SUPER-1 study) are presented in **Figure 2**.

The Cox regression analysis to investigate the relationship between change in 6MWD over the first 12 weeks of sildenafil treatment and subsequent survival suggested an interaction between baseline walk in SUPER-1 and change in 6MWD. For patients whose baseline walk was <325 m, deterioration in 6MWD during the first 12 weeks of sildenafil treatment was associated with subsequent poor survival (HR 0.241, 95% CI 0.117 to 0.498); there was a lesser association between change in 6MWD and survival for

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those whose baseline 6MWD was ≥325 m (HR 1.967, 95% CI 0.687 to 5.628) (**Figures 3A and 3B**).

Time since diagnosis (initiation of sildenafil treatment within/beyond 0.3 years of diagnosis) was not associated with survival from SUPER-1 baseline (HR 0.921, 95% CI 0.522 to 1.624).

Safety

Sildenafil appeared to be generally well tolerated in the extension study, and AEs were consistent with the known adverse effects of sildenafil, including headache, dyspepsia, diarrhea, and blurred vision. Most AEs were mild or moderate in severity (**Table 5**). Serious AEs (SAEs) were reported by 153 patients. Perceived treatment-related SAEs included grand mal seizure, drug hypersensitivity, urticaria and angioedema, gastroesophageal reflux disease, posterior subcapsular cataract, and hypotension. Thirty-nine patients permanently discontinued due to AEs, including 9 patients who discontinued because of perceived sildenafil-related AEs (chest tightness, neck stiffness, myalgia, headache, visual field constriction, dyspnea, abdominal pain, diarrhea, nausea, vomiting, dizziness, worsening hypotension, and drug hypersensitivity). Because of the nature of the study design, many patients were treated for >3 years with sildenafil; at study end, 64 patients died overall, of whom 59 had entered the extension study and received treatment (Figure 1). None of the deaths was considered to be related to treatment. Seven patients underwent lung transplantation.

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Discussion

In this open-label, uncontrolled, observational extension study of PAH patients treated with sildenafil for ≥3 years, 46% of patients increased their 6MWD relative to SUPER-1 baseline (with or without the initiation of additional approved PAH therapies), and 60% maintained or improved their baseline functional status at 3 years. These estimates are downwardly biased because all patients with missing assessments and all patients who discontinued are thereby assumed to have deteriorated. The Kaplan-Meier estimated 3-year survival rate for the overall patient population from the start of the double-blind SUPER-1 study was 79%; the most conservative estimate (assuming that all censored patients had died) places this number at 68%. Patients with baseline 6MWD <325 m in SUPER-1 who lacked improvement in 6MWD during the first 12 weeks of sildenafil treatment had poor survival (<35%). Most AEs were mild to moderate in severity; headache, dyspepsia, diarrhea, and blurred vision were reported most frequently.

In SUPER-1, sildenafil improved 6MWD and functional class in the short-term. Because PAH is a progressive, degenerative condition, if 46% of subjects are walking further than they did at baseline (ie, the start of SUPER-1 for all patients, regardless of randomization to placebo or sildenafil) and 60% have maintained or improved their functional class (whilst being predominantly on sidenafil monotherapy) after 3 years, these data suggest that sildenafil has long term efficacy. However, a long term randomized controlled trial would be needed to reliably assess the benefit-to-risk profile.

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Interventions are needed to improve PAH survival.[15] Drugs from 3 classes, prostacyclin analogues, endothelin receptor antagonists, and PDE5 inhibitors,[16,17] have been approved to treat PAH.[2,3] Prostacyclin analogues are administered by continuous intravenous infusion (epoprostenol, treprostinil, and iloprost), continuous subcutaneous infusion (treprostinil), or inhalation 4–≥6 times per day (iloprost, treprostinil[18]).[2] Continuous intravenous infusion therapies have delivery systems that can be associated with clinically significant complications, such as bacteremia and thromboembolic events. The PDE5 inhibitors and endothelin receptor antagonists are administered orally.

Two long-term, open-label, uncontrolled observational studies of epoprostenol infusion monotherapy in New York Heart Association FC III or IV patients with idiopathic PAH/familial PAH (IPAH/HPAH) showed survival rates of 85%, 70%, 63%, and 55% at 1, 2, 3, and 5 years, respectively,[19] and 88%, 76%, and 63% at 1, 2, and 3 years, respectively.[20] The 1- and 2-year survival estimates for FC III IPAH/HPAH patients treated with bosentan monotherapy (to which additional medication could be added during the extension studies) was 96% and 89%, respectively.[21]

These survival estimates are difficult to compare with those of the long-term sildenafil study reported here; the patient population in the current study was not limited to patients with IPAH/HPAH (37% had PAH associated with other conditions [APAH]) and 39% of patients were FC II at SUPER-1 baseline (3% FC IV). In an open-label study with sitaxsentan and a bosentan comparator arm, the patient population was more like that of the current study, with both IPAH/HPAH and APAH patients who were mostly FC II and

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III at baseline. The 1-year survival rate was 96% with sitaxsentan, and 88% with bosentan.[22] Again, however, one must be cautious in making comparisons between these interventions.

When to initiate treatment, change treatment, or add a second agent in PAH patients are unanswered questions. Placebo treatment (for 12 weeks in SUPER-1) was associated with poorer longer-term survival compared with the 3 groups receiving sildenafil treatment from the start of SUPER-1. However, this association must be viewed with caution. It is consistent with recent reviews that found that placebo-treated patients are more likely to experience clinical deterioration in short-term studies (eg, 12–24 weeks), although the long-term implications (*i.e.*, survival) remain unclear due to the *post-hoc* nature of the analysis.[23]

Targeted therapies significantly improved 6MWD and relative risk of death in a meta-analysis of studies in PAH patients.[24] Our finding that poor walkers (<325 m) at SUPER-1 enrollment whose 6MWD failed to improve after the first12 weeks of sildenafil treatment had reduced survival at 3 years may aid in the early identification of patients who have particularly poor prognosis and may be appropriate candidates for additional early therapy. Thus, patients with poor baseline 6MWD should be monitored closely during the first several months after initiating sildenafil; patients who do not improve or deteriorate should be considered for more aggressive approved therapy (if available).

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Long-term uncontrolled extension studies, such as this one, can provide useful descriptive information about the longer-term clinical course of patients; however, the lack of a randomized comparator limits causal inference. Although no guidance was provided for additional therapy during our study, subjective opinion drives clinical management decisions and therfore our study is applicable in "real-world" clinical settings with patients having similar disease characteristics to our study population. An additional limitation of this study is that most patients (87% of those on treatment at 3 years) were titrated to sildenafil 80 mg TID. When the double-blind and extension studies were designed, it was anticipated that this highest evaluated dose would be the most efficacious. However, the 20-mg dose remains the only approved dose based upon statistical benefit at 12 weeks; long-term extension studies do not provide a solid base to determine if additional benefit is achieved with a larger dose or if the higher dose is necessary for maintenance of apparent effect. Therefore, the results of this study may not be predictive of outcomes for patients treated long-term with lower doses of sildenafil.

In conclusion, in PAH, long-term treatment initiated as sildenafil monotherapy was generally well tolerated. After 3 years in the SUPER-2 extension study, the majority of patients (60%) who entered the SUPER-1 trial improved or maintained their functional status, and 46% maintained or improved 6MWD.

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the final version for publication. Drs. Rubin, Badesch, Galiè, Simonneau, Barst, Ghofrani, and Fleming significantly contributed to the study design and conception. Dr. Oakes and Mr. Layton were responsible for statistical analyses.

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Figure Legends

Figure 1. Study flowchart.

Figure 2. Kaplan-Meier estimates of survival by treatment group in the SUPER-1 study. HR=hazard ratio.

Figure 3. Kaplan Meier survival following 12 weeks of sildenafil treatment (i.e., for SUPER-1 patients treated with any dose of sildenafil, weeks 0 to 12; for SUPER-1 patients treated with placebo, weeks 12 to 24) by change in 6-minute walk distance (6MWD; ≤0 m or >0 m). Top panel shows patients whose SUPER-1 baseline 6MWD was <325 m; bottom panel shows patients whose SUPER-1 baseline 6MWD was ≥325 m.

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List of abbreviations:

APAH: associated pulmonary arterial hypertension

6MWD: 6-minute walk distance

cGMP: cyclic guanosine monophosphate

FC: functional class

HPAH: heritable pulmonary arterial hypertension

IPAH: idiopathic pulmonary arterial hypertension

PAH: pulmonary arterial hypertension

PDE5: phosphodiesterase type 5

SUPER: Sildenafil Use in Pulmonary Arterial Hypertension

TID: three times daily

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Table 1. Comparison of baseline patient characteristics in the SUPER-1 and SUPER-2 studies based on SUPER-1 randomization group

	Assigned group at SUPER-1 baseline*			
	Placebo	Sildenafil 20 mg	Sildenafil 40 mg	Sildenafil 80 mg
Number of patients				
SUPER-1	70	69	67	71
SUPER-2†	67	65	63	64
Age, mean (range) y				
SUPER-1	49 (18–78)	47 (19–78)	51 (23–81)	48 (20–81)
SUPER-2†	50 (23–78)	47 (19–78)	50 (24–77)	47 (20–71)
Females, n (%)				
SUPER-1	57 (81%)	49 (71%)	47 (70%)	56 (79%)
SUPER-2†	54 (81%)	45 (69%)	46 (73%)	50 (78%)
IPAH-HPAH/APAH, n/n				
SUPER-1	42/28	44/25	43/24	46/25
SUPER-2†	41/26	41/24	39/24	43/21
WHO FC I, n				
SUPER-1	1	0	0	0
SUPER-2†	1	0	0	0
WHO FC II, n				
SUPER-1	32	24	23	28
SUPER-2†	32	22	21	25
WHO FC III, n				
SUPER-1	34	40	44	42
SUPER-2†	32	38	42	38
WHO FC IV, n				
SUPER-1	3	5	0	1
SUPER-2†	2	5	0	0

IPAH=idiopathic PAH; HPAH=heritable PAH; APAH=PAH associated with connective tissue disease or repaired congenital systemic-to-pulmonary shunts.

*Because the double-blind phase included a placebo arm that did not receive treatment for 12 weeks, the original SUPER-1 randomization groups were retained for analysis of SUPER-2.

†Includes only patients entering SUPER-2. Three patients from the placebo group, 4 from the sildenafil 20 mg, 4 from the sildenafil 40 mg, and 7 from the sildenafil 80 mg TID groups (total of 18 patients) from the SUPER-1 study did not enter SUPER-2.

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Table 2. Change in Categorized 6-Minute Walk Distance at 3 Years Relative to SUPER-1 Baseline*

Walk Category†	n	Percent
>60 m Improvement	81	29.2
>30 – 60 m Improvement	22	7.9
>0 – 30 m Improvement	24	8.7
≥0 – 30 m Worsening	18	6.5
>30 – 60 m Worsening	12	4.3
>60 m Worsening	19	6.9
Discontinued	41	14.8
Died	53	19.1
Missing	7	2.5

*Analysis includes 18 patients from the double-blind study who did not enter the extension trial.
†These categories were specified post-hoc.
Analysis description: When a patient had a missing baseline walk, the screening walk was used. The analysis relates to 3 calendar years (1095 days). If a patient died before 3 years, then the patient was classified as 'died'; if a patient discontinued before 3 years, then the patient was classified as 'discontinued'. If 6MWD was missing in the visit window, the worst score of the non-missing neighbors was used. If a patient was enrolled on the target day but had a missing 6MWD and no subsequent 6MWD, then the data were classified as 'missing.'

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Table 3. Functional Class: Change from SUPER-1 Baseline at 3 Years in All Patients*

Change in Functional Class	n	%
Improved 2 classes	10	3.6
Improved 1 class	71	25.6
No change	86	31.0
Worsened 1 class	15	5.4
Discontinued	41	14.8
Died	53	19.1
Missing	1	0.4

*Analysis includes 18 patients from the double-blind study who did not enter the extension trial.
Analysis description: The analysis relates to 3 calendar years (1095 days). If a patient died before 3 years then the patient was classified as 'died'; if a patient discontinued before 3 years then the patient was classified as 'discontinued'. If functional class was missing in the visit window, the worst score of the non-missing neighbors was used. If a patient was enrolled on the target day but was missing a functional class score with no subsequent assessment, then the data were classified as 'missing.'

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Table 4. Kaplan-Meier Survival Estimates (All Patients)*

		SUPER -1 Randomized Treatment				
Survival Period		All N=277	Placebo n=70	Sildenafil 20 mg n=69	Sildenafil 40 mg n=67	Sildenafil 80 mg n=71
1 Year	Percent survived	94	86	96	100	93
	(95% CI)	(91, 97)	(78, 95)	(95, 100)	(100, 100)	(86, 99)
2 Years	Percent survived	88	81	91	95	86
	(95% CI)	(84, 92)	(72, 91)	(84, 98)	(89, 100)	(78, 95)
3 Years	Percent survived	79	68	84	84	78
	(95% CI)	(74, 84)	(57, 80)	(75, 93)	(75, 94)	(68, 88)

*Analysis includes 18 patients from the double-blind phase who did not enter the extension trial.

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Table 5. Adverse Events Occurring During SUPER-2 Treatment

	All Cause				Treatment Related			
Adverse event, n (%)	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**
Peripheral edema	64 (25)	28	34	2	7 (3)	4	3	0
Diarrhea	61 (24)	26	31	4	21 (8)	12	8	1
Cough	60 (23)	39	20	1	6 (2)	4	2	0
Pulmonary hypertension aggravated	60 (23)	7	26	27	0	0	0	0
Arthralgia	56 (22)	26	27	3	8 (3)	5	3	0
Chest pain	56 (22)	27	22	7	1 (<1)	1	0	0
Headache	56 (22)	16	32	8	42 (16)	11	26	5
Nasopharyngitis	56 (22)	29	27	0	4 (2)	2	2	0
Back pain	51 (20)	26	20	5	10 (4)	8	2	0
Dizziness	49 (19)	25	22	2	11 (4)	9	2	0
Upper respiratory tract infection	46 (18)	21	23	2	1 (<1)	1	0	0
Dyspnea	46 (18)	19	18	9	2 (1)	0	2	0
Dyspnea exacerbated	45 (17)	9	23	13	2 (1)	0	1	1
Dyspepsia	43 (17)	21	22	0	27 (10)	13	14	0
Nausea	43 (17)	25	14	4	15 (6)	10	4	1
Palpitations	41 (16)	29	9	3	2 (1)	1	1	0
Influenza	39 (15)	16	22	1	0	0	0	0
Limb pain	37 (14)	17	17	3	7 (3)	3	4	0
Fatigue	36 (14)	23	11	2	4 (2)	3	1	0
Pharyngitis	36 (14)	18	17	1	1 (<1)	1	0	0
Vomiting	36 (14)	18	16	2	11 (4)	7	4	0
Pyrexia	34 (13)	20	14	0	1 (<1)	1	0	0
Vision blurred	33 (13)	28	5	0	19 (7)	17	2	0
Abdominal pain	32 (12)	11	15	6	14 (5)	5	7	2
Upper abdominal pain	30 (12)	16	11	3	13 (5)	6	4	3
Asthenia	30 (12)	14	13	3	3 (1)	3	0	0
Bronchitis	30 (12)	9	17	4	1 (<1)	0	1	0
Epistaxis	30 (12)	23	4	3	4 (2)	3	1	0
Urinary tract infection	30 (12)	9	20	1	0	0	0	0
Syncope	28 (11)	5	13	10	3 (1)	0	3	0
Insomnia	27 (10)	13	14	0	1 (<1)	0	1	0
Pneumonia	26 (10)	0	13	13	0	0	0	0
Right ventricular	26 (10)	0	10	16	0	0	0	0

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failure								
Anemia	25 (10)	13	8	4	2 (1)	1	0	1
Conjunctival hyperemia	25 (10)	22	3	0	9 (4)	7	2	0
Hypotension	21 (8)	9	9	3	10 (4)	4	6	0
Sinusitis	20 (8)	7	12	1	0	0	0	0
Myalgia	19 (7)	11	8	0	11 (4)	6	5	0
Edema	19 (7)	8	10	1	0	0	0	0
Retinal hemorrhage	19 (7)	19	0	0	5 (2)	5	0	0
Depression	17 (7)	7	9	1	0	0	0	0
Lower respiratory tract infection	17 (7)	1	11	5	0	0	0	0
Cyanosis	16 (6)	12	4	0	0	0	0	0
Episcleral hyperemia	16 (6)	15	1	0	11 (4)	10	1	0
Gastroenteritis	16 (6)	9	4	3	0	0	0	0
Pruritus	16 (6)	10	6	0	6 (2)	3	3	0
Constipation	15 (6)	8	7	0	3 (1)	1	2	0
Hypokalemia	15 (6)	9	4	2	0	0	0	0
Productive cough	15 (6)	5	9	1	0	0	0	0
Vertigo	15 (6)	8	6	1	2 (1)	2	0	0
Visual disturbance	15 (6)	11	4	0	8 (3)	7	1	0
Anorexia	14 (5)	8	6	0	3 (1)	1	2	0
Cardiac murmur	14 (5)	14	0	0	0	0	0	0
Flushing	14 (5)	9	4	1	9 (4)	7	1	1
Muscle cramp	14 (5)	4	7	3	5 (2)	2	3	0
Jaw pain	14 (5)	11	3	0	3 (1)	3	0	0
Toothache	14 (5)	8	5	1	0	0	0	0
Gastritis	13 (5)	5	7	1	6 (2)	3	3	0
Decreased hemoglobin	13 (5)	4	8	1	3 (1)	2	1	0
Increased international normalized ratio	13 (5)	7	6	0	1 (<1)	1	0	0
Weight gain	13 (5)	5	8	0	1 (<1)	1	0	0

*Includes only patients who entered the extension trial. Adverse events occurring in ≥5% of patients are reported.

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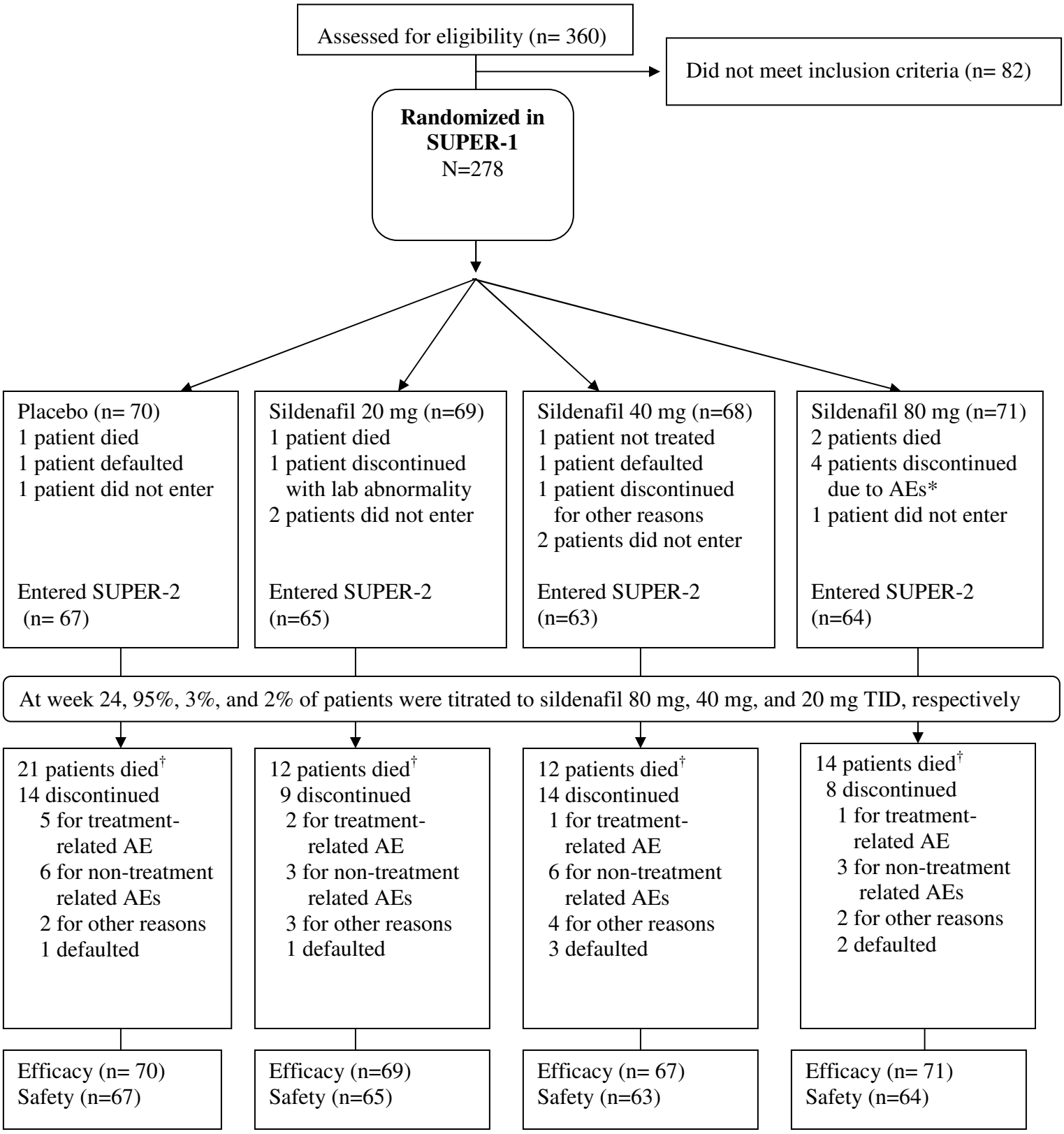
Figure 1



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AE=adverse event; TID=three times daily. Default includes lost to follow up or patient withdrawn consent.
*One of the patients who discontinued later died.
†Of the 59 patients who entered the extension study and died, death was the reason for discontinuation in 44 patients.

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Figure 2

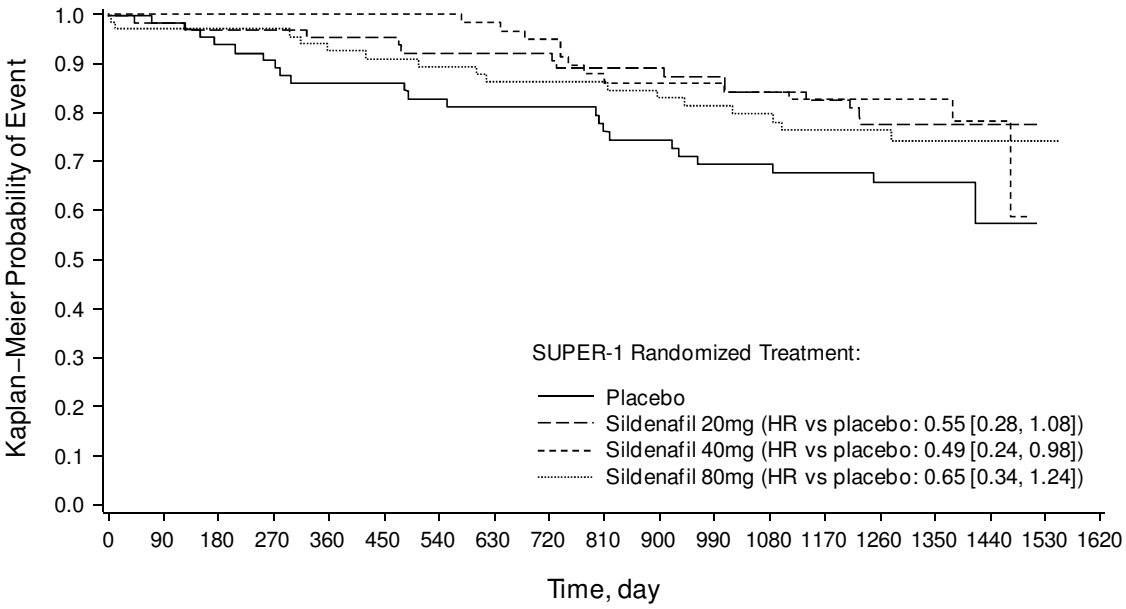

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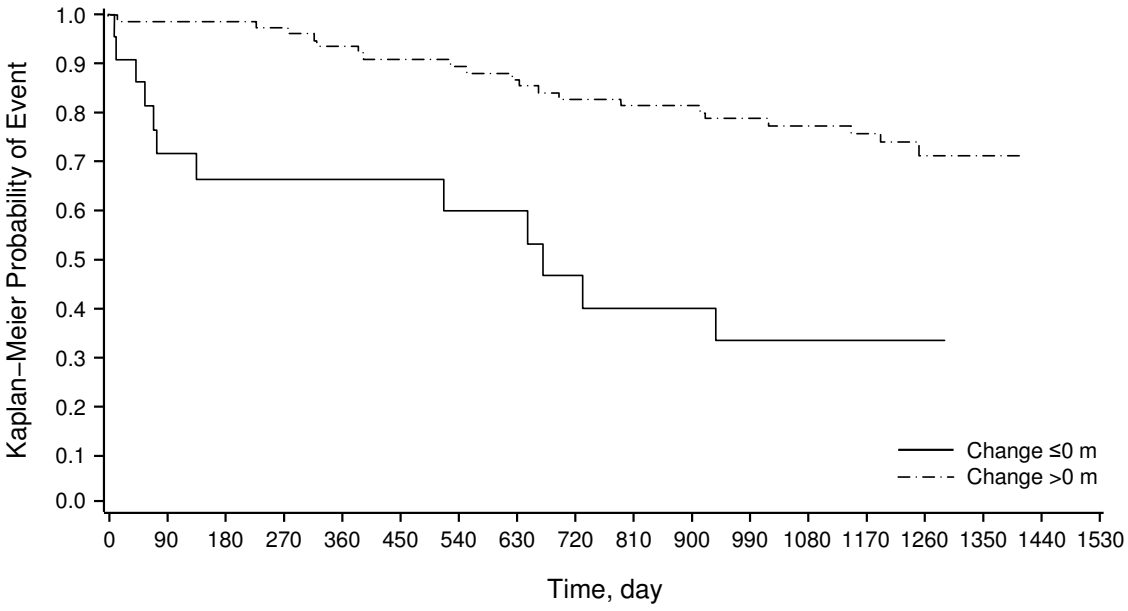
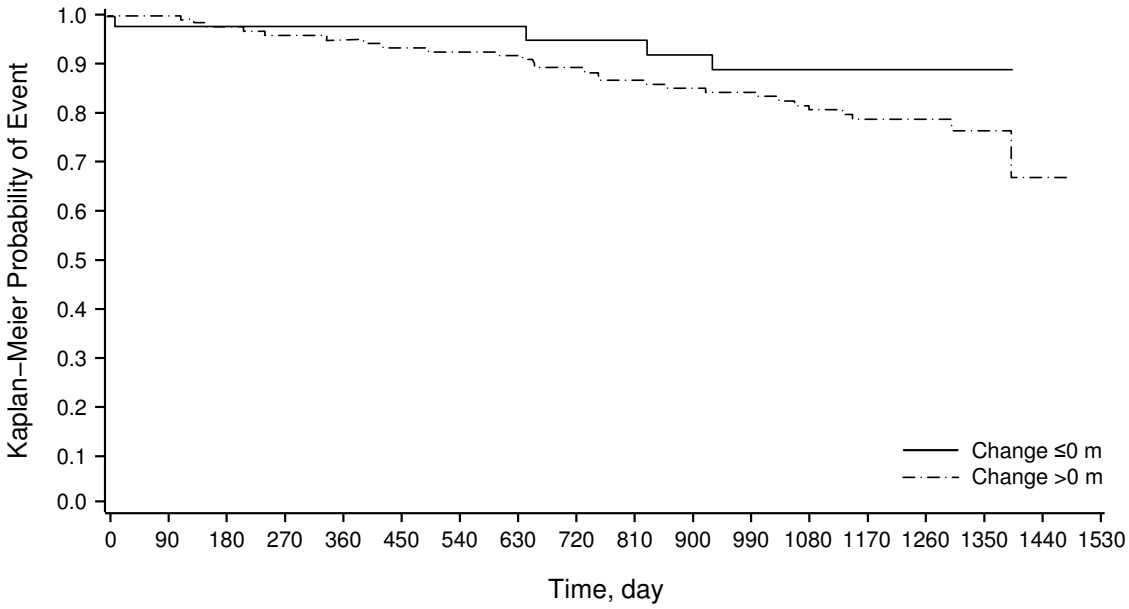
Figure 3





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Long-Term Treatment with Sildenafil Citrate in Pulmonary Arterial Hypertension: SUPER-2

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