CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-845

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA:	21-845
Drug:	sildenafil citrate (Revatio™)
Indication:	Treatment of pulmonary hypertension
Sponsor:	Pfizer, Inc.
Review date:	May 23, 2005
Reviewer:	Thomas A. Marciniak, M.D. Lead Medical Officer

Recommendation and Conclusions

I recommend approval of sildenafil for the treatment of pulmonary arterial hypertension (PAH). The single pivotal study shows convincingly and highly statistically significantly that sildenafil use improves function, i.e., walking distance, in patients with PAH. The lowest dose test, 20 mg TID, appears to be as effective as the higher doses tested. The adverse effect profile seems acceptable relative to the benefit and compared to adverse event profiles of other approved drugs. I do recommend that a post-marketing study be performed testing lower doses of sildenafil and a sildenafil-warfarin interaction study be done.

Materials Used in Review

1. NDA 21-845 submissions
2. Clinical Review by Maryann Gordon, M.D., dated May 3, 2005
3. Statistical Review by Valeria Freidlin, Ph.D., dated May 4, 2005
4. Pharmacology/Toxicology Review by Thomas Papoian, Ph.D., dated May 12, 2005
5. Chemistry Review by William C. Timmer, Ph.D., dated May 10, 2005
6. Clinical Pharmacology and Biopharmaceutics Review by Elena V. Mishina, Ph.D., draft

Background

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). It is approved for the treatment of erectile dysfunction and marketed since 1998 as Viagra®. This application is for the indication of the treatment of pulmonary arterial hypertension (PAH) in adults. Nitric oxide (NO) activation of the enzyme guanylate cyclase results in increased levels of cGMP, which produces vascular smooth muscle relaxation and vasodilatation. As an inhibitor of PDE5, sildenafil enhances the effect of NO and the effects on vascular smooth muscle tone. NO and cGMP function in modulating vascular tone in the pulmonary and other vascular beds and there are high levels of PDE5 in the pulmonary epithelium. Hence the sponsor pursued a development program for PAH. This applications includes the results of one double-blind, randomized, placebo-controlled trial as the major evidence supporting

efficacy and safety and the results of a long-term extension of that trial to provide additional data on safety.

Chemistry

The chemistry reviewer, Dr. William Timmer, recommends approval from a chemistry, manufacturing, and controls perspective. The composition of the 20 mg film-coated tablet is essentially the same as that of the tablets marketed for erectile dysfunction. The differences of the new tablet are (1) removal of the blue dye from the film-coat; (2) change in the shape from diamond to oval; and (3) the 20 mg strength. Dr. Timmer judges that the physical and chemical characteristics, impurity profile, and stability are adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product and acceptable batch-to-batch variations. Based on analysis of the stability data the approved shelf life is 60 months at room temperature when protected from light. The sponsor claims a categorical exclusion of the environmental assessment. The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities. Dr. Timmer's review does not note any deficiencies and he does not recommend any post-marketing commitments.

Pre-Clinical Pharmacology and Toxicology

The pharmacology reviewer, Dr. Thomas Papoian, recommends approvability of sildenafil for PPH from a nonclinical perspective. He notes that several primary and secondary pharmacodynamic studies, pharmacokinetic studies, and safety pharmacology studies were submitted to support the new indication. No toxicology studies were submitted, since these have already been submitted for NDA #20-895 (Viagra), and have been cross-referenced in the current NDA.

Dr. Papoian reviewed the following studies: (1) The Effect of Intravenously-Administered UK-92,480,27 on Hypoxic Pulmonary Vasoconstriction in the Anesthetized Dog; (2) Inhibition of the Novel Human Recombinant Cyclic Nucleotide Phosphodiesterase (PDE) Enzymes 7 to 11 by Sildenafil, UK-103,320, UK-114,542, UK-150,564, UK-343,664 and UK-347,334; (3) Determination of cGMP-hydrolyzing PDE Isozyme Activity in Human Cardiac Muscle; (4) To Determine Whether Sildenafil (UK-92,480-10) Has Agonist/Antagonist Activity at Human A2a Receptors Expressed in HEK Cells; (5) An In Vitro Evaluation of the Effect of Sildenafil (UK-92,480) on Isoprenaline-induced Contractility in Rabbit Isolated Papillary Muscle; and (6) Determination of Brain Penetration of [14C]-Sildenafil in Male Rat Following Single Subcutaneous (2 mg/kg) Administration. There are no clinical issues suggested by these studies. Please see his review for relevant comments on the studies.

Dr. Papoian has the following labeling recommendation: Due to the differences between the dose used for erectile dysfunction (100 mg Viagra) versus the 20 mg three times a day (TID) dosing recommended for pulmonary hypertension (60 mg/day Revatio), the sections of the Revatio draft labeling for "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" differ from the labeling for Viagra, specifically the dose-exposure multiples of animals relative to the human exposure. The draft labeling for carcinogenesis was erroneous in that

Dr. Papoian recommends a correction. The pregnancy labeling was correct as stated, since the daily animal doses were correctly compared to the human dose of 20 mg TID.

Dr. Papoian also notes some additional unresolved labeling issues. These include the rationale for using: (1) , (2) e; (3) surface area to calculate dose-exposure multiples in pregnant rats when systemic exposures in normal rats are available; and (4) the km values selected to estimate exposure multiples based on surface area.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics reviewer, Dr. Elena Mishina, finds the clinical pharmacology and biopharmaceutics sections acceptable provided labeling comments are adequately addressed. She also recommends that a warfarin interaction study be done and that doses lower than 20 mg be studied. Her review focuses on studies involving drug-drug interaction studies (5 total: sildenafil with oral contraceptives, atorvastatin, phenprocoumon, acenocoumarol and bosentan) and population PK and PK/PD studies in PAH patients (one pivotal study and one hemodynamics study). I've summarized below the most pertinent findings from her review:

- Regarding pharmacokinetics in PAH patients, the mean average steady state concentrations of sildenafil after 20 mg TID were about 50% higher compared to healthy volunteers. After 40 and 80 mg TID, average steady state concentrations in patients with pulmonary arterial hypertension were about 30% higher compared to healthy volunteers. The trough levels of sildenafil in pulmonary arterial hypertension patients were twice higher compared to healthy volunteers at all doses.
- Bosentan is a CYP3A4 inducer and the main metabolic pathway of sildenafil occurs through CYP3A4. In the presence of bosentan (125 mg BID), mean sildenafil C_{max} and AUC_t were 55% and 63% lower compared to placebo. In the presence of sildenafil, mean bosentan C_{max} and AUC_t increased by 42% and 50% compared to placebo, most likely due to CYP3A4 induction.
- No clinically relevant PK interactions were observed between sildenafil (up to 100 mg dose) and atorvastatin or oral contraceptives. There were no difference between the treatment groups in the pharmacodynamic interaction studies with anti-coagulants (for both phenprocoumon and acenocoumarol). The design of the interaction studies with anti-coagulants was similar: Daily doses of phenprocoumon or acenocoumarol were given for 14 days. The anti-coagulant was continued and sildenafil 100 mg was administered for two daily doses. INRs for the last two days were compared to preceding two days. PK was not done. The mean INRs by time for the phenprocoumon are shown in Figure 1.

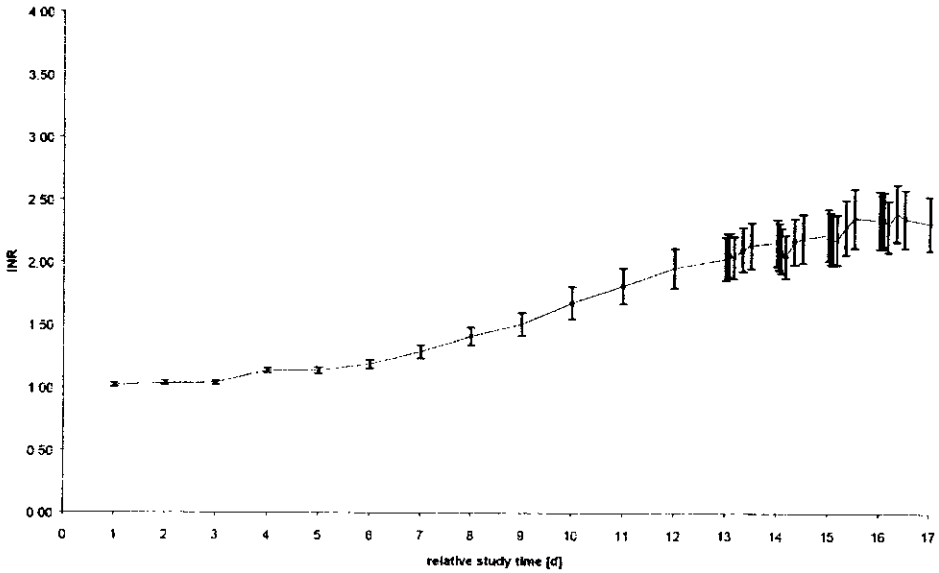


Figure 1: Mean INR values (± SD) for the phenprocoumon interaction study

COMMENT: Note that the INR values are not stable even at the end of the 14-day phenprocoumon-alone period. To show that sildenafil does not affect INR increases from phenprocoumon with this study design, one would have to continue both drugs for at least another 14-day period. Furthermore, this study and the matching one with acenocoumarol do not address whether coumarin derivatives can affect sildenafil PK.

- There was no correlation between the primary clinical endpoint, 6-minute walk distance and sildenafil plasma concentrations. The sponsor described the relationship between the pulmonary vascular resistance (PVRi) and sildenafil plasma concentrations with a linear model. The model describing the relationship between PVRi and sildenafil plasma concentrations showed that this relationship has a very shallow slope. The estimated EC_{50} value of 2.92 ng/mL suggests that a low dose of sildenafil is needed to lower PVRi. However, Dr. Mishina notes that PVRi is not a good surrogate for efficacy because the data show high variability and the tested dose range was not great.

- Dr. Mishina supports the proposed to-be-marketed dosage of 20 mg TID. She notes that sufficient efficacy and safety were shown in the pivotal clinical trials using the proposed regimen. Although sildenafil was well tolerated at doses up to 80 mg TID in PAH patients, the incidence and severity of most adverse events was higher in the 80 mg dose group. The sufficient sildenafil plasma concentrations to significantly increase a 6 minute walking distance were achieved at the low dose of 20 mg TID. However, she also advocates studying lower doses post-marketing.

COMMENT: I agree with recommendation regarding studying doses lower than 20 mg TID post-marketing and I present more of the clinical evidence regarding dose-response below. If the phenprocoumon and acenocoumarol studies were adequate, I would have argued that a warfarin interaction study is not needed. However, given their inadequacies, I also recommend that a warfarin interaction study be done.

Statistical Review

The statistical review, Dr. Valeria Freidlin, corroborated the sponsor's 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. This conclusion is based on the results of one randomized, double-blind, placebo-controlled, parallel group trial, Study A1481140. In this international study 278 patients with pulmonary arterial hypertension (PAH) confirmed by right heart cath (mean pulmonary artery pressure [PAP] =25 and wedge pressure =15) and baseline walking distance 100-450 meters were randomized 1:1:1:1 to placebo or sildenafil 20, 40, or 80 mg TID. Randomization was stratified by etiology (three categories: primary, connective tissue disorder, post-surgical) and baseline walk distance (< or = 325 m). All but one randomized subject received treatment. Of these 63% had primary PAH, 30% PAH secondary to a connective tissue disorder, and 6.5% at least five years post-surgical repair of an atrial or ventricular septal defect, patent ductus arteriosus, or aorto-pulmonary window. The mean age was 49 and 75% were female. The majority were white (75%) with 7% Asians but only 2% blacks.

Most demographic and clinical baseline factors were well balanced among the treatment groups. However, baseline hemodynamic parameters were not well balanced. I show the mean pulmonary artery pressures by treatment group in Table 1 and address the effects upon the primary endpoint later.

Table 1: Reviewer's baseline mean pulmonary artery pressures by group

	Sildenafil dose, mg			
	Placebo	**20**	**40**	**80**
Systolic	87	84	77	80
Diastolic	37	36	31	34
Mean	56	48	54	52

The primary efficacy endpoint was the change from baseline to 12 weeks in 6-minute walking distance at least four hours after the last dose. Walks at estimated peak effect were not done. The primary analysis 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 (using a T-test stratified for the randomization strata) in a step-down fashion. Subjects missing the 6-minute walk at week 12 and having earlier post-treatment walks had the value imputed using last observation carried forward (LOCF). Three secondary endpoints were specified to be tested sequentially: mean PAP, time to clinical worsening, and Borg dyspnea score.

For the primary endpoint 11 patients were not evaluated because of missing baseline or all post-treatment walks, leaving a primary analysis set of 277. Mean walking distances for all sildenafil dose groups were significantly greater than for the placebo group as shown in Table 2 confirmed by Dr. Freidlin.

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

To verify the sponsor's primary efficacy results Dr. Freidlin 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. Her 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. She also found that there was no statistically significant difference between the three sildenafil doses ($p>0.74$). I repeated the ANOVA adding baseline systolic PAP as a covariate and found that the treatment group effect remained highly statistically significant. Dr. Freidlin also performed a sensitivity analysis on all randomized and treated subjects in which she assigned the baseline value to subjects lacking all post-baseline walks and subjects who died. The sensitivity analysis supported the primary analysis ($p<0.001$).

Dr. Freidlin's review notes that there were significant decreases in mean PAP, the first secondary endpoint, but that there was no significant difference for the second secondary endpoint, time to clinical worsening. I show the results for all secondary endpoints in Table 3.

Table 3: Secondary endpoints for Study A1481140

			Sildenafil dose, mg		
		Placebo	20	40	80
Mean PAP	?	0.6	-2.1	-2.6	-4.7
	P	-	0.021	0.006	0.001
Clinical worsening	%	10	4.4	3.0	7.1
	P	-	ND	ND	0.42
BORG dyspnea	?	0	-0.8	-0.5	-0.9
	P	-	ND	ND	ND

PAP = pulmonary artery pressure; ND = not done

The higher rate of clinical worsening in the placebo group was predominantly due to more hospitalizations for PAH in the placebo group (7 vs. 2 each in the sildenafil groups).

Dr. Freidlin also notes in her review that the 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. I discuss safety in more detail in the next section.

COMMENT: Dr. Freidlin's review confirms that Study A1481140 supports efficacy of sildenafil in the treatment of PAH. The magnitude of the effect at trough is reasonable (41-47 meters improvement in 6-minute walking distance) and the effects for all sildenafil doses tested are highly statistically significant. The significant decrease in mean PAP provides supporting evidence that sildenafil beneficially affects a physiological parameter that is related to the disease. The baseline imbalance in PAP does not appear to affect the significance of the results. The combination of the highly statistically significant results for the primary endpoint and some supporting evidence makes it reasonable to accept the results of this one study as supporting approval.

One major question that is not answered clearly is what is the optimal dosage. For the primary endpoint all dosages of sildenafil test (20-80 mg) appear to produce a similar effect. The results for the secondary endpoints also don't suggest a dose-response relationship for this range of doses. There is some suggestion that the highest dose tested, 80 mg, has more adverse effects. I examine the clinical evidence for justifying dosage in the next section.

Clinical Review

The primary clinical reviewer, Dr. Maryann Gordon, recommends an approvable action for this application. She also recommends two postmarketing studies: an efficacy study using lower doses and an interaction study with warfarin. I summarize the most pertinent observations from her review regarding these recommendations below.

Efficacy

Dr. Gordon notes the same data regarding the success of the primary endpoint as I summarized above from Dr. Freidlin's review, so I will not repeat it here. Dr. Gordon does quote some additional relevant details. She included in her review the following sponsor's figure showing changes in walk distance by visit:

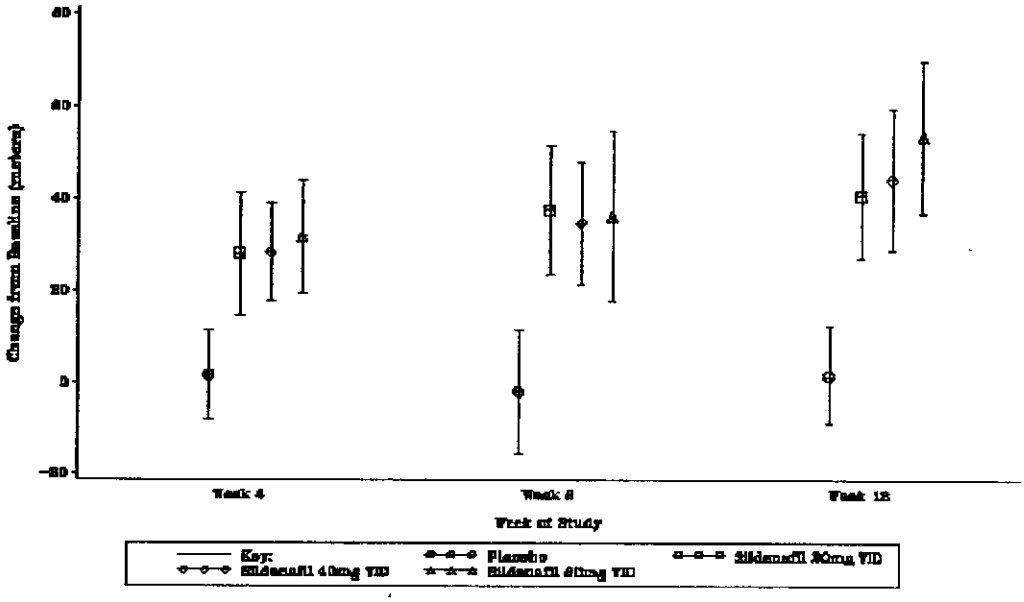


Figure 2: Sponsor's change from baseline in 6-minute walk by visit (mean and 95% confidence limits)

COMMENT: The above figure shows well the overlap in the confidence intervals for the change from baseline in walk distance in the three sildenafil groups. It also suggests that while most of the benefit is evident at 4 weeks, there may be slight continuing improvement through week 12. (See also comments below about the extension study results.) To appreciate better the distribution of walking distance changes I plotted histograms of the changes for each group at week 12 and show them in Figure 3. There isn't a clear pattern distinguishing the three sildenafil treatment groups.

The evidence suggesting no dose-response in the range 20-80 mg appears fairly strong. I summarize what clinical evidence there is suggesting a dose-response relationship following Figure 3.

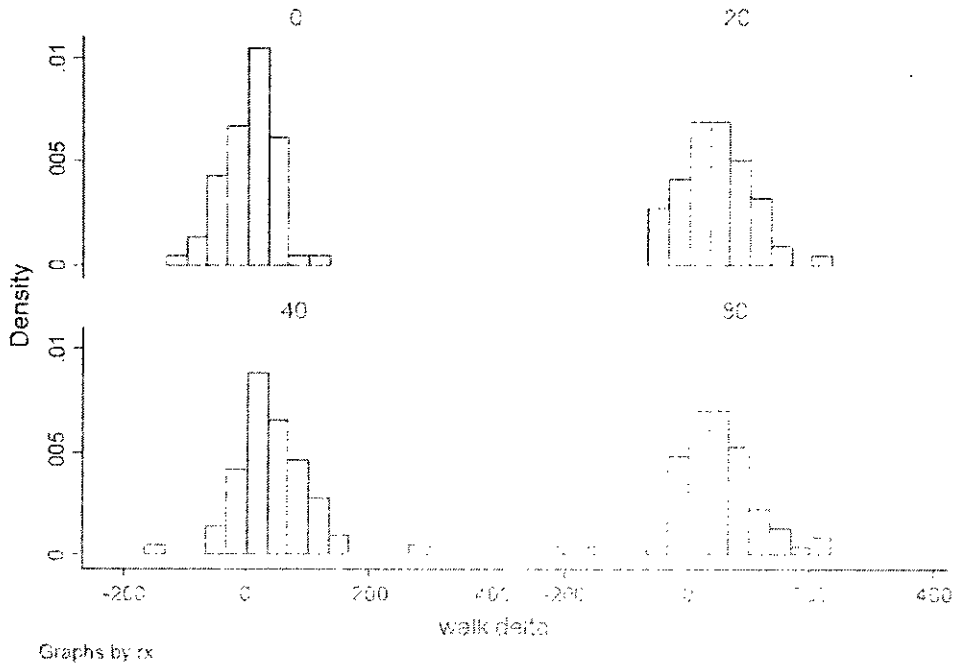


Figure 3: Reviewer's distributions of walk distance changes at week 12 by sildenafil dose

The data suggesting that there may be a dose-response relationship are the following:

- The reduction in mean PAP increases with dose as shown in Table 3. To make this interpretation one has to ignore the similar values for the 20 and 40 mg dosages. However, the change in systolic PAP is more suggestive of a dose response. I show the other most relevant parameters, PAP and pulmonary vascular resistance (PVR) in Table 4. Systolic PAP shows a good dose-response. PVR mirrors the changes in mean PAP, with similar changes for the 20 and 40 mg groups.

Table 4: Reviewer's mean changes from baseline to week 12 in PAP and PVR

		Sildenafil dose, mg		
	Placebo	**20**	**40**	**80**
Systolic PAP	1.6	-1.2	-3.0	-5.9
Diastolic PAP	0.6	-1.8	-3.2	-3.8
PVR	49	-140	-153	-261

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance

- There appears to be more of a dose-response in patients whose baseline walk distance was < 325 m compared to those whose baseline walk distance was > 325 m. I show the comparisons in Table 5. The dose-response for patients with a baseline walk distance < 325 m is not pronounced.

Table 5: Reviewer's changes from baseline to week 12 in 6-minute walk distance by baseline walk distance

		Sildenafil dose, mg		
Baseline walk distance	**Placebo**	**20**	**40**	**80**
< 325 m	-12	52	56	72
= 325 m	10	40	36	30

- In the open-label extension (Study A1481142) to Study A1481140, all patients were titrated to 80 mg TID if tolerated. Patients at the higher Study A1481140 doses were less likely to show an improvement in functional class as shown in Table 6.

Table 6: Sponsor's changes of at least one functional class from A1481142 baseline to week 24 by A1481140 randomized treatment

	1140 Treatment Group			
	Placbo	**Sildenafil 20mg**	**Sildenafil 40mg**	**Sildenafil 80mg**
N	61	64	63	63
Improvement	20 (32.8)	12 (18.8)	10 (15.9)	2 (3.2)
Deterioration	4 (6.6)	3 (4.7)	4 (6.3)	6 (9.5)

The discussion of dosing recommendations in the NDA (Section 2.7.3.4) notes the following: "The efficacy results from Study A1481140 demonstrated statistically significant increases in 6-minute walk distance compared to placebo at all dose levels. However, there was little evidence of a dose response between the sildena fil treated groups, with 20 mg TID providing comparable efficacy to 40mg TID and 80mg TID. Additionally, there was no evidence of an incremental efficacy benefit when patients dose escalated." This section interprets an earlier study (A1481024) as suggesting that a maximum effect could be achieved at the approximate C_{max} (100 ng/ml) resulting from oral dosing with 25 mg sildenafil. Study A1481024 was a pilot study measuring hemodynamic parameters in patients with PAH given IV sildenafil to targeted blood levels. This study showed that IV sildenafil reduced PVR with a trend of increased reductions with increasing dose across the plasma concentrations of 10 to 100 ng/ml, but at concentrations of 100 to 500ng/ml the reduction in PVR appeared to plateau. The investigators concluded that a maximum reduction in PVR was reached at plasma concentrations of 100 ng/ml.

COMMENT: I agree with the conclusion of the sponsor: There is little evidence of a dose response in the range 20-80 mg TID. Whether a dose lower than 20 mg is effective with lower toxicity is an issue that should be explored post-marketing. That a lower dose

may be effective is suggested by the published data on PE5 inhibition with sildenafil. The IC_{50} for PDE5 for sildenafil has been estimated as 3.5-3.9 nM, or about 2 ng/mL. This value is much less than the C_{max} for the 20 mg TID dose (about 100 ng/mL). While concentrations later in the dosing interval are lower and the high protein binding of sildenafil might also affect its receptor interaction, that PDE5 is maximally inhibited even at the 20 mg TID dosage is a possibility.

In addition to primary question of efficacy addressed above, there are some other interesting efficacy issues. I have the following comments about other efficacy issues:

- As the tables in Dr. Gordon's review show, there were no apparent differences in efficacy by age, gender, or race (although the numbers of male and nonwhite patients are too small to exclude any gender or race variations.) Another subgroup variation of interest is efficacy by region. I show the 6-minute walk changes by region in Table 7.

Table 7: Reviewer's changes from baseline to week 12 in 6-minute walk distance by region

Region	N	Placebo	Sildenafil dose, mg		
			20	40	80
Europe	137	7	53	51	58
US	62	-8	33	37	19
S. America	10	5	22	30	130
Asia	15	48	35	18	35
Other	37	-4	24	32	50

COMMENT: All regions showed increases in walking distance with sildenafil, although the numbers are too small in South America and Asia to estimate accurately and the placebo increase in Asia of 48 m is the result for one patient. The increases with sildenafil in the US are lower than those in Europe. Note, however, that the placebo group showed an increase in walking distance in Europe while the placebo group in the US showed a decrease. Hence the region-specific placebo-corrected increases in walking distance are similar in Europe and the US. Whether this is a random variation or whether it represents differences in how walks are conducted in Europe and the US are questions that would be interesting to explore with other data sets.

- To try to understand the relationship between 6-minute walking distances and other factors, particularly the hemodynamic parameters, I performed linear regression modeling of walking distance by other baseline factors. While many of the hemodynamic parameters are interrelated, the best predictors of walking distance appeared to be cardiac index and pulmonary capillary wedge pressure as shown in the model in Table 8.

Table 8: Reviewer's linear regression model of 6-minute walk distance

Source	SS	df	MS		
Model	322129.898	7	46018.5569	Number of obs	218
Residual	991260.983	210	4720.29039	F(7, 210)	9.75
Total	1313390.88	217	6052.49254	Prob > F	0.0000
				R-squared	0.2453
				Adj R-squared	0.2201
				Root MSE	68.704

walkbase	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ht	2.485991	.591682	4.20	0.000	1.319593	3.652388
wt	-.7753012	.3060233	-2.53	0.012	-1.378573	-.1720298
pcwpb	-3.629734	1.529667	-2.37	0.019	-6.645205	-.6142629
cib	11.93204	6.655096	1.79	0.074	-1.187312	25.0514
plmclass 2	-68.96392	69.9486	-0.99	0.325	-206.8553	68.92748
plmclass 3	-111.6443	69.79418	-1.60	0.111	-249.2313	25.94274
plmclass 4	-184.1541	74.52336	-2.47	0.014	-331.0638	-37.24431
_cons	95.38024	121.286	0.79	0.433	-143.7139	334.4744

pcwpb = baseline pulmonary capillary wedge pressure; cib = baseline cardiac index

In a model without pulmonary class, cardiac index is more significant as a predictor and age also is a significant predictor. Note that height is a positive and weight a negative predictor of walk distance.

- I also modeled change from baseline in 6-minute walk distance and show the results in Table 9.

Table 9: Reviewer's linear regression model of change from baseline in 6-minute walk distance

Source	SS	df	MS		
Source	SS	df	MS	Number of obs	218
				Number of obs	264
Model	204701.374	5	40940.2748	F(5, 258)	14.34
Residual	736389.884	258	2854.22436	Prob > F	0.0000
				R-squared	0.2175
Total	941091.258	263	3578.29376	Adj R-squared	0.2024
				Root MSE	53.425

walkdelt	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
walkbase	-.1525645	.0435512	-3.50	0.001	-.2383256	-.0668033
age	-1.175736	.2283012	-5.15	0.000	-1.625307	-.7261651
ht	.9865896	.4304746	2.29	0.023	.1388984	1.834281
wt	-.414212	.2212668	-1.87	0.062	-.8499308	.0215068
sildenafil	40.8402	7.687877	5.31	0.000	25.70123	55.97918
_cons	-19.01169	66.36493	-0.29	0.775	-149.6976	111.6742

Adding baseline hemodynamic parameters does not improve the prediction of the above model, suggesting that the baseline imbalances in hemodynamic parameters are not important. Sildenafil use is a highly significant predictor of change in walk distance. It is a better predictor when included as a binary value compared to inclusion of the actual doses. It ceases being a predictor if it is included as the

actual doses but the analysis is restricted to the sildenafil groups. These latter analyses confirm that there is no dose-response relationship for sildenafil in the dose range 20-80 mg for change in 6-minute walk.

I also modeled using the ratio of the week 12 walk distance to baseline rather than the difference. The model results for the walk ratio were very similar to those for the walk difference.

- I also modeled the change in 6-minute walk by the change in the hemodynamic parameters. None of the hemodynamic parameters was a great predictor of change in 6-minute walk. Change in right atrial pressure and in diastolic PAP appeared to be the best predictors. The prediction also appeared to be slightly better if I used the ratios to baseline rather than the differences. I show one such model using right atrial pressure in Table 10.

Table 10: Reviewer's linear regression model of ratio to baseline of 6-minute walk distance with right atrial pressure ratio

Source	SS	df	MS		
Model	2.04163432	5	.408326864	Number of obs	= 242
Residual	9.77649634	236	.041425832	F(5, 236)	= 9.86
				Prob > F	= 0.0000
Total	11.8181307	241	.049037887	R-squared	= 0.1728
				Adj R-squared	= 0.1552
				Root MSE	= .20353

walkrat	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
walkbase	-.0010171	.0001732	-5.87	0.000	-.0013582	-.000676
age	-.0033874	.0009464	-3.58	0.000	-.0052518	-.0015229
ht	.0039661	.00171	2.32	0.021	.0005973	.0073349
wt	-.0020239	.0008832	-2.29	0.023	-.0037637	-.000284
rapr	-.0247383	.010952	-2.26	0.025	-.0463144	-.0031622
_cons	1.157648	.2621698	4.42	0.000	.6411558	1.67414

walkrat = ratio of 6-minute walk distance at week 12 to baseline
rapr = ratio of right atrial pressure at week 12 to baseline

COMMENT: Changes in the hemodynamic parameters are not very good predictors of 6-minute walk performance. The ratio to baseline may be slightly better than the difference from baseline. Similar analyses may be useful in planning future studies of sildenafil or other PDE5 inhibitors in PAH.

Safety

Dr. Gordon in her review of safety identified only one special concern: Bleeding events, particularly epistaxis, were more frequent with sildenafil given concomitantly with a vitamin K antagonist compared to sildenafil alone or placebo. She recommends that a post-marketing drug interaction study with warfarin be done. I discuss the findings regarding bleeding below as well as some other safety issues that warrant comment. Please see Dr. Gordon's excellent summary of the full spectrum of safety issues for the details on all aspects of sildenafil safety in PAH patients. Note also that sildenafil is a

drug with substantial post-marketing experience and demonstration of safety, although its current use is for a different indication and with intermittent dosing.

Regarding bleeding, overall bleeding events were similar among the placebo and sildenafil groups in Study A1481140 as shown in Table 11.

Table 11: Sponsor's bleeding events in Study A1481140

Adverse Event (MedDRA Preferred Term)	Number of All Events (%)				
	Placebo N = 70	Sildenafil (mg TID)			
		20 mg N = 69	40 mg N = 67	80 mg N = 71	Total N = 207
Epistaxis	1 (1.4)	6 (8.7)	5 (7.5)	3 (4.2)	14 (6.8)
Retinal Hemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)	4 (1.9)
Eye Hemorrhage NOS	1 (1.4)	1 (1.4)	1 (1.5)	1 (1.4)	3 (1.4)
Menorrhagia	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Haemoglobin Decreased	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Blood in Stool	0	0	0	1 (1.4)	1 (<1)
Conjunctival Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Gastritis Haemorrhagic	0	1 (1.4)	0	0	1 (<1)
INR Increased	2 (2.9)	1 (1.4)	0	0	1 (<1)
Rectal Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Metrorrhagia	1 (1.4)	0	1 (1.5)	0	1 (<1)
Vaginal Haemorrhage	0	1 (1.4)	0	0	1 (<1)
Hematoma NOS	3 (4.3)	1 (1.4)	0	0	1 (<1)
Gingival Bleeding	0	0	1 (1.5)	0	1 (<1)
Anal Haemorrhage	1 (1.4)	0	0	0	0
Hematuria	1 (1.4)	0	0	0	0
Venipuncture Site Haemorrhage	1 (1.4)	0	0	0	0
TOTAL PATIENTS WITH BLEEDING EVENTS	11 (15.7)	14 (20.3)	12 (17.9)	8 (11.3)	34 (16.4)

One bleeding event that is increased substantially in sildenafil patients is epistaxis (including one serious adverse event), and another bleeding event (retinal hemorrhage) also appears to be more frequent in sildenafil patients. Note that the epistaxis does not appear to be dose-related and that INR increased adverse events are not more frequent in the sildenafil groups. Dr. Gordon notes in her review that vitamin K antagonists were prescribed frequently in Study A1481140 (74% of patients) and that epistaxis was more frequent in sildenafil patients treated with a vitamin K antagonist as shown in Table 12.

Table 12: Bleeding events by vitamin K antagonist use in Study A1481140

	Placebo		Sildenafil	
	Vitamin K antagonist (n=56) n (%)	None (n=14) n (%)	Vitamin K antagonist (n=148) n (%)	None (n=59) n (%)
All bleeding	7 (13)	4 (29)	30 (20)	3 (5)
Epistaxis	1 (2)	0	13 (9)	1 (2)
Retinal hemorrhage	0	0	4 (3)	0

She also notes that patients with PAH secondary to connective tissue disease were more likely to report epistaxis (13%) compared to those with primary PAH (2%). In the long term follow-up Study A1481142 epistaxis was reported in 9% of patients, retinal hemorrhage in 5%, and retinal or other eye hemorrhages in 8%. Most of the retinal hemorrhages are described as small or punctuate. There does not appear to be substantial visual loss associated with them.

Both epistaxis and retinal bleeding are mentioned in the current Viagra label as adverse events that have been reported post-marketing. I searched AERS Datamart and found 48 (27 initial, 21 follow-up) post-marketing reports of epistaxis associated with Viagra use. Two were also associated with warfarin use. Four were associated with rhinitis. I also found 70 (42 initial, 38 follow-up) post-marketing reports of eye or retinal hemorrhage associated with Viagra use. Six of the reports report blindness and several others report visual disturbances. None mentioned concomitant warfarin use. Epistaxis is also mentioned in the labeling for the two other approved PDE5 inhibitors, tadalafil and vardenafil.

COMMENT: If increased bleeding in patients taking sildenafil and a vitamin K antagonist represented a pharmacokinetic interaction between the two drugs, I would expect to see a general increase in bleeding and increases at a variety of bleeding sites, e.g., gastrointestinal, urinary. The marked differences at two specific sites (nose, retina) and the reports of bleeding at these sites without warfarin use and with other PDE5 inhibitors suggests to me that the increased bleeding at these sites is a pharmacodynamic effect of PDE inhibitors (maybe PDE5, but possibly one of the other PDE receptor types). However, there is no way to rule out an effect of sildenafil on warfarin PK or PD from this study. Given that warfarin is commonly prescribed for PAH patients (74% in this study) and that bleeding is the most serious drug-related adverse effect, we need to have good data on any possible interactions between these two drugs. The interactions studies with the coumarin derivatives used in Europe were inadequate as documented in the Clinical Pharmacology and Biopharmaceutics section above. I recommend that a sildenafil-warfarin interaction study be done.

The following are the other safety issues from the randomized, placebo-controlled Study A1481140 that I consider worthy of comment:

- There were four deaths in the sildenafil groups and one in the placebo group. Three of deaths were typical complications of PAH (including the placebo death), one was a myocardial infarction, and one was septic shock in a patient with a history of leucopenia. The myocardial infarction occurred early in an 81 year old female randomized to sildenafil 80 mg. This distribution of deaths is entirely within chance distribution.

- There were five withdrawals because of adverse events and one because of increased serum creatinine. The latter was in a patient randomized to 20 mg sildenafil and occurred on day 1. In the absence of other signals of nephrotoxicity it is difficult to interpret. The other five withdrawals all occurred in patients receiving sildenafil 80 mg TID. In addition to myocardial infarction noted above under deaths, the causes for withdrawal were chest pain, trigeminy, and syncope;

chromatopsia and dyspepsia; fluid retention; and hepatic cirrhosis. The latter occurred at day 27 in a patient who had experienced liver function abnormalities and abnormal biopsy with bosentan, which was discontinued five months earlier. Temporary discontinuations were more common in the placebo and sildenafil 20 mg groups (5 each, compared to 1 each in the 40 and 80 mg groups.)

- Serious adverse events were reported in 42 patients: 12 randomized to placebo; 13 randomized to sildenafil 20 mg; 8 randomized to sildenafil 40 mg; and 9 randomized to sildenafil 80 mg. The events included worsening of PAH symptoms but were otherwise diverse and without obvious patterns.
- Sildenafil is an inhibitor of PDE6, an enzyme involved in the phototransduction in the retina. Altered vision, color tinge to vision, increase perception of light, blurred vision were reported in clinical trials conducted with sildenafil in male erectile dysfunction. Ocular testing was performed by ophthalmologists at baseline, Week 12, and at visit when a visual adverse event was reported. The eye disorder adverse events reported by more than one patient are shown in Table 13.

Table 13: Eye disorder adverse events reported by >1 patient in Study A1481140

Adverse Event (MedDRA preferred term)	Number of all events (%)			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Abnormal sensation in eye	0	2 (2.9)	1 (1.5)	0
Blepharitis	1 (1.4)	1 (1.4)	0	0
Cataract bilateral NOS	1 (1.4)	0	1 (1.5)	0
Chromatopsia	1 (1.4)	1 (1.4)	1 (1.5)	3(4.2)
Conjunctival hyperaemia	0	1 (1.4)	1 (1.5)	0
Conjunctivitis	1 (1.4)	0	1 (1.5)	1 (1.4)
Cyanopsia	0	0	1 (1.5)	3 (4.2)
Diplopia	0	1 (1.4)	1 (1.5)	1 (1.4)
Episcleral hyperaemia	2 (2.9)	0	0	0
Eye haemorrhage NOS	1 (1.4)	1 (1.4)	1 (1.5)	1 (1.4)
Eye irritation	0	2 (2.9)	0	2 (2.8)
Eye pain	1 (1.4)	1 (1.4)	0	3 (4.2)
Eye Puritus	1 (1.4)	0	1 (1.5)	0
Eye redness	1 (1.4)	0	1 (1.5)	0
Eyelid oedema	1 (1.4)	1 (1.4)	0	0
Halo vision	1 (1.4)	0	0	2 (2.8)
Lenticular opacities	1 (1.4)	0	1 (1.5)	0
Photophobia	0	0	0	4 (5.6)
Retinal haemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)
Vision blurred	4 (5.7)	3 (4.3)	2 (3.0)	4 (5.6)
Visual acuity reduced	0	0	2 (3.0)	1 (1.4)
Visual brightness	0	0	0	2 (2.8)
Visual disturbance NOS	0	0	3 (4.5)	5 (7.0)

NOS: Not otherwise specified

Note that the frequencies of chromatopsia, cyanopsia, eye pain, photophobia, visual brightness and visual disturbance NOS increase with increasing dose.

- There were some adverse events that occurred more frequently in the sildenafil groups. Those occurring in at least six sildenafil patients and more frequent in the sildenafil groups are shown in Table 14.

Table 14: Adverse events more frequent in sildenafil patients in Study A1481140

	Placebo (n=70) n (%)	Sildenafil (n=207) n (%)	Placebo Subtracted %
Headache	27 (38.6)	95 (45.9)	7.3
Flushing	3 (4.3)	24 (11.6)	7.3
Epistaxis	1 (1.4)	14 (6.8)	5.4
Insomnia	1 (1.4)	13 (6.3)	4.9
Myalgia	3 (4.3)	19 (9.2)	4.9
Diarrhea nos	4 (5.7)	21 (10.1)	4.4
Pain in limb	4 (5.7)	21 (10.1)	4.4
Dyspepsia	5 (7.1)	23 (11.1)	4.0
Visual disturbances	0	8 (3.9)	3.9
Pyrexia	2 (2.9)	12 (5.8)	2.9
Gastritis nos	0	6 (2.9)	2.9
Sinusitis	0	6 (2.9)	2.9
Rhinitis nos	0	6 (2.9)	2.9
Paresthesia	0	6 (2.9)	2.9
Influenza	2 (2.9)	11 (5.3)	2.4
Anxiety	1 (1.4)	6 (2.9)	1.5
Erythema	1 (1.4)	6 (2.9)	1.5
Vertigo	1 (1.4)	6 (2.9)	1.5
Cough	4 (5.7)	14 (6.8)	1.1
Dyspnea exacerbated	2 (2.9)	7 (3.4)	0.5
Hot flushed nos	3 (4.3)	10 (4.8)	0.5
Back pain	8 (11.4)	24 (11.6)	0.2

nos = not otherwise specified

There is also one analysis in the report of the long term safety Study A1481142 that is worthy of comment. The sponsor compared survival rates of the patients in this study to predicted survival rates based on a published NIH registry prognostic index for primary pulmonary hypertension subjects. Patients who underwent lung transplantation, electively discontinued sildenafil or were lost to follow-up in the base study or extension study were

censored. The observed survival rates by Study A1481140 randomization group at one year were consistently higher than the predicted survival rates (0.93-1.00 vs. 0.71-0.72).

COMMENT: Note the occurrence of rhinitis with sildenafil use. Rhinitis is also reported with other PDE5 inhibitors. This effect is another suggestion that sildenafil acts upon nasal vasculature and that the epistaxis is likely a PD effect of sildenafil.

The comparison of survival in Study A1481142 to the NIH registry prediction is worthless. One does not have any idea of how the patient population in this study compares to the patient population in the registry. Furthermore, the NIH registry enrolled patients beginning in 1981. PAH investigators in recent years have reported much improved survival compared to the NIH registry results. Whether the improvement represents advances in therapy or patient selection is impossible to determine. The only study in which survival may legitimately be compared (the randomized, placebo-controlled Study A1481140) is too small and too short to yield any confidence in survival comparisons. The clinical data base for sildenafil in PAH is too small to provide conclusive evidence regarding whether sildenafil affects survival in PAH, either adversely or beneficially. We can be slightly reassured by the similar mortality rates in the sildenafil and placebo groups in Study A1481140.

Overall the adverse effects profile of sildenafil in PAH seems acceptable relative to the reasonable benefit of increased function, i.e., increased walking distance. The color vision aberrations are the one set of AEs that appear to be dose-related and hence should be less problematic with the initial proposed to-be-marketed dose (20 mg TID) and even less so if a lower dose is proved to be effective in a subsequent study. The bleeding AEs don't appear to be dose-related (at least at the dosages tested in the one pivotal study) and are somewhat worrisome—the retinal hemorrhages have been reported to result in visual loss in post-marketing reports. However, given the reasonable benefit and the significant problems with other approved therapies, I believe that the risk/benefit assessment still favors approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Marciniak
5/23/05 01:43:06 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21845
Reviewer Name	Maryann Gordon, M.D.
Review Completion Date	May 3, 2005
Established Name	sildenafil
(Proposed) Trade Name	Revatio™
Therapeutic Class	cGMP specific phosphodiesterase type-5 inhibitor
Applicant	Pfizer, Inc
Priority Designation	P
Formulation	oral
Indication	treatment of pulmonary arterial hypertension

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approvable

1.2 Recommendation on Postmarketing Actions

Efficacy study using lower doses and interaction study with warfarin.

1.3 Summary of Clinical Findings

1.3.1 Introduction and Brief Overview of Clinical Program

Sildenafil, phosphodiesterase 5 inhibitor, is currently approved for the treatment of male erectile dysfunction and is now seeking approval for the treatment of pulmonary arterial hypertension.

Pulmonary arterial hypertension (PAH)
Adult studies-efficacy and safety
One double blind, randomized, placebo controlled trial (A1481140)

Adult studies-safety
One ongoing, open label, uncontrolled, extension study (A1481142) defending long term safety in PAH.

Not included in NDA

Pediatric studies
There are three ongoing double blind, placebo controlled trials (A1481131 and A1481134 (IV formulation) and A1481157 (IV formulation)). There is one extension trial (A1481156). Limited safety information is available.

Additional studies/database included in safety review

There is one completed, double blind, placebo controlled trial (—) in — adults.

Clinical Pharmacology
There are 35 completed trials.

Miscellaneous studies
There is one completed trial in pulmonary hypertension (A1481024) and numerous chronic dosing studies for multiple indications.

Post marketing surveillance
Spontaneous reports from 25,963 patients.

1.3.2 Efficacy summary

Conclusion
The efficacy of sildenafil in subjects with PAH was demonstrated in one well-controlled study (A1481140). All doses of sildenafil tested prolonged walking distance compared to baseline by up to 50 m ($p<0.0001$). Limited information indicates that there is no dose response, i.e., sildenafil 20 mg tid was as efficacious as 80 mg tid. There was very little change in walk distance beyond 12 weeks despite continuation of sildenafil in an open label, uncontrolled extension study. Sildenafil also significantly decreased the mean pulmonary artery pressure from baseline compared to placebo.

The review of safety of sildenafil doses 20, 40, and 80 mg tid for 12 weeks in subjects with PAH did not raise major concerns. Reports of serious safety events including deaths were similar across treatment groups. More adverse events and discontinuations for adverse events were reported for subjects receiving sildenafil 80 mg tid.

Adverse events with the largest placebo subtracted incidence rates included headache (7%), flushing (7%), and epistaxis (5%). Other adverse events that were reported with greater frequency in the sildenafil treated groups included visual disturbance, diarrhea, dyspepsia, gastritis, and myalgia. Ocular testing did not reveal serious eye adverse events. Bleeding events, particularly epistaxis, were more frequent in the sildenafil plus vitamin K antagonists compared to sildenafil alone. For those taking vitamin K antagonists (74% of all subjects), the incidence rate for sildenafil groups reporting any bleeding was 20% compared to 13% for placebo. In addition, those sildenafil subjects with PAH secondary to connective tissue disease were more likely to report epistaxis (13%) compared to those on placebo (0%) and those with primary PAH (2%). In conjunction with this finding, there were minor decreases in mean hemoglobin/ hematocrit.

After reviewing both adverse events and laboratory values, there was no convincing evidence that sildenafil has an adverse effect on the liver, kidney, or bone marrow.

Background
Protocol 1481140 was a double blind, randomized, 12-week study with subjects with PAH. The primary objective was to evaluate the effect of three doses of oral sildenafil (20, 40 and 80 mg three times daily) on exercise capacity, as measured by the 6-Minute Walk test (conducted at least 4 hours after the last dose).

Subjects were those at least 18 years of age with either primary pulmonary hypertension (PPH), or pulmonary hypertension secondary to connective tissue disease (SPH-CT), or pulmonary

hypertension with surgical repair, at least 5 years previously, of atrial septal defect, ventricular septal defect, patent ductus arteriosus, aorto-pulmonary window. The mean pulmonary artery pressure had to be ≥ 25 mmHg, pulmonary artery wedge pressure < 15 mmHg at rest, and baseline 6-Minute Walk test distance between 100 m and 450 m. Excluded patients included those who had congenital heart disease (other than those specified in the inclusion criteria.), PAH due to thromboembolism, HIV, chronic obstructive airway disease, congestive heart failure or schistosomiasis, and subjects with significant (*i.e.* >2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation. Disallowed concomitant medication included chronic prostacyclin therapy, bosentan (or those who showed no improvement when taking bosentan), nitrates or nitric oxide donors (including nicorandil), and potent CYP3A4 inhibitors.

Dosing was three times daily with a 4-hour interval between doses. After the first dose, patients remained in the hospital for at least 8 hours with vital signs measured at hours 1, 2, 4, and 8. Subjects randomized to 80 mg started with 40 mg tid for one week and then up titrated to 80 mg tid because of the reporting of muscle aches at high doses.

Primary efficacy endpoint was change from baseline in exercise capacity at week 12 as measured by the 6-minute walk test conducted 4 hours after the previous dose. Subjects with missing Week 12 tests were to have an assessment imputed using the last observation carried forward. Those who died or underwent lung transplantation were to have their change from baseline walk distance assessed as zero.

Additional efficacy parameters included BORG dyspnea scale at the end of the 6-minute walk test, right heart catheterization with changes in pulmonary artery pressure, time to first occurrence of clinical worsening (defined as death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin or bosentan therapy), functional capacity and therapeutic class, quality of life questionnaires, patient overall preference assessment, and change in chronic use of background therapy for PAH.

Results

A total of 278 subjects were randomized and 277 were analyzed. The majority of subjects were white, female, had a mean age of about 50 years, and had PPH. The mean time from diagnosis was around 2.5 years. The drug classes taken by more than 50% of the subjects included analgesics, anticoagulants, antihypertensive drugs, diuretics, drugs used for local anesthesia, and mydriatics and cycloplegics.

6-minute walk test

The details of the primary efficacy endpoint are shown below.

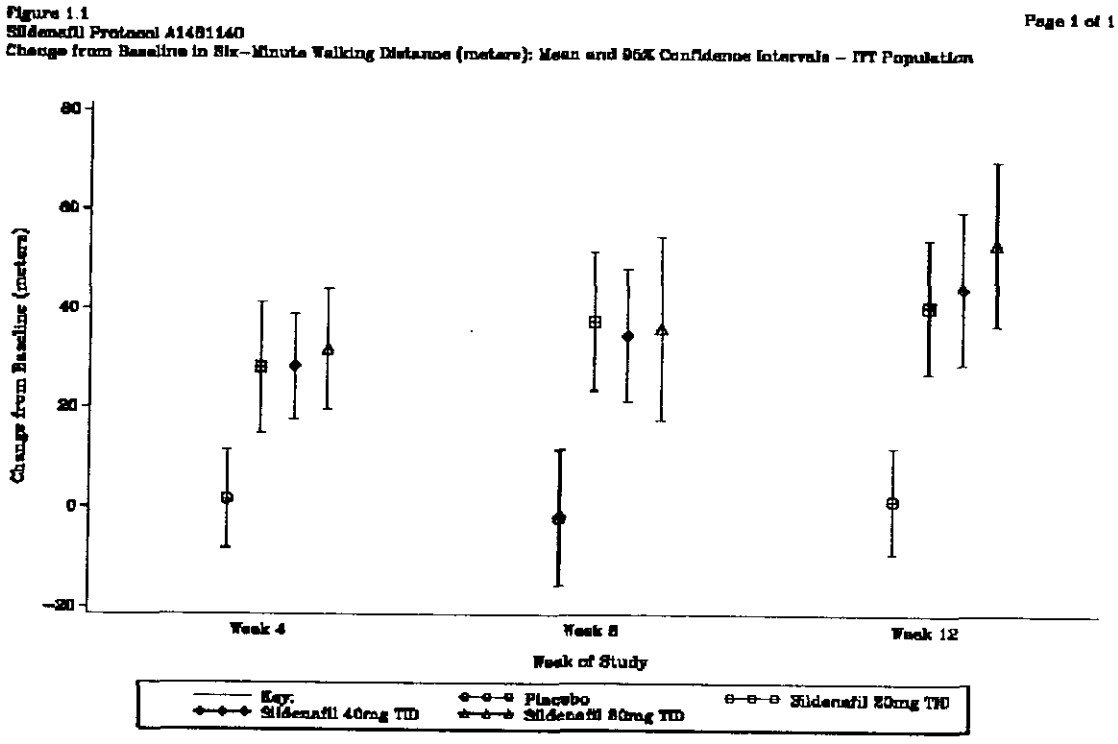
	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
Total subjects randomized	70	69	68	71
Total subjects included in ITT+	66	67	64	69
Mean baseline walk distance (m)	347.6	345.7	342.8	337.9

Mean change from baseline (m) at week 12 (LOCF) walk distance	-3.7	41.4	44.1	46.8
Std dev (m)	52.8	54.8	60.7	70.9
Min, max (m)	-263, 106	-77, 204	-139, 298	-230, 229
Placebo subtracted walk distance (m)	-	45.1***	47.8***	50.5***
99% CI	-	20.5, 70	19.9, 72.4	22.9, 76.5

+ includes those subjects who received at least one dose of study drug and had both baseline and post baseline walking distance assessments.
***compared to placebo, p value for each active treatment group was <0.0001.

Sildenafil increased walk distance between 45-51 m compared to placebo. There was no evidence of a dose response.

The figure below shows the change from baseline at each visit for the ITT population, by treatment group.



Long term effects

The open label, uncontrolled extension study (A1481142) recorded walk distance up to 9 months of treatment. The table below shows the results for those subjects who were receiving sildenafil 80 mg tid.

Change from Week 24 6-Minute Walk distance for subjects whose final optimised dose was 80mg sildenafil

Change from Week 24 baseline	Month 9	Month 12	Month 15	Month 18	Month 21
N	228	213	155	80	17
Mean (meters)	1.6	1.5	-5.2	2.5	-37.9
95% Confidence Interval	(-5.8,9.0)	(-5.7,8.7)	(-11.8,1.5)	(-9.7,14.7)	(-79.3, 3.6)

Source: Table: 5.2.3

These results suggest that the effect of sildenafil 80 mg tid wanes over time, perhaps because many of the subjects are getting sicker.

Subgroups

The mean placebo-subtracted walk distances for selected subgroups are shown below. See study report for sample sizes.

Mean change from baseline at week 12 (LOCF) - walk distance (m)

	Sildenafil 20 mg tid	Sildenafil 40 mg tid	Sildenafil 80 mg tid
<325 m/ ≥325 walk at baseline	57/38	69/36	86/29
PPH/SPH-CT	40/55	48/49	62/28
NHYA class II/III	50/45	10/71	50/53
Male/Female	81/37	69/45	101/39
<49 yrs/≥ 49 yrs of age	55/31	61/35	67/24

There is no indication that sildenafil is not efficacious in a particular subgroup.

Secondary endpoints

Changes in pulmonary artery pressure (PAP)

Mean baseline (mmHg) and mean change (mmHg) from baseline at week 12 LOCF

Placebo n=65		Sild 20 mg tid n=65		Sild 40 mg tid n=63		Sild 80 mg tid n=65	
Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
53.6	0.6	54.5	-2.1*	48.6	-2.6**	52.0	-4.7***

*p<0.05
**p< 0.01
***p<0.001

There was a statistically significant decrease in mean PAP in all sildenafil groups compared to placebo.

Clinical worsening

Clinical worsening was defined as death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin therapy or initiation of bosentan therapy.

Number and (percent) of subjects

	Placebo n=70	Sild 20 mg tid n=69	Sild 40 mg tid n=67	Sild 80 mg tid n=71
Worsening: any	7 (10)	3 (4.3)	2 (3.0)	5 (7.0)
Death	1	1	0	2
Hosp for PAH	7	2	2	2
Init of prostac	1	0	0	0
Init of bosen	0	0	1	2

Subjects could have more than 1 event

Overall, there were few of these particular events and no reports of subjects undergoing lung transplantation. However, more subjects in the placebo group experienced clinical worsening (primarily because of greater need for hospitalization) compared to the other treatment groups. There was no statistical significance when sildenafil 80 mg tid was compared with placebo in reducing time to clinical worsening.

BORG score

There were 266 subjects who had both baseline and post baseline BORG assessments. The mean scores at baseline and the mean changes from baseline at endpoint are shown below, by treatment group.

Mean baseline and mean changes from baseline at week 12 LOCF

Placebo n=66		Sild 20 mg tid n=67		Sild 40 mg tid n=64		Sild 80 mg tid n=69	
Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
3.4	0	3.8	-0.8	2.9	-0.5	3.4	-0.9

Table 5.5.1

There were improvements in the mean BORG score for the active treatment groups. There was no change in the placebo group.

1.3.3 Safety summary

PAH

Deaths

There were 5 deaths in the 12-week efficacy study A1481140 (1 placebo, 2 sildenafil 20 mg, 2 sildenafil 80 mg). None seemed linked to the use of study drug. None of the deaths in the rest of the data base indicates an association with the use of sildenafil.

Survival rates (based on data from ongoing follow up study A1481142)

Predicted survival rates were based on the NIH-Registry prognostic index for primary pulmonary hypertension subjects. The observed survival rate at 1 year was calculated using Kaplan Meier estimates. Subjects who underwent lung transplantation, electively discontinued sildenafil or were lost to follow-up in the base study or extension study were censored. Subjects who were event-free at the time of the interim data-cut were censored at 1 year.

Table 5.7
Sildenafil Protocol A1481142
Summary of Prognostic Index by 1140 Treatment

1140 Randomized Treatment*		Years after start of active treatment	Predicted Survival	Observed Survival (Kaplan-Meier Estimate)
Placebo	(N=32)	1 Year	0.70	0.93
		2 Years	0.58	
		3 Years	0.49	
Sildenafil 20mg TID	(N=32)	1 Year	0.72	0.97
		2 Years	0.61	
		3 Years	0.52	
Sildenafil 40mg TID	(N=37)	1 Year	0.72	1.00
		2 Years	0.60	
		3 Years	0.51	
Sildenafil 80mg TID	(N=40)	1 Year	0.71	0.94
		2 Years	0.59	
		3 Years	0.50	

* The numbers in parentheses show the number of subjects included in the analysis for prognostic index. For the Sildenafil groups this represents subjects randomized to and treated with Sildenafil in 1140 who have a valid mean PAP, RAP and cardiac index (CI) at 1140 baseline. For the Placebo group this represents the number of subjects randomized to Placebo in 1140 who extended into (and were treated in) 1142 and who have a valid mean PAP, RAP and CI at 1142 baseline.

The observed survival was always higher than the predicted survival. However, this information only implies that there is no effect of sildenafil on decreasing survival in patients with PAH.

Other serious safety

There were few drop outs for adverse events in the efficacy study A1481140 (5 subjects randomized to sildenafil 80 mg tid). The events included decreased creatinine clearance, trigeminy, headache/visual disturbances/dyspepsia, myocardial infarction, fluid retention, and hepatic cirrhosis. There were 15 subjects who withdrew from the ongoing extension trial A1481142 because of adverse events. Most of the events were either similar to those probably associated with sildenafil (diarrhea, weakness, headache, allergic reaction) or the underlying disease (hypotension, dyspnea, worsening heart failure, worsening of symptoms of PAH). There was one report of suicide attempt.

All adverse events

Adverse events reported by at least 6 subjects during study A1481140 are shown below.

Number and (percent) of subjects

	Placebo n=70	Total sild n=207	Placebo Subtracted %
Headache	27 (38.6)	95 (45.9)	7.3
Flushing	3 (4.3)	24 (11.6)	7.3

Epistaxis	1 (1.4)	14 (6.8)	5.4
Insomnia	1 (1.4)	13 (6.3)	4.9
Myalgia	3 (4.3)	19 (9.2)	4.9
Diarrhea nos	4 (5.7)	21 (10.1)	4.4
Pain in limb	4 (5.7)	21 (10.1)	4.4
Dyspepsia	5 (7.1)	23 (11.1)	4.0
Visual disturbances	0	8 (3.9)	3.9
Pyrexia	2 (2.9)	12 (5.8)	2.9
Gastritis nos	0	6 (2.9)	2.9
Sinusitis	0	6 (2.9)	2.9
Rhinitis nos	0	6 (2.9)	2.9
Paraesthesia	0	6 (2.9)	2.9
Influenza	2 (2.9)	11 (5.3)	2.4
Anxiety	1 (1.4)	6 (2.9)	1.5
Erythema	1 (1.4)	6 (2.9)	1.5
Vertigo	1 (1.4)	6 (2.9)	1.5
Cough	4 (5.7)	14 (6.8)	1.1
Dyspnea exacer	2 (2.9)	7 (3.4)	0.5
Hot flushed nos	3 (4.3)	10 (4.8)	0.5
Back pain	8 (11.4)	24 (11.6)	0.2

Headache and flushing had the highest placebo subtracted rates followed by epistaxis, insomnia, and myalgia.

Possible dose related adverse events include flushing, visual disturbances, myalgia, and pyrexia.

Pooled adverse events from studies A1481140 (PAH) and A1481165 (hypertension) included dyspepsia (9.9%), flushing (9.8%), headache (7.5%), myalgia (5.2%), headache (4.0%), diarrhea (3.8%), epistaxis (3.8%), insomnia (3.5%), and pain in limb (3.3%).

Eye disorders
Sildenafil is an inhibitor of PDE6, an enzyme involved in the phototransduction in the retina. Altered vision, color tinge to vision, increase perception of light, blurred vision were reported in clinical trials conducted with sildenafil in male erectile dysfunction. Visual disturbances NOS and chromatopsia (placebo subtracted incidence rates 3.9% and 1.0%, respectively) were the most commonly reported eye disorders in study A1481140.

The most commonly reported eye events in the extension study A1481142 included vision blurred (8.1%), visual disturbance nos (5.8%), conjunctival hyperemia (4.6%), episcleral hyperemia (3.9%), retinal hemorrhage (3.9), chromatopsia (2.7%), and eye hemorrhage (2.3%).

Bleeding disorders
The overall reporting rate for bleeding was slightly higher in the sildenafil group compared to placebo in study A1481140 (16.4% and 15.7%, respectively). However, there was a sizable increase in the incidence rate of reporting epistaxis in the sildenafil groups compared to placebo

(6.8% versus 1.4%, respectively). This effect is probably linked to concomitant vitamin K antagonists.

Number and (percent) of patients

	Placebo		sildenafil	
	vitK ant n=56	No vitK ant N=14	vitK ant n=148	No vitK ant N=59
All bleeding	7 (12.5)	4 (28.6)	30 (20.3)	3 (5.1)
Epistaxis	1 (1.8)	0	13 (8.8)	1 (1.7)
Retinal hemor	0	0	4 (2.7)	0

In the open label extension study A1481142, the reporting rate for epistaxis was 8.5%. One subject (11205) on warfarin was hospitalized for epistaxis and low hemoglobin and required blood transfusion.

In the — study — bleeding was reported by 2.1% sildenafil subjects and 1.7% placebo subjects.

Conclusion: there is a probable interaction between vitamin K antagonists and sildenafil.

Clinical laboratory values

There was one PAH subject who discontinued for a laboratory parameter abnormality (decrease in creatinine clearance study A1481140). No subject in the extension study discontinued sildenafil because of an abnormal laboratory value. Two hypertensive subjects discontinued because of elevated glucose levels.

Hematology

There were small but consistent decreases in hemoglobin, hematocrit, RBC counts in study A1481140.

Liver, Renal, Electrolytes

There is no evidence that sildenafil influences any of these laboratory parameters.

Vital signs

In a normotensive population, there was little effect of sildenafil on blood pressure and a small decrease in heart failure. There was a hypotensive effect, however, in a population with essential hypertension (9/6 mmHg decrease from baseline for sildenafil 80 mg tid).

1.3.4 Dose regimen and administration

Oral doses of 20 mg tid (4-6 hours apart). Although 80 mg tid was tested, there was no evidence of increased efficacy with this dose and there was evidence of a decline in the safety profile.

1.3.5 Drug-drug interactions

(Additions to the current label for Viagra®)
Bosentan: In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg tid) with the endothelin antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady state (125 mg bid.) resulted in a 62.6% decrease of sildenafil AUC and a 55.4% decrease in sildenafil C_{max}. Sildenafil at steady state (80 mg tid) resulted in a 49.8% increase in AUC and a 42% increase in C_{max} of bosentan (125 mg bid.).

1.3.6 Special populations

No additions to current label.

2 EFFICACY STUDY A1481140

This was a double blind randomized 12-week study in patients with pulmonary hypertension.

The objective of this study was to evaluate the effect of three doses of oral sildenafil (20, 40 and 80 mg three times daily) on exercise capacity, as measured by the 6-Minute Walk test (conducted at least 4 hours after the last dose), after 12 weeks of treatment in subjects with pulmonary arterial hypertension who are aged 18 years and over.

2.1 Study conduct

Inclusion criteria
-18 years (and given written consent and, if female, have adequate forms of birth control) with any of the following conditions:
–Primary pulmonary arterial hypertension, or
–Pulmonary hypertension secondary to connective tissue disease, or
–Pulmonary hypertension with surgical repair, at least 5 years previously, of atrial septal defect, ventricular septal defect, patent ductus arteriosus, aorto-pulmonary window.

And with the following:
- mean pulmonary artery pressure ≥25 mmHg and a pulmonary artery wedge pressure of < 15 mmHg at rest, via right heart catheterization within 21 days prior to randomization[1].
-baseline 6-Minute Walk test distance is >100 m and <450 m.

Those subjects who underwent right heart catheterization and who fulfill the following criteria:

[1] In the event that a wedge pressure was unable to be obtained during right heart catheterization, then subjects with a left ventricular end diastolic pressure (LVEDP) of < 14mmHg and absence of any mitral stenosis on echo-cardiograpy could be eligible for entry into the study after discussion with the sponsor's study clinician.

1. background therapy (class of drug) has not been changed for at least 30 days prior to right heart catheterization measurement,
2. the doses of background therapy have not changed within 7 days of catheterization, and
3. the drugs and doses used for background therapy have not changed since catheterization for inclusion (subjects can undergo repeat right heart catheterization prior to randomization).

Selected exclusion criteria

-Subjects who had congenital heart disease (other than those specified in the inclusion criteria), PAH due to thromboembolism, HIV, chronic obstructive airway disease, congestive heart failure or schistosomiasis.

- Subjects with significant (*ie* >2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation (In the event that subjects in whom a wedge pressure was not obtained were entered into the study, there must have been no evidence of any mitral stenosis on echocardiography. Subjects with previous surgical replacement of a valve could be eligible for entry into the study after consultation with the sponsor.

2.1.2 Disallowed medication

Subjects who were receiving any form of chronic prostacyclin or bosentan (or those who showed no improvement when taking bosentan), nitrates or nitric oxide donors (including nicorandil) in any form, protease inhibitors such as ritonavir and saquinavir, erythromycin, ketoconazole, itraconazole, and alpha blockers. Chronic use of arginine enriched products was not allowed. Subjects previously receiving any of these drugs must have stopped use for a period of at least 1 month except in the case of bosentan (4 months) or prostacyclin (3 months).

2.1.3 Study investigators

A total of 54 investigators from Australia, Europe, North and South America, Asia, Middle East, Central America, and Africa enrolled subjects into this study[2]. Sites in Germany, Italy, and Poland had the largest number of subjects per site (between 19-22 subjects each).

Study procedures are shown below.

[2] The efficacy results were independent of the results from these centers (per Dr. Freidlin).

STUDY FLOWCHART

	Visit 1 Screening	Visit 2 Baseline	Telephone Week 1	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12	Visit 6 Follow-Up
	Day -21 to -1	Day 1	Day 7	Day 28	Day 56	Day 84	Day 114
Eligibility							
Informed consent – study	X						
Inf. consent -genotyping				X			
Inclusion/exclusion criteria	X	X					
Demography	X						
Diagnosis	X						
Functional classification*	X	X		X	X	X	X
Medical history	X						
Efficacy							
Physical examination	X	X		X	X	X	X
Vital signs	X	X		X	X	X	X
Laboratory tests	X	X		X	X	X	X
Lung function(**)	X						
ECG		X				X	
Pregnancy test	X	X		X	X	X	
Ocular tests (***)		X		(X)	(X)	X	X
Adverse events		X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Evaluation							
6-Minute Walk test	X	X		X	X	X	X
BORG dyspnoea score	X	X		X	X	X	X
Right heart catheterisation		X				X	
SF-36 questionnaire		X		X		X	
EQ.5d questionnaire		X		X		X	
Population PK blood samples		X			X	X	
Events defining clinical - worsening				X	X	X	
Overall patient preference - questionnaire						X	
Others							
Dispense study medication		X		X	X		
Dispense subject diary		X		X	X		
Review dosing log			X	X	X	X	X
Dose titration			X				
Collect drug/containers				X	X	X	X
Collect diary pages				X	X	X	X

* Functional classification = Pulmonary hypertension criteria for functional capacity and therapeutic class

** for subjects with a diagnosis of scleroderma

*** when ocular adverse events are reported

Dosing

Dosing intervals were a minimum of 6 hours. After the first dose, patients remained in the hospital for at least 8 hours with vital signs measured at hours 1, 2, 4, and 8. Subjects randomized to 80 mg started with 40 mg tid for one week and then up titrated to 80 mg tid because of the reporting of muscle aches at high doses.

Pharmacokinetics

Blood draws for PK sampling were obtained on day 1, week 8, and week 12.

Randomization

A central randomization scheme was used in a 1:1:1 ratio. Subjects were stratified according to walking distance (<325m and ≥325m) and etiology of PAH (primary, secondary to connective tissue disease, hypertension with surgical repair).

Procedures

6-minute walk

The 6-minute walk test and BORG dyspnea score were performed at screening, day 1, weeks 4, 8, 12, and follow-up day 114. The primary endpoint was the distance walked at week 12 at trough (just before the next dose and ≥ 4 hours after the last dose). The BORG dyspnea score was obtained at the end of the walk test (maximum exertion).

Right heart hemodynamics

Hemodynamic parameters measured on day 1 and week 12 included right atrial pressure, systolic pulmonary artery pressure, diastolic pulmonary arterial pressure, mean pulmonary artery pressure, cardiac output, pulmonary capillary wedge pressure and systemic venous pressure. At week 12, hemodynamic measurements were performed twice at least 15 minutes apart with the time of previous dose of study medication having been recorded. At least one of these readings was to be recorded at trough.

Symptoms

Time to clinical worsening was defined as: death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin therapy or initiation of bosentan therapy.

Other evaluations included SF-36 and EQ.5d questionnaires as well as overall patient preference.

Efficacy endpoints

Primary efficacy endpoint was change from baseline in exercise capacity at week 12 as measured by the 6-minute walk test. Subjects with missing Week 12 tests were to have an assessment imputed using the last observation carried forward. Those who died or underwent lung transplantation were to have their change from baseline walk distance assessed as zero.

Secondary endpoints included change from baseline at week 12 in mean PAP, time from randomization to the first occurrence of clinical worsening (defined as death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin or bosentan therapy), change from baseline at week 12 in the BORG dyspnea score (assessed at

the end of the 6-minute walk and reflect the maximum degree of dyspnea at any time during the walking test).

Tertiary endpoints included functional capacity and therapeutic class, quality of life questionnaires, patient overall preference assessment, change in chronic use of background therapy for PAH.

2.2 Results

Disposition of subjects

The study was conducted in the US (18 center), South America (2 centers), Europe (25 centers), and other (6 centers).

The numbers randomized, treated, and eventual outcome are shown below by treatment group.

Number of subjects

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
No. randomized	70	69	68	71
Treated	70	69	67^	71
Completed and entered extension	67	65	63	64
Completed without extension	1	2	2	1
Did not complete	2 (2.9)	2 (2.9)	2 (2.9)	6 (4.3)
Included in ITT 6-minute walk	66	67	64	69

^patient #10271

Table 1.1

A total of 278 subjects were randomized to one of four treatment groups. All but one subject received at least one dose of study drug. Subject #10271 (sild 40 mg) was manually randomized and took a medication pack that was not allocated by the sponsor. The total number of subjects included in the study report was 277.

There were 12 patients (4.3%) who did not complete the study. The highest percent of drop outs occurred in the group randomized to sildenafil 80 mg tid (6 subjects, 8.5%). The other groups had less than 3% drop out rate.

The reasons for the 12 subjects not completing the study are shown below by treatment group.

No. of patients not completing for any reason

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
Did not complete	2	2	2	6^
Death	1	1	0	1

Adverse event	0	0	0	5+
Lab abnormal	0	1	0	0
Other	1	0	2	0

^ patient 10743 was randomized to 80mg and discontinued the study on day 7 while still receiving 40mg. She died on day 8 from septic shock.
+subject 10484 discontinued because of an adverse event and died 2 days later of MI.
Table 4.1.2

There were three deaths (one each for placebo, sild 20 mg tid, sild 80 mg tid). Only the 80 mg group had drop outs for adverse event (5 subjects). There was one drop out (sild 20 mg tid) because of a laboratory abnormality, and 2 (sild 40 mg tid) who did not complete for other reasons.

Demographics
The number of subjects by gender, the mean ages, the percent that was white, and the mean age are shown below by treatment group.

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
male/female (n)	13/57	20/49	20/47	15/56
Mean age (yrs)	49.1	47.2	51.4	48.1
White (%)	87.1	85.5	86.6	81.7
Mean weight (kg)	73.9	71.0	74.5	70.6

Table 2.1

The majority of subjects were female, mean age was around 50 years, most were white, and mean weight was around 72 kgs.

Type of pulmonary hypertension
Eligible subjects were those with either primary (PPH) or secondary pulmonary hypertension (SPH). The table below shows the numbers in each of the 2 categories and the mean number of years since diagnosis at time of study entry.

Number of subjects

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid	total
PPH	42	44	43	46	175
Mean since dx (yrs)	2.2	2.5	3.2	2.5	
SPH	28	25	24	25	102
Mean since dx (yrs)	4.3	2.4	0.9	2.7	

Table 2.2.1

There were 175 subjects (63%) with PPH and 102 (37%) with SPH. Mean years from diagnosis was around 2.5.

Etiology of SPH

The SPH could be secondary to 1) connective tissue (CT) disease, or 2) with surgical repair (occurring at least 5 years previously) of atrial or ventricular septal defect, patent ductus arteriosus, or aorto-pulmonary window. The numbers of subjects in each category are shown below.

Number of subjects

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
CT disease	22	21	20	21
Scleroderma	8	9	11	10
SLE	4	6	3	6
CREST	3	3	2	4
Mixed CT	2	1	3	0
Other CT	5	2	1	1
Surgical repair	6	4	4	4

Table 2.2.2

Most of the subjects with SPH had it because of connective tissue disease (84, 30.3%); far fewer had SPH with surgical repair (18, 6.5%).

Duration of treatment

The table below shows the number of days subjects received study drug, by treatment group.

Days of treatment (includes missed dosing days)

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
Median duration of treatment	85	85	85	84
Range	55-96	1-103	2-91	7-94

Table 3.1.1

The median durations of treatment were similar across treatment groups.

Concomitant medication

The drug classes taken by more than 50% of the subjects were analgesics, anticoagulants, antihypertensive drugs, diuretics, drugs used for local anesthesia, and mydriatics and cycloplegics.

2.2.1 Efficacy

Primary efficacy endpoint

The table below shows the number of subjects who were randomized, the number included in the intent to treat analysis (ITT), and the number were excluded from the ITT analysis. 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.

No. of patients

	Placebo	sild 20 mg tid	sild 40 mg tid	sild 80 mg tid
randomized	70	69	68+	71
ITT population^	66	67	64	69
lacking walk test	4	2	3	2

+one patient randomized but not treated.
^These subjects were randomized to study drug, received at least one dose of study drug, and have both baseline and post baseline walking distance assessments.
Table 5.1.1

Of the 278 subjects randomized, 266 (95.7%) were included in the ITT.

Walk test
The numbers of subjects without a baseline walk test, without a post baseline walk test, and the mean baseline walk test (meters) are shown below by treatment group.

	Placebo n=66	sild 20 mg tid n=67	sild 40 mg tid n=64	sild 80 mg tid n=69
No. lacking baseline walk test	4	1	2	0
No. lacking post baseline walk test	0	1	1	2
6 min walk (m)+	347.6	345.7	342.8	337.9
Std dev (m)	74.8	90.3	76.7	79.2

+inclusion criterion limited subjects to those who walked more than 100 m but less than 450 m.
Table 5.2.1

The numbers of subjects lacking either a baseline or post baseline walk test and, therefore, excluded from the ITT analysis were similar across treatment groups. Mean baseline walk distances were similar across treatment groups (about 345 m).

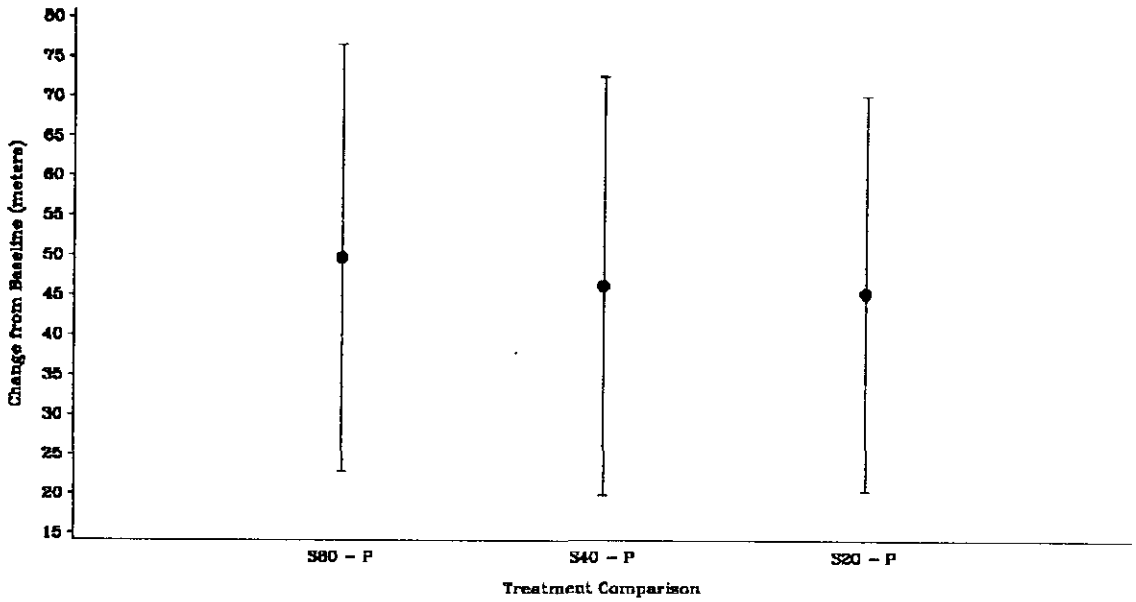
Mean change from baseline (m) at week 12 LOCF

	Placebo n=66	sild 20 mg tid n=67	sild 40 mg tid n=64	sild 80 mg tid n=69
6 min walk (m)	-3.7	41.4	44.1	46.8
Std dev	52.8	54.8	60.7	70.9
Min, max	-263, 106	-77, 204	-139, 298	-230, 229
Placebo subtracted	-	45.1***	47.8***	50.5***
99% CI	-	20.5, 70	19.9, 72.4	22.9, 76.5

***compared to placebo, p value for each active treatment group was <0.0001.
Table 5.2.1

The mean increases in walk distance for the active treatment groups compared to baseline (placebo subtracted) were 45.1 m, 47.8 m, and 50.5 m for sildenafil 20 mg, 40 mg, and 80 mg, respectively.

Figure 1.2.1
Sildenafil Protocol A1481140
Treatment Differences in Changes from Baseline in Six-Minute Walking Distance (meters) at Week 12 (LOCF) : Mean and 95% Confidence Intervals - ITT Population



ITT population for walking distance includes all subjects who have been randomized to study treatment, received at least one dose of study medication, and who have both a baseline and post-baseline walking distance assessment.

All 3 dose groups were significantly better than placebo, but not different from each other.

Walk test by visit

The mean changes from baseline at weeks 4, 8, and 12 are shown below by treatment group.

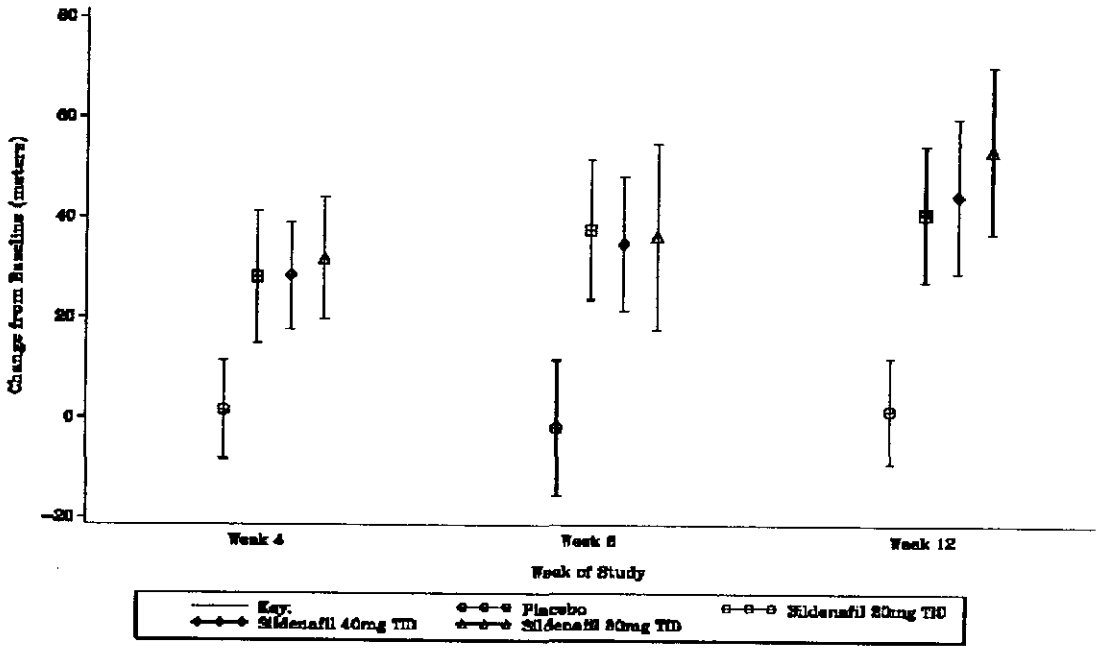
Change from baseline (m) at each visit/no. of patients

	Week 4	Week 8	Week 12
placebo	1.7/66	-1.9/64	1.6/62
Sild 20 mg tid	28.1/66	37.7/64	40.8/66
Sild 40 mg tid	28.3/63	34.8/62	44.3/63
Sild 80 mg tid	31.8/69	36.3/66	53.4/64

Table 5.2.1

The placebo group changed their walk distance very little during the entire treatment period. The active treatment groups showed improvement by week 4 and maintained this improvement over the remaining 8 weeks. This is displayed in the figure below.

Figure 1.1
Sildenafil Protocol A1481145
Change from Baseline in Six-Minute Walking Distance (meters): Mean and 95% Confidence Intervals – ITT Population



ITT population for walking distance includes all subjects who have been randomised to study treatment, received at least one dose of study medication, and who have both a baseline and post-baseline walking distance assessment.

Subgroups

Baseline walking distance (<325m and > 325 m)

Mean changes from baseline at endpoint for the 6-minute walk tests grouped by baseline walk distance are shown below.

APPEARS THIS WAY
ON ORIGINAL

Mean change from baseline at week 12 LOCF minus placebo^

	Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
	<325 m n=23	≥325 m n=44	<325 m n=23	≥325 m n=41	<325 m n=26	≥325 m n=43
Means change from baseline	56.9	38.6	69.0	36.1	86.7	29.2
95% CI	25.3, 88.5	15.4, 61.8	34.2, 103.7	11.9, 60.3	57.3, 116.2	0.9, 57.6

^placebo: n=23 for <325 m and n=43 for ≥ 325 m
Table 5.2.8

Compared to those at baseline who could walk longer than the mean, those with a lower baseline walk test had greater increases in walk at endpoint.

Type of PH
Walk test results by type of pulmonary hypertension (primary, secondary connective tissue disease, and secondary surgical repair) are shown below.

Mean change from baseline (m) at week 12 LOCF minus placebo^

	Sild 20 mg tid n=43/20/4+	Sild 40 mg tid n=42/18/4+	Sild 80 mg tid n=46/19/4+
Primary PH	39.7	47.9	62.2
95% CI	13.8, 65.6	19.7, 76.0	35.4, 89.1
Secondary PH- Connective tissue dis	54.9	49.3	28.1
95% CI	24.4, 85.4	18.5, 80.0	-14.3, 70.5
Surgical repair	49.2	33.4	14.9
95% CI	5.1, 93.2	-8.5, 75.4	-3.8, 33.6

^placebo: n=39 for primary PH, 21 for secondary: connective tissue, and 6 for secondary: surgical repair.
+n=primary PH/secondary: connective tissue/secondary: surgical repair
table 5.2.8

None of the actively treated PH groups walked less than placebo. The group with the poorest results was secondary with surgical repair sildenafil 80 mg tid. The importance of this is unclear since the sample size was extremely small.

By disease severity (except NYHA I- too few subjects)
The mean walk distance by NYHA class at baseline is shown below.

Mean change from baseline (m) at week 12 LOCF minus placebo^

	Sild 20 mg tid n=22/40/5+	Sild 40 mg tid n=21/43/0+	Sild 80 mg tid n=27/41/1+
NYHA II	50.2	9.7^^	50.1
NYHA III	44.5	71.3	52.5
NYHA IV	78.6	-	122

^placebo: n= 30 for Class II, 33 for Class III, and 2 for Class IV.
+number of subjects with NYHA II/III/IV
^^median was 12 m
Table 5.2.5.3

There were few NYHA class IV subjects and only one who was class I. No group walked less than placebo. Sample sizes are too small to draw a conclusion.

By gender
The majority of subjects were female. The mean changes from baseline at endpoint by gender and treatment groups are shown below.

Mean change from baseline (m) at week 12 LOCF

placebo		Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
male n= 12	female n=54	male n= 19	female n=48	male n= 19	female n=45	male n= 15	female n=54
-37.0	3.7	43.7	40.3	32.4	49.0	63.7	42.2

Table 5.2.5.4

The male group randomized to placebo had the poorest performance in the walk test (a decline of 37 m from baseline at week 12 LOCF). However, all active treatment groups had a sizable increase over baseline regardless of gender. Again, the sample sizes, especially for the male subjects, are small.

By age (<49 years and > 49 years)
Results by age group are shown below.

Mean change from baseline (m) at week 12 LOCF

placebo		Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
<49 n=31	≥49 n=35	<49 n=38	≥49 n=29	<49 n=27	≥49 n=37	<49 n=35	≥49 n=34
-2.4	-4.9	52.9	26.0	63.0	30.2	64.5	28.7

Table 5.2.5.5

All groups on active treatment improved their walk distance compared to baseline. Younger subjects tended to walk longer compared to their older counterparts.

By race
Results by race are shown below.

Mean change from baseline (m) at week 12 LOCF minus placebo^

Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
white n= 57	nonwhite n=10	white n= 55	nonwhite n=9	white n= 57	nonwhite n=12
42.0	64.8	44.1	70.9	44.3	87.2

^placebo: n=57 for white and n=9 for nonwhite
Table 5.2.8

There were few non white subjects. All groups on active treatment improved their walk distance compared to baseline.

By location
The majority of subjects were located in either Europe or the US. Walk distance results by location are shown below.

Mean change from baseline (m) at week 12 LOCF

placebo		Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
Europe n=34	US n=17	Europe n=39	US n= 15	Europe n=37	US n=12	Europe n= 30	US n=18
5.9	-8.2	48.8	33.3	51.3	37.3	55.6	21.1

Table 5.2.5.7

The walk distance increases in the treatment groups were similar regardless of location.

By median baseline pulmonary arterial pressure (PAP)
Results by median baseline PAP are shown below.

Mean change from baseline (m) at week 12 LOCF minus placebo^

Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
<52 mmHg n=30	>52 mmHg n=36	<52 mmHg n=39	>52 mmHg n=24	<52 mmHg n=31	>52 mmHg n=38
32.0	56.3	30.5	69.0	33.4	64.2

^placebo: n=29 for <52 mmHg and n=37 for PAP≥ 52 mmHg.
Table 5.2.8

There could be a tendency for those with a higher PAP to have a better response to active treatment compared to those with a lower PAP. This is consistent with the results for subjects whose baseline walk distance was shorter than the median.

By median baseline peripheral vascular resistance index (PVRI)
Results by median baseline PVRI are shown below.

Mean change from baseline (m) at week 12 LOCF minus placebo^

Sild 20 mg tid		Sild 40 mg tid		Sild 80 mg tid	
<1648	≥1648	<1648	≥1648	<1648	≥1648

dyne.s/cm^5/m^2 n=23	dyne.s/cm^5/m^2 n=26	dyne.s/cm^5/m^2 n=28	dyne.s/cm^5/m^2 n=24	dyne.s/cm^5/m^2 n=35	dyne.s/cm^5/m^2 n=26
37.0	51.8	38.4	53.3	34.9	59.5

^placebo: n=22 for <1648 dyne.s/cm5/m2 and n=32 for ≥ 1648 dyne.s/cm5/m2.
Table 5.2.8

There appears to be a tendency for those with a higher PVRI to have a better response to active treatment compared to those with a lower PVRI.

Secondary efficacy endpoints

The protocol stated that the following secondary endpoints will provide supportive evidence of efficacy[3]:

1. Change from baseline at Week 12 in mean PAP.
2. Time from randomization to the first occurrence of clinical worsening defined as death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin therapy or initiation of bosentan therapy.
3. Change from baseline at Week 12 in the BORG dyspnea score.

Pulmonary artery pressure (PAP)

Of the 277 treated subjects, only 258 had adequate assessment of their PAP. There were two subjects (20mg: 1; 40mg: 1) with missing baseline values and 17 subjects (Placebo: 5; 20mg: 3; 40mg: 3; 80mg: 6 including 2 deaths) with missing post baseline. The mean changes are shown below.

Mean baseline (mmHg) and mean change(mmHg) from baseline at week 12 LOCF

Placebo n=65		Sild 20 mg tid n=65		Sild 40 mg tid n=63		Sild 80 mg tid n=65	
Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
53.6	0.6	54.5	-2.1	48.6	-2.6	52.0	-4.7

Table 5.3.1

The comparisons to placebo are shown below (subjects were excluded if there was no baseline walk distance).

[3] If a statistically significant treatment effect was observed in the primary endpoint, then statistical tests on these three secondary endpoints were to be conducted in a hierarchical order as follows. First, mean PAP will be evaluated. If no significant treatment effect is found, then no further secondary endpoints will be evaluated. If a statistically significant treatment effect is observed in mean PAP, then the time to clinical worsening will be evaluated. If no significant treatment effect is found, then no further secondary endpoints will be evaluated. If a statistically significant treatment effect is observed in the time to clinical worsening, then the BORG dyspnea score will be evaluated.

Table 5.3.2 Page 1 of 1
Sildenafil Protocol A1481140
Treatment Comparisons of Change from Baseline in Mean PAP (mmHg) at Week 12 (LOCF) - ITT Population

Statistic	Treatment Comparison With Placebo (N=61) Sildenafil 20mg TID (N=64)	Sildenafil 40mg TID (N=61)	Sildenafil 80mg TID (N=63)
Mean Difference (SE)	-2.7 (1.3)	-3.9 (1.2)	-5.1 (1.2)
p-value (1-sided)	0.021	0.0059	0.000023
95% Confidence Interval	(-5.4, -0.1)	(-6.3, -0.7)	(-7.5, -2.6)

As specified in the step-down procedure, treatment comparisons of Mean PAP are performed because there was a significant treatment effect (at least one dose significantly different from placebo at the 0.005 level (one-sided)) in the parameter six minute walking distance. The step-down procedure also specifies that when a contrast of a specific dose level for Mean PAP is found to be significant at the 0.025 level (one-sided), the contrast for the next lower dose level can be tested. Significance tests of Mean PAP are performed using a stratified t-test (one-sided), with baseline walking distance and etiology as the stratification factors The number of subjects included in this analysis is less than the number in the ITT population for hemodynamics due to subjects with a missing baseline walking distance (stratification factor).
ITT population for all hemodynamic assessments includes all subjects who have been randomized to study treatment, received at least one dose of study medication, and who have both a baseline and post-baseline Mean PAP assessment.
Source Data: Section 11, Item 11, Table 2.1.1 Date of Reporting Dataset Creation: 22MAY2004 Date of Table Generation: 27MAY2004 (13:14)

Compared to placebo, there were significant improvements in PAP in all active treatment groups.

Clinical worsening

Clinical worsening was defined as death or lung transplantation or hospitalization because of pulmonary hypertension or initiation of prostacyclin therapy or initiation of bosentan therapy.

No. and (percent) of subjects

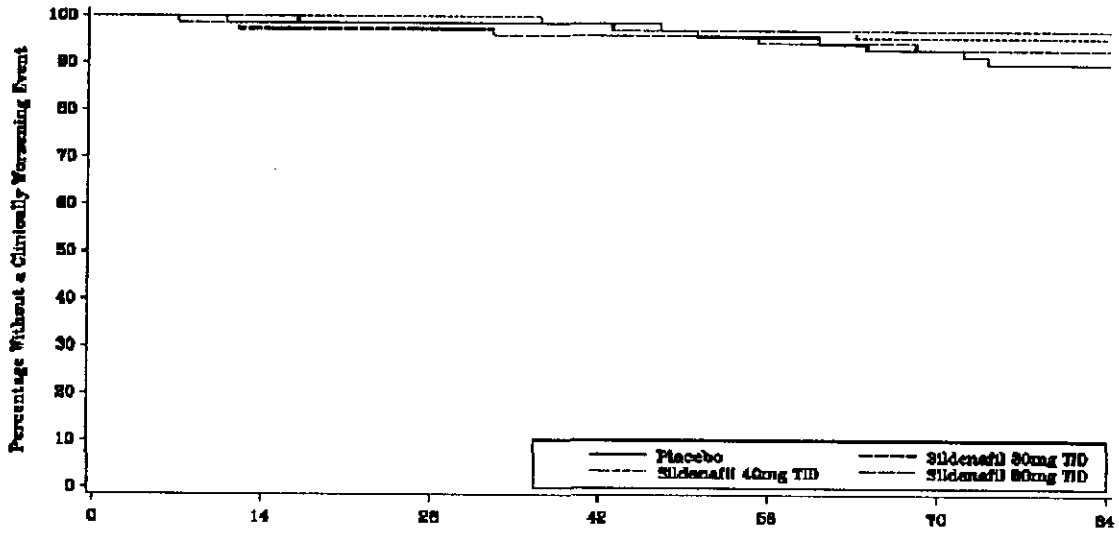
	Placebo n=70	Sild 20 mg tid n=69	Sild 40 mg tid n=67	Sild 80 mg tid n=71
Worsening: any	7 (10)	3 (4.3)	2 (3.0)	5 (7.0)
Death	1	1	0	2
Hosp for PAH	7	2	2	2
Init of prostac	1	0	0	0
Init of bosen	0	0	1	2

Subjects could have more than 1 event
Table 5.4.1

There were no reports of subjects undergoing lung transplantation. More subjects in the placebo group experienced clinical worsening (mostly because of greater need for hospitalization) compared to the other treatment groups.

There was no difference in the time to clinical worsening for the placebo group compared to the active treatment groups. According to the sponsor's statistical plan, no further statistical testing of secondary endpoints was done..

Figure 2
Sildenafil Protocol A1481140
Kaplan–Meier Plot of Time to Clinical Worsening (Days) – ITT Population



Number at Risk (number censored)	Day 0	(a) Day 28	(b) Day 56	(c) Day 84
Placebo	70	(0) 66	(0) 57	(22) 41
Sildenafil 20mg TID	68	(1) 65	(0) 56	(23) 42
Sildenafil 40mg TID	67	(0) 58	(0) 53	(22) 43
Sildenafil 80mg TID	71	(0) 59	(2) 55	(28) 38

The numbers censored are given in parentheses and represent (a) the number censored between days 0 and 27, (b) the number censored between days 28 and 55, (c) the number censored between days 56 and 83. There are 26,21,22 and 25 subjects censored between days 56 and 83 in the Placebo, Sildenafil 20mg, 40mg and 80mg groups respectively. This is due to subjects completing their week 12 visit according to the protocol specified windows (day 84+/– 3 days).
ITT population for clinical worsening includes all subjects who have been randomised to study treatment and received at least one dose of study medication.
Source Data: Section 11, Item 11, Table 2.2.2 Date of Data Extraction: 22MAY2004 Date of Table Generation: 25MAY2004 (08:47)

BORG score

There were 266 subjects who had both baseline and post baseline BORG assessments. The mean scores at baseline and the mean changes from baseline at endpoint are shown below, by treatment group.

Mean baseline and mean changes from baseline at week 12 LOCF

Placebo n=66		Sild 20 mg tid n=67		Sild 40 mg tid n=64		Sild 80 mg tid n=69	
Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
3.4	0	3.8	-0.8	2.9	-0.5	3.4	-0.9

Table 5.5.1

There were improvements in the mean BORG score for the active treatment groups. There was no change in the placebo group.

Tertiary Endpoints

These included functional capacity and therapeutic class, change in chronic use of background therapy, additional hemodynamic parameters, and quality of life questionnaires.

Pulmonary Hypertension Criteria For Functional Capacity And Therapeutic Class
The changes in functional class from baseline class at week 12 LOCF are shown below.

No. of patients

Placebo n=70		Sild 20 mg tid n=68		Sild 40 mg tid n=66		Sild 80 mg tid n=69	
Worse	Better	Worse	Better	Worse	Better	Worse	Better
7	5	2	19	2	24	2	29

Table 5.6

The subjects in the active treatment groups were more likely to improve and less likely to worsen their functional class compared to the placebo group.

Change in Chronic Use of Background Therapy for Pulmonary Arterial Hypertension:
Background therapy included anticoagulants, oxygen, diuretics, calcium channel blockers and digoxin. Additions and discontinuations of these medications were reviewed for all randomized subjects.

The numbers of subjects who added to their background therapy, by treatment group, are shown below.

Number (%) of subjects who added at least one class of background medication

Class	Treatment Group			
	Placebo N=70	Sildenafil 20mg N=69	Sildenafil 40mg N=67	Sildenafil 80mg N=71
Any addition	14 (20)	9 (13)	11 (16)	7 (10)
Anticoagulants	2 (3)	3 (4)	3 (5)	3 (4)
Oxygen	7 (10)	2 (3)	1 (2)	2 (3)
Diuretics	7 (10)	5 (7)	7 (10)	2 (3)
Calcium channel blockers	0 (0)	0 (0)	0 (0)	0 (0)
Digoxin	3 (4)	0 (0)	3 (5)	2 (3)

The groups were quite similar regarding the number of medication additions.

There were few subjects (2 sildenafil 80 mg tid) who discontinued background therapy.

Additional Hemodynamic Parameters

Change from baseline to Week 12 LOCF in haemodynamics parameters†

Haemodynamic Parameter Mean (95% CI)	Treatment Group			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
RAP (mmHg)				
N	64	65	63	65
Baseline	8.6 (7.5,9.8)	8.1 (6.8, 9.4)	8.7 (7.2, 10.2)	8.7 (7.3, 10.0)
Change from Baseline	0.3 (-0.9, 1.5)	-0.8 (-1.9, 0.3)	-1.1 (-2.4, 0.2)	-1.0 (-2.1, 0.1)
Systolic PAP (mmHg)				
N	65	65	63	65
Baseline	84.7 (79.4, 90.0)	85.1 (80.6, 89.5)	76.7 (71.0, 82.4)	79.6 (73.7, 85.6)
Change from Baseline	1.7 (-1.0, 4.3)	-1.2 (-4.2, 1.8)	-3.0 (-5.5, -0.4)	-5.9 (-9.1, -2.8)
Diastolic PAP (mmHg)				
N	65	65	63	65
Baseline	34.9 (32.2, 37.7)	35.9 (33.3, 38.5)	31.6 (29.0, 34.1)	34.6 (31.4, 37.9)
Change from Baseline	0.6 (-0.7, 1.8)	-1.8 (-3.7, 0.0)	-3.2 (-4.6, -1.8)	-3.8 (-5.4, -2.1)
Mean PAP (mmHg)				
N	65	65	63	65
Baseline	53.6 (50.1, 57.0)	54.5 (51.3, 57.6)	48.6 (45.3, 51.9)	52.0 (48.0, 56.0)
Change from Baseline	0.6 (-0.8, 2.0)	-2.1 (-4.3, 0.0)	-2.6 (-4.4, -0.9)	-4.7 (-6.7, -2.8)
Cardiac Output* (litres/min)				
N	52	49	52	58
Baseline	4.0 (3.7, 4.3)	4.30 (3.90, 4.70)	4.23 (3.83, 4.63)	4.31 (3.92, 4.70)
Change from Baseline	-0.1 (-0.4, 0.2)	0.4 (0.1, 0.7)	0.4 (0.1, 0.8)	0.7 (0.4, 1.0)
PCWP (mmHg)				
N	64	61	57	61
Baseline	9.4 (8.6, 10.2)	8.8 (8.1, 9.6)	8.5 (7.6, 9.5)	9.2 (8.4, 9.9)
Change from Baseline	-0.4 (-1.3, 0.5)	-0.2 (-1.6, 1.1)	0.2 (-0.7, 1.2)	0.2 (-0.9, 1.2)
Systolic SAP (mmHg)				
N	61	65	63	65
Baseline	126.2 (121.3, 131.0)	124.1 (118.9, 129.3)	125.0 (120.6, 129.4)	122.9 (117.4, 128.3)
Change from Baseline	-3.1 (-6.9, 0.8)	-2.9 (-6.5, 0.7)	0.5 (-3.4, 4.4)	-4.3 (-7.4, -1.2)
Diastolic SAP (mmHg)				
N	61	65	63	65
Baseline	78.9 (75.7, 82.0)	76.1 (73.4, 78.9)	76.2 (73.3, 79.0)	76.0 (72.8, 79.1)
Change from Baseline	-3.9 (-7.1, -0.7)	-2.3 (-5.2, 0.7)	-2.4 (-4.8, -0.1)	-5.4 (-7.8, -3.0)
Mean SAP (mmHg)				
N	61	65	61	64
Baseline	95.1 (91.6, 98.7)	93.5 (90.4, 96.6)	93.9 (90.7, 97.1)	92.5 (88.8, 96.3)
Change from Baseline	-3.1 (-6.2, -0.1)	-2.6 (-5.1, -0.1)	-0.9 (-3.8, 1.9)	-4.9 (-7.8, -2.0)

APPEARS THIS WAY
ON ORIGINAL

Change from baseline to Week 12 LOCF in haemodynamics parameters (continued)

Haemodynamic Parameter Mean (95% CI)	Treatment Group			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Heart Rate (beats/min)				
N	64	65	63	65
Baseline	80.8 (76.8, 84.9)	81.9 (78.9, 85.0)	76.5 (73.7, 79.2)	79.3 (76.7, 81.9)
Change from Baseline	-1.3 (-4.1, 1.4)	-3.7 (-5.9, -1.4)	-3.3 (-5.5, -1.0)	-4.7 (-7.3, -2.2)
MVO_2 (%)				
N	60	63	60	60
Baseline	60.6 (57.8, 63.4)	63.1 (61.0, 65.3)	61.7 (59.2, 64.2)	62.6 (59.9, 65.3)
Change from Baseline	-2.4 (-4.7, -0.2)	1.1 (-0.5, 2.7)	2.2 (-0.2, 4.6)	2.0 (-0.2, 4.1)
SVR* (dyne.sec/cm^5)				
N	50	49	50	57
Baseline	1888.7 (1702.9, 2074.5)	1732.1 (1585.5, 1878.8)	1807.7 (1633.3, 1982.1)	1696.2 (1536.1, 1856.4)
Change from Baseline	-77.6 (-196.5, 41.4)	-166.6 (-307.3, -25.8)	-257.5 (-401.4, -113.6)	-323.4 (-451.3, -195.4)
SVRI* (dyne.sec/cm^5/m^2)				
N	50	49	50	57
Baseline	3354.5 (3049.6, 3659.4)	3043.5 (2808.1, 3278.9)	3165.2 (2904.1, 3426.2)	2960.1 (2680.0, 3240.2)
Change from Baseline	-132.3 (-342.0, 77.5)	-305.4 (-539.7, -71.2)	-418.5 (-663.2, -173.8)	-579.2 (-801.8, -356.7)
PVR* (dyne.sec/cm^5)				
N	51	47	47	55
Baseline	1011.7 (874.9, 1148.5)	959.6 (827.1, 1092.1)	850.0 (717.2, 982.8)	917.5 (751.3, 1083.6)
Change from Baseline	49.1 (-54.4, 152.7)	-121.7 (-216.8, -26.6)	-143.3 (-218.0, -68.7)	-261.0 (-365.3, -156.7)
PVRI* (dyne.sec/cm^5/m^2)				
N	51	47	47	55
Baseline	1810.2 (1579.2, 2041.2)	1662.8 (1449.1, 1876.5)	1478.5 (1257.3, 1699.6)	1601.6 (1322.2, 1880.9)
Change from Baseline	113.2 (-99.9, 326.2)	-220.4 (-381.5, -59.2)	-240.9 (-364.6, -117.1)	-456.3 (-634.2, -278.4)

The number of subjects included in this summary table may be less than the number in the ITT population for haemodynamics due to missing assessments

**Subjects with CO determined using the Fick technique and subjects with shunts who have had their CO determined by thermodilution rather than the Fick technique are excluded from this summary.*

There were improvements in PVRI but not PCWP. Cardiac output improved somewhat. Blood pressure was similar across treatment groups. Heart rates tended to decrease in a dose related manner.

SF-36 and EQ-5D questionnaires

The SF-36 is described as a generic measure of quality of life assessing physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The EQ-5D current health state VAS scale and utility index is an assessment of overall perception of health including mobility, self care, usual activities, pain/discomfort, and anxiety/depression.

Change from baseline to Week 12 LOCF in SF-36 domains

SF-36 Domain Mean (95% CI)	Treatment Group			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Physical Functioning				
N	70	67	64	69
Baseline	34.9 (29.8,40.0)	37.9 (32.4,43.4)	35.5 (30.5,40.5)	38.2 (32.6,43.7)
Change from Baseline	4.5 (0.7,8.3)	12.0 (7.8,16.3)	14.5 (9.1,19.8)	14.6 (9.9,19.4)
Role-Physical				
N	68	67	64	69
Baseline	22.1 (13.7,30.4)	29.6 (20.4,38.9)	26.6 (17.2,35.9)	25.6 (17.4,33.8)
Change from Baseline	15.4 (5.6,25.3)	11.1 (2.8,19.3)	26.2 (15.8,36.5)	22.2 (11.9,32.5)
Bodily Pain				
N	69	67	64	69
Baseline	69.0 (62.6,75.5)	70.7 (64.4,76.9)	59.4 (53.5,65.3)	65.3 (58.7,71.9)
Change from Baseline	4.9 (0.1,9.7)	7.3 (0.9,13.8)	5.4 (-1.3,12.1)	8.5 (1.1,15.9)
General Health				
N	70	66	64	68
Baseline	39.0 (34.9,43.0)	36.5 (31.8,41.3)	38.8 (34.5,43.1)	36.3 (31.8,40.7)
Change from Baseline	0.3 (-3.4,4.0)	6.1 (2.0,10.2)	9.6 (5.1,14.1)	8.3 (4.8,11.8)
Vitality				
N	70	67	64	69
Baseline	40.4 (35.6,45.2)	39.1 (33.5,44.7)	42.6 (37.2,48.0)	41.5 (36.0,47.0)
Change from Baseline	5.5 (1.4,9.6)	11.6 (6.3,16.8)	12.3 (6.4,18.3)	11.2 (5.5,16.9)
Social Functioning				
N	70	67	64	69
Baseline	59.3 (52.9,65.7)	57.5 (50.4,64.5)	57.0 (50.0,64.1)	61.6 (55.4,67.8)
Change from Baseline	7.3 (1.4,13.2)	15.1 (9.1,21.1)	15.4 (8.2,22.6)	8.3 (2.2,14.4)
Role-Emotional				
N	68	67	63	69
Baseline	52.5 (41.4,63.5)	54.2 (43.3,65.2)	60.3 (49.8, 70.9)	53.1 (42.8,63.4)
Change from Baseline	12.3 (0.9,23.7)	15.9 (4.9,26.9)	10.1 (-2.3,22.4)	17.9 (6.3,29.5)
Mental Health				
N	70	67	64	69
Baseline	64.9 (60.3,69.5)	59.0 (53.6,64.4)	65.5 (59.9,71.0)	65.7 (60.7,70.6)
Change from Baseline	5.3 (1.5,9.2)	10.2 (5.3,15.1)	10.4 (5.0,15.7)	7.0 (2.1,11.9)

Compared to placebo, there were more improvements in the various domains in the active treatment groups.

Change from baseline to Week 12 LOCF in EQ-5D

EQ-5D Component Mean (95% CI)	Treatment Group			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Current Health State (VAS)				
N	69	66	63	67
Baseline	60.7 (56.5,64.9)	54.8 (50.2,59.4)	60.9 (56.1,65.7)	58.9 (54.9,63.0)
Change from Baseline	0.6 (-3.1,4.3)	9.8 (6.1,13.4)	6.0 (1.1,10.9)	7.9 (4.6,11.1)
Utility Index				
N	70	67	64	68
Baseline	0.7 (0.6, 0.7)	0.6 (0.5, 0.7)	0.7 (0.6, 0.7)	0.6 (0.6, 0.7)
Change from Baseline	0.0 (0.0, 0.1)	0.1 (0.1, 0.2)	0.0 (0.0, 0.1)	0.1 (0.1, 0.2)

There were larger improvements in the active treatment groups compared to placebo for current health state. For the utility index, there were improvements in the sildenafil 20 mg and 80 mg groups.

Patient overall preference assessment at week 12

The results of this questionnaire are shown below.

Overall Preference and willingness to use Medication Again – ITT Population

N (%)	Treatment Group			
	Placebo N=68	Sildenafil 20mg N=65	Sildenafil 40mg N=63	Sildenafil 80mg N=68
Overall Preference For Treatment				
Definite preference for current treatment	27 (40)	42 (65)	37 (59)	46 (68)
Slight preference for current treatment	15 (22)	9 (14)	11 (18)	12 (18)
No preference	18 (27)	12 (19)	12 (19)	6 (9)
Slight preference for previous treatment	3 (4)	2 (3)	2 (3)	2 (3)
Definite preference for previous treatment	2 (3)	0 (0)	0 (0)	1 (2)
Not recorded	3 (4)	0 (0)	1 (2)	1 (2)
Willingness To Use Medication Again				
Definitely would use same medication again	37 (54)	48 (74)	47 (75)	51 (75)
Might want to use same medication again	16 (24)	7 (11)	7 (11)	7 (10)
Not sure	13 (19)	9 (14)	7 (11)	6 (9)
Might not want to use same medication again	0 (0)	1 (2)	1 (2)	1 (2)
Definitely would not use same medication again	1 (2)	0 (0)	1 (2)	2 (3)
Not recorded	1 (2)	0 (0)	0 (0)	1 (2)

Compared to placebo, more subjects taking active treatment stated a definite preference for current treatment and more would definitely use the same medication again.

2.2.2 Safety

Serious safety
Deaths
There were 5 deaths. These are described in the table below.

Treatment	ID/sex/ Age/etiology	Days on drug	Day of death	comments
Placebo tid	10965/F/18/surgical repair	72	73	Aggravated PAH. Hospitalized day 73 for **pulmonary hypertensive crisis**. Died 5 hours after resuscitation was started.
Sild 20 mg tid	10487/F/40/ rheumatoid arthritis	44	44	Admitted because of fever. Dx was septic shock and urosepsis. Bilateral **pulmonary embolism** leading to death 1 day after hospitalization.
Sild 20 mg tid	10016/F/47/ primary	85	142	Reported weight gain, fluid retention, declining renal function starting day 58. Treated with diuretics but admitted on day 108 for aggravated **right-sided heart failure**. Completed study and died of heart failure 57 days later.
Sild 80 mg tid	10484/ F/81/ scleroderma	11	13	Admitted day 11 because of feeling unwell. Grew worse and **myocardial infarction** was considered. Died day 13. No autopsy.
Sild 80 mg tid	10743/ F/38/SLE	7	8	Admitted day 7 with nausea, vomiting. **Septic shock** diagnosed. Died one day later. History of leukopenia.

Tables 6.5 and 6.7.1

The 5 subjects who died had been randomized to placebo (1), sild 20mg (2), and sild 80 mg (2). Causes of death included pulmonary hypertensive crisis, pulmonary embolism, right sided heart failure, myocardial infarction, and septic shock. There is no obvious link between any of these deaths and the use of sildenafil.

Discontinuations for adverse events

There were 5 permanent discontinuations because of adverse event(s) and 1 for abnormal laboratory value. All six subjects are discussed below.

Treatment	ID/sex/ Age/etiology	Event onset day/disc.	Severity/ outcome	comments
Sild 20 mg	10331/F/65	1/1	Mild/ resolved	Day 1 the subject experienced mild **decreased creatinine clearance** (creatinine 1.8mg/dl; normal range 0.6-1.3mg/dl two days prior to Day 1). Study drug permanently discontinued after the first dose.
Sild 80 mg	10037/F/56	69/70	Moderate/ resolved	Day 69 hospitalized for symptoms of chest pain, **trigeminy**, syncope, and increased edema. No evidence of worsening pulmonary hypertension. Day 70 discontinued and started on bosentan. Other reported events included influenza, photophobia, headaches, peripheral edema, increased immunoglobulin, nausea, myalgia, chest pain, and night sweats.
Sild 80 mg	10345/F/46	4/7	Moderate/ Resolved	Day 1 reported **headache** and **flushing**; day 3 reported **dyspepsia**, **leg pain**, **hot flash** (all on 40 mg tid); day 4 reported **chromatopsia**, **photophobia**; day 6 **dyspepsia**, **salty taste** (all on 80 mg). All resolved by day 17.
Sild 80 mg	10484/F/81	11/13	Severe/ died	**Myocardial infarction**. See death table
Sild 80 mg	10749/F/61	9/14	Moderate/ Resolved	Day 9 reported moderate peripheral edema and increased weight; Day 14 reported moderate **fluid retention**. Treated with torsemide and spironolactone. All three adverse events resolved on Day 28.
Sild 80 mg	10752/F/68	27	Moderate/ Present	Day 27 hospitalized for new onset ascites, portal hypertension, and possible pericardial effusion. Day 28 an ultrasound and CT scan of the abdomen revealed a new finding of **hepatic cirrhosis.** Sildenafil was permanently discontinued. Ruled out hepatitis A, B,

				and C. ANA was positive. Report of a positive challenge rechallenge with Tracleer associated with abnormal LFTs. Tracleer was permanently discontinued 5 months prior to study start. Results of a liver biopsy prior to start of study showed focal mild hepatic changes consistent with grade 1-2 inflammation and stage 2 fibrosis.

Tables 4.2.1, 6.4, and 6.7.1

All the permanent discontinuations occurred in subjects randomized to active treatment, primarily sildenafil 80 mg tid. There was 1 death (possible myocardial infarction) and one case of liver cirrhosis (possible autoimmune, possible bosentan induced). The other events leading to discontinuation include decreased creatinine clearance, cardiac arrhythmias (trigeminy), and chromatopsia.

Temporary discontinuation/dose reduction

There were 12 subjects (5 placebo, 5 sild 20 mg tid, 1 sild 40 mg tid, and 1 sild 80 mg tid) who had temporary study drug discontinuations.

Summary of temporary discontinuations

Subject	Adverse Event	Start/Stop Day of AE
Treatment: Placebo		
10017	Upper respiratory tract infection	35 to 48
10340	Vomiting NOS	46 to 46
10725	Right ventricular failure Right lower lobe pneumonia	75 ongoing 75 ongoing
10759	Orthostatic hypotension	15 to 22
10962	Toothache	48 to 51
Treatment: Sildenafil 20mg		
10012	Increased liver function tests	27 ongoing
10031	Diarrhea Upper respiratory tract infection	30 to 31 56 to 59
10728	Abdominal pain	4 to 6
10732	Small bowel obstruction Cholelithiasis	2 to 15 49 to 82 83 ongoing
10769	Nausea	51 to 51 78 to 81
Treatment: Sildenafil 40mg		
10743	Septic shock	5 ongoing
Treatment: Sildenafil 80mg		
10061	Gastritis	34 to 40

Source: Table 4.2.2

While the placebo group tended to temporarily discontinue study drug for a variety of reasons, the sildenafil groups tended to temporarily discontinue study drug because of gastrointestional complaints.

Serious events

There were 42 subjects who reported at least 1 serious adverse event. These are shown in the table below.

Subject	Serious Adverse Event Term	Onset Day
Treatment: Placebo		
10506	Thrombocytopenia	40
10030	Syncopal episode	38
10256	Right heart decompensation	51
10965*	Acute pulmonary hypertensive crisis	73
10725	Right lower lobe pneumonia	76
	PAH with right heart failure	76
10059	Chest pain	64
	Dyspnoea	64
10059	Back pain	88
10326	Dyspnoea	11
	Chest pain	11
10326	Chest pain	59
10759	Orthostatic hypotension	15
10265	Pneumonia	43
10004	Worsening PAH	48
10252	Acute right sided heart failure	57
Treatment: Sildenafil 20mg		
10760	Vertigo	60
10503	Chest pain	N/a
10732*	Small bowel obstruction	2
10028**	Bronchial infection	6
	Hemorrhagic gastritis	6
	Peptic ulcer esophagitis	6
	Left ventricular dysfunction	94
10750	Respiratory infection	52
10315	Squamous cell carcinoma of right lung lower lobe	11
10315	Pneumonia	91
10031	Upper respiratory tract infection	56
10031	Exacerbation of dyspnoea	76
	Fever	76
	Weakness	76
10267	Pericardial effusion	417
10040	Unconsciousness	38
10034	Epistaxis	5

N.B. Subject 10732 is mislabeled in the above table. This subject did not die but temporarily discontinued study drug because of small bowel obstruction (email from sponsor dated 1-25-05).

Subject	Serious Adverse Event Term	Onset Day
Treatment: Sildenafil 20mg (continued)		
10487*	Septic shock	43
	Bilateral distal pulmonary embolism	44
	Urosepsis	43
	Bilateral acute interstitial nephritis	N/A
10016*	Weight gain due to fluid retention	N/A
	Aggravated right sided heart failure	N/A
	Renal failure	N/A
10062	Worsening of polycythaemia	29
Treatment: Sildenafil 40mg		
10258	Syncopal episode	82
10036	Right heart decompensation	43
10297**	Breathing difficulties	20
	Right sided heart failure	18
10297**	Right heart failure	51
10049	Acute anemia	1
	Hypotension	1
	Metrorrhagias	N/A
10002	Postural hypotension	2
11202	Anaphylactic reaction	91
10739	Pneumonia	2
10738	Psychological problems	36
Treatment: Sildenafil 80mg		
10037**	Cardiac arrhythmias	69
10752**	Ascites	2
10743*	Septic shock	7
10009	Upper respiratory tract infection	6
10009	Worsened edema	N/A
	Dyspepsia	58
	Right sided heart failure exacerbation	58
	Exacerbation of PHT	58
10272	Right heart failure	31
10484*	Myocardial infarction	12
10338	Collapse	84
	Weakness in both lower extremities	118
10505	Gouty Tophi	9
10505	Fever	61
10767	Recurrance of vulval nodule	57

*subject died

**subject permanently discontinued

Of the 42 subjects with events, 12 were randomized to placebo, 13 randomized to sildenafil 20 mg tid, 8 randomized to sildenafil 40 mg tid, and 9 randomized to sildenafil 80 mg tid.

Serious events reported by subjects taking placebo included thrombocytopenia, syncope, orthostatic hypotension, back pain, right sided heart failure, pneumonia, and chest pain.

Serious events reported by subjects taking sildenafil 20 mg tid included events suggestive of worsening PAH, as well as chest pain, small bowel obstruction, lung cancer, epistaxis, worsening polycythemia.

Serious events reported by subjects taking sildenafil 40 mg tid included events suggestive of worsening PAH, as well as acute anemia, anaphylactic reaction, and psychological problems.

Serious events reported by subjects taking sildenafil 80 mg tid included events suggestive of worsening PAH, as well as cardiac arrhythmias, myocardial infarction, gout, fever, and recurrence of vulval nodule.

There is no obvious link between any of these events and the use of sildenafil.

All (reported) adverse events

Review of systems
The table below shows the adverse events reported by body system.

Number and (percent) of subjects

	Placebo n=70	Total sild n=207	Placebo Subtracted %
Eye	14 (20.0)	57 (27.5)	7.5
Gastrointestinal disorders	27 (38.6)	90 (43.5)	4.9
Nervous system/psych.	43 (61.4)	136 (65.7)	4.3
Hepatobiliary	0	8 (3.9)	3.9
Metabolism and nutrition	3 (4.3)	16 (7.7)	3.4
Reproductive and breast	5 (7.1)	16 (7.7)	0.6
Musculoskeletal and connective tissue	24 (34.3)	71 (34.3)	0
Blood and lymphatic	4 (5.7)	9 (4.3)	-1.4
Cardiac	12 (17.1)	26 (12.5)	-4.6
Ear and labyrinth	3 (4.3)	8 (3.9)	-0.4
Endocrine	2 (2.9)	2 (1.0)	-1.9
Immune	4 (5.7)	3 (1.4)	-4.3
Renal and urinary	5 (7.1)	7 (3.4)	-3.7
Respiratory	24 (34.3)	66 (31.9)	-2.4
Skin	13 (18.6)	38 (18.4)	-0.2
Vascular	17 (24.3)	38 (18.4)	-5.9

Table 6.1.2.2

Eye disorders were reported more frequently by sildenafil subjects compared to placebo subjects (7.5%), as were adverse events grouped under gastrointestinal (4.9%), nervous (4.3%), hepatobiliary (3.9%), metabolism (3.4%), and reproductive/breast (0.6%) systems.

Individual adverse events
The following table show all adverse events reported by at least six subjects randomized to sildenafil and reported more often in the sildenafil group compared to placebo.

Number and (percent) of subjects

	Placebo n=70	Total sild n=207	Placebo Subtracted %
Headache	27 (38.6)	95 (45.9)	7.3
Flushing	3 (4.3)	24 (11.6)	7.3
Epistaxis	1 (1.4)	14 (6.8)	5.4
Insomnia	1 (1.4)	13 (6.3)	4.9
Myalgia	3 (4.3)	19 (9.2)	4.9
Diarrhea nos	4 (5.7)	21 (10.1)	4.4
Pain in limb	4 (5.7)	21 (10.1)	4.4
Dyspepsia	5 (7.1)	23 (11.1)	4.0
Visual disturbances	0	8 (3.9)	3.9
Pyrexia	2 (2.9)	12 (5.8)	2.9
Gastritis nos	0	6 (2.9)	2.9
Sinusitis	0	6 (2.9)	2.9
Rhinitis nos	0	6 (2.9)	2.9
Paraesthesia	0	6 (2.9)	2.9
Influenza	2 (2.9)	11 (5.3)	2.4
Anxiety	1 (1.4)	6 (2.9)	1.5
Erythema	1 (1.4)	6 (2.9)	1.5
Vertigo	1 (1.4)	6 (2.9)	1.5
Cough	4 (5.7)	14 (6.8)	1.1
Dyspnea exacer	2 (2.9)	7 (3.4)	0.5
Hot flushed nos	3 (4.3)	10 (4.8)	0.5
Back pain	8 (11.4)	24 (11.6)	0.2

Table 6.1.3.2

Headache and flushing had the highest placebo subtracted rates followed by epistaxis, insomnia, and myalgia.

The most common placebo-subtracted adverse events are shown below, by dose.

No. and (percent) of subjects

	Placebo n=70	Sild 20 mg tid n=69	Sild 40 mg tid n=67	Sild 80 mg tid n=71
Headache	27 (38.6)	32 (46.4)	28 (41.8)	35 (49.3)
Flushing	3 (4.3)	7 (10.1)	6 (9.0)	11 (15.5)
Epistaxis	1 (1.4)	6 (8.7)	5 (7.5)	3 (4.2)
Insomnia	1 (1.4)	5 (7.2)	5 (3.6)	3 (4.3)
Myalgia	3 (4.3)	5 (7.2)	4 (6.0)	10 (14.1)
Diarrhea nos	4 (5.7)	6 (8.7)	8 (11.9)	7 (9.9)
Pain in limb	4 (5.7)	5 (7.2)	10 (14.9)	6 (8.5)
Dyspepsia	5 (7.1)	9 (13.0)	5 (7.5)	9 (12.7)
Visual disturbances	0	0	3 (4.5)	5 (7.0)
Pyrexia	2 (2.9)	4 (5.8)	2 (3.0)	7 (9.9)
Influenza	2 (2.9)	4 (5.8)	4 (6.0)	3 (4.2)
Anxiety	1 (1.4)	5 (7.2)	0	1 (1.4)
Dyspnea exacer	2 (2.9)	5 (7.2)	1 (1.5)	1 (1.4)
Cough	4 (5.7)	5 (7.2)	3 (4.5)	6 (8.5)
Back pain	8 (11.4)	9 (13.0)	9 (13.4)	6 (8.5)
Hot flush	3 (4.3)	7 (10.1)	2 (3.0)	1 (1.4)
Erythema	1 (1.4)	4 (5.8)	1 (1.5)	1 (1.4)
Vertigo	1 (1.4)	1 (1.4)	3 (4.5)	2 (2.8)
Back pain	8 (11.4)	9 (13.0)	9 (13.4)	6 (8.5)
Gastritis nos	0	2 (2.9)	2 (3.0)	3 (4.2)
Sinusitis	0	2 (2.9)	3 (4.5)	1 (1.4)
Rhinitis nos	0	3 (4.3)	1 (1.5)	2 (2.8)
Paraesthesia	0	2 (2.9)	3 (4.5)	1 (1.4)

Table 6.1.3.2

Possible dose related adverse events include flushing, visual disturbances, myalgia, and pyrexia.

Eye related adverse events

Ocular testing was performed by ophthalmologists at baseline, Week 12, and at visit when a visual adverse event was reported.

Sildenafil is an inhibitor of PDE6, an enzyme involved in the phototransduction in the retina. Altered vision, color tinge to vision, increase perception of light, blurred vision were reported in clinical trials conducted with sildenafil in male erectile dysfunction.

Ocular adverse events reported by at least 1 sildenafil subject with PAH and reported by $\geq$ 1% more sildenafil subjects compared to placebo subjects are shown below.

Number and (percent) of patients

	Placebo n=70	Sild 20 mg tid n=69	Sild 40 mg tid n=67	Sild 80 mg tid n=71
At least one eye disorder	14 (20.0)	14 (20.3)	19 (28.4)	24 (33.8)
Visual disturbances	0	0	3 (4.5)	5 (7.0)
Photophobia	0	0	0	4 (5.6)
Chromatopsia	1 (1.4)	1 (1.4)	1 (1.5)	3 (4.2)
Cyanopsia	0	0	1 (1.5)	3 (4.2)
Eye pain	1 (1.4)	1 (1.4)	0	3 (4.2)
Abnormal sensation in eye	0	2 (2.9)	1 (1.5)	0
Conjunctival hemorrhage	0	1 (1.4)	1 (1.5)	0
Diplopia	0	1 (1.4)	1 (1.5)	1 (1.4)
Eye irritation	0	2 (2.9)	0	2 (2.8)
Halo vision	1 (1.4)	0	0	2 (2.8)
Retinal hemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)
Visual acuity reduced	0	0	2 (3.0)	1 (1.4)
Visual brightness	0	0	0	2 (2.8)

Table 6.1.3.2

Overall, there were more eye events reported in the total sildenafil group compared to placebo (27.5% and 20.0%, respectively). Unlike the incidence rates of reporting in the 80 mg tid dose, the overall rate for the 20 mg tid dose was similar to placebo. Eye events were rarely reported as serious or resulted in drug discontinuation.

Overall changes in visual correction, abnormal visual field changes, contract sensitivity changes, or intraocular pressures were absent (Tables 10.2-10.5).

Bleeding related adverse events

Reported bleeding events are shown below by treatment group.

Table 38. All Causality Bleeding Events Reported by Patients in Pivotal Study A1481140

Adverse Event (MedDRA Preferred Term)	Number of All Events (%)				
	Placebo	Sildenafil (mg TID)			
	N = 70	20 mg N = 69	40 mg N = 67	80 mg N = 71	Total N = 207
Epistaxis	1 (1.4)	6 (8.7)	5 (7.5)	3 (4.2)	14 (6.8)
Retinal Hemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)	4 (1.9)
Eye Hemorrhage NOS	1 (1.4)	1 (1.4)	1 (1.5)	1 (1.4)	3 (1.4)
Menorrhagia	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Haemoglobin Decreased	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Blood in Stool	0	0	0	1 (1.4)	1 (<1)
Conjunctival Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Gastritis Haemorrhagic	0	1 (1.4)	0	0	1 (<1)
INR Increased	2 (2.9)	1 (1.4)	0	0	1 (<1)
Rectal Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Metrorrhagia	1 (1.4)	0	1 (1.5)	0	1 (<1)
Vaginal Haemorrhage	0	1 (1.4)	0	0	1 (<1)
Hematoma NOS	3 (4.3)	1 (1.4)	0	0	1 (<1)
Gingival Bleeding	0	0	1 (1.5)	0	1 (<1)
Anal Haemorrhage	1 (1.4)	0	0	0	0
Hematuria	1 (1.4)	0	0	0	0
Venipuncture Site Haemorrhage	1 (1.4)	0	0	0	0
TOTAL PATIENTS WITH BLEEDING EVENTS	11 (15.7)	14 (20.3)	12 (17.9)	8 (11.3)	34 (16.4)

Source: SCS Table 9.3.61

The overall reporting rate for bleeding is slightly higher in the sildenafil group. However, there is a sizable increase in the incidence rate of reporting epistaxis in the sildenafil groups compared to placebo (6.8% versus 1.4%, respectively).

The table below lists reports of bleeding in the study categorized by the concomitant medication vitamin K antagonists.

Table 39. All Causality Bleeding Events Reported by Patients Co-prescribed Vitamin K Antagonists in Pivotal Study A1481140

MedDRA PT	PBO N (%)		Sildenafil N (%)	
	VitK Ant (N = 56)	No VitK Ant (N = 14)	VitK Ant (N = 148)	No VitK Ant (N = 59)
Conjunctival Haemorrhage	0	0	0	1 (1.7)
Eye Haemorrhage NOS	1 (1.8)	0	3 (2.0)	0
Retinal Haemorrhage	0	0	4 (2.7)	0
Anal Hemorrhage	0	1 (7.1)	0	0
Gastritis Hemorrhagic	0	0	1 (<1)	0
Gingival Bleeding	0	0	1 (<1)	0
Rectal Haemorrhage	0	0	0	1 (1.7)
Venipuncture Site Haemorrhage	0	1 (7.1)	0	0
Blood in Stool	0	0	1 (<1)	0
Haemoglobin Decreased	0	0	2 (1.4)	0
INR Increased	2 (3.6)	0	1 (<1)	0
Menorrhagia	0	0	2 (1.4)	0
Metrorrhagia	1 (1.8)	0	0	0
Vaginal Hemorrhage	0	0	1 (<1)	0
Epistaxis	1 (1.8)	0	13 (8.8)	1 (1.7)
Hematoma NOS	1 (1.8)	2 (14.3)	1 (<1)	0
Haematuria	1 (1.8)	0	0	0
TOTAL PATIENTS WITH BLEEDING EVENTS	7 (12.5)	4 (28.6)	30 (20.3)	3 (5.1)

Source: SCS Table 3.7.12.1C

For those taking vitamin K antagonists (74% of all subjects), the incidence rate for sildenafil groups reporting any bleeding was 20.3% compared to 12.5% for placebo. Epistaxis, the most commonly reported bleeding event, had an incidence rate of 14.3% (all sildenafil) compared to 1.8% (placebo). For those not taking vitamin k antagonists, there was little difference in the reporting rate for epistaxis (1.7% and 0%). The reporting rate for retinal hemorrhage was 2.7% and reported only by the sildenafil plus vitamin K antagonists group.

Laboratory evaluations

There was one subject (10331) who discontinued study because of decreased creatinine clearance (discussed in "discontinuations").

Hematology

The table below shows the number and percent of subjects with a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects+

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
Any abnormality		22 (31)	22 (32)	21 (32)	22 (32)
hemoglobin	<0.8xbaseline	0	0	2 (4)	3 (6)
hematocrit	<0.8xbaseline	0	1 (2)	4 (8)	2 (3)
RBC count	<0.8xbaseline	0	0	2 (4)	0

platelets	< 75 $10^3/mm^3$	2 (4)	0	1 (2)	0
WBC	<2.5 $10^3/mm^3$	2 (3)	0	0	0
lymphocytes	<0.8 xLLN	8	6	5	11
	>1.2xULN	0	2	0	0
Total neutrophils	<0.8 xLLN	2 (3)	0	0	0
	>1.2xULN	8 (13)	3 (6)	3 (5)	3 (5)
Basophils	>1.2xULN	4 (6)	6 (11)	3 (5)	2 (3)
Eosinophils	>1.2xULN	2 (3)	1 (1)	0	0
Monocytes	>1.2xULN	3 (5)	5 (8)	6 (10)	2 (3)

+total numbers of subjects are limited to those with normal or missing baseline and with at least one observation post baseline.
Table 7.1.1

There were 2%-8% of sildenafil patients with normal baseline values and abnormally low values during treatment for hemoglobin/hematocrit/RBC count. There were no placebo subjects with comparable changes. Changes for other parameters in the sildenafil treated groups were variable and similar to changes in the placebo group.

Mean changes from baseline to last observation for selected hematology parameters are shown below.

Lab parameter	units	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
hemoglobin	g/dl	0.1	-0.2	-0.3	-0.6
hematocrit	%	0.8	-0.2	-1.1	-1.9
RBC count	$10^6/mm^3$	0.1	-0.06	-0.11	-0.16
platelets	$10^3/mm^3$	-16	-2	1	-1
WBC	$10^3/mm^3$	0	-0.3	-0.4	-0.6
lymphocytes	$10^3/mm^3$	-0.03	-0.11	-0.25	-0.2

Table 9.4.120C

There are mean decreases from baseline for hemoglobin, hematocrit and RBC counts in the sildenafil groups, with a dose response. There is also a mean decrease in the active treatment groups for WBC.

There is a suspicion of minor blood loss with chronic use of sildenafil. The placebo subtracted incidence rate for reporting epistaxis was 5.4% and it was 2.6% for gastritis.

Chemistry parameters
Liver function
The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects+

Lab	Definition of	Placebo	Sild 20 mg	Sild 40 mg	Sild 80 mg

parameter	abnormality		tid	tid	tid
Any abnormality		1 (2)	2 (3)	2 (4)	0
Total bili	>1.5xULN	1 (2)	1 (2)	1 (2)	0
AST	>3.0xULN	0	1 (2)	0	0
ALT	>3.0xULN	0	0	1 (2)	0

Table 7.1.1

The incidence rates of abnormalities are similar across treatment groups.

There were no subjects with values for alk phos, total protein, albumin that met the definition of abnormality. The mean changes from baseline were unremarkable (Table 9.4.120C).

There is no indication that sildenafil has an adverse effect on the liver.

Renal function

The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
BUN	>1.3xULN	2 (3)	3 (5)	1 (2)	2 (4)

Table 7.1.1

There were no subjects meeting the definition of abnormal creatinine. Abnormalities for BUN were similar across treatment groups. The mean changes from baseline were unremarkable (Table 9.4.120C).

There is no indication that sildenafil has an adverse effect on the kidney.

Electrolytes

The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
sodium	<0.9xLLN	1 (2)	0	0	0
potassium	<0.9xLLN	1 (2)	2 (3)	1 (2)	2 (3)
potassium	>1.1xULN	2 (3)	1 (2)	1 (2)	0

Table 7.1.1

The incidence rates of abnormalities are similar across treatment groups. The mean changes from baseline were unremarkable (Table 9.4.120C).

There is no indication that sildenafil has an adverse effect on electrolytes.

Vital signs
Median blood pressure and heart rate changes are shown below.

Median Changes from Baseline to Last Observation - by Randomised Treatment

Number of subjects	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Systolic blood pressure (mmHg)	1.0	1.5	5.0	-2.0
Diastolic blood pressure (mmHg)	0.0	0.0	0.0	-2.0
Heart Rate (bpm)	0.0	-0.5	-2.0	-3.0

There are no consistent changes in blood pressure. Compared to placebo, heart rate in the active treatment groups decreased in a dose related manner.

3 INTERIM REPORT FOR PROTOCOL A1481142

This was an open, uncontrolled long-term extension study in pulmonary arterial hypertension (PAH) subjects who have completed study A1481140 (referred to as the base study).

3.1 Study conduct

Number of subjects and subject type
A total of 259 subjects entered this study:
-63 % (164) of subjects diagnosed with primary pulmonary hypertension (PPH),
-30% (79) with pulmonary hypertension secondary to connective tissue disease (SPH-CT), and
-6% (16) with pulmonary hypertension with surgical repair.

Dose
Depending on their dose in the base study, subjects were assigned to either
-sildenafil 40 mg tid up titrated after six weeks to sildenafil 80 mg tid, or
-sildenafil 80 mg tid. Dosing was every 4 hours.

The goal was to treat all subjects with 80 mg tid. However, if a subject could not tolerate the highest dose, the dose could be decreased to 40 mg tid or 20 mg tid. Subjects were maintained on their "final optimized dose" based on tolerability.

Disallowed medications
Bosentan, nitrates or nitric oxide donors in any form (including Nicorandil), Ritonovir, and alpha blockers were not permitted during the study were.

Allowed background medication

Background medications for PAH permitted during the study included warfarin, calcium channel blockers, digoxin, oxygen and diuretics. In addition, subjects were able to use alternative therapies for PAH (arginine, epoprostenol, iloprost, prostacyclin and treprostinal) at the discretion of the investigator if deemed clinically necessary.

The safety evaluations
Recording of adverse events, physical examinations, laboratory tests, ocular tests, vital signs, and a 12-lead electrocardiogram.

An exploratory analysis compared the observed survival at 1-year with predicted survival based on the NIH prognostic index for PPH subjects.

The efficacy evaluations
6-Minute Walk test (measured before next dose or at 4 hours after last dose), BORG dyspnea score, Pulmonary Hypertension Criteria for Functional Capacity and Therapeutic Class, Quality of Life, and pharmacokinetic measurements.

3.2 Results

Subject disposition

Subject Evaluation Groups by final optimised dose

	Sildenafil		
	20 mg	40 mg	80 mg
Treated	5	10	244
Discontinued	3	6	28
Ongoing at date of cut-off	2	4	216
Analysed for efficacy	5	10	244
Analysed for Adverse Events	5	10	244
Analysed for Laboratory Data	4	9	244
Analysed for Visual Safety	5	10	244

The three treatment groups represent the final optimised dose for subjects who continue in the study beyond 24 weeks and is the last scheduled dose for subjects who discontinue prior to week 24.

A total of 259 subjects met the criteria for enrollment into the extension study. Most subjects were able to tolerate the 80 mg dose of sildenafil (244, 94.2%). However, 15 subjects had to reduce their dose of sildenafil.

Subject type
There were 164 subjects with PPH, 79 with SPH-CT, and 16 with SPH with surgical repair.

Demographics

Baseline Demographic Characteristics by final optimised dose

Characteristic	Sildenafil		
	20 mg N= 5	40 mg N= 10	80 mg N= 244
Gender, n (%)			
Men	0	2 (20)	62 (25)
Women	5 (100)	8 (80)	182 (75)
Age, Years			
Mean (SD)	47.0 (19.8)	56.5 (13.5)	48.4 (14.8)
Min, Max	25-74	31-74	19-78
Race, n (%)			
White	3 (60)	10 (100)	206 (84)
Black	0	0	5 (2)
Asian	1 (20)	0	18 (7)
Other	1 (20)	0	15 (6)
Weight (kg)			
Mean (SD)	55.6 (7.4)	76.4 (21.6)	72.7 (17.5)
Min, Max	45-64	51-129	41-137

The three treatment groups represent the final optimised dose for subjects who continue in the study beyond 24 weeks and is the last scheduled dose for subjects who discontinue prior to week 24.

Most subjects were female, white, and approximately 50 years of age (range 19-78 years).

Duration of treatment

Table 3.1.1.2
Sildenafil Protocol A1481142
Duration of 1142 Treatment - Actual Time

	Sildenafil 20mg TID	Sildenafil 40mg TID	Sildenafil 80mg TID
Number of Subjects	5	10	244
Duration Category (Days)			
<=1	0	1	0
2-7	0	1	0
8-14	0	0	0
15-28	1	0	0
29-60	0	1	0
61-90	0	3	2
91-180	0	0	8
181-364	4	2	147
365-547	0	2	87
548-729	0	0	0
730-912	0	0	0
913-1094	0	0	0
>=1095	0	0	0
Median Duration	246.0	76.0	335.5
Range	15-306	1-509	61-511

N.B. Any gaps in treatment of any duration are not counted in this total. The durations summarized therefore include the dose titration phase (which may be at a different dose from the final dose used in the treatment grouping).

Most subjects (242, 93.4%) received sildenafil for at least 181 days.

Discontinuations

No. of subjects

	Sild 20 mg tid n=5	Sild 40 mg tid n=10	Sild 80 mg tid n=244
Total Discontinuations	3	6	28
Death	0	1	10
Adverse events	1	5	9
Other^	2	0	9

^Other classification consisted of: 3 subjects due to lack of efficacy, 1 subject with addition of bosentan therapy, 1 subject planning on becoming pregnant, 1 subject became pregnant, and 1 subject had worsening PAH, 4 subjects refused to continue in study.

Table 4.1

A total of 37 subjects (14.2%) did not complete 24 weeks of treatment. Of these 37, 11 subjects died[4], 15 subjects discontinued because of an adverse event, and 11 subjects discontinued for a variety of other reasons.

3.2.1 Safety

Deaths

There were 14 subjects who died either while receiving sildenafil or within 40 days of stopping drug and 2[5] who died after the 40 days follow up. The 16 deaths are shown below.

ID/dose of sildenafil	Sex/age	Last day of dosing/day of death	Comments
100110771/80 mg tid	F/70	188/191	Acute intestinal pneumonitis. Other events included cerebral hemorrhage, GI bleeding, bowel pseudo-obstruction.
101710251/80 mg tid	F/61	144/511^	Right heart failure.
101710504/80 mg tid	F/69	Ukn/191	Pulmonary embolism.
101810498/80 mg tid	F/69	114/124	Renal dysfunction, acute hepatitis, right heart failure, worsening PAH
101910056/40 mg tid	M/74	8/40	Worsening pulmonary edema. Systemic hypotension starting day 1, discontinued drug day 8, elevated hepatic enzymes post therapy day 4
102010506/80 mg tid	F/46	91/91	Cardiac arrest following worsening right heart failure
102310769/80 mg tid	F/69	225/242	Septic arthritis

[4]Additionally, 3 subjects died after discontinuing from the study, and a further 2 died after the follow-up period.

[5] Subject 10251 died 164 days after their final dose of sildenafil, and Subject 10047 died 139 days after their final dose of sildenafil.

103710047/80 mg tid	F/78	61/200^	Worsening PAH
103910333/80 mg tid	F/25	205/211	Worsening PAH with hemoptysis and respiratory failure
104010488/80 mg tid	M/57	334/394	Right heart and renal failure
104410053/80 mg tid	F/58	43/68	Acute myocardial infarction
104510265/80 mg tid	M/68	Na/470	Probable pneumonia
104910260/80 mg tid	F/23	218/219	Pulmonary arterial aneurysm dissection
11209/80 mg tid	F/32	394/395	Cardiac arrest, pneumonia
106210004/80 mg tid	F/77	401/402	Few details of death; mention of "abdominal problem"
106210259/80 mg tid	F/53	400/401	Died at home; worsening pulmonary hypertension
107010051/80 mg tid	F/67	At least 365/unk	Died at home; worsening PAH

^died after the 40 day follow up period
Tables 6.5 and 6.6

Causes of death were mostly related to the underlying pulmonary arterial hypertension and similar to deaths reports from the base study.

Survival rates

Predicted survival rates were based on the NIH-Registry prognostic index for primary pulmonary hypertension subjects. The observed survival rate at 1 year was calculated using Kaplan Meier estimates. Subjects who underwent lung transplantation, electively discontinued sildenafil or were lost to follow-up in the base study or extension study were censored. Subjects who were event-free at the time of the interim data-cut were censored at 1 year.

Table 5.7
Sildenafil Protocol A1481142
Summary of Prognostic Index by 1140 Treatment

1140 Randomized Treatment*		Years after start of active treatment	Predicted Survival	Observed Survival (Kaplan-Meier Estimate)
Placebo	(N=32)	1 Year	0.70	0.93
		2 Years	0.58	
		3 Years	0.49	
Sildenafil 20mg TID	(N=32)	1 Year	0.72	0.97
		2 Years	0.61	
		3 Years	0.52	
Sildenafil 40mg TID	(N=37)	1 Year	0.72	1.00
		2 Years	0.60	
		3 Years	0.51	
Sildenafil 80mg TID	(N=40)	1 Year	0.71	0.94
		2 Years	0.59	
		3 Years	0.50	

* The numbers in parentheses show the number of subjects included in the analysis for prognostic index. For the Sildenafil groups this represents subjects randomized to and treated with Sildenafil in 1140 who have a valid mean

PAP, RAP and cardiac index (CI) at 1140 baseline. For the Placebo group this represents the number of subjects randomized to Placebo in 1140 who extended into (and were treated in) 1142 and who have a valid mean PAP, RAP and CI at 1142 baseline.

The observed survival was always higher than the predicted survival. However, this information only implies that there is no effect of sildenafil on decreasing survival in PAH patients.

Discontinuations because of adverse events

There were 15 subjects who discontinued sildenafil because of an adverse event.

Summary of permanent discontinuations due to adverse events*

Subject A1481140 treatment	Adverse Event Investigator Term (Severity)	Start/Stop Day of AE**	Causality	SAE	Day of last dose
Treatment at event onset: 20mg sildenafil					
10017 placebo	Chest tightness (moderate)	100 to 103	Study drug	No	101
	Neck stiffness (moderate)	94 to 103	Study drug	No	
	Myalgia (moderate)	89 to 103	Study drug	No	
	Dizziness (mild)	92 to 103	Study drug	No	
	Headache (moderate)	98 to 103	Study drug	No	
	Visual field constriction (moderate)	90 to 103	Study drug	No	
	Dyspnoea (moderate)	95 to 103	Study drug	No	
Treatment at event onset: 40mg sildenafil					
10056 placebo	Worsening systemic hypotension (severe)	85 to 106 106 to 115	Disease under study Disease under study	No Yes	95
10481 placebo	Diarrhoea (moderate)	145 to 156	Study drug	No	156
	Diarrhea (severe)	157 to >217	Study drug	No	
	Nausea (moderate)	145 to 156	Study drug	No	
	Nausea (severe)	157 to 170	Study drug	No	

This table continues on the following page

Summary of permanent discontinuations due to adverse events* (continued)

Subject At481140 treatment	Adverse Event Investigator Term (Severity)	Start/Stop Day of AE**	Causality	SAE	Day of last dose
10494 placebo	Diarrhoea (moderate) Vomiting (moderate)	108 to 171 108 to 171	Study drug Study drug	No No	162
10737 placebo	Worsening of hypotension (severe)	86 to 162	Study drug	Yes	86
10761 80mg	Allergic reaction (moderate) Allergic reaction (severe)	[131] to 175 176 to 196	Study drug Study drug	No Yes	174
Treatment at event onset: 80mg sildenafil					
10031 *** 20mg	Weakness (mild) Dyspnoea (mild)	460 to [>460] 460 to [>460]	Disease under study Disease under study	No No	406
10047 placebo	Deterioration of congestive heart failure (mild) Progression of PAH (moderate)	146 to [>148] 144 to [>148]	Disease under study Disease under study	No Yes	144
10054 40mg	Intratentorial haemorrhage (severe)	319 to 323	Suicide attempt	Yes	318
10059 placebo	Dyspnoea (moderate) Dyspnoea (mild) Dyspnoea (moderate)	262 to 266 267 to 300 301 to [>301]	Study drug Disease under study Disease under study	No No No	261
10312 20mg	Headache (severe) Headache (mild)	129 to 130 169 to 357	Study drug Study drug	No No	357
10344 40mg	Worsening PAH (severe)	168 to [>289]	Disease under study	No	257
10498 placebo	Worsening PAH (severe)	150 to [>199]	Disease under study	Yes	199
10766 20mg	Worsening symptoms of PAH (moderate)	127 to [>210]	Disease under study	No	176
10769 20mg	Septic joints	277 to [>328]	Arthritis	Yes	311

**start and stop day of event are measure from start of base study
***post treatment event

There was one serious allergic reaction and one cerebral hemorrhage. Most other events leading to discontinuation were similar to those reported for the base study.

<u>All adverse events</u>
Events reported by at least 10 subjects (3.9%) are shown below.

Adverse Event (MedDRA preferred term)	Sil All causality events N (%)
Anaemia NOS	11 (4.2)
Palpitations	22 (8.5)
Right ventricular failure	13 (5.0)
Conjunctival hyperaemia	12 (4.6)
Episcleral hyperaemia	10 (3.9)
Retinal haemorrhage	10 (3.9)
Vision blurred	21 (8.1)
Visual disturbance NOS	15 (5.8)
Abdominal pain NOS	24 (9.3)
Abdominal pain upper	20 (7.7)
Diarrhoea NOS	47 (18.1)
Dyspepsia	43 (16.6)
Nausea	37 (14.3)
Toothache	11 (4.2)
Vomiting NOS	30 (11.6)
Asthenia	16 (6.2)
Chest pain	41 (15.8)
Fatigue	20 (7.7)
Peripheral oedema	55 (21.2)
Pyrexia	15 (5.8)
Influenza	26 (10.0)
Lower respiratory tract infection NOS	11 (4.2)
Pneumonia NOS	11 (4.2)
Sinusitis NOS	11 (4.2)
Upper respiratory tract infection NOS	29 (11.2)
Urinary tract infection NOS	11 (4.2)
Arthralgia	39 (15.1)
Back pain	38 (14.7)
Muscle cramp	10 (3.9)
Myalgia	18 (6.9)
Neck pain	11 (4.2)
Pain in limb	31 (12.0)
Dizziness	48 (18.5)
Headache	82 (31.7)
Syncope	16 (6.2)
Depression	10 (3.9)
Insomnia	14 (5.4)
Bronchitis NOS	18 (6.9)
Cough	39 (15.1)
Dyspnoea NOS	37 (14.3)
Dyspnoea exacerbated	21 (8.1)
Epistaxis	22 (8.5)
Nasopharyngitis	46 (17.8)
Pharyngitis	28 (10.8)
Productive cough	10 (3.9)
PAH NOS aggravated	15 (5.8)
Pruritus	10 (3.9)
Flushing	15 (5.8)
Hypotension NOS	13 (5.0)

Most events were similar to the events reported in the controlled study. Commonly reported events included headache (31.7%), peripheral edema (21.2%), dizziness (18.5%), diarrhea (18.1%), nasopharyngitis (17.8%), and abdominal pain including upper (17.0%).

Incidence rates for reporting anemia and epistaxis were 4.2% and 8.5%, respectively,

Serious adverse events

There were numerous reports of serious adverse events, not an unexpected occurrence in a seriously ill population taking multiple medications. The most frequently reported serious adverse events were right ventricular failure (13 subjects), pulmonary hypertension (10 subjects), dyspnea (10 subjects) and pneumonia (9 subjects).

Laboratory parameters

There were no discontinuations from study drug because of laboratory values. Abnormal values reported during the study are shown below.

Incidence of Laboratory Test Abnormalities by actual dose

Parameter	Primary Abnormality Criteria	Number of subjects with abnormal tests		
		Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
Hemoglobin	<0.8 x baseline	2	1	20
Hematocrit	<0.8 x baseline	2	2	23
Red blood cell count	<0.8 x baseline	1	1	11
Platelets	<0.8 x baseline			3
White blood cell count	<0.75 x baseline			3
Lymphocytes (Absolute)	<0.8 x LLN	2	2	84
Lymphocytes (%)	<0.8 x LLN			1
Total Neutrophils (Absolute)	>1.2 x ULN	1		43
Basophils (Absolute)	>1.2 x ULN	1	1	18
Eosinophils (Absolute)	>1.2 x ULN	1		6
Monocytes (Absolute)	>1.2 x ULN			23
Total bilirubin	>1.5 x ULN			20
Aspartate transaminase	>3.0 x ULN	1	1	1
Alanine transaminase	>3.0 x ULN	1	1	3
Gamma GT	>3.0 x ULN	1		
Blood urea nitrogen	>1.3 x ULN	1	3	21
Creatinine	>1.3 x ULN	1	2	9
Sodium	<0.95 x LLN			2
Potassium	<0.9 x LLN			15

The most common abnormalities were decreased lymphocytes, elevated total neutrophils, and decreased hematocrit.

Median laboratory changes from baseline to last observation

Table 7.4.1
Sildenafil Protocol A1481142
Laboratory Test Data: Median Changes from Baseline to Last Observation

		Sildenafil 20mg TID			Sildenafil 40mg TID			Sildenafil 80mg TID		
PARAMETER	UNITS	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE
Hemoglobin (HGB)	G/DL	4	15.7	-0.5	8	15.8	-0.8	242	16.5	-0.2
Hematocrit (HCT)	%	4	50	-2.1	8	48	-2.1	242	50.6	-0.9
RBC Count	10**6/MM**3	4	5.08	0	8	5.17	-0.14	242	5.3	0
Platelets	10**3/MM**3	4	265	-21	8	269	5	241	224	6
WBC Count	10**3/MM**3	4	8	-0.8	8	9.2	-1.2	242	7.8	-0.1
Lymphocytes (Abs)	10**3/MM**3	4	1.27	-0.41	7	1.49	-0.3	238	1.51	-0.15
Total Neutrophils (Abs)	10**3/MM**3	4	5.52	-0.19	7	5.97	-0.83	238	4.6	0.17
Basophils (Abs)	10**3/MM**3	4	0.05	-0.01	7	0.1	0	237	0.07	-0.02
Eosinophils (Abs)	10**3/MM**3	4	0.17	0	7	0.14	0	237	0.11	0.01
Monocytes (Abs)	10**3/MM**3	4	0.28	0.05	7	0.45	-0.15	237	0.39	-0.02
Total Bilirubin	MG/DL	4	0.4	0.1	9	0.8	-0.2	241	0.7	-0.1
AST (SGOT)	IU/L	4	25	-2	9	27	-1	243	28	-2
ALT (SGPT)	IU/L	4	26	-7	9	24	-1	243	26	-2
Alkaline Phosphatase	IU/L	4	82	2	9	78	5	243	87	-1
Total Protein	G/DL	1	8.5	0.5	.	.	.	9	7.2	0.5
Albumin	G/DL	1	3.6	-0.1	.	.	.	9	4.2	0.1
BUN	MG/DL	4	31.8	1.2	9	40.5	7.4	243	33.8	0
Creatinine	MG/DL	4	1.1	0	9	1.6	0	243	1.2	0
Sodium	MEQ/L	4	138	0	9	138	0	243	139	1
Potassium	MEQ/L	4	4.3	-0.4	9	4.2	0.1	243	4	-0.1

Last observation is defined as last observation while on study drug or during the lag.
Normalized data has been used in the computations.

There were minor decreases in hemoglobin and hematocrit.

Ocular tests

Ocular safety testing was performed at baseline, at Week 24 and yearly thereafter by ophthalmologists at each center. In addition, these tests were repeated at any visit where a visual adverse event was reported.

Events reported as eye disorders by at least two subjects are shown in the table below.

APPEARS THIS WAY
ON ORIGINAL

Incidence of All Causality Eye Disorder Adverse Events Reported by ≥2 Subject (0.8%)

Adverse Event (MedDRA preferred term)	Number of all events (%)
	Sildenafil
Cataract	2 (0.8)
Cataract unilateral	2 (0.8)
Chromatopsia	7 (2.7)
Conjunctival hyperaemia	12 (4.6)
Conjunctivitis	2 (0.8)
Cyanopsia	4 (1.5)
Diplopia	2 (0.8)
Dry eye NOS	2 (0.8)
Episcleral hyperaemia	10 (3.9)
Eye disorder NOS	2 (0.8)
Eye haemorrhage NOS	6 (2.3)
Eye irritation	3 (1.2)
Eye pain	3 (1.2)
Eye redness	3 (1.2)
Eyelid ptosis	2 (0.8)
Halo vision	2 (0.8)
Keratitis	2 (0.8)
Lacrimation increased	2 (0.8)
Lenticular opacities	4 (1.5)
Macular degeneration	2 (0.8)
Ocular discomfort	5 (1.9)
Ocular vascular disorder	2 (0.8)
Photopsia	5 (1.9)
Punctate keratitis	2 (0.8)
Refractive errors (NOS)	4 (1.5)
Retinal haemorrhage	10 (3.9)
Retinal pigmentation	3 (1.2)
Retinal tear	2 (0.8)
Vision blurred	21 (8.1)
Visual acuity reduced	3 (1.2)
Visual brightness	4 (1.5)
Visual disturbance NOS	15 (5.8)

The most commonly reported events included blurred vision (8.1%), visual disturbances not otherwise specified (5.8%), conjunctival hyperemia (4.6%), episcleral hyperemia (3.9%), and retinal hemorrhage (3.9%). Eye disorders reported by subjects who permanently or temporarily discontinued sildenafil included visual field constriction (sildenafil 20 mg tid) and red eye flashes (sildenafil 40 mg tid).

3.2.2 Walk distance

The descriptive summaries of 6-Minute Walk distance, BORG dyspnea score and functional class, and estimated survival rats.

6-minute walk test

Week 24

The table shows increase in walk distance at week 24 for the 232 subjects who were taking 80 mg tid at week 24. The baseline is from the base study and the subjects are grouped by randomized treatment group in the base study.

Change from baseline Study A1481140 6-Minute Walk distance at Week 24 for subjects whose Week 24 dose was 80mg sildenafil

Change from A1481140 baseline	Randomised Group in A1481140			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
N	52	61	58	61
Mean (meters)	45.7	47.7	53.6	49.8
95% Confidence Interval	(32.9, 58.5)	(30.4,65.0)	(32.4,74.8)	(28.6, 71.0)

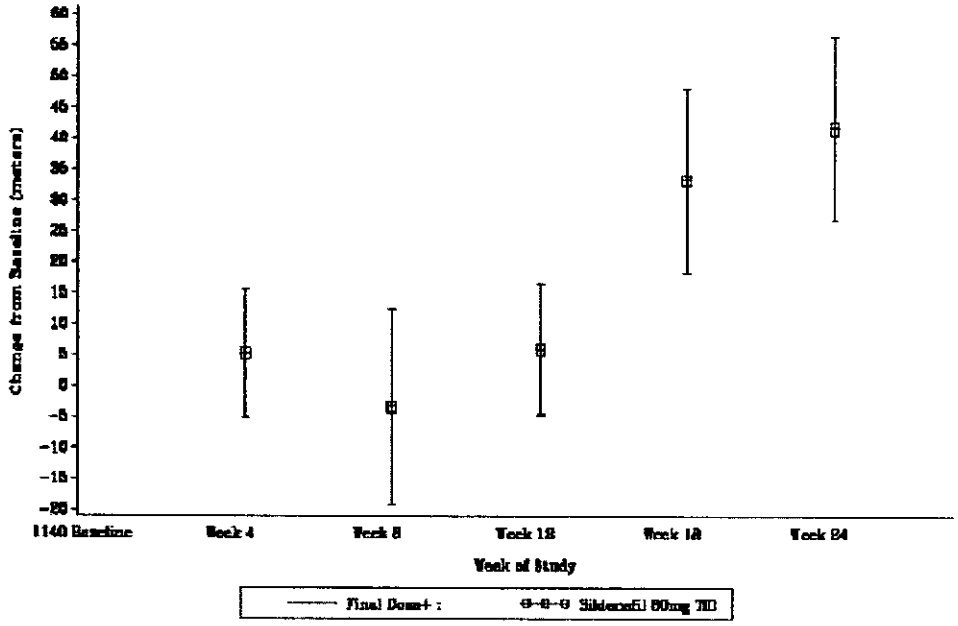
Source: Table: 5.2.1

The increase in walk distance was similar regardless of dose for the first 12 weeks.

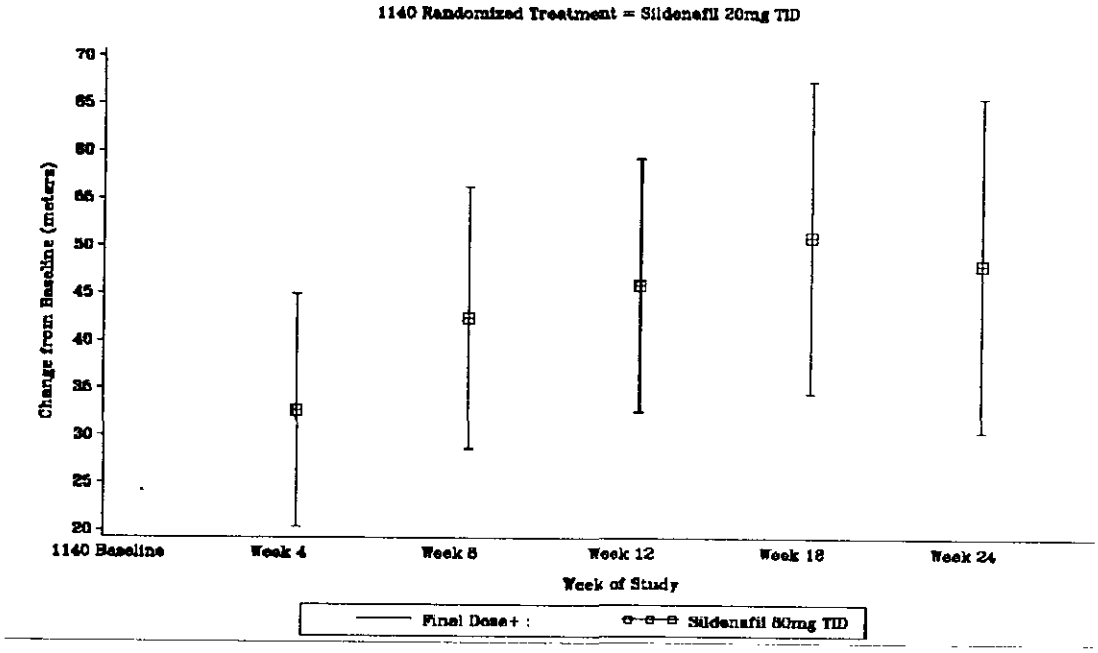
The figures below shows mean change from baseline of the base study by visit, grouped by randomized dose during base study (dose received up to week 12).

Placebo (n=52)

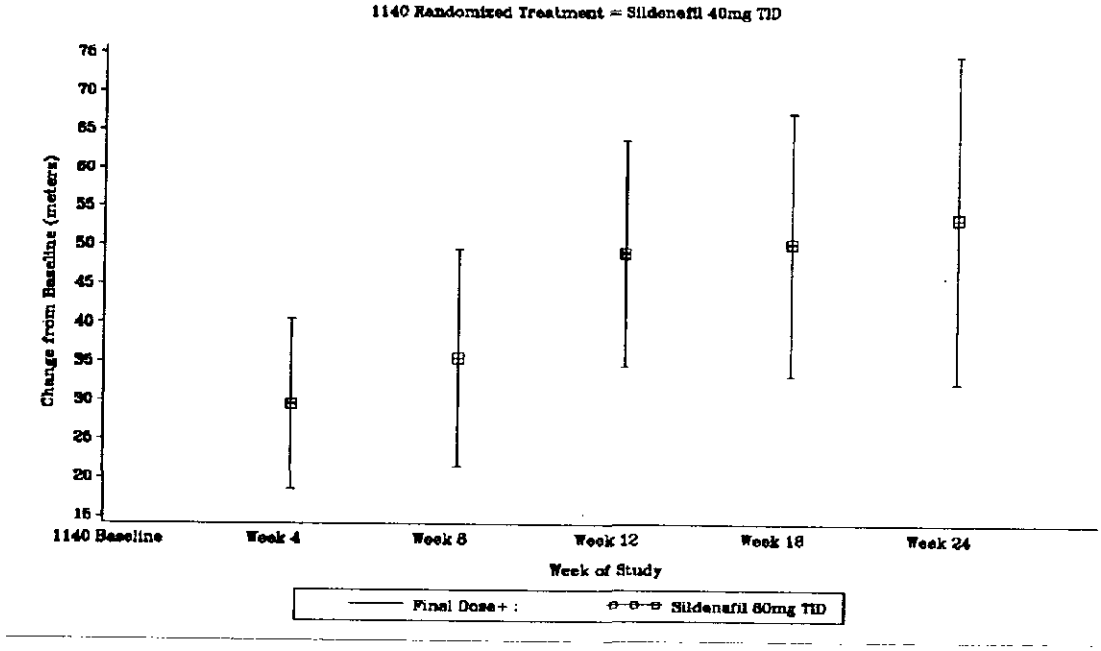
Change from A1481140 baseline in 6-Minute Walk Distance to Week 24 for Subjects Randomised to Placebo in Study A1481140.



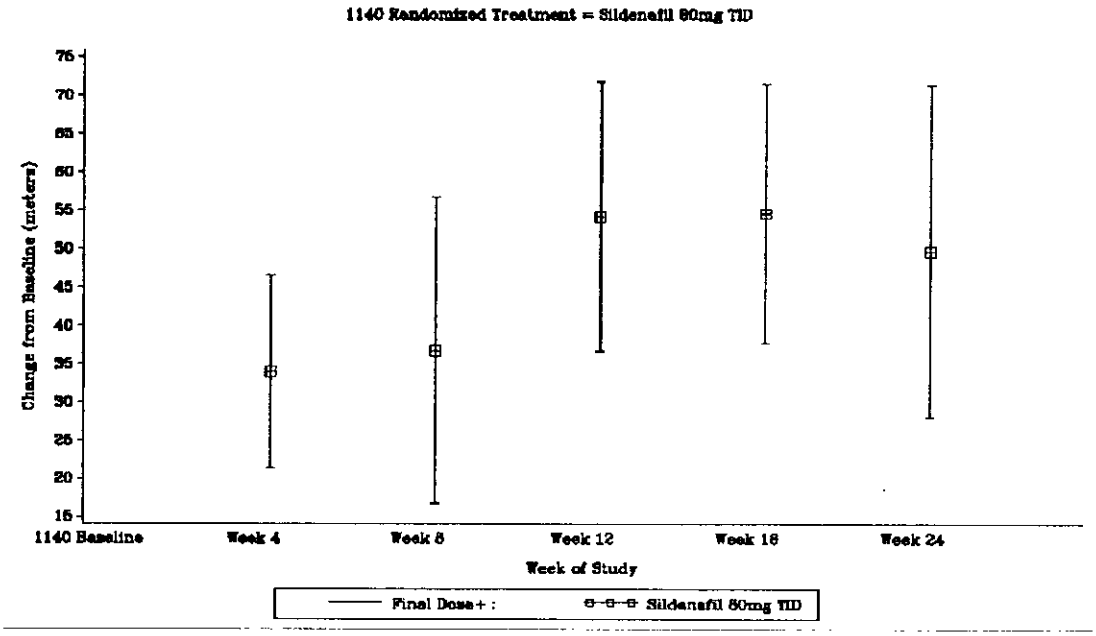
Sildenafil 20 mg tid (n=61)



Sildenafil 40 mg tid (n=58)



Sildenafil 80 mg tid (n=61)



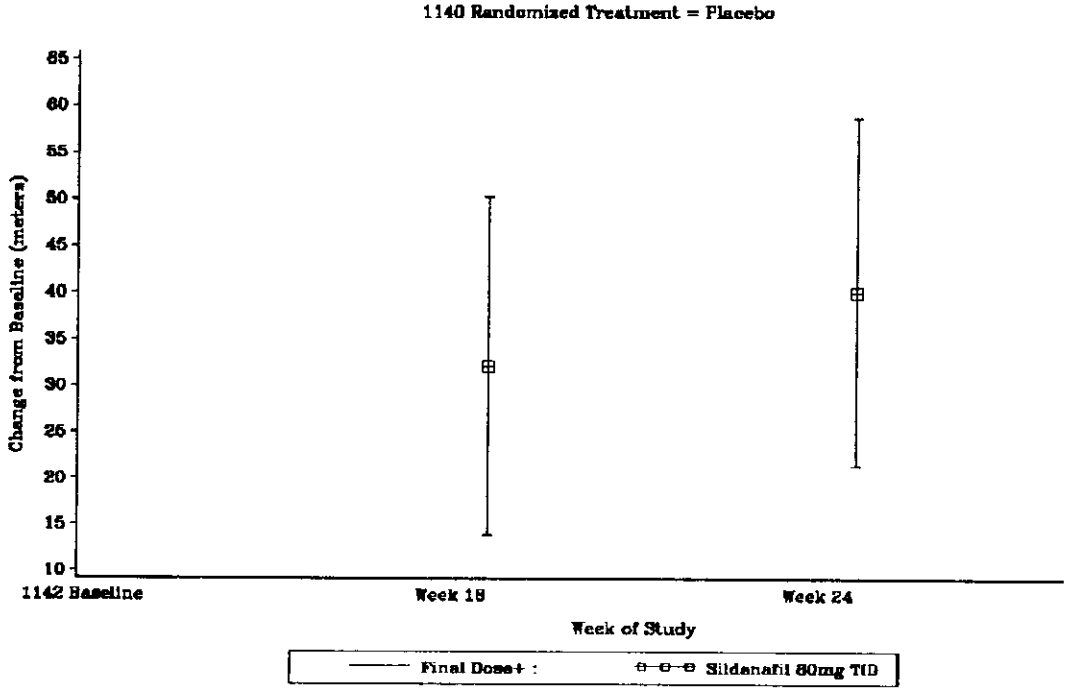
The group that received placebo for the first 12 weeks walked about 46 m longer at weeks 18 and 24 while receiving sildenafil 80 mg tid.

The groups that received active treatment during the base study experienced little change in walk distance from week 12 at weeks 18 and 24 despite continuation of sildenafil.

Walk distances using baseline of extension study (grouped by base study randomized treatment group).
The figures below show walk distance change from baseline (with baseline being walk distance observed at visit 12 of the base study). (N.B. y axis changes values)

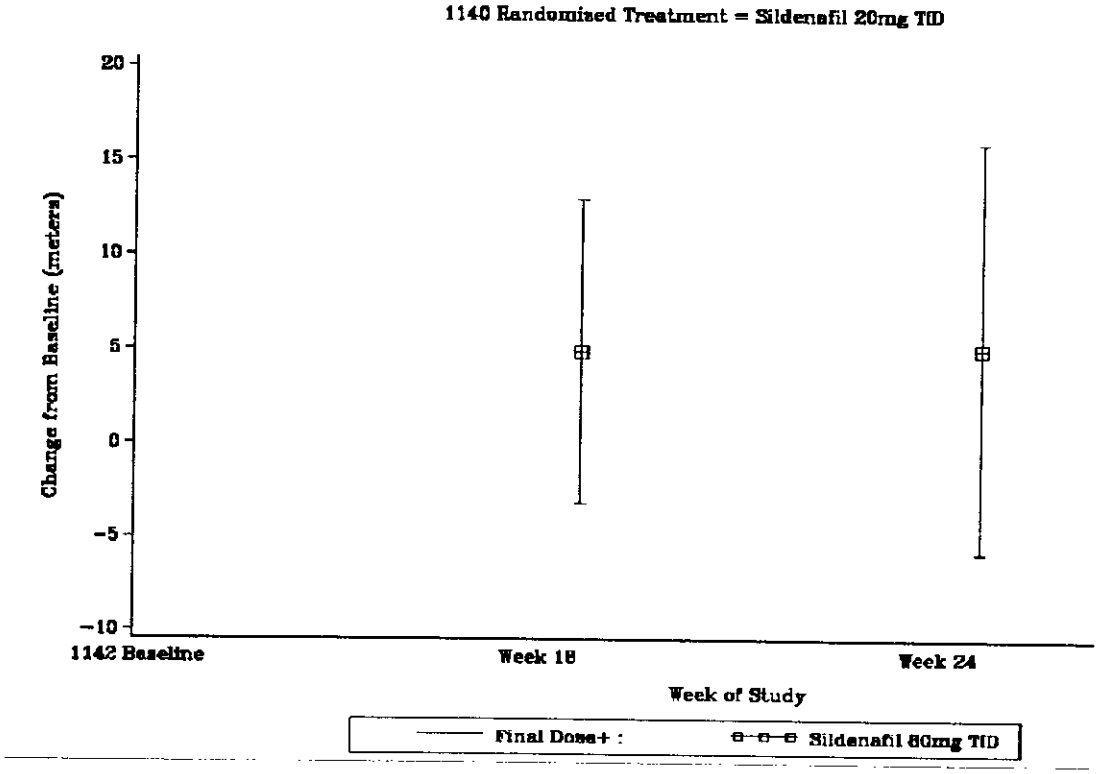
APPEARS THIS WAY
ON ORIGINAL

Figure 1.2
Sildenafil Protocol A1481142
Six Minute Walking Distance (meters) to Week 24 by 1140 Treatment and 1142 Final Dose (Change from 1142 Baseline) - Full Analysis Set: Mean and 95% Confidence Intervals



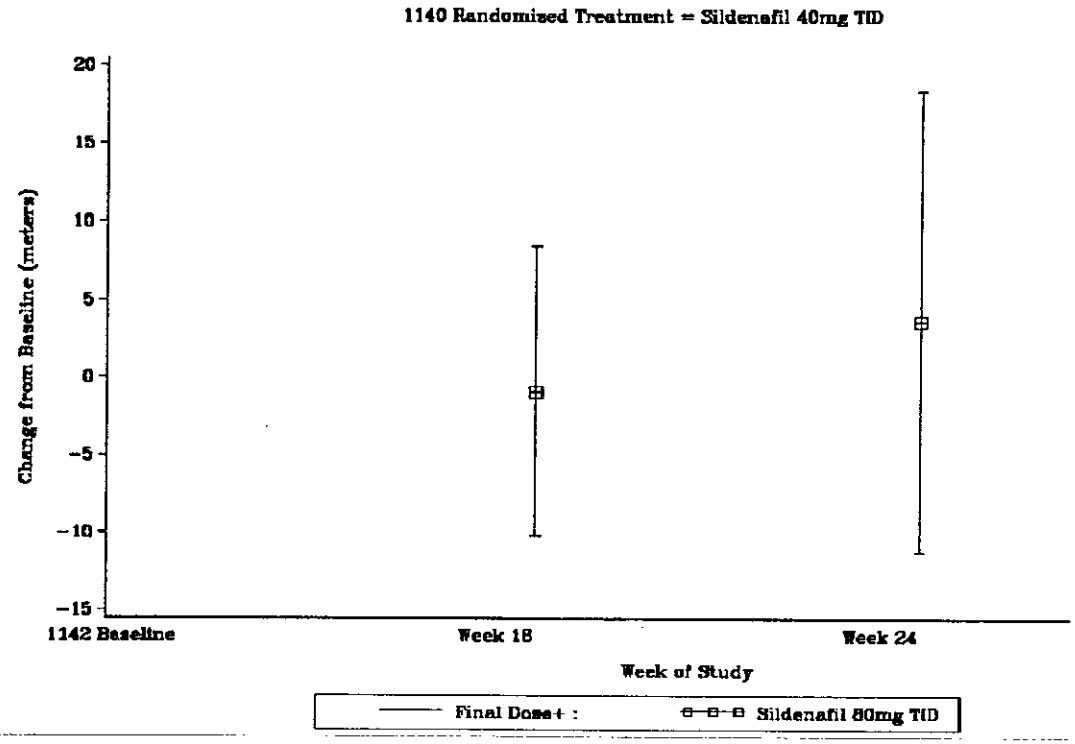
APPEARS THIS WAY
ON ORIGINAL

Figure 1.2
Sildenafil Protocol A1481142
Six Minute Walking Distance (meters) to Week 24 by 1140 Treatment and 1142 Final Dose (Change from 1142
Full Analysis Set: Mean and 95% Confidence Intervals



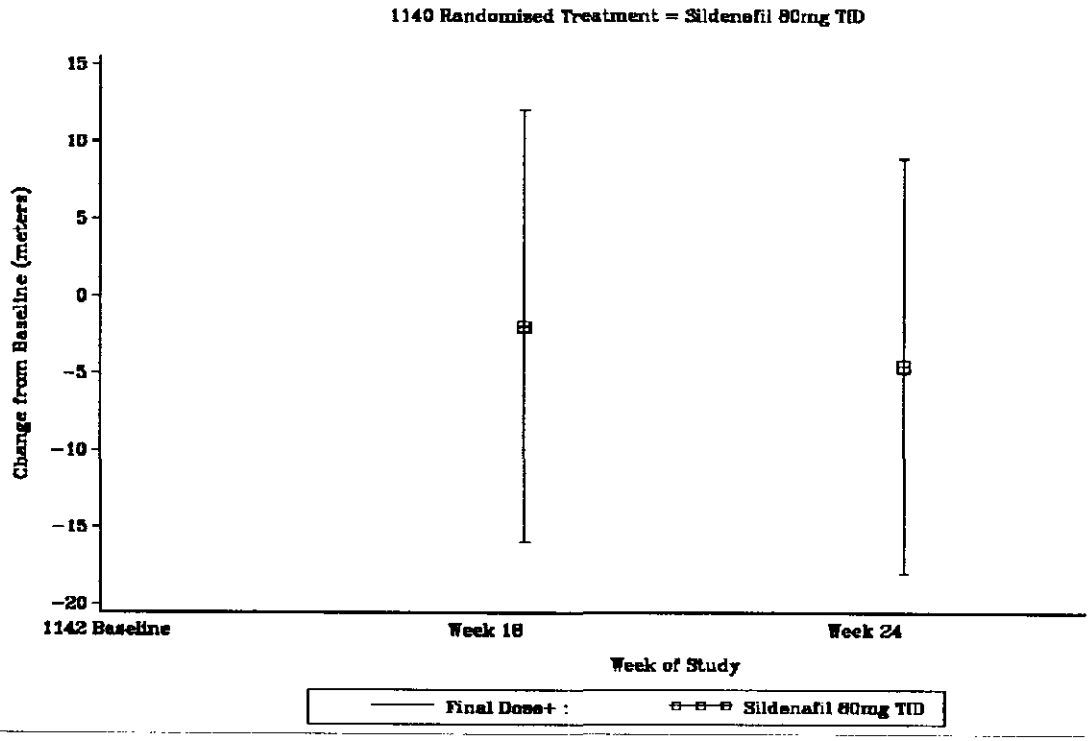
APPEARS THIS WAY
ON ORIGINAL

Figure 1.2
Sildenafil Protocol A1481142
Six Minute Walking Distance (meters) to Week 24 by 1140 Treatment and 1142 Final Dose (Change from 1142 Bas
Full Analysis Set: Mean and 95% Confidence Intervals



APPEARS THIS WAY
ON ORIGINAL

Figure 1.2
Sildenafil Protocol A1481142
Six Minute Walking Distance (meters) to Week 24 by 1140 Treatment and 1142 Final Dose (Change from 1142 Baselin
Full Analysis Set: Mean and 95% Confidence Intervals



After 12 weeks of treatment, it seems that the effect of sildenafil on walk distance declines over time and/or subjects are getting sicker.

Beyond week 24

Change from Week 24 6-Minute Walk distance for subjects whose final optimised dose was 80mg sildenafil

Change from Week 24 baseline	Month 9	Month 12	Month 15	Month 18	Month 21
N	228	213	155	80	17
Mean (meters)	1.6	1.5	-5.2	2.5	-37.9
95% Confidence Interval	(-5.8,9.0)	(-5.7,8.7)	(-14.8,4.5)	(-9.7,14.7)	(-79.3, 3.6)

Source: Table: 5.2.3

These results suggest that the effect of sildenafil 80 mg tid wanes over time as many of the subjects get sicker.

3.2.3 Other efficacy

BORG Dyspnea score

The mean changes in BORG scores from baseline (obtained during the base study) at week 24 for subjects who reached a dose of 80mg are shown below by randomized treatment group.

Change from baseline Study A1481140 BORG Dyspnoea score at Week 24 for subjects whose Week 24 dose was 80mg sildenafil

Change from A1481140 baseline	Randomised Group in A1481140			
	Placebo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
N	52	61	58	60
Median difference	-1	-1	0	-1
95% Confidence Interval	(-1.8,-0.8)	(-1.5,-0.5)	(-1.0,0.0)	(-1.3,-0.5)

These improvements are consistent to what was observed for the base study.

The mean changes from baseline (week 12) at various time points during the extension study are shown in the table below.

Change from Week 24 BORG Dyspnoea score for subjects whose final optimised dose was 80mg sildenafil

Change from Week 24 baseline	Month 9	Month 12	Month 15	Month 18	Month 21
N	227	212	153	79	16
Median difference	0	0	0	0	0
95% Confidence Interval	(0.0,0.0)	(0.0,0.3)	(0.0,0.5)	(0.0,0.5)	(-0.3,1.0)

There were neither further improvements nor worsening in the BORG dyspnea score in subjects taking sildenafil 80 mg tid.

Functional class

Changes of at least one functional class from A1481142 baseline to Week 24 by A1481140 randomised treatment

	1140 Treatment Group			
	Placbo	Sildenafil 20mg	Sildenafil 40mg	Sildenafil 80mg
N	61	64	63	63
Improvement	20 (32.8)	12 (18.8)	10 (15.9)	2 (3.2)
Deterioration	4 (6.6)	3 (4.7)	4 (6.3)	6 (9.5)

There were far fewer improvements in subjects who were randomized to sildenafil 80 mg tid and received this dose for 24 weeks (3.2%) compared to subjects who were on placebo for the first 12 weeks and then switched to sildenafil 80 mg tid for the final 12 weeks (32.8%). The incidence rates of deterioration were similar across treatment groups.

4 INTEGRATED SUMMARY OF SAFETY

4.1 Data sources

This data base contains clinical trials with patients with pulmonary arterial hypertension (PAH) and essential hypertension, as well as patients and healthy volunteers in clinical pharmacology studies and post marketing surveillance.

PAH

Adult studies

There is one completed double blind, placebo controlled trial (A1481140) and an ongoing follow-up open label extension study (A1481142). There is an ongoing randomized, double blind, placebo controlled trial (A1481141) assessing the safety and efficacy of sildenafil when used in combination with intravenous prostacyclin (epoprostenol)[6]. There is limited safety information about this study at this time.

Pediatric studies

There are three ongoing double blind, placebo controlled trials (A1481131 and A1481134 (IV formulation) and A1481157 (IV formulation)). There is one extension trial (A1481156).

There is one completed double blind, placebo controlled trial — , in — adults.

Clinical Pharmacology

There are 35 completed trials.

Miscellaneous studies

There is one completed trial in pulmonary hypertension (A1481024) and numerous chronic dosing studies for multiple indications.

Post marketing surveillance

Spontaneous reports from 25,963 patients.

Details of these data sources are shown in the following table.

[6] Meeting held with the Division of Cardio-renal Drugs, Food and Drug Administration, July 14, 2004, the Agency agreed that the data from a single pivotal study, Study A1481140 would be sufficient to support the NDA.

Table 1. Sources of Clinical Safety Data

Dataset/Status	Patient Population/Number of Patients	Type of Study	Dose
A1481140 Completed	PAH/ N = 277 (207 sildenafil, 70 PBO)	Phase 3, DB, PBO-controlled	20, 40, or 80 mg TID
A1481142 Extension to A1481140 Ongoing (Interim data cut 30 July 2004)	PAH/ N = 259 (not unique patients)	Long-term extension to 1140; Phase 3 (DB and OL phase)	20, 40, or 80 mg TID; maximum tolerated dose; no PBO group
Completed	N = 199 (139 sildenafil, 60 PBO)	Phase 2, DB, PBO-controlled	20, 40, or 80 mg TID
A1481141 Ongoing (SAEs only)	PAH NA (study remains blinded)	Phase 3, DB, PBO-controlled	20, 40, or 80 mg TID; optimised treatment
A1481153 Extension to A1481141 Ongoing (SAEs only)	PAH Not unique patients	Phase 3, OL	20, 40, or 80 mg TID; optimised treatment
A1481131 Ongoing (SAEs only)	PAH, Pediatric NA (study remains blinded)	Phase 3, DB, PBO-controlled in children aged 1-16 years	10, 20, 40, or 80 mg TID, depending on body weight
A1481156: Extension to A1481131 Ongoing (SAEs only)	PAH, Pediatric NA (study remains blinded)	Phase 3, DB, PBO-controlled in children aged 1-16 years	10, 20, 40, or 80 mg TID, depending on body weight
A1481134 Ongoing (SAEs only)	PAH (IV); Pediatric NA (study remains blinded)	Phase 3, DB, PBO-controlled in children aged 0-17 years	IV dosing
A1481157 Ongoing (SAEs only)	(IV); Pediatric NA (study remains blinded)	Phase 3, DB, PBO-controlled in neonates ≤72 hours old	IV dosing
Completed	N = 85	Phase 2 pilot, DB, PBO-controlled	IV dosing; short-term
Clinical Pharmacology 35 Completed Studies	Subjects N = 721 sildenafil treated patients	38 Phase 1 Studies	Varies
Postmarketing Adverse Events	Multiple Indications N = 25,963 (180 PH, 25,783 other indications)	Spontaneous Reports[a]	prn and chronic; various dose regimens
Chronic Dosing Studies Completed Studies	Multiple Indications N = 972	Phase 2, DB, PBO-controlled	Varies
Literature Review and Unpublished Data	61 publications, N = 481 Unpublished data: N = 128, case-series from 6 sites	Randomised controlled studies and case-series	Varies
Viagra Label	MED	Varies	Varies

PAH = Pulmonary arterial hypertension; IV = Intravenous; MED = Male erectile dysfunction; DB = Double-blind; PBO = Placebo; SAE = Serious adverse event; OL = Open-label; NA = Not applicable.

Number of unique subjects (oral formulation only)

dataset	Placebo	sildenafil
PAH Completed (1 study)	70	207
Hypertension Completed (1 study)	60	139
Clinical pharmacology (35 studies)	-	721
Post marketing	-	25,963
Chronic dosing studies	-	972

The majority of safety data for support of PAH indication is from one trial (A1481140).

Duration of exposure
Range of dosing for PAH subjects was 1-614 days with 96 subjects having received sildenafil between 181 and 364 days and 149 subjects having received sildenafil for more than 1 year.

4.2 Serious safety

Deaths
PAH
The deaths reported in the completed double blind, placebo controlled 12-week study (A1481140) are shown below.

Treatment	ID/sex/ Age/etiology	Days on drug	Day of death	comments
Placebo tid	10965/F/18/ surgical repair	72	73	Aggravated PAH. Hospitalized day 73 for **pulmonary hypertensive crisis**. Died 5 hours after resuscitation was started.
Sild 20 mg tid	10487/F/40/ connective tissue disease	44	44	Admitted because of fever. Dx was septic shock and urosepsis. Bilateral **pulmonary embolism** leading to death 1 day after hospitalization.
Sild 20 mg tid	10016/F/47/ primary	85	142	Reported weight gain, fluid retention, declining renal function starting day 58. Treated with diuretics but admitted on day 108 for aggravated **right-sided heart failure**. Completed study and died of heart failure 57 days later.
Sild 80 mg tid	10484/ F/81/ scleroderma	11	13	Admitted day 11 because of feeling unwell. Grew worse and **myocardial infarction** was considered. Died day 13. No autopsy.
Sild 80 mg tid	10743/ F/38/SLE	7	8	Admitted day 7 with nausea, vomiting. **Septic shock** diagnosed. Died one day later.

There were 5 deaths: placebo (1), sild 20mg (2), and sild 80 mg (2). Causes of death included pulmonary hypertensive crisis, pulmonary embolism, right sided heart failure, myocardial infarction, and septic shock.

The deaths reported in the ongoing[7] extension study (A1481142) are shown below.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

[7] As of 9-1-2004

ID/dose of sildenafil	Sex/age	Last day of dosing/day of death	Comments
100110771/80 mg tid	F/70	188/191	Acute intestinal pneumonitis. Other events included cerebral hemorrhage, GI bleeding, bowel pseudo-obstruction.
101710251/80 mg tid	F/61	423/423	Right heart failure.
101710504/80 mg tid	F/69	230/230	Pulmonary embolism.
101810498/80 mg tid	F/69	114/124	Renal dysfunction, acute hepatitis, right heart failure, worsening PAH
101910056/40 mg tid	M/74	8/40	Worsening pulmonary edema. Systemic hypotension starting day 1, discontinued drug day 8, elevated hepatic enzymes post therapy day 4
102010506/80 mg tid	F/46	91/91	Cardiac arrest following worsening right heart failure
102310769/80 mg tid	F/69	225/242	Septic arthritis
103710047/80 mg tid	F/78	61/200	Worsening PAH
103910333/80 mg tid	F/25	205/211	Worsening PAH with hemoptysis and respiratory failure
104010488/80 mg tid	M/57	334/394	Right heart and renal failure
104410053/80 mg tid	F/58	43/68	Acute myocardial infarction
104510265/80 mg tid	M/68	Na/470	Probable pneumonia
104910260/80 mg tid	F/23	218/219	Pulmonary arterial aneurysm dissection
2004045637/80 mg tid	F/32	394/395	Cardiac arrest, pneumonia
106210004/80 mg tid	F/77	401/402	Few details of death; mention of "abdominal problem"
106210259/80 mg tid	F/53	400/401	Died at home; worsening pulmonary hypertension
107010051/80 mg tid	F/67	At least 365/unk	Died at home; worsening PAH

There were 17 subjects who had died by the time of the study report cut-off date.

Causes of death appear to be related to the underlying pulmonary arterial hypertension and similar to deaths reported in the base study.

Survival rates (based on data from ongoing follow up study A1481142)
Predicted survival rates were based on the NIH-Registry prognostic index for primary pulmonary hypertension subjects. The observed survival rate at 1 year was calculated using Kaplan Meier estimates. Subjects who underwent lung transplantation, electively discontinued sildenafil or were lost to follow-up in the base study or extension study were censored. Subjects who were event-free at the time of the interim data-cut were censored at 1 year.

Table 5.7
Sildenafil Protocol A1481142
Summary of Prognostic Index by 1140 Treatment

1140 Randomized Treatment*		Years after start of active treatment	Predicted Survival	Observed Survival (Kaplan-Meier Estimate)
Placebo	(N=32)	1 Year	0.70	0.93
		2 Years	0.58	
		3 Years	0.49	
Sildenafil 20mg TID	(N=32)	1 Year	0.72	0.97
		2 Years	0.61	
		3 Years	0.52	
Sildenafil 40mg TID	(N=37)	1 Year	0.72	1.00
		2 Years	0.60	
		3 Years	0.51	
Sildenafil 80mg TID	(N=40)	1 Year	0.71	0.94
		2 Years	0.59	
		3 Years	0.50	

* The numbers in parentheses show the number of subjects included in the analysis for prognostic index. For the Sildenafil groups this represents subjects randomized to and treated with Sildenafil in 1140 who have a valid mean PAP, RAP and cardiac index (CI) at 1140 baseline. For the Placebo group this represents the number of subjects randomized to Placebo in 1140 who extended into (and were treated in) 1142 and who have a valid mean PAP, RAP and CI at 1142 baseline.

The observed survival was always higher than the predicted survival. However, this information only implies that there is no effect of sildenafil on decreasing survival in PAH patients.

There were no deaths in study

Ongoing clinical studies (excluding A1481142)
There was a total of 9 randomized subjects who died in studies A1481141 (3 patients with PAH), A1481153 (4 patients with PAH in extension study), and A1481134 (2 pediatric patients with PAH). There were 3 subjects who died prior to randomization. All deaths are shown below.

Table 28. Listing of Patients Who Died in Ongoing Studies (A1481141, A1481153, A1481131, A1481156, A1481134, and A1481157)

Study Number	Patient Number	Sex/Age/Race	Dose/Route	Event Day Onset	Event Term	Outcome/Investigator Causality
Adult Trials						
A1481141	101610028	M/66/W	Blinded therapy/NA	12	Worsening PAH	Death/Disease under study; not related
	103210029	F/35/W	Blinded therapy/NA	33	Massive exsanguinating hemoptysis	Death/Other (PH/coagulopathy/con meds); not related
	104510017	M/57/W	Blinded therapy/NA	Not available	Severe pulmonary hypertension	Death/Disease under study; not related
A1481153[4]	100710014	F/43/W	Sildenafil 240 mg daily	Not available	Right heart failure	Death/Disease under study; not related
	103010002	F/45/W	Sildenafil 120 mg daily	Not available	Posttherapy: Worsening thrombocytopenia	Death/Concomitant treatment (heparin), not related
	103510271	F/75/W	Sildenafil 240 mg	54 61	Worsening PAH Digoxin toxicity	Death/Disease under study; not related
	103810005	F/55/W	Sildenafil 240 mg	193	Abdominal catastrophe and acute abdominal event	Death/Other (possible abdominal perforation and mesenteric perforation or emboli), not related
Paediatric Trials						
A1481134	100710418	F/6 months/W	Blinded therapy/NA	Not available	Persistent pulmonary hypertension	Death/Disease under study; not related
	10090010	M/15/W	Blinded therapy/NA	Not available	Posttherapy: Fungal sepsis	Death/Other illness (unknown illness); not study drug related
	10330002	F/1/W	Died prior to randomisation	Not available	Prerandomisation; Death Cause Unknown	Death/Unknown cause, not related
	10210006	F/Unk/ Unk	Died prior to randomisation	Not available	Prerandomisation; resistant pulmonary hypertension	Death/Disease under study; not related
A1481131	10268034	M/15 months/ W	Died prior to randomisation	Not available	Pulmonary hypertensive crisis	Death/Other (general anaesthesia); not related

Of the 9 deaths, one resulted from hemoptysis (case still blinded), one from worsening thrombocytopenia (open label sildenafil), and one from an abdominal catastrophe (open label sildenafil).

One death in study A1481141 was reported to the Division on 2-22-2005. The subject was a 62 year old female with PAH secondary to CREST who was receiving sildenafil 40 mg tid plus iv epoprostenol. After 17 months of treatment, she collapsed while refilling the epoprostenol pump and could not be resuscitated. Cause of death was reported as cardiac arrest.

study with IV formulation

One subject died from pneumonia 40 days post dose.

Adverse events leading to discontinuation

PAH

The numbers of subjects who discontinued in the completed PAH study for any reason are shown below, by dose group.

Number of subjects

	Placebo n=70	sild 20 mg tid n=69	sild 40 mg tid n=67	sild 80 mg tid n=71
Total discontinued	2	2	2	6^
Deaths	1	1	0	1
Adverse event	0	0	0	5
Lab abnormal	0	1	0	0
Other	0	0	1	0
Defaulted	1	0	1	0

^ patient 10743 was randomized to 80mg and discontinued the study on day 7 while still receiving 40mg. She died on day 8 from septic shock.

Table 4.1.2

Slightly more subjects in the 80 mg tid sildenafil group discontinued from the study--mainly for adverse events--compared to placebo and lower sildenafil doses. The five subjects who discontinued because of an adverse event plus the one subject who discontinued for a laboratory abnormality are discussed in the table below.

Permanent discontinuations for adverse events

ID/sex/age	Dose/days on drug	comments
10037/F/56	Sild 80 mg tid/68	Cardiac arrhythmia (trigeminy). Other events included chest pain, syncope, and increased edema
10345/F/46	Sild 80 mg tid/8	Chromatopsia, photophobia, dyspepsia, swollen ankles, leg pain, salty taste, headache, flushing, hot flash
10484/F/81	Sild 80 mg tid/11	Myocardial infarction, edema, weight increased, fluid retention. Subject died day 13
10752/F/68	Sild 80 mg tid/27	Hepatic cirrhosis (autoimmune hepatitis)
10749/F/61	Sild 80 mg tid/14	Edema, increased weight, fluid retention
10331/F/65	Sild 20 mg tid/2	Decreased creatinine clearance

Table 4.2.1

Temporary discontinuation/dose reduction

There were 12 subjects (5 placebo, 5 sild 20 mg tid, 1 sild 40 mg tid, and 1 sild 80 mg tid) who had temporary study drug discontinuations. These are shown in the following table.

Summary of temporary discontinuations

Subject	Adverse Event	Start/Stop Day of AE	Causality	SAE
Treatment: Placebo				
10017	Upper respiratory tract infection	35 to 48	Other event- unstable temperature	No
10340	Vomiting NOS	46 to 46	Illness - hiatus hernia	No
10725	Right ventricular failure Right lower lobe pneumonia	75 ongoing 75 ongoing	Disease under study Other event- infection	Yes Yes
10759	Orthostatic hypotension	15 to 22	Concomitant treatment-felodipine induced	Yes
10962	Toothache	48 to 51	Illness - caries	No
Treatment: Sildenafil 20mg				
10012	Increased liver function tests	27 ongoing	Concomitant treatment- xanax	No
10031	Diarrhea Upper respiratory tract infection	30 to 31 56 to 59	Study drug illness- cold	No Yes
10728	Abdominal pain	4 to 6	Study drug	No
10732	Small bowel obstruction Cholelithiasis	2 to 15 49 to 82 83 ongoing	illness- unknown illness- unknown illness- unknown	Yes No Yes
10769	Nausea	51 to 51 78 to 81	illness- viral illness- viral	No No
Treatment: Sildenafil 40mg				
10743	Septic shock	5 ongoing	Other event-pneumococcal sepsis	Yes
Treatment: Sildenafil 80mg				
10061	Gastritis	34 to 40	Other event- viral / bacterial infection	No

There were 15 subjects who withdrew from the ongoing extension trial A1481142 because of adverse events. Most of the events were either similar to those probably associated with sildenafil (diarrhea, weakness, headache, allergic reaction) or the underlying disease (hypotension, dyspnea, worsening heart failure, worsening of symptoms of PAH). There was one report of suicide attempt.

study

The 10 sildenafil subjects who permanently discontinued study treatment because of an adverse event/laboratory abnormality:
-subject 10011004 dizziness and blurred vision (40 mg tid),
-subject 10011014 myalgia (40 mg tid),
-subject 10061001 and subject 10061010 myalgia (both 40 mg tid),
-subject 10071022 diabetes (40 mg tid),
-subject 10091021 severe accidental injury (possible concussion during assault, 40 mg tid),
-subject 10051010 and subject 10111020 myocardial infarct (40 mg tid and 80 mg tid),
-subject 10141003 asthenia and headache (80 mg tid),
-subject 10181002) back pain (40 mg tid)
(Table 13 study report).

The most often reported event leading to drop out from the sildenafil group was myalgia (3 subjects).

There were 3 placebo subjects who discontinued because of diarrhea/dyspepsia/nausea, lab abnormality, and chest tightness.

In addition, seven (3.5%) subjects had temporary discontinuations or dose reductions because of adverse events. The events included dyspepsia, myalgia, and headache (doses were 40 and 80mg tid).

Serious adverse events

PAH

All reported serious adverse events from study A1481140 are shown below.

Subject	Serious Adverse Event Term	Onset Day
Treatment: Placebo		
10506	Thrombocytopenia	40
10030	Syncopal episode	38
10256	Right heart decompensation	51
10965*	Acute pulmonary hypertensive crisis	73
10725	Right lower lobe pneumonia PAH with right heart failure	76 76
10059	Chest pain Dyspnoea	64 64
10059	Back pain	88
10326	Dyspnoea Chest pain	11 11
10326	Chest pain	59
10759	Orthostatic hypotension	15
10265	Pneumonia	43
10004	Worsening PAH	48
10252	Acute right sided heart failure	57
Treatment: Sildenafil 20mg		
10760	Vertigo	60
10503	Chest pain	N/a
10732*	Small bowel obstruction	2
10028**	Bronchial infection Hemorrhagic gastritis Peptic ulcer esophagitis Left ventricular dysfunction	6 6 6 94
10750	Respiratory infection	52
10315	Squamous cell carcinoma of right lung lower lobe	11
10315	Pneumonia	91
10031	Upper respiratory tract infection	56
10031	Exacerbation of dyspnoea Fever Weakness	76 76 76
10267	Pericardial effusion	417
10040	Unconsciousness	38
10034	Epistaxis	5

Subject	Serious Adverse Event Term	Onset Day
Treatment: Sildenafil 20mg (continued)		
10487*	Septic shock	43
	Bilateral distal pulmonary embolism	44
	Urosepsis	43
	Bilateral acute interstitial nephritis	N/A
10016*	Weight gain due to fluid retention	N/A
	Aggravated right sided heart failure	N/A
	Renal failure	N/A
10062	Worsening of polycythaemia	29
Treatment: Sildenafil 40mg		
10258	Syncopal episode	82
10036	Right heart decompensation	43
10297**	Breathing difficulties	20
	Right sided heart failure	18
10297**	Right heart failure	51
10049	Acute anemia	1
	Hypotension	1
	Metrorrhagias	N/A
10002	Postural hypotension	2
11202	Anaphylactic reaction	91
10739	Pneumonia	2
10738	Psychological problems	36
Treatment: Sildenafil 80mg		
10037**	Cardiac arrhythmias	69
10752**	Ascites	2
10743*	Septic shock	7
10009	Upper respiratory tract infection	6
10009	Worsened edema	N/A
	Dyspepsia	58
	Right sided heart failure exacerbation	58
	Exacerbation of PHT	58
10272	Right heart failure	31
10484*	Myocardial infarction	12
10338	Collapse	84
	Weakness in both lower extremities	118
10505	Gouty Tophi	9
10505	Fever	61
10767	Recurrance of vulval nodule	57

**subject died*

***subject was permanently discontinued*

The numbers of subjects reporting event and the types of event are similar across treatment groups.

Ongoing PAH studies

Serious events reported by subjects in ongoing studies are shown below.

Table 32. Summary of Serious Adverse Events Reported by ≥2 Patients in Ongoing Studies (A1481141, A1481153, A1481131, A1481134)

Body System[a]/Adverse Event (MedDRA Preferred Term)		Number of All Causality Events (%)		
		Placebo	Blinded Therapy	Sildenafil (All Doses)
I&I	Catheter-Related Infection	0	1	4
C	Right Ventricular Failure	0	2	3
C	Cardiac Failure	0	1	2
C	Palpitations	0	0	2
GI	Ascites	0	0	2
GD	Asthenia	0	0	2
I&I	Catheter Sepsis	0	3	1
I&I	Catheter Site Infection	0	0	2
I&I	Pneumonia	0	2	2
I&I	Sepsis	0	0	2
M&N	Fluid Overload	0	4	0
GD	Syncope	0	4	2
R	Dyspnoea	0	1	2
R	Dyspnoea Exacerbated	1	3	1
R	Pneumothorax	0	0	2
R	Pulmonary Hypertension	0	7	2
V	Haemorrhage	0	0	2
V	Hypotension	0	2	2
C	Cardiac Arrest	0	2	0
C	Left Ventricular Failure	0	2	0
C	Tachycardia	1	0	1
GD	Oedema Peripheral	0	1	1
M&N	Hypoglycemia	0	1	1
M	Pain in Extremity	0	1	1
RU	Renal Failure Acute	0	3	0
R	Haemoptysis	0	1	1

NOS = Not otherwise specified; URTI = Upper respiratory tract infection.

[a] B&L = Blood and lymphatic disorders; C = Cardiac; Ear = Ear and labyrinth; E = Endocrine; Eye = Eye disorders; GI = Gastrointestinal; GD = General disorders & administrative site conditions; HB = Hepatobiliary; IS = Immune system; I&I = Infections and infestations; IP&P = Injury, poisoning, and procedural complications; I = Investigations; M&N = Metabolism & nutrition; M = Musculoskeletal and connective tissue disorders; N = Neoplasms benign, malignant, and unspecified, NS = Nervous system, P = Psychiatric disorders; RU = Renal and urinary disorders; Repro = Reproductive system and breast disorders; R = Respiratory, thoracic, and mediastinal disorders; S = Skin and subcutaneous tissue; V = Vascular.

Events reported by more than 2 sildenafil subjects include catheter-related infection and right ventricular failure.

Stridor was reported[8] in study A1481131 in a 21 month old boy with Down's syndrome. He was taken to the hospital and re-challenged. The event recurred; the patient was treated with

[8] 2-16-05 IND safety report.

prednisone, epinephrine, and benadryl and recovered. One additional report of (non serious) stridor was found in the sildenafil data base.

4.3 All adverse events

PAH

The following table show all adverse events reported by at least six subjects randomized to sildenafil and reported more often in the sildenafil group compared to placebo.

No. and (percent) of subjects

	Placebo n=70	Total sild n=207	Placebo Subtracted %
Headache	27 (38.6)	95 (45.9)	7.3
Flushing	3 (4.3)	24 (11.6)	7.3
Epistaxis	1 (1.4)	14 (6.8)	5.4
Insomnia	1 (1.4)	13 (6.3)	4.9
Myalgia	3 (4.3)	19 (9.2)	4.9
Diarrhea nos	4 (5.7)	21 (10.1)	4.4
Pain in limb	4 (5.7)	21 (10.1)	4.4
Dyspepsia	5 (7.1)	23 (11.1)	4.0
Visual disturbances	0	8 (3.9)	3.9
Pyrexia	2 (2.9)	12 (5.8)	2.9
Gastritis nos	0	6 (2.9)	2.9
Sinusitis	0	6 (2.9)	2.9
Rhinitis nos	0	6 (2.9)	2.9
Paraesthesia	0	6 (2.9)	2.9
Influenza	2 (2.9)	11 (5.3)	2.4
Anxiety	1 (1.4)	6 (2.9)	1.5
Erythema	1 (1.4)	6 (2.9)	1.5
Vertigo	1 (1.4)	6 (2.9)	1.5
Cough	4 (5.7)	14 (6.8)	1.1
Dyspnea exacer	2 (2.9)	7 (3.4)	0.5
Hot flushed nos	3 (4.3)	10 (4.8)	0.5
Back pain	8 (11.4)	24 (11.6)	0.2

Table 6.1.3.2

The events with the highest placebo-subtracted incidence rates include headache (7.3%), flushing (7.3%), and epistaxis (5.4%).

199 subjects (60 placebo, 139 sildenafil) were enrolled into [redacted] (20, 40, 80 mg tid dosing as in PAH study).

Median duration on drug was 29 days.

Adverse events reported by the _ subjects are shown below.

Table 16. All Causality Common Adverse Events (≥3% Incidence in Sildenafil-treated Patients) by Preferred Term and Decreasing Frequency That Occurred More Frequently on Sildenafil Than Placebo: Study A1481165

Body System[a]/Adverse Event (MedDRA Preferred Term)		Number of All Causality Events (%)				
			Sildenafil (mg TID)			
		Placebo N = 60	20 mg N = 28	40 mg N = 57	80 mg N = 54	Total N = 139
NS	Headache NOS	5 (8.3)	5 (17.9)	14 (24.6)	8 (14.8)	27 (19.4)
GI	Dyspepsia	1 (1.7)	3 (10.7)	13 (22.8)	11 (20.4)	27 (19.4)
V	Flushing	0	4 (14.3)	8 (14.0)	6 (11.1)	18 (12.9)
M	Myalgia	3 (5.0)	1 (3.6)	7 (12.3)	7 (13.0)	15 (10.8)
GI	Diarrhoea NOS	2 (3.3)	4 (14.3)	1 (1.8)	3 (5.6)	8 (5.8)
M	Back Pain	0	0	6 (10.5)	2 (3.7)	8 (5.8)
GI	Nausea	2 (3.3)	3 (10.7)	2 (3.4)	2 (3.5)	7 (5.0)
GD	Fatigue	0	1 (3.6)	0	3 (5.6)	6 (4.3)
I&I	Nasopharyngitis	0	1 (3.6)	0	3 (5.6)	4 (2.9)
M	Arthralgia	0	1 (3.6)	1 (1.8)	2 (3.7)	4 (2.9)
I&I	Upper Respiratory Tract Infection	1 (1.7)	1 (3.6)	0	2 (3.7)	3 (2.2)
GI	Frequent Bowel Movements	0	0	1 (1.8)	2 (3.7)	3 (2.2)

NOS = Not otherwise specified.

[a] GD = General disorders & administrative site conditions; GI = Gastrointestinal; M = Musculoskeletal and connective tissue disorder; NS = Nervous system; R = Respiratory, thoracic, and mediastinal disorders, V = Vascular.

Events most commonly reported by sildenafil subjects (placebo subtracted incidence rate ≥ 2.9%) include dyspepsia (17.7%), flushing (12.9%), headache (11.1%), myalgia (5.8%), back pain (5.8%), fatigue (4.3%), nasopharyngitis (2.9%), and arthralgia (2.9%).

Pooled adverse events from A1481140 (PAH) and —) studies are shown below.

APPEARS THIS WAY
ON ORIGINAL

Table 17. All Causality Common Adverse Events (≥3% Incidence in any Sildenafil Dose Group) by Preferred Term and Decreasing Frequency: Pooled Data (Studies A1481140 and

Body System*/Adverse Event (MedDRA Preferred Term)		Placebo N = 130	Sildenafil (All Doses Combined) N = 346
Incidence of AEs: Sildenafil >Placebo			
NS	Headache	27 (20.8)	95 (27.5)
GI	Dyspepsia	6 (4.6)	50 (14.5)
V	Flushing	3 (2.3)	42 (12.1)
M	Myalgia	6 (4.6)	34 (9.8)
M	Back Pain	8 (6.2)	32 (9.2)
GI	Diarrhoea NOS	6 (4.6)	29 (8.4)
NS	Headache NOS	5 (3.8)	27 (7.8)
M	Pain in Limb	4 (3.1)	22 (6.4)
I&I	Nasopharyngitis	7 (5.4)	19 (5.5)
GI	Abdominal Pain Upper	6 (4.6)	17 (4.9)
GI	Vomiting NOS	6 (4.6)	17 (4.9)
R	Cough	4 (3.1)	16 (4.6)
R	Epistaxis	1 (0.8)	16 (4.6)
P	Insomnia	1 (0.8)	15 (4.3)
I&I	Pyrexia	2 (1.5)	13 (3.8)
I&I	Influenza	2 (1.5)	12 (3.5)

Adverse events with placebo subtracted incidence rates > 3.0% include dyspepsia (9.9%), flushing (9.8%), headache (7.5%), myalgia (5.2%), headache (4.0%), diarrhea (3.8%), epistaxis (3.8%), insomnia (3.5%), and pain in limb (3.3%).

4.3.1 Selected adverse events

4.3.1.1 Ocular events

PAH

Events related to the eye that were reported by at least 2 subjects are shown below.

Table 36. Incidence of All Causality Eye Disorder Adverse Events Reported by ≥2 Patients: Study A1481140

Adverse Event (MedDRA Preferred Term)	Number of all events (%)				
	Placebo N = 70	Sildenafil (mg TID)			
		20 mg N = 69	40 mg N = 67	80 mg N = 71	Total N = 207
Incidence of AEs: Sildenafil > Placebo					
Visual Disturbance NOS	0	0	3 (4.5)	5 (7.0)	8 (3.9)
Chromatopsia	1 (1.4)	1 (1.4)	1 (1.5)	3(4.2)	5 (2.4)
Eye Irritation	0	2 (2.9)	0	2 (2.8)	4 (1.9)
Eye Pain	1 (1.4)	1 (1.4)	0	3 (4.2)	4 (1.9)
Retinal Haemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)	4 (1.9)
Photophobia	0	0	0	4 (5.6)	4 (1.9)
Cyanopsia	0	0	1 (1.5)	3 (4.2)	4 (1.9)
Diplopia	0	1 (1.4)	1 (1.5)	1 (1.4)	3 (1.4)
Abnormal Sensation in Eye	0	2 (2.9)	1 (1.5)	0	3 (1.4)
Visual Acuity Reduced	0	0	2 (3.0)	1 (1.4)	3 (1.4)
Conjunctival Hyperaemia	0	1 (1.4)	1 (1.5)	0	2 (<1)
Visual Brightness	0	0	0	2 (2.8)	2 (<1)
Incidence of AEs: Sildenafil ≤ Placebo					
Vision Blurred	4 (5.7)	3 (4.3)	2 (3.0)	4 (5.6)	9 (4.3)
Eye Haemorrhage NOS	1 (1.4)	1 (1.4)	1 (1.5)	1 (1.4)	3 (1.4)
Conjunctivitis	1 (1.4)	0	1 (1.5)	1 (1.4)	2 (<1)
Halo Vision	1 (1.4)	0	0	2 (2.8)	2 (<1)
Eye Pruritus	1 (1.4)	0	1 (1.5)	0	1 (<1)
Eye Redness	1 (1.4)	0	1 (1.5)	0	1 (<1)
Eyelid Oedema	1 (1.4)	1 (1.4)	0	0	1 (<1)
Lenticular Opacities	1 (1.4)	0	1 (1.5)	0	1 (<1)
Blepharitis	1 (1.4)	1 (1.4)	0	0	1 (<1)
Cataract Bilateral NOS	1 (1.4)	0	1 (1.5)	0	1 (<1)
Episcleral Hyperaemia	2 (2.9)	0	0	0	0

NOS = Not otherwise specified.

Visual disturbance NOS was the most often reported eye disorder followed by chromatopsia (placebo subtracted incidence rates of 3.9% and 1.0%, respectively).

Eye disorders reported by more than 2 subjects in the open label extension study A1481142 are shown below.

Adverse Event (MedDRA Preferred Term)	Number of All Events (%)
	Sildenafil N = 259
Vision Blurred	21 (8.1)
Visual Disturbance NOS	15 (5.8)
Conjunctival Hyperaemia	12 (4.6)
Episcleral Hyperaemia	10 (3.9)
Retinal Haemorrhage	10 (3.9)
Chromatopsia	7 (2.7)
Eye Haemorrhage NOS	6 (2.3)
Ocular Discomfort	5 (1.9)
Photopsia	5 (1.9)
Cyanopsia	4 (1.5)
Visual Brightness	4 (1.5)
Lenticular Opacities	4 (1.5)
Refractive Errors (NOS)	4 (1.5)
Eye Irritation	3 (1.2)
Eye Pain	3 (1.2)
Eye Redness	3 (1.2)
Retinal Pigmentation	3 (1.2)
Visual Acuity Reduced	3 (1.2)

The most commonly reported eye events include vision blurred, visual disturbance nos, conjunctival hyperemia, episcleral hyperemia, retinal hemorrhage, chromatopsia, and eye hemorrhage.

Eye disorders were infrequently reported. There were 3 reports of conjunctivitis in sildenafil 40 mg tid (5.2%) versus 1 in placebo (1.7%). Chromatopsia was reported once in the highest dose sildenafil group.

Conclusion: there is an increase in the reporting of seemingly minor visual disturbances in a PAH population taking sildenafil.

4.3.1.2 Bleeding events

PAH

Table 38. All Causality Bleeding Events Reported by Patients in Pivotal Study A1481140

Adverse Event (MedDRA Preferred Term)	Number of All Events (%)				
	Placebo N = 70	Sildenafil (mg TID)			
		20 mg N = 69	40 mg N = 67	80 mg N = 71	Total N = 207
Epistaxis	1 (1.4)	6 (8.7)	5 (7.5)	3 (4.2)	14 (6.8)
Retinal Hemorrhage	0	1 (1.4)	2 (3.0)	1 (1.4)	4 (1.9)
Eye Hemorrhage NOS	1 (1.4)	1 (1.4)	1 (1.5)	1 (1.4)	3 (1.4)
Menorrhagia	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Haemoglobin Decreased	0	1 (1.4)	1 (1.5)	0	2 (1.0)
Blood in Stool	0	0	0	1 (1.4)	1 (<1)
Conjunctival Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Gastritis Haemorrhagic	0	1 (1.4)	0	0	1 (<1)
INR Increased	2 (2.9)	1 (1.4)	0	0	1 (<1)
Rectal Haemorrhage	0	0	0	1 (1.4)	1 (<1)
Metrorrhagia	1 (1.4)	0	1 (1.5)	0	1 (<1)
Vaginal Haemorrhage	0	1 (1.4)	0	0	1 (<1)
Hematoma NOS	3 (4.3)	1 (1.4)	0	0	1 (<1)
Gingival Bleeding	0	0	1 (1.5)	0	1 (<1)
Anal Haemorrhage	1 (1.4)	0	0	0	0
Hematuria	1 (1.4)	0	0	0	0
Venipuncture Site Haemorrhage	1 (1.4)	0	0	0	0
TOTAL PATIENTS WITH BLEEDING EVENTS	11 (15.7)	14 (20.3)	12 (17.9)	8 (11.3)	34 (16.4)

Source: SCS Table 9.3.61

The overall reporting rate for bleeding is slightly higher in the sildenafil group. However, there is a sizable increase in the incidence rate of reporting epistaxis in the sildenafil groups compared to placebo (6.8% versus 1.4%, respectively). Details of the subjects with epistaxis are shown below.

Table 40. Summary of Actions, Causality and Outcomes of Epistaxis Adverse Events

Patient Number	PH Class at Baseline	Treatment Group	Sex/Age Race	Severity	Action	Causality	Outcome	Abnormal Baseline Renal Function	Abnormal Baseline Platelets	On Immuno-suppressant	INR Nearest Bleeding Event
10307*	PPH	PBO	F/59/W	Mild	Withhold warfarin	Warfarin	Resolved	N	N	Y (Prednisone)	1.3
10034*	PPH	20 tid	F/51/W	Moderate	Electrocoagulation	PHx of nosebleed	Resolved	N	Y (114L)	N	3.55
10503*	CTD/scleroderma	20tid	F/61/W	Moderate	NA	Oxygen Therapy	Resolved	N	N	N	1-2.7
10750*	CTD/SjS	20 tid	F/43/W	Mild	NA	Phencoumarin	Resolved	N	N	N	3
10760*	CTD/scleroderma	20 tid	F/78/W	Mild	NA	Dry Mucosa	Resolved	N	N	N	2
10774*	CTD/CREST	20 tid	F/75/W	Mild	Pinch nose	Sildenafil	Resolved	Y BUN. 10.7H Creatinine 120H	N	N	3.1
11205*	Surgical Repair	20 tid	M/47/W	Mild	NA	Warfarin	Resolved	N	N	N	2.49
10486	CTD/CREST	40 tid	F/63/W	Mild	NA	Environmental	Resolved	Y (9.5H)	N	N	N/A
10497*	CTD/Mixed	40 tid	F/44/B	Mild	Withhold warfarin	Warfarin	Resolved	N	N	Y (Prednisone)	5.9
10727*	CTD/SLE	40 tid	F/58/W	Mild	NA	Warfarin + dry air	Resolved	N	Y (414H)	Y (Fluticasone)	1.1
10748*	CTD/Mixed	40 tid	F/48/W	Mild	NA	Acenocoumarol	Resolved	N	N	N	1.34
10963*	Surgical Repair	40 tid	F/45/W	Mild	NA	Warfarin	Resolved	N	N	N	1.12
10039*	PPH	80 tid	F/25/W	Mild	NA	Anticoagulant	Resolved	N	Y (125L)	N	1.6
10061*	PPH	80 tid	F/66/W	Mild	NA	Warfarin	Resolved	N	N	N	1.75
10337*	PPH	80 tid	M/22/W	Mild	NA	Acenocoumarol	Resolved	N	Y (139L)	N	1.22-1.28

NOTE: No patient with epistaxis was reported as having abnormal platelets. Platelets Normal limit: 140-370 10**9/l; Blood urea nitrogen (BUN) normal limits: 2.1-8.9 mmol/L; Creatinine normal limits: 53-115 umol/L.
W = White; F = Female; M = Male; A = Asian; B = Black; INR = International normalized ratio; NA = No action; * = Patient on anticoagulation; CTD = Connective tissue disease; SjS = Sjogrens syndrome; SLE = Systemic lupus erythematosis; PPH = Primary pulmonary hypertension; Sx Repair = Surgical repair; ASD = Atrial septal defect; PDA = Patent ductus arteriosis; NL = Normal limit; H = High; L = Low.
Source: CSR, Section 13, Table 3

The table below lists reports of bleeding in study A1481140 categorized by the concomitant medication vitamin K antagonists.

Table 39. All Causality Bleeding Events Reported by Patients Co-prescribed Vitamin K Antagonists in Pivotal Study A1481140

MedDRA PT	PBO N (%)		Sildenafil N (%)	
	VitK Ant (N = 56)	No VitK Ant (N = 14)	VitK Ant (N = 148)	No VitK Ant (N = 59)
Conjunctival Haemorrhage	0	0	0	1 (1.7)
Eye Haemorrhage NOS	1 (1.8)	0	3 (2.0)	0
Retinal Haemorrhage	0	0	4 (2.7)	0
Anal Hemorrhage	0	1 (7.1)	0	0
Gastritis Hemorrhagic	0	0	1 (<1)	0
Gingival Bleeding	0	0	1 (<1)	0
Rectal Haemorrhage	0	0	0	1 (1.7)
Venipuncture Site Haemorrhage	0	1 (7.1)	0	0
Blood in Stool	0	0	1 (<1)	0
Haemoglobin Decreased	0	0	2 (1.4)	0
INR Increased	2 (3.6)	0	1 (<1)	0
Menorrhagia	0	0	2 (1.4)	0
Metrorrhagia	1 (1.8)	0	0	0
Vaginal Hemorrhage	0	0	1 (<1)	0
Epistaxis	1 (1.8)	0	13 (8.8)	1 (1.7)
Hematoma NOS	1 (1.8)	2 (14.3)	1 (<1)	0
Haematuria	1 (1.8)	0	0	0
TOTAL PATIENTS WITH BLEEDING EVENTS	7 (12.5)	4 (28.6)	30 (20.3)	3 (5.1)

Source: SCS Table 3.7 12.1C

For those taking vitamin K antagonists (74% of all subjects), the incidence rate for sildenafil groups reporting any bleeding was 20.3% compared to 12.5% for placebo. Epistaxis, the most commonly reported bleeding event, had an incidence rate of 14.3% (all sildenafil) compared to 1.8% (placebo). For those not taking vitamin k antagonists, there was little difference in the reporting rate for epistaxis (1.7% and 0%). The reporting rate for retinal hemorrhage was 2.7% and reported only by the sildenafil plus vitamin K antagonists group.

In addition, those subjects with PAH secondary to connective tissue disease were more likely to report epistaxis (12.9%) compared to those with primary PAH (2.3%).

In the open label extension study A1481142, the reporting rate for epistaxis was 8.5%. One subject (11205) on warfarin was hospitalized for epistaxis and low hemoglobin and required blood transfusion. He was rehospitalized for epistaxis about 2 months later. Episode resolved and sildenafil treatment continued.

Table 41. Bleeding Events Reported by Patients in Study A1481142 by 1140 Randomized Dose

MedDRA Preferred Term	Placebo (N = 67)	Sildenafil (mg TID)			
		20 mg (N = 65)	40 mg (N = 63)	80 mg (N = 64)	Total Sildenafil (N = 259)
Abdominal Haematoma	0	0	1 (1.6)	0	1 (<1)
Antepartum Haemorrhage	0	1 (1.5)	0	0	1 (<1)
Cerebral Haemorrhage	1 (1.5)	0	0	0	1 (<1)
Coagulation Time NOS Abnormal	0	1 (1.5)	0	0	1 (<1)
Cystitis Haemorrhagic	0	1 (1.5)	0	0	1 (<1)
Epistaxis	4 (6)	7 (10.8)	7 (11.1)	4 (6.3)	22 (8.5)
Eye Haemorrhage NOS	1 (1.5)	3 (4.6)	2 (3.2)	3 (4.7)	9 (3.5)
Gastrointestinal Haemorrhage NOS	2 (3)	0	1 (1.6)	0	3 (1.2)
Gingival Bleeding	1 (1.5)	0	2 (3.2)	0	3 (1.2)
Haematemesis	0	1 (1.5)	1 (1.6)	0	2 (<1)
Haematoma NOS	1 (1.5)	1 (1.5)	1 (1.6)	1 (1.6)	4 (1.5)
Haematuria	2 (3)	0	0	0	2 (<1)
Haemoglobin Decreased	1 (1.5)	3 (4.6)	2 (3.2)	2 (3.1)	8 (3.1)
Haemoptysis	3 (4.5)	0	3 (4.8)	1 (1.6)	7 (2.7)
INR Abnormal NOS	1 (1.5)	0	0	0	1 (<1)
INR Increased	1 (1.5)	2 (3.1)	1 (1.6)	1 (1.6)	5 (1.9)
Lower Gastrointestinal Haemorrhage	1 (1.5)	0	0	0	1 (<1)
Menometrorrhagia	0	1 (1.5)	0	0	1 (<1)
Menorrhagia	2 (3)	3 (4.6)	1 (1.6)	1 (1.6)	7 (2.7)
Metrorrhagia	2 (3)	0	2 (3.2)	0	4 (1.5)
Oesophageal Varices Haemorrhage	0	1 (1.5)	0	0	1 (<1)
Pulmonary Alveolar Haemorrhage	0	0	0	1 (1.6)	1 (<1)
Rectal Haemorrhage	1 (1.5)	0	0	1 (1.6)	2 (<1)
Retinal Haemorrhage	2 (3)	3 (4.6)	5 (7.9)	4 (6.3)	14 (5.4)
Subdural Haematoma	0	0	1 (1.6)	0	1 (<1)
Uterine Haemorrhage	0	0	0	1 (1.6)	1 (<1)
Vaginal Haemorrhage	0	0	2 (3.2)	1 (1.6)	3 (1.2)
Total Bleeding Events	**26 (38.8)**	**28 (43.0)**	**32 (50.8)**	**21 (32.8)**	**107 (41.3)**

INR = International normalized ratio.
Source: SCS Table 9.3.62D

In the study bleeding was reported by 2.1% sildenafil subjects and 1.7% placebo subjects.

Conclusion: there is a probable interaction between vitamin K antagonists and sildenafil.

4.3.2 Laboratory evaluations

PAH
There was one subject (10331) who discontinued study drug because of decreased creatinine clearance.

Hematology

The table below shows the number and percent of subjects with a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects+

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
Any abnormality		22 (31)	22 (32)	21 (32)	22 (32)
hemoglobin	<0.8xbaseline	0	0	2 (4)	3 (6)
hematocrit	<0.8xbaseline	0	1 (2)	4 (8)	2 (3)
RBC count	<0.8xbaseline	0	0	2 (4)	0
platelets	$< 75\ 10^3/mm^3$	2 (4)	0	1 (2)	0
WBC	$<2.5\ 10^3/mm^3$	2 (3)	0	0	0
lymphocytes	<0.8 xLLN	8	6	5	11
	>1.2xULN	0	2	0	0
Total neutrophils	<0.8 xLLN	2 (3)	0	0	0
	>1.2xULN	8 (13)	3 (6)	3 (5)	3 (5)
Basophils	>1.2xULN	4 (6)	6 (11)	3 (5)	2 (3)
Eosinophils	>1.2xULN	2 (3)	1 (1)	0	0
Monocytes	>1.2xULN	3 (5)	5 (8)	6 (10)	2 (3)

+total numbers of subjects are limited to those with normal or missing baseline and with at least one observation post baseline.

Table 7.1.1

There were 2%-8% of sildenafil patients with normal baseline values and abnormally low values during treatment for hemoglobin/hematocrit/RBC count. There were no placebo subjects with comparable changes. Changes for other parameters were variable and similar to changes in the placebo group.

There were increased numbers of reports of epistaxis and gastritis within the sildenafil group (1.4% and 6.8% for placebo and sildenafil, respectively).

Mean changes from baseline to last observation for selected hematology parameters are shown below.

Lab parameter	units	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
hemoglobin	g/dl	0.1	-0.2	-0.3	-0.6
hematocrit	%	0.8	-0.2	-1.1	-1.9
RBC count	$10^6/mm^3$	0.1	-0.06	-0.11	-0.16
platelets	$10^3/mm^3$	-16	-2	1	-1
WBC	$10^3/mm^3$	0	-0.3	-0.4	-0.6
lymphocytes	$10^3/mm^3$	-0.03	-0.11	-0.25	-0.2

Table 9.4.120C

There are mean decreases from baseline for hemoglobin, hematocrit and RBC counts in the sildenafil groups, with a dose response. There is also a mean decrease in the active treatment groups for WBC.

Chemistry parameters

Liver function

The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects+

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
Any abnormality		1 (2)	2 (3)	2 (4)	0
Total bili	>1.5xULN	1 (2)	1 (2)	1 (2)	0
AST	>3.0xULN	0	1 (2)	0	0
ALT	>3.0xULN	0	0	1 (2)	0

Table 7.1.1

The incidence rates of abnormalities are similar across treatment groups.

There were no subjects with values for alk phos, total protein, albumin that met the definition of abnormality. The mean changes from baseline were unremarkable (Table 9.4.120C).

There is no indication that sildenafil has an adverse effect on the liver.

Renal function

The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
BUN	>1.3xULN	2 (3)	3 (5)	1 (2)	2 (4)

Table 7.1.1

There were no subjects meeting the definition of abnormal creatinine. Abnormalities for BUN were similar across treatment groups. The mean changes from baseline were unremarkable (Table 9.4.120C).

There is no indication that sildenafil has an adverse effect on the kidney.

Electrolytes

The table below shows the number and percent of subjects who had a normal lab value at baseline that became abnormal anytime during the study.

No. and (percent) of subjects

Lab parameter	Definition of abnormality	Placebo	Sild 20 mg tid	Sild 40 mg tid	Sild 80 mg tid
sodium	<0.9xLLN	1 (2)	0	0	0
potassium	<0.9xLLN	1 (2)	2 (3)	1 (2)	2 (3)
potassium	>1.1xULN	2 (3)	1 (2)	1 (2)	0

Table 7.1.1

There percent of abnormalities are similar across treatment groups. The mean changes from baseline were unremarkable (Table 9.4.120C).

Two subjects, one randomized to placebo and one to sildenafil 40 mg tid, were discontinued from study drug because of abnormal laboratory values. Both abnormalities were elevated glucose levels.

Mean changes from baseline for hematology parameters.

Mean changes from baseline at endpoint (LOCF) for haemoglobin, hematocrit and RBC in Study — are provided in the table below

Parameter	Placebo – mean change from baseline	Sildenafil 20mg – mean change from baseline	Sildenafil 40mg – mean change from baseline	Sildenafil 80mg – mean change from baseline
Haemoglobin (G/DL)	0	-0.3	-0.2	-0.2
Hematocrit (%)	-0.1	-0.5	-0.8	-0.7
RBC count (10**6/MM**3)	-0.03	-0.06	-0.08	-0.07

The minor decreases from baseline are larger in the sildenafil groups.

4.3.3 Vital signs

PAH

Changes in vital signs after approximately 12 weeks of treatment for placebo and sildenafil groups are shown below.

	Placebo			Sildenafil 20mg TID			Sildenafil 40mg TID			Sildenafil 80mg TID		
	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs	N	Median Baseline	Median Change From Baseline To Last Obs
Sitting												
Systolic BP (mmHg)	70	115.0	1.00	68	115.0	1.50	136	115.0	0.00	67	114.0	-1.00
Diastolic BP (mmHg)	70	72.0	0.00	68	74.5	0.00	136	73.0	0.00	67	75.0	-1.00
Heart Rate (bpm)	69	79.0	0.00	68	80.0	-0.50	136	77.5	0.00	67	78.0	-3.00

Source Data: Section 13, Table 13 Date of Reporting Dataset Creation: 22MAY2004 Date of Table Generation: 22MAY2004 11:45:

It seems that sildenafil has little effect on systolic and diastolic blood pressure in a population with normal vital signs. Heart rate tended to decrease a small amount.

Blood pressure responses to sildenafil in a population over 28 days of treatment are shown below.

Systolic:

Table 5.4.2.2 Page 1 of 1
Sildenafil Protocol
Summary of Statistical Analysis of Mean Change from Baseline in Systolic Blood Pressure (Day 28) (ITT)

Treatment	N	Baseline Mean	Average Mean Change From Baseline: Unadjusted	Adjusted+	Difference From Placebo*: Mean	Standard Error	95% CI	p-value
Double Blind Placebo	60	153.0	-1.1	-1.8				
Sildenafil 20mg (tid)	28	151.4	-0.4	-0.7	0.2	2.69	(-4.9, 5.3)	0.933
Sildenafil 40mg (tid)	57	151.7	-6.8	-7.8	-6.1	2.10	(-10.2, -1.9)	0.004
Sildenafil 80mg (tid)	54	153.1	-10.1	-9.9	-8.9	2.13	(-13.1, -4.8)	<0.001

Note: The Sildenafil 80mg treatment group received 40mg (tid) from day 0 to day 6 and 80mg (tid) on days 7 to 28.
The mean change from baseline is calculated as the difference between the mean on-treatment blood pressure
and the mean blood pressure pre-dose at baseline.
*The difference from placebo is calculated from an ANCOVA analysis with baseline as a covariate. The mean difference to placebo is adjusted for baseline.
+Adjusted for baseline.

There were mean decreases in systolic blood pressure of 6.1 and 8.9 mmHg for sildenafil 40 mg tid and 80 mg tid, respectively.

Diastolic:

Table 5.8.2 Page 1 of 1
Sildenafil Protocol
Summary of Statistical Analysis of Mean Change from Baseline in Diastolic Blood Pressure (Day 28) (PP)

Treatment	N	Baseline Mean	Average Mean Change From Baseline: Unadjusted	Adjusted+	Difference From Placebo*: Mean	Standard Error	95% CI	p-value
Double Blind Placebo	51	89.3	-2.9	-2.8				
Sildenafil 20mg (tid)	19	87.6	-4.4	-4.5	-1.7	1.69	(-5.0, 1.7)	0.326
Sildenafil 40mg (tid)	51	87.9	-6.9	-6.9	-4.1	1.25	(-6.6, -1.7)	0.001
Sildenafil 80mg (tid)	41	87.4	-9.1	-9.2	-6.4	1.32	(-9.0, -3.7)	<0.001

Note: The Sildenafil 80mg treatment group received 40mg (tid) from day 0 to day 6 and 80mg (tid) on days 7 to 28.
The mean change from baseline is calculated as the difference between the mean on-treatment blood pressure
and the mean blood pressure pre-dose at baseline.
*The difference from placebo is calculated from an ANCOVA analysis with baseline as a covariate. The mean difference to placebo is adjusted for baseline.
+Adjusted for baseline.

There were mean decreases in diastolic blood pressure of 4.1 and 6.4 mmHg for sildenafil 40 mg tid and 80 mg tid, respectively.

5 CLINICAL PHARMACOLOGY

5.1 Adverse events

The integrated safety data base for the clinical pharmacology includes 15 interactions studies and 1 study in macular degeneration. These studies are listed below.

Table 1. Listing of Clinical Pharmacology PAH and Post-Marketing Studies

Study Number (148-)	PAH Stimulation
PAH Studies	
1149	Bosentan Interaction Study
MED Post-Marketing Studies	
005	Subjects with Macular Degeneration
230	Hemodynamic Study with ISMN
231	GTN Interaction
234	Erythromycin Interaction
238	Azithromycin Interaction
236	Oral Contraceptives Interaction
239	Saquinavir Interaction
240	Ritonavir Interaction
1031	Hemodynamic Study with ISMN
242	Doxazosin Interaction
1068	Doxazosin Interaction
1163	Doxazosin Interaction
1053	Phenprocoumon Interaction
1054	Acenocoumarol Interaction
258-002	Atorvastatin Interaction

A total of 327 subjects received sildenafil (oral formulation) and 169 received placebo.

The table below shows the adverse events reported by at least 30 (4.3%) sildenafil subjects and reported more often by sildenafil subjects than placebo subjects.

No. and (percent) of subjects

Adverse event	All placebo n=360	All sildenafil n=691	Placebo subtracted %
Headache	66 (18.3)	243 (35.2)	16.9
Vasodilatation	9 (2.5)	89 (12.9)	10.4
Penile erection	2 (<1)	89 (12.9)	12.9
Back pain	10 (2.8)	72 (10.4)	7.6
Abnormal vision	11 (3.1)	66 (9.6)	6.5
Dyspepsia	3 (<1)	41 (5.9)	5.9
Dizziness	28 (7.8)	94 (13.6)	5.8
Myalgia	11 (3.1)	58 (8.4)	5.3
Rhinitis	12 (3.3)	57 (8.2)	4.9
Asthenia	5 (1.4)	42 (6.1)	4.7
Nausea	8 (2.2)	44 (6.4)	4.2
Pain	5 (1.4)	34 (4.9)	3.5
Diarrhea	1 (<1)	18 (2.6)	2.6

With the exception of penile erection, events reported in the clinical pharmacology studies were similar to those reported in the PAH study A1481140.

Macular degeneration

Study 148-005 was a single dose study with 100 mg sildenafil given to 9 subjects with early age-related macular degeneration and visual acuity of 20/40 or better in at least one eye. Results are shown below.

Table 5. Statistical Analysis of Visual Parameters Measured in Study 148-005

Test	Eye Comparison	Difference	95% CIs
Humphrey Perimetry			
Mean Deviation	Left Eye: Sildenafil - Placebo	0.745	0.084, 1.406
	Right Eye: Sildenafil - Placebo	0.314	-1.147, 1.774
Corrected PSD	Left Eye: Sildenafil - Placebo	0.878	-0.426, 2.182
	Right Eye: Sildenafil - Placebo	-0.466	-1.761, 0.829
Photostress Test (Time to Recovery)	Left Eye: Sildenafil - Placebo	-19.921	-46.203, 6.360
	Right Eye: Sildenafil - Placebo	-6.632	-34.678, 21.414
D-15 Color Discrimination			
Confusion Angle	Left Eye: Sildenafil - Placebo	0.462	-28.942, 29.866
	Right Eye: Sildenafil - Placebo	-5.250	-29.401, 18.900
Confusion Index	Left Eye: Sildenafil - Placebo	-0.015	-0.338, 0.307
	Right Eye: Sildenafil - Placebo	0.024	-0.147, 0.194
Selectivity Index	Left Eye: Sildenafil - Placebo	0.013	-0.492, 0.519
	Right Eye: Sildenafil - Placebo	-0.004	-0.181, 0.173

This study, because of its small sample size and single dosing, is difficult to evaluate. That said, there is no strong evidence linking the use of sildenafil and the development of serious eye disease.

Miscellaneous studies

IV dosing

Protocol 1481024 administered iv sildenafil (and NO by inhalation to 50%) to subjects with PAH. There was one death from pneumonia, one serious event (bacteremia), and three drop outs for adverse events (nausea, hypotension, sepsis). There were numerous reports of drops in blood pressure of at least 10%. Commonly reported adverse events included vasodilatation, hypotension, headache, and nausea.

Additional chronic oral dosing studies

There were 8 additional double blind, placebo controlled, randomized studies with a variety of indications. Doses ranged from 10 mg to 200 mg once daily used for a median of 57 days. There were 2 deaths: one placebo subject died of a myocardial infarct and one sildenafil subject died of "myocardial fibrosis and atheroma." Adverse events reported by at least 2% of subjects are shown below.

Table 49. Adverse Events (All Causality) Reported by ≥2% of Patients by Study Treatment

Adverse Event	% Patients Reporting Event	
	Placebo (N = 312)	Sildenafil (N = 660)
Incidence of AEs: Sildenafil (All Doses Combined) >Placebo		
Headache	9.6	17.1
Dyspepsia	2.9	11.1
Vasodilatation	0.6	6.1
Myalgia	2.2	4.7
Pain	1.9	3.5
Arthralgia	1.9	3.3
Diarrhea	1.9	3.5
Nausea	1.6	3.8
Flu Syndrome	2.2	3.0
Hypoglycemia	1.9	2.9
Back Pain	1.6	2.7
Leg Cramps	1.9	3.0
Rhinitis	1.0	2.3
Abnormal Vision	0.6	2.1

As with the other databases, headache, dyspepsia, vasodilatation, and myalgia were the most frequently reported events. Along with nausea, visual events, and diarrhea, these also were the events most commonly leading to study discontinuation.

Overview of Post-Marketing Non-Clinical Study Sildenafil Cases

Exposure

As of June 2004, an estimated — patients have taken sildenafil worldwide. The United States accounts for the majority of patients that have taken Viagra® with an estimated → patients.

The adverse events reported by at least 3.2% Viagra® patients (from the nonstudy clinical sildenafil cases) are shown below.

Percent of patients

	Sildenafil patients n=25,783+
Headache	12.9
Flushing	9.0
Erectile dysfunction	5.7
Dizziness	3.6
Myocardial infarction	3.4
Nasal congestion	3.3
Dyspepsia	3.2

+nonstudy clinical sildenafil cases

Module 5 section 5.3.6

This is a familiar list of events reported by individuals taking sildenafil.

Warfarin interaction reports (increases in INR)

Case (2004016429) involved a 64-year-old male with an unknown history who experienced increased INR. He had been taking warfarin for a long time, with an INR within therapeutic range. At an unknown time, sildenafil was increased to 125mg/day and his INR increased to 4 - 6. Sildenafil was discontinued and INR returned to 1.7 - 1.8.

Case 2003114255 involved a female child with a history of an unknown heart condition who was started on sildenafil solution 28mg/day which was compounded by the hospital pharmacy. At an unknown time, the same month, warfarin was initiated and titrated to 1.5mg/day. After the warfarin dosage increase, labs revealed INR 8.0.

Case 200115485 provided limited information and involved a female approximately 60 years of age taking sildenafil and warfarin. At an unknown time, she experienced aggravated rectal bleeding.

Case 2003123666 involved a 40-year-old female taking warfarin and epoprostenol and was initiated on sildenafil. She was titrated to sildenafil 100mg/day. Twenty-two days after sildenafil initiation, her period began. By ten days after her period had begun, she had developed anemia, general malaise, tachycardia, and headache due to prolonged menstruation. She was hospitalized and warfarin was discontinued. Her INR at the time of bleeding was not reported. She was administered hydroxyprogesterone and a blood transfusion. Seventeen days after the start of her period, the bleeding stopped. Over the next two months, she had three additional episodes of menstrual hemorrhage and was hospitalized.

Case 2003013485 involved a 61-year-old female with a history of ischemic heart disease and hypertension who started sildenafil 75mg/day and warfarin on unknown dates. Six days after sildenafil was increased to 150mg/day, she experienced bruises, petechiae, and vaginal bleeding. She had been hospitalized for observation of deep vein thrombosis and labs revealed an INR 6.0. She was treated with paracetamol and phytomenadione. The following day, INR was 1.6 and the bruises and petechiae had disappeared.

Case 2004039275 involved a female of unknown age taking sildenafil 75mg/day and warfarin who experienced persistently low INR that was between 1-1.5, since commencing sildenafil. Her medical history was significant for hemoptysis.

6 4-MONTH SAFETY UPDATE

Database

This update contains information an update on safety in patients with PAH from an ongoing open-label extension study (A1481142) as well as a discussion of serious safety for ongoing blinded studies in adults and children with PAH. Relevant dates include July 30, 2004 (Oracle cutoff date for NDA submission), September 1, 2004 (serious safety cutoff date for NDA submission), February 4, 2005 (Oracle cutoff date for 4-month safety update), and March 1, 2005 (serious safety cutoff date for 4 month safety update).

Table 1. Overview of Source and Number of Participants Who Received Study Medication as of 01 March 2005

	Number of Patients in NDA		Number of Patients With New Data[a]		Total Number of Patients in Safety Update	
	PBO	Sildenafil	PBO	Sildenafil	PBO	Sildenafil
Clinical Phase 2/3 Safety Database in PH Patients						
Controlled PAH Studies						
A1481140: Study Completed	70	207	0	0	0[b]	0[b]
A1481141: Ongoing Study; Data Not Unblinded	NDA patients = 170[c]		New patients = 37[c]		Total patients = 207[c]	
A1481131: Ongoing Pediatric Study; Data Not Unblinded	NDA patients = 38[c]		New patients = 43[c]		Total patients = 81[c]	
A1481134: Ongoing Pediatric Study; Data Not Unblinded	NDA patients = 11[c]		New patients = 7[c]		Total Patients = 18[c]	
A1481157: IV Study, Ongoing Pediatric; Data Not Unblinded	NDA patients = 16[c]		New patients = 16[c]		Total Patients = 32[c]	
A1481024: Study Completed	NA	85	0	0	0	0
Uncontrolled PAH Studies						
A1481142: Ongoing, Extension to A1481140	NA	259[d]	Not unique patients[d]		NA	259[d]
A1481153: Ongoing, Extension to A1481141	NDA patients = 112[e,c]		Not unique patients[e,c]		Total Patients = 164[e,c]	
A1481156: Ongoing, Extension to A1481131	NDA patients = 16[f,c]		Not unique patients[f,c]		Total Patients = 49[f,c]	
Postmarketing Spontaneous Reports of Adverse Events						
Patients With PAH	NA	180	NA	45	NA	225

NA = Not Applicable; NDA Patients = Number of Patients Enrolled in the Study at the Time of Data Cutoff (01 September 2004) for NDA 21-845
New Patients = Number of Patients Enrolled in the Time Period Between Submission of the NDA and the Cutoff Date (01 March 2005) of the 4-Month SU; PH = Pulmonary Hypertension.

[a] New data may include any or all of the following: exposure to study drug, common AEs, SAEs, deaths, withdrawals due to AEs, and/or laboratory data
[b] All safety data from the completed pivotal trial (A1481140) were submitted in NDA 21-845; ongoing patients have now been enrolled in the extension study (A1481142).
[c] Treatment group assignment not unblinded for the study; some patients with SAEs who had moved into extension studies may have had individual treatment group assignment unblinded (see Table 11 within this document, Serious Adverse Events in Ongoing Blinded Studies)
[d] Not unique patients, Extension to A1481140
[e] Not unique patients, Extension to A1481141
[f] Not unique patients, Extension to A1481131

There is a small amount of new safety information.

Exposure

The exposure data for subjects discussed in NDA and additional information for new subjects in the safety update are shown below.

APPEARS THIS WAY
ON ORIGINAL

Table 2. Summary of Exposure to Study Medication: Combined Across the Pivotal Study (A1481140) and Extension (A1481142)

Total Exposure [Number (%) of Patients]	NDA Data A1140/1142 Combined N = 274	Safety Update Data A1140/1142 Combined N = 274
Total Exposure Time[a]	Any Dose[b]	Any Dose[b]
Exposure ≤1 Day	2 (0.7)	2 (0.7)
1 Day > Exposure ≤1 Weeks	3 (1.1)	3 (1.1)
1 Week > Exposure ≤2 Weeks	3 (1.1)	3 (1.1)
2 Weeks > Exposure ≤4 Weeks	3 (1.1)	3 (1.1)
1 Month > Exposure ≤2 Months	2 (0.7)	2 (0.7)
2 Months > Exposure ≤3 Months	8 (2.9)	8 (2.9)
3 Months > Exposure ≤6 Months	8 (2.9)	7 (2.6)
6 Months > Exposure ≤1 Year	96 (35.0)	15 (5.5)
1 Year > Exposure ≤1.5 Years	133 (48.5)	83 (30.3)
1.5 Years > Exposure ≤2 Years	16 (5.8)	124 (45.3)
2 Years > Exposure ≤2.5 Years	0	24 (8.8)
Median Duration	414.0 days	585.5 days
Range	1-614 days	1-844 days

[a] Duration is defined as the total number of dosing days regardless of missed dosing days. The total exposure time includes titration and fixed-dose phases.

[b] The "*Any Dose*" column includes all patients who received any active treatment (at least 1 dose) in the pivotal trial (A1481140) or the extension (A1481142). Duration is counted from the time a patients began active treatment (either in A1481140 or A1481142).

Source Data: Appendix C, Table 3.1.3

Mean duration of treatment has increased to 586 days. There are 24 PAH subjects with at least 2 years of exposure to sildenafil.

Safety

The table below shows the number of adverse events reported by September 1, 2004 and the total events reported by February 4, 2005.

All adverse events

The numbers of subjects with events are shown below.

Table 3. Study A1481142: Overall Summary of Adverse Events in Study A1481142 as of Cutoff Date of 04 February 2005

	NDA Data Start of Study Until 01 Sep 2004 N = 259	4-Month Safety Update Start of Study Until 04 Feb 2005 N = 259
Subjects Evaluable for Adverse Events	259	259
Number of Adverse Events	2137	2766
Subjects With Adverse Events	249 (96.2)	254 (98.1)
Subjects With Severe Adverse Events	81 (31.3)	102 (39.4)

Adverse events reported by at least 3% of sildenafil subjects are shown below.

Table 4. Study A1481142: All Causality Common Adverse Events (≥3% Incidence in Sildenafil-Treated Patients) as of Cutoff Date of 04 February 2005

(Page 1 of 3)

Body System[a]/Adverse Event (MedDRA Preferred Term)		NDA Data From Start of Study Until 30 Jul 2004 N = 259			4-Month Safety Update From Start of Study Until 04 Feb 2005 N = 259		
		Cumulative Incidence		Incidence Rate[b] (per 100 PY)	Cumulative Incidence		Incidence Rate[c] (per 100 PY)
NS	Headache	82	(31.7)	34.7	90	(34.7)	26.1
GD	Oedema Peripheral	55	(21.2)	23.3	59	(22.8)	17.1
NS	Dizziness	48	(18.5)	20.3	53	(20.5)	15.4
GI	Diarrhoea NOS	47	(18.1)	19.9	58	(22.4)	16.8
R	Nasopharyngitis	46	(17.8)	19.5	51	(19.7)	14.8
GI	Dyspepsia	43	(16.6)	18.2	46	(17.8)	13.4
GD	Chest Pain	41	(15.8)	17.4	50	(19.3)	14.5
M	Arthralgia	39	(15.1)	16.5	47	(18.1)	13.6
R	Cough	39	(15.1)	16.5	47	(18.1)	13.6
M	Back Pain	38	(14.7)	16.1	49	(18.9)	14.2
R	Dyspnoea NOS	37	(14.3)	15.7	40	(15.4)	11.6
GI	Nausea	37	(14.3)	15.7	43	(16.6)	12.5
M	Pain in Limb	31	(12.0)	13.1	39	(15.1)	11.3
GI	Vomiting NOS	30	(11.6)	12.7	35	(13.5)	10.2
I&I	URTI NOS	29	(11.2)	12.3	43	(16.6)	12.5
R	Pharyngitis	28	(10.8)	11.9	32	(12.4)	9.3
I&I	Influenza	26	(10.0)	11.0	31	(12.0)	9.0
GI	Abdominal Pain NOS	24	(9.3)	10.2	29	(11.2)	8.4
R	Epistaxis	22	(8.5)	9.3	28	(10.8)	8.1
C	Palpitations	22	(8.5)	9.3	28	(10.8)	8.1
R	Dyspnoea Exacerbated	21	(8.1)	8.9	28	(10.8)	8.1
Eye	Vision Blurred	21	(8.1)	8.9	22	(8.5)	6.4
GI	Abdominal Pain Upper	20	(7.7)	8.5	24	(9.3)	7.0
GD	Fatigue	20	(7.7)	8.5	27	(10.4)	7.8
R	Bronchitis NOS	18	(6.9)	7.6	26	(10.0)	7.5
M	Myalgia	18	(6.9)	7.6	20	(7.7)	5.8
GD	Asthenia	16	(6.2)	6.8	17	(6.6)	4.9
NS	Syncope	16	(6.2)	6.8	21	(8.1)	6.1
GD	Pyrexia	15	(5.8)	6.4	22	(8.5)	6.4
V	Flushing	15	(5.8)	6.4	16	(6.2)	4.6

[a] B&L = Blood and Lymphatic Disorders; C = Cardiac; Ear = Ear and Labyrinth; Eye = Eye Disorders; GD = General Disorders and Administrative Site Conditions; GI = Gastrointestinal; I = Investigations; I&I = Infections and Infestations; M = Musculoskeletal and Connective Tissue Disorders; M&N = Metabolism and Nutrition; NOS = Not Otherwise Specified; NS = Nervous System; P = Psychiatric Disorders; R = Respiratory, Thoracic, and Mediastinal Disorders; Repro = Reproductive System and Breast Disorders; S = Skin and Subcutaneous Tissue; URTI = Upper Respiratory Tract Infection; UTI = Urinary Tract Infection, V = Vascular; PH=pulmonary hypertension; LRTI=lower respiratory tract infection

[b] Based on a total exposure of 236.2 PY (exposure time in Study A1481142) at the time of data cutoff for the NDA submission for A1481142 data (30 July 2004).

[c] Based on a total exposure of 344.5 PY (exposure time in Study A1481142) at the time of the cutoff date for this SU for A1481142 data (04 February 2005).

Body System[a]/Adverse Event (MedDRA Preferred Term)		NDA Data From Start of Study Until 30 Jul 2004 N = 259		4-Month Safety Update From Start of Study Until 04 Feb 2005 N = 259	
		Cumulative Incidence	Incidence Rate[b] (per 100 PY)	Cumulative Incidence	Incidence Rate[c] (per 100 PY)
R	PH Aggravated NOS	15 (5.8)	6.4	24 (9.3)	7.0
Eye	Visual Disturbance NOS	15 (5.8)	6.4	14 (5.4)	4.1
P	Insomnia	14 (5.4)	5.9	18 (6.9)	5.2
V	Hypotension NOS	13 (5.0)	5.5	16 (6.2)	4.6
C	Right Ventricular Failure	13 (5.0)	5.5	16 (6.2)	4.6
Eye	Conjunctival Hyperemia	12 (4.6)	5.1	19 (7.3)	5.5
I&I	UTI NOS	11 (4.2)	4.7	17 (6.6)	4.9
M	Neck Pain	11 (4.2)	4.7	11 (4.2)	3.2
B&L	Anemia NOS	11 (4.2)	4.7	15 (5.8)	4.4
I&I	LRTI NOS	11 (4.2)	4.7	11 (4.2)	3.2
I&I	Pneumonia NOS	11 (4.2)	4.7	18 (6.9)	5.2
I&I	Sinusitis NOS	11 (4.2)	4.7	18 (6.9)	5.2
GI	Toothache	11 (4.2)	4.7	13 (5.0)	3.8
S	Pruritus	10 (3.9)	4.2	11 (4.2)	3.2
R	Productive Cough	10 (3.9)	4.2	12 (4.6)	3.5
P	Depression	10 (3.9)	4.2	12 (4.6)	3.5
Eye	Episcleral Hyperemia	10 (3.9)	4.2	13 (5.0)	3.8
Eye	Retinal Hemorrhage	10 (3.9)	4.2	13 (5.0)	3.8
M	Muscle Cramp	10 (3.9)	4.2	12 (4.6)	3.5
GD	Fatigue Aggravated	9 (3.5)	3.8	9 (3.5)	2.6
GI	Gastroenteritis NOS	9 (3.5)	3.8	12 (4.6)	3.5
GI	Abdominal Distension	9 (3.5)	3.8	9 (3.5)	2.6
GD	Malaise	8 (3.1)	3.4	10 (3.9)	2.9
M	Pain in Jaw	8 (3.1)	3.4	9 (3.5)	2.6
GD	Pain NOS	7 (2.7)	3.0	8 (3.1)	2.3
I	Hemoglobin Decreased	7 (2.7)	3.0	9 (3.5)	2.6
M&N	Hypokalemia	7 (2.7)	3.0	11 (4.2)	3.2
NS	Paresthesia	7 (2.7)	3.0	9 (3.5)	2.6
B&L	Iron Deficiency Anemia	6 (2.3)	2.5	8 (3.1)	2.3

(Page 3 of 3)

Body System[a]/Adverse Event (MedDRA Preferred Term)		NDA Data From Start of Study Until 30 Jul 2004 N = 259		4-Month Safety Update From Start of Study Until 04 Feb 2005 N = 259	
		Cumulative Incidence	Incidence Rate[b] (per 100 PY)	Cumulative Incidence	Incidence Rate[c] (per 100 PY)
Ear	Vertigo	6 (2.3)	2.5	11 (4.2)	3.2
Eye	Eye Hemorrhage NOS	6 (2.3)	2.5	11 (4.2)	3.2
R	Hemoptysis	6 (2.3)	2.5	8 (3.1)	2.3
S	Rash NOS	6 (2.3)	2.5	8 (3.1)	2.3
Eye	Ocular Discomfort	5 (1.9)	2.1	8 (3.1)	2.3
GI	Gastritis NOS	5 (1.9)	2.1	8 (3.1)	2.3
I	INR Increased	5 (1.9)	2.1	8 (3.1)	2.3
I	Weight Increased	5 (1.9)	2.1	11 (4.2)	3.2
M	Chest Wall Pain	5 (1.9)	2.1	8 (3.1)	2.3
M	Pain in Foot	5 (1.9)	2.1	8 (3.1)	2.3
Repro	Menorrhagia	5 (1.9)	2.1	8 (3.1)	2.3
R	Dyspnea Exertional	5 (1.9)	2.1	8 (3.1)	2.3
Eye	Lenticular Opacities	4 (1.5)	1.7	9 (3.5)	2.6
C	Cyanosis NOS	3 (1.2)	1.3	11 (4.2)	3.2
I	Cardiac Murmur NOS	2 (<1)	0.85	8 (3.1)	2.3

There was little change in the incidence rates for the individual adverse events between July 30, 2004 and February 4, 2005. The events with the highest reporting rates (per 100 patient years) include headache, peripheral edema, dizziness, diarrhea, nasopharyngitis, and dyspnea.

Serious adverse events

Deaths

There were 8 additional deaths between September 1, 2004 and March 01, 2005. These deaths are listed below.

Table 6. Study A1481142: Listing of Deaths That Occurred Between 01 September 2004 (SAE Cutoff Date for NDA Submission) and 01 March 2005 (SAE Cutoff Date for 4-Month Safety Update)

Patient Number	Sex/Age/ Race	Dose	Event Onset Day[a]	Event Term	Outcome/ Investigator Causality
Study A1481142 (Ongoing Extension to Study A1481140)					
10734	M/44/W	80 mg TID[b]	Day 637	Multiorgan Failure	Death/Not study drug related
10001	F/65/W	40 mg TID[b]	Day 684	Worsening PAH	Death/Disease Under Study
10482	F/51/W	80 mg TID[b]	Day 263	Cardiac Arrest	Death/Disease Under Study
10027	M/61/W	80 mg TID[b]	Day 644	Respiratory Insufficiency	Death/Pneumonia
10286	F/25/W	80 mg TID[b]	Day 317[c]	Respiratory Arrest, Cardiac Arrest, Worsening PAH, Right Heart Failure	Death/Disease Under Study/Unknown
10328	F/37/W	80 mg TID[b]	Day 338	Acute Back Pain/Dilated Pulmonary Trunk	Death/Death Cause Unknown
10044	M/73/W	80 mg TID[b]	Day 615	Pneumonia	Death/Other (Bacterial) Infection
10739	F/49/W	80 mg TID[b]	Day 491	Acute Respiratory Failure; Intracranial Bleeding	Death/Other Illness (Disease Under Study)

F = Female; M = Male; NA = Not Available; PH = Pulmonary Hypertension; SAE = Serious Adverse Event, TID = 3 Times Daily; W = White.

[a] Event onset day is measured from start of treatment

[b] Final dose in Study A1481142

[c] Data taken from Serious Adverse Event narrative (see Appendix B)

Most of the new deaths were similar to those reported in the NDA. One subject (10328) experienced rupture of the pulmonary trunk aneurysm. It seems unlikely that sildenafil was associated with any of these deaths.

Other serious events

Serious events reported for the NDA and the safety update are shown below.

Table 7. Study A1481142: Summary of Serious Adverse Events Reported by ≥2 Patients as of Cutoff Date of 01 March 2005 (SAE Cutoff Date for 4-Month Safety Update)

(Page 1 of 2)

Body System[a]/Adverse Event (MedDRA Preferred Term)		NDA Data From Start of Study Until 01 Sep 2004 N = 259		4-Month Safety Update From Start of Study Until 01 Mar 2005 N = 259	
		Cumulative Incidence	Incidence Rate[b] (per 100 PY)	Cumulative Incidence	Incidence Rate[c] (per 100 PY)
C	Right Ventricular Failure	13 (5.0)	5.5	14 (5.4)	4.1
R	Pulmonary Hypertension	10 (3.9)	4.2	16 (6.2)	4.6
R	Dyspnoea	10 (3.9)	4.2	13 (5.0)	3.8
I&I	Pneumonia	9 (3.5)	3.8	16 (6.2)	4.6
GD	Chest Pain	8 (3.1)	3.4	8 (3.1)	2.3
C	Cardiac Failure	6 (2.3)	2.5	10 (3.9)	2.9
NS	Syncope	6 (2.3)	2.5	6 (2.3)	1.7
R	Hemoptysis	5 (1.9)	2.1	5 (1.9)	1.5
R	Dyspnoea Exacerbated	4 (1.5)	1.7	5 (1.9)	1.5
V	Hypotension	4 (1.5)	1.7	4 (1.5)	1.2
RU	Renal Failure	4 (1.5)	1.7	5 (1.9)	1.5
IP&P	Fall	4 (1.5)	1.7	4 (1.5)	1.2
C	Pericardial Effusion	3 (1.2)	1.3	3 (1.2)	0.87
GD	Peripheral Oedema	3 (1.2)	1.3	4 (1.5)	1.2
GD	Pyrexia	3 (1.2)	1.3	5 (1.9)	1.5
I&I	Lower Respiratory Tract Infection	3 (1.2)	1.3	4 (1.5)	1.2
B&L	Anemia	2 (<1)	0.85	3 (1.2)	0.87
C	Pericarditis	2 (<1)	0.85	2 (<1)	0.58
C	Atrial Flutter	2 (<1)	0.85	3 (1.2)	0.87
C	Cardiac Arrest	2 (<1)	0.85	4 (1.5)	1.2
GI	Abdominal Pain	2 (<1)	0.85	2 (<1)	0.58
GI	Nausea	2 (<1)	0.85	2 (<1)	0.58
GI	Small Intestinal Obstruction	2 (<1)	0.85	3 (1.2)	0.87
HB	Cholelithiasis	2 (<1)	0.85	2 (<1)	0.58
IS	Hypersensitivity	2 (<1)	0.85	2 (<1)	0.58
I&I	Sepsis	2 (<1)	0.85	2 (<1)	0.58
I&I	Urosepsis	2 (<1)	0.85	2 (<1)	0.58
I&I	Viral Infection	2 (<1)	0.85	2 (<1)	0.58

[a] B&L = Blood and Lymphatic Disorders; C = Cardiac; GD = General Disorders and Administrative Site Conditions; GI = Gastrointestinal; HB = Hepatobiliary; I = Investigations; I&I = Infections and Infestations; IS = Immune System; M = Musculoskeletal and Connective Tissue Disorders; M&N = Metabolism and Nutrition; N=Neoplasms Benign, Malignant, and Unspecified; NS = Nervous System; P = Psychiatric Disorders; R = Respiratory, Thoracic, and Mediastinal Disorders; Repro = Reproductive System and Breast Disorders; RU = Renal and Urinary Disorders; V = Vascular.

[b] Based on a total exposure of 236.2 PY (exposure time in Study A1481142) at the time of data cutoff for the NDA submission for A1481142 data (30 July 2004).

[c] Based on a total exposure of 344.5 PY (exposure time in Study A1481142) at the time of the cutoff date for this SU for A1481142 data (04 February 2005). Exposure data were not available up to the 01 March 2005 cutoff date; therefore, the incidence rate for SAEs for the 4-month SU is slightly overestimated.

(Page 2 of 2)

Body System[a]/Adverse Event (MedDRA Preferred Term)		NDA Data From Start of Study Until 01 Sep 2004 N = 259		4-Month Safety Update From Start of Study Until 01 Mar 2005 N = 259	
		Cumulative Incidence	Incidence Rate[b] (per 100 PY)	Cumulative Incidence	Incidence Rate[b] (per 100 PY)
I	Hepatic Enzymes Increased	2 (<1)	0.85	2 (<1)	0.58
M&N	Fluid Overload	2 (<1)	0.85	2 (<1)	0.58
M	Pain in Extremity	2 (<1)	0.85	3 (1.2)	0.87
N	Metastases to Liver	2 (<1)	0.85	2 (<1)	0.58
Repro	Menorrhagia	2 (<1)	0.85	2 (<1)	0.58
R	Hypoxia	2 (<1)	0.85	3 (1.2)	0.87
R	Pulmonary Embolism	2 (<1)	0.85	2 (<1)	0.58
C	Cardiac Failure Congestive	0	--	2 (<1)	0.58
GI	Diarrhoea	1 (<1)	0.42	2 (<1)	0.58
GI	Gastrointestinal Hemorrhage	1 (<1)	0.42	2 (<1)	0.58
GI	Inguinal Hernia	0	--	2 (<1)	0.58
I&I	Bronchitis	1 (<1)	0.42	3 (1.2)	0.87
I&I	Central Line Infection	0	--	2 (<1)	0.58
I&I	Gastroenteritis	1 (<1)	0.42	2 (<1)	0.58
I&I	Respiratory Tract Infection	1 (<1)	0.42	2 (<1)	0.58
I	Hemoglobin Decreased	0	--	2 (<1)	0.58
M&N	Hyperkalemia	1 (<1)	0.42	2 (<1)	0.58
M&N	Hypokalemia	1 (<1)	0.42	2 (<1)	0.58
M&N	Hyponatremia	1 (<1)	0.42	2 (<1)	0.58
M	Arthralgia	0	--	2 (<1)	0.58
NS	Dizziness	1 (<1)	0.42	2 (<1)	0.58
P	Suicide Attempt	1 (<1)	0.42	2 (<1)	0.58
RU	Renal Failure Acute	0	--	2 (<1)	0.58
R	Epistaxis	1 (<1)	0.42	2 (<1)	0.58
R	Respiratory Arrest	1 (<1)	0.42	2 (<1)	0.58
R	Respiratory Failure	1 (<1)	0.42	4 (<1)	1.2

There was little change between serious adverse events reported in the NDA and those reported in the safety update. The most commonly reported events included right ventricular failure, pulmonary hypertension, and pneumonia.

Discontinuations

The table below shows the subjects who discontinued for any reason between July 30, 2004 and February 4, 2005.

Table 8. Study A1481142: Listing of Discontinuations That Occurred Between 30 July 2004 (Oracle Cutoff Date for NDA Submission) and 04 February 2005 (Oracle Cutoff Date for 4-Month Safety Update)

Patient Number	Treatment Group (mg Sildenafil TID)	Reason for Discontinuation
10001[a]	40 mg	Patient died (worsening PAH)
10027[a]	80 mg	Patient died (respiratory insufficiency due to pneumonia)
10044[a]	80 mg	Patient died (pneumonia)
10265[b]	80 mg	Patient died (pneumonia, PAH)
10281	80 mg	Adverse Event: Bilateral lung transplant
10296	80 mg	Adverse Event: Syncope and nausea (related)
10328[a]	80 mg	Patient died (pulmonary trunk aneurysm)
10482[a]	80 mg	Patient died (cardiac arrest)/pneumonia
10729	80 mg	Adverse event: Myocardial infarction
10734[a]	80 mg	Patient died (multiorgan failure)
10739[a]	80 mg	Patient died (acute heart and respiratory failure)
11213	80 mg	Patient no longer willing to participate

[a] Patient also included on previous Table 6, Listing of Patients Who Died
[b] Patient's death reported in NDA

Other than one subject who refused to continue and one subject reporting syncope and nausea, new discontinuations were the result of adverse events most likely linked to their underlying disease.

Abnormal laboratory values

The table below shows the abnormal values reported in the extension study and listed according to whether the subject's value at baseline was normal or abnormal.

There were relatively few increases in liver function tests. About 9% of subjects in the safety update had increases in BUN, but far fewer had increases in serum creatinine.

Ongoing blinded studies

Deaths

There were 10 additional subjects who died in one of the ongoing blinded studies (9 adults and 1 child). Of the 9 adults who died, 5 patients were on concomitant sildenafil and epoprostenol therapy, 1 was on placebo, 3 were on medication still blinded.

Table 10. Ongoing Blinded Studies (A1481141, A1481153, A1481131, A1481156, A1481134, A1481157): Listing of Deaths That Occurred Between 01 September 2004 (SAE Cutoff Date for NDA Submission) and 01 March 2005 (SAE Cutoff Date for 4-Month Safety Update)

Patient Number	Sex/Age/ Race	Dose	Event Onset Day[a]	Event Term	Outcome/ Investigatory Causality
Study A1481141 (Ongoing Blinded Study)					
10033	F/65/W	Blinded	Day 109[b]	Progressive right heart failure, hypoxemia, progressive PAH	Death/Disease Under Study or Other (Not Study Drug Related)
10038	F/56/A	24 days post-therapy[c]	Day 40, 25	Worsening PAH, cardiopulmonary arrest	Death/Disease Under Study
28248	M/30/B	Blinded	Day 7	Right heart failure	Death/Disease Under Study
Study A1481153 (Ongoing Extension Study to A1481141)					
10602	F/62/W	40 mg TID	Not Available	Cardiac Arrest	Death/Related to study drug
10403	M/67/W	40 mg TID	Day 27[b]	Cardiac Arrest	Death/Disease Under Study
10033	F/65/W	Blinded	Not Available	Worsening PAH, right heart failure	Death/Other (Not Study Drug Related)
10224	F/59/B	80 mg TID	Day 257	Worsening PAH	Death/Disease Under Study
10409	F/54/W	80 mg TID	Day 122	Death	Death/Other (Sepsis)
10410	F/59/W	40 mg TID	Day 38	Cardiac arrest	Death/Disease Under Study
Study A1481157 (Ongoing Pediatric Study)					
10031	F/1 day/B	Intravenous	Day 1	Tension pneumothorax	Death/Disease Under Study

A = Asian; B = Black; F = Female; M = Male; NA = Not Available; PH = Pulmonary Hypertension; SAE = Serious Adverse Event; SU = Safety Update; W = White; TID = 3 Times Daily.

[a] Event onset day is measured from start of treatment

[b] Data taken from Serious Adverse Event narrative (see Appendix B)

[c] Data taken from Serious Adverse Event narrative (see Appendix B); patient was on placebo

Source: SU Table A6.1b, Appendix C

One subject (10602) who was receiving both sildenafil and epoprostenol for an unknown amount of time, had interruption of the epoprostenol infusion followed by collapsed. She could not be resuscitated. The cause of death was listed as cardiac arrest; the autopsy revealed no acute pathology. The other deaths seem to be unremarkable.

Serious adverse events

Serious events reported in the ongoing blinded studies are shown below.

There were relatively few increases in liver function tests. About 9% of subjects in the safety update had increases in BUN, but far fewer had increases in serum creatinine.

Ongoing blinded studies

Deaths

There were 10 additional subjects who died in one of the ongoing blinded studies (9 adults and 1 child). Of the 9 adults who died, 5 patients were on concomitant sildenafil and epoprostenol therapy, 1 was on placebo, 3 were on medication still blinded.

Table 10. Ongoing Blinded Studies (A1481141, A1481153, A1481131, A1481156, A1481134, A1481157): Listing of Deaths That Occurred Between 01 September 2004 (SAE Cutoff Date for NDA Submission) and 01 March 2005 (SAE Cutoff Date for 4-Month Safety Update)

Patient Number	Sex/Age/ Race	Dose	Event Onset Day[a]	Event Term	Outcome/ Investigatory Causality
Study A1481141 (Ongoing Blinded Study)					
10033	F/65/W	Blinded	Day 109[b]	Progressive right heart failure, hypoxemia, progressive PAH	Death/Disease Under Study or Other (Not Study Drug Related)
10038	F/56/A	24 days post-therapy[c]	Day 40, 25	Worsening PAH, cardiopulmonary arrest	Death/Disease Under Study
28248	M/30/B	Blinded	Day 7	Right heart failure	Death/Disease Under Study
Study A1481153 (Ongoing Extension Study to A1481141)					
10602	F/62/W	40 mg TID	Not Available	Cardiac Arrest	Death/Related to study drug
10403	M/67/W	40 mg TID	Day 27[b]	Cardiac Arrest	Death/Disease Under Study
10033	F/65/W	Blinded	Not Available	Worsening PAH, right heart failure	Death/Other (Not Study Drug Related)
10224	F/59/B	80 mg TID	Day 257	Worsening PAH	Death/Disease Under Study
10409	F/54/W	80 mg TID	Day 122	Death	Death/Other (Sepsis)
10410	F/59/W	40 mg TID	Day 38	Cardiac arrest	Death/Disease Under Study
Study A1481157 (Ongoing Pediatric Study)					
10031	F/1 day/B	Intravenous	Day 1	Tension pneumothorax	Death/Disease Under Study

A = Asian; B = Black; F = Female; M = Male; NA = Not Available; PH = Pulmonary Hypertension, SAE = Serious Adverse Event; SU = Safety Update, W = White, TID = 3 Times Daily.

[a] Event onset day is measured from start of treatment

[b] Data taken from Serious Adverse Event narrative (see Appendix B)

[c] Data taken from Serious Adverse Event narrative (see Appendix B); patient was on placebo

Source: SU Table A6.1b, Appendix C

One subject (10602) who was receiving both sildenafil and epoprostenol for an unknown amount of time, had interruption of the epoprostenol infusion followed by collapsed. She could not be resuscitated. The cause of death was listed as cardiac arrest; the autopsy revealed no acute pathology. The other deaths seem to be unremarkable.

Serious adverse events

Serious events reported in the ongoing blinded studies are shown below.

Table 11. Ongoing Blinded Studies (A1481141, A1481153, A1481131, A1481156, A1481134, A1481157): Summary of Serious Adverse Events Reported by ≥2 Patients as of Cutoff Date of 01 March 2005 (SAE Cutoff Date for 4-Month Safety Update)

(Page 1 of 2)

Body System[a]/Adverse Event (MedDRA Preferred Term)		Number of All Causality Events					
		NDA Data From Start of Study Until 01 Sep 2004			4-Month Safety Update From Start of Study Until 01 Mar 2005[b]		
		Placebo	Blinded Therapy	Sildenafil (All Doses)	Placebo	Blinded Therapy	Sildenafil (All Doses)
I&I	Catheter-Related Infection	0	1	4	0	1	11
C	Right Ventricular Failure	0	2	3	0	9	6
C	Cardiac Failure	0	1	2	0	1	2
C	Palpitations	0	0	2	0	0	2
C	Cyanosis	0	1	1	0	3	0
GI	Ascites	0	0	2	0	1	2
GI	Pancreatitis Acute	0	0	0	0	0	3
GD	Asthenia	0	0	2	0	1	2
HB	Cholelithiasis	0	1	0	0	0	2
I&I	Catheter Sepsis	0	3	1	0	3	2
I&I	Catheter Site Infection	0	0	2	0	0	2
I&I	Cellulitis	0	1	0	0	1	2
I&I	Pneumonia	0	2	2	0	2	3
I&I	Sepsis	0	0	2	0	0	6
I&I	URTI	0	1	0	0	2	0
M&N	Fluid Overload	0	4	0	0	4	0
NS	Syncope	0	4	2	0	5	2
R	Dyspnoea	0	1	2	0	4	3
R	Dyspnoea Exacerbated	1	3	1	1	4	2
R	Pneumothorax	0	0	2	0	0	3
R	Pulmonary Hypertension	0	6	2	0	13	6
V	Hemorrhage	0	0	2	0	0	2
V	Hypotension	0	2	2	0	2	3

NOS = Not otherwise specified; URTI = Upper respiratory tract infection.

[a] B&L = Blood and Lymphatic Disorders; C = Cardiac; GD = General Disorders and Administrative Site Conditions; GI = Gastrointestinal; HB = Hepatobiliary; I&I = Infections and Infestations; IP&P = Injury, Poisoning, and Procedural Complications; M = Musculoskeletal and Connective Tissue Disorders; M&N = Metabolism and Nutrition; NS = Nervous System; P = Psychiatric Disorders; R = Respiratory, Thoracic, and Mediastinal Disorders; RU = Renal and Urinary Disorders; V = Vascular.

[b] Prerandomization events not included on this table.

(Page 2 of 2)

Body System[a]/Adverse Event (MedDRA Preferred Term)		Number of All Causality Events					
		NDA Data From Start of Study Until 01 Sep 2004			4-Month Safety Update From Start of Study Until 01 Mar 2005[b]		
		Placebo	Blinded Therapy	Sildenafil (All Doses)	Placebo	Blinded Therapy	Sildenafil (All Doses)
C	Cardiac Arrest	0	2	0	0	2	4
C	Left Ventricular Failure	0	2	0	0	2	0
GD	Oedema Peripheral	0	1	1[c]	0	1	0[c]
M&N	Hypoglycemia	0	1	1	0	1	1
M	Pain in Extremity	0	1	1	0	1	1
RU	Renal Failure Acute	0	3	0	0	3	0
R	Hemoptysis	0	1	1	0	2	2
B&L	Anemia	0	0	0	0	0	2
B&L	Thrombocytopenia	0	0	0	0	0	3
C	Atrial Fibrillation	0	0	0	0	0	2
C	Supraventricular Tachycardia	0	0	0	0	0	2
GI	Abdominal Distension	0	1	0	0	1	1
GI	Abdominal Pain	0	0	1	0	0	2
GI	Gastrointestinal Hemorrhage	0	0	0	0	0	2
GI	Nausea	0	0	0	0	1	2
GD	Catheter-Related Complication	0	0	0	0	1	1
GD	Chest Pain	0	0	0	0	3	1
I&I	Bacteremia	0	0	0	0	2	0
I&I	Gastroenteritis	0	0	0	0	2	0
I&I	Gastroenteritis Viral	0	0	0	0	2	1
IP&P	Device Failure	0	0	0	0	0	2
RU	Renal Failure	0	0	0	0	1	2
R	Hypoxia	1	0	0	1	2	0
R	Respiratory Arrest	0	0	0	0	1	1

The most common events included pulmonary hypertension, right ventricular failure, and syncope.

Post marketing

The sponsor searched their early alert safety database for sildenafil nonclinical study cases reported from September 2, 2004 through March 1, 2005 reporting an indication of pulmonary hypertension.

Adverse events from this database are shown below for adults (table 12) followed by pediatric patients (table 14).

Table 12. Comparison of Adverse Events From Sildenafil PII Cases Received Between 02 September 2004 and 01 March 2005 (Safety Update)[a] With Cases Received Cumulatively Through 01 September 2004 and Cases Received Through 01 March 2005

Meddra SOC	Preferred Term	Safety Update 02 Sep 2004 Through 01 Mar 2005	Cumulative Through 01 Sep 2004	Cumulative Through 01 Mar 2005
		Number (% of 45 Cases)	Number (% of 180 Cases)	Number (% of 225 Cases)
Cardiac Disorders	Tachycardia	3 (6.7%)	2 (1.1%)	5 (2.2%)
General Disorders and Administration Site Conditions	Death	2 (4.4%)	7 (3.9%)	9 (4.0%)
	Drug ineffective	6 (13.3%)	--	7 (3.1%)
	Fatigue	2 (4.4%)	4 (2.2%)	6 (2.7%)
Injury, Poisoning, and Procedural Complications	Drug exposure during pregnancy	2 (4.4%)	--	2 (0.9%)
	Intentional misuse	2 (4.4%)	--	2 (0.9%)
	Overdose	2 (4.4%)	45 (25.0%)	45 (20.0%)
Investigations	Platelet count decreased	2 (4.4%)	--	2 (0.9%)
	Prothrombin time prolonged	3 (6.7%)	1 (0.6%)	4 (1.8%)
Nervous System Disorders	Headache	2 (4.4%)	14 (7.8%)	17 (7.6%)
Pregnancy, Puerperium, and Perinatal Conditions	Pre-eclampsia	2 (4.4%)	--	2 (0.9%)
Respiratory, Thoracic, and Mediastinal Disorders	Pulmonary hypertension	6 (13.3%)	24 (13.3%)	30 (13.3%)

[a] Events reported in 2 or more cases

Overdose[9] was the most commonly reported event followed by pulmonary hypertension and headache.

APPEARS THIS WAY
ON ORIGINAL

[9] From the sponsor "In reference to your question of 15 April regarding the 4-month Safety Update Report for REVATIO, we wish to clarify the reporting of "overdose" as presented in table 17 of that report. The 45 cases presented (as also identified in table 12 of the report) are all from spontaneous reports from physicians, patients, literature sources, or others wherein pulmonary hypertension patients are being treated "off-label" with Viagra - available only in doses of 25 mg, 50 mg, and 100 mg tablets at the time of these reports. As such, all cases would be coded per Pfizer SOP as overdose because they report dosing that is different than the recommended dosing for the approved indication in erectile dysfunction. Therefore, as only the VIAGRA label was approved at the time of the reported events, any dosing regimen more frequent than once-daily would also be reported as "overdose". In fact, none of the reported cases involve a patient consistently dosed at 20 mg TID, the regimen proposed in the REVATIO draft labeling from NDA 21-845."

Table 14. A Comparison of Adverse Events Received For the Sildenafil Safety Update With Sildenafil Original PH Submission Involving Pediatric Patients

MedDRA (Version 7.1) SOC	Preferred Term	Sildenafil Update 02 Sep 2004 Through 01 Mar 2005	Cumulative Review Through 01 Sep 2004
		Number (% of 11 Cases)	Number (% of 28 Cases)
General Disorders and Administration Site Conditions	Death	1 (9.1%)	--
	Drug ineffective	2 (18.2%)	--
Injury, Poisoning, and Procedural Complications	Drug exposure during pregnancy	2 (18.2%)	--
	Intentional misuse	1 (9.1%)	--
Investigations	Prothrombin time prolonged	2 (18.2%)	1 (3.6%)
Nervous System Disorders	Cerebrovascular accident	1 (9.1%)	--
Pregnancy, Puerperium, and Perinatal Conditions	Foetal growth retardation	1 (9.1%)	--
	Premature labour	1 (9.1%)	--
	Small for dates baby	1 (9.1%)	--
Respiratory, Thoracic, and Mediastinal Disorders	Pulmonary hypertension	1 (9.1%)	5 (17.9%)
Skin and Subcutaneous Tissue Disorders	Erythema	1 (9.1%)	1 (3.6%)
	Rash follicular	1 (9.1%)	--

Death

All deaths reported between September 2, 2004 and March 1, 2005 are shown below.

Table 15. Sildenafil Nonclinical Study PH Cases Received Between 02 September 2004 Through 01 March 2005 and Reporting Case Outcome as Death

AER Number	Gender	Age	Reported Cause of Death	Comments
2004066791	F	UNK	Death Cause Unknown	Limited information provided
2004083002	F	UNK	Aspiration of GI contents into airways	Death unrelated to sildenafil per reporting physician
2004085082	M	UNK	Pulmonary hypertension	Postmortem tests revealed no evidence death was drug-related. Patient showed improvement on sildenafil with BNP level falling from 115 fmol/mL at baseline to 65 fmol/mL at Week 4.
2004089247	F	Child	Death cause unknown	Limited information provided
2004098654	F	70 Years	Cardiac decompensation	Patient was well-adjusted to sildenafil and was hospitalized with acute respiratory disease
2005006440	M	47 Years	Pulmonary hemorrhage	Medical history of Tetralogy of fallot with hypoplastic pulmonary arteries, large major aorta pulmonary collateral's and Eisenmenger syndrome.
2005025042	F	Adolescent	Pulmonary hypertension	Patient had taken sildenafil for 3 years with improvement in functional class
2005025047	F	UNK	Sudden death after a hypertensive crisis	Unclear if patient was taking sildenafil at time of death.

Nothing seems unusual in this limited database.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maryann Gordon
5/3/05 10:38:35 AM
MEDICAL OFFICER

Safety Update Review: See page 97 of Dr. Gordon's Medical Review