

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-845

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Pharmacometrics Addendum to Clinical Pharmacology & Biopharmaceutics Review

NDA: 21-845 N 000 Submission date: December, 2 2004
Drug: Sildenafil citrate 20 mg tablets, Revatio™
Indication: Treatment of Pulmonary Arterial Hypertension

Reviewer: B. Nhi Beasley, Pharm.D.
Team Leader: Joga Gobburu, Ph.D.

Executive Summary

The purpose of this addendum is to determine if there is a concentration response relationship for sildenafil in the treatment of pulmonary arterial hypertension (PAH). The response measure evaluated was pulmonary vascular resistance (PVR) or pulmonary vascular resistance index (PVRI) and six minute walk distance (6MWD). Specifically, we were tasked to determine if the dose of 20 mg is too high for the treatment of PAH and if the dosing interval of three times daily (TID) is too frequent for the treatment of PAH.

The dose of 20 mg does not seem too high for the treatment of PAH. The adverse effect of concern, bleeding events (primarily manifested as epistaxis), was not dose dependent. Since 74% of the patients in the pivotal study 1140 were taking vitamin K antagonists, the data were further analyzed by concomitant warfarin use since both S-warfarin and sildenafil are metabolized by CYP2C9. The percent of subjects taking warfarin with bleeding events was 8, 29, 26 and 7 % for placebo, sildenafil 20, 40 and 80 mg TID, respectively. Thus, analysis by dose did not show signs of saturation or dose related bleeding events, although the actual number of events was small and information on warfarin dose adjustments was unavailable. On another note, the IC50 for PDE5 inhibition is approximately 47 ug/L while the mean maximum concentration from 20 mg is approximately 100 ug/L. Thus, if bleeding events are related to PDE inhibition, then all doses produced concentrations above the IC50.

In terms of effectiveness from the 20 mg dose, all doses were effective for 6 MWD compared to placebo. However, there was not much difference between doses (45, 48, and 51 meters for 20, 40 and 80 mg TID, respectively) despite the difference in trough concentrations. There was, however, a relationship between concentration and PVR (measured more frequently than 6 MWD). Given the concentration PVR relationship, it seems likely that since PVR affects 6MWD that there should be a relationship between concentration and 6MWD. However, the change in PVR required to significantly affect 6MWD is unknown. Further, we, as well as the sponsor, were not able to discern the relationship between concentration or dose and 6MWD. This is likely because of the lack of 6MWD data collected at times other than at trough concentrations. Since all 6MW tests were measured around trough concentrations, this prevents one from building a relationship between concentration and 6MWD.

Twenty milligrams TID was the lowest dose studied in the pivotal trial 1140, thus conclusions for the lowest effective dose cannot be made based on the NDA. However, there is a concentration response relationship that follows an Emax model with respect to PVR change

from baseline, and literature data suggest that a dose as low as 12.5 mg is effective hemodynamically (change in PVR). The PVR response seems to plateau around 100 ug/L, or the approximate mean maximum concentration from 20 mg.

It is most likely that sildenafil cannot be administered less frequently than TID for the treatment of PAH. From the NDA, the EC50 from study 1024 is around 17 ug/L, while the mean minimum concentration from the 20 mg TID dose is around 30 ug/L. Outside literature on PVR time course suggests that administering the drug less frequent than TID is not an option. The literature suggests that the effect on PVR starts to decrease after two hours. Although metabolite was not measured in these studies, the hemodynamic decrease in PVR effect after two hours suggest that any hemodynamic contribution to duration of effect past 8 hours from an active metabolite is unlikely.

There is a relatively large discrepancy between the two population PK/PD models developed by the sponsor (an EC50 of 3 ug/L and 17 ug/L). The explanations for these discrepancies are unsatisfactory (different patient populations and outliers included in analysis). However, the reviewer believes that the study design in study 1024 allows for better model development and thus better estimates than the design of study 1140. Thus, the EC50 for sildenafil is around 17 ug/L and the concentration that produces the maximal effect is around 100 ug/L. On another note, the sponsor modeled drug effect in both studies without accounting for the placebo effect. However, when we correctly accounted for the drug effect by including the placebo effect, we did not find a large difference in model parameters.

Given the totality of the data it seems that the only way to determine if a dose lower than 20 mg is effective for the treatment of PAH is to conduct another study using lower doses, however the literature suggest that the lowest effective dose for change in PVR is 12.5 mg. The adverse event of bleeding does not seem to be dose related and does not seem to be caused by an interaction with coumadin. We recommend that the 20 mg TID dose be approved for the treatment of PAH.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the information included in the sNDA 19-922. The Office of Clinical Pharmacology and Biopharmaceutics finds that:

1. The effects of sildenafil on PVRI are concentration dependent, at least acutely. There is no clear reason why this relationship would be altered after chronic treatment. However, the effects on 6 min walk distance (6MWD) seem to be similar at 20, 40 and 80 mg doses. The desired change in PVRI to obtain maximal effects on the 6MWD is unknown.
2. It is unlikely that sildenafil could be dosed less frequently than tid. The concentrations of the parent and metabolite (which has about 1/3rd of parent activity) exhibit a 5:1 fluctuation between peak and trough levels at steady state. Again, if the effects on PVRI are of clinical relevance then dosing, say, bid would lead to lack of adequate effects on PVRI between bid doses.

Date _____

Joga Gobburu, Ph. D.
Pharmacometrics Reviewer (on behalf of Dr. Nhi Beasley)

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 21, 845, MeहुलM, MarroumP, MishinaE, BeasleyN, StockbridgeN, MarciniakT,
GordonM, HFD 110 BIOPHARM

Review

1. Background

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5. Sildenafil increases intracellular concentrations of nitric oxide (NO) derived cGMP, and is expected to reverse metabolic and vascular defects due to reduction of NO in patients with PAH. Endothelial NO dilates pulmonary blood vessels and ultimately reduces pulmonary arterial pressure and PVR. The sponsor is developing sildenafil for the treatment of PAH.

Dr. Gordon's medical review highlights the higher incidence of reported bleeding in the sildenafil group versus the placebo group in the pivotal clinical trial, A148 1140. A total of 74 % of patients were taking vitamin K antagonists. The reported bleeding incidence rates were 21 % in the sildenafil groups compared to 13% in the placebo group. The incidence rate of epistaxis, the most commonly reported bleeding event, was 14% in the sildenafil group compared to 2 % in the placebo group. There was little difference in reported epistaxis rates in patients not taking vitamin K antagonists. Thus, there is concern that since sildenafil is metabolized by CYP2C9 (minor pathway) and S-warfarin is metabolized by CYP2C9, then concomitant sildenafil with warfarin may increase plasma concentrations of S-warfarin, through competition of the same pathway, and consequently increase the risk for bleeding events.

Additionally, in the pivotal trial the tested oral doses of 20 mg, 40 mg, and 80 mg TID had a flat dose response with respect to the primary endpoint of 6MWD, however each dose was statistically better than placebo (Table 1), suggesting that these doses are at the top of the dose response curve. The sponsor is proposing 20 mg orally TID for the treatment of PAH.

Table 1. 6MWD in meters at week 12, placebo corrected, LOCF

ITT population (pbo n =66)	20 mg (n=67)	40 mg (n=64)	80 mg (n=69)
Mean difference (SE)	45 (10)*	48 (10)*	51 (10)*
99 % CI	(21, 70)	(20, 72)	(23, 77)

*p<0.0001

ITT = intent to treat

LOCF = last observation carried forward

Given the flat dose response and the higher incidence of bleeding events in the clinical trial, two important questions arose that are also the primary purpose of this addendum.

- 1) Is the dose of 20 mg too high for the treatment of PAH?, and
- 2) Can sildenafil be administered less frequently than TID?

2. Is the dose of 20 mg too high for the treatment of PAH?

2.1. Summary

The dose of 20 mg does not seem too high for the treatment of PAH. The adverse effect of concern, bleeding events (primarily manifested as epistaxis), was not dose dependent. Since 74% of the patients in the pivotal study 1140 were taking vitamin K antagonists, the data were further analyzed by concomitant warfarin use since both S-warfarin and sildenafil are metabolized by CYP2C9. The percent of subjects taking warfarin with bleeding events was 8, 29, 26 and 7 % for placebo, sildenafil 20, 40 and 80 mg TID, respectively. Thus, analysis by dose did not show signs of saturation or dose related bleeding events, although the actual number of events was small. Additionally, the clinical pharmacology review of the drug interaction study with acenocoumarol and phenprocoumon, derivatives of coumadin that are also metabolized by CYP2C9, showed no increase in bleeding time with concomitant sildenafil. On another note, the IC50 for PDE5 inhibition is approximately 47 ug/L while the mean maximum concentration from 20 mg is approximately 100 ug/L. Thus, if bleeding events are related to PDE inhibition, then all doses produced concentrations above the IC50.

In terms of effectiveness from the 20 mg dose, all doses were effective, however, there was not much difference between doses in relation to 6MWD (45, 48, and 51 meters for 20, 40 and 80 mg TID, respectively). There was, however, a relationship between concentration and PVR (measured more frequently than 6 MWD). Given the concentration PVR relationship, it seems likely that since PVR affects 6MWD that there should be a relationship between concentration and 6MWD. However, we, as well as the sponsor, were not able to discern this relationship between concentration or dose and 6MWD. This lack of relationship is not explainable by the fact that the sampling of 6MWD occurred at trough. Figure 6 shows that the trough concentrations of 20 mg, 40 mg and 80 mg are reasonably separated. Should there be a dose response, it might have been possible to detect it even at trough.

Twenty milligrams TID was the lowest dose studied in the pivotal trial 1140, thus conclusions for the lowest effective dose cannot be made based on the NDA. However, there is a concentration response relationship that follows an Emax model with respect to PVR change from baseline, and literature data suggest that a dose as low as 12.5 mg is effective hemodynamically (change in PVR). The PVR response seems to plateau around 100 ug/L, or the approximate mean maximum concentration from 20 mg. The degree of PVR change needed for a significant effect on 6MWD is unknown. Thus, the lowest effective dose can only be speculated to be 12.5 mg.

2.2 Details of analysis

Two studies in the NDA provide insight on the concentration response relationship or proper dose selection, study A148 1024 (target concentration hemodynamic study) and study A148 1140 (pivotal study measuring 6MWD and hemodynamics).

2.2.1 Design

2.2.1.1. Study 1024

Study 1024 was a double blind, placebo controlled, target concentration escalation study that measured hemodynamics (primary endpoint - PVR) in 85 patients with pulmonary HTN. The target concentrations of 10, 50, 100, 300, and 500 ug/L correspond to the mean maximum concentrations achieved with single oral doses of 5, 10, 25, 50, and 100 mg.

Patients were stratified into three groups prior to randomization: Group 1a – PAH, Group 1b – pulmonary venous HTN due to congestive heart failure, and Group 2 hypoxic pulmonary HTN. Patients in groups 1a and 1b were randomized 3:1 to sildenafil or placebo, group 2 received only sildenafil. The original study was conducted in 37 patients. The sildenafil infusion initially targeted a concentration of 100, 300 and 500 ug/L. An amendment for Groups 1a and 1b randomized 48 more patients to sildenafil target concentrations of 10, 50, and 100 ug/L or placebo and added observations from NO dosing. Patients enrolled in the original study were not enrolled in the extension study. A total of 45 patients received treatment in group 1a, 34 received treatment in group 1b, and six received treatment in Group 2.

For each target concentration, the initial intravenous infusion was given over five minutes followed by a maintenance infusion given over 15 minutes. Concentrations were measured at the end of each infusion.

Hemodynamics were measured at baseline and at each target concentration step. There were four possible baseline HD measurement times: baseline 1, during NO, after NO (received 40 ppm for five minutes), and baseline 2 (when PAP returned to $\pm 5\%$ of baseline 1). If subjects did not receive NO in the extension study, then only two baselines were recorded. Hemodynamics were also measured at the three target plasma concentrations during the treatment phase (ten minutes after the start of every maintenance infusion).

2.2.1.2 Study 1140

Study A148 1140 was a phase 3, randomized, double blind, placebo controlled, study in 277 patients with PAH (207 sildenafil, 70 placebo) with a primary endpoint of distance walked in six minutes (6MWD) after twelve weeks of treatment. Patients were randomized to placebo, 20, 40 or 80 mg orally TID. Patients randomized to the 80 mg dose were given 40 mg TID for the first seven days. Drug was taken three times a day at least six hours apart.

Blood samples for PK were drawn at baseline, Week 8 and 12. Baseline samples were collected after the first dose between 15 minutes to 3 hours, > 3 to 6 hours, and >6 to 8 hours. At Week 8, two samples were taken, the first as soon as the patient arrived and the second as close as possible to the end of the dosing interval (at least 30 minutes apart). At Week 12, samples were collected after the first dose of the day in the same three sampling windows as baseline. Additionally two samples were taken during the hemodynamic assessments.

Six minute walk distance was assessed at screening, baseline, Week 4, Week 8, Week 12 and if applicable at a follow-up visit around Week 16. The time of day of the 6MW was as close to predicted trough levels of sildenafil and at least four hours post dose. Hemodynamics were assessed at baseline and Week 12. At Week 12, the hemodynamics were performed at least 15 minutes apart and at least one of these readings was taken close to the expected time of trough sildenafil levels.

Most of these patients were female (73 %) and White (85%). A total of 64% had primary PAH, 30% had PAH due to connective tissue disease and 6% had PAH associated with surgical repair of cardiac defects.

**APPEARS THIS WAY
ON ORIGINAL**

2.2.2 Concentration PVR data

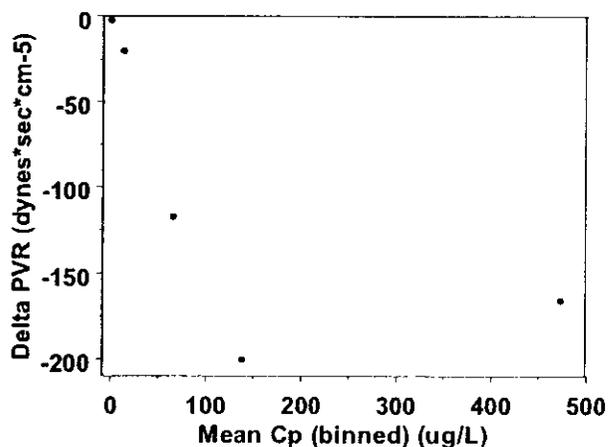
2.2.2.1. Study 1024

Table 2. and Figure 1 show that there is a concentration - change in PVR relationship. Since concentrations varied widely within the target concentration, the reviewer binned the patients by concentration percentiles of 0, >0-25th, >25th-50th, >50th-75th, >75th-100 so that an approximately equal number of patients composed each percentile, other than the placebo group. The PVR effect seems to plateau around the 100 ug/L concentration (approximate c_{max} of 20 mg dose). The reviewer calculated change in PVR as treatment PVR minus baseline 1 PVR. The reviewer excluded two patients (ids 304 and 237) because they had concentrations at zero time. Incidentally, these patients did not have a concentration - change in PVR relationship; change in PVR was fairly flat over the target concentrations of 10-100 ug/L.

Table 2. PVR mean change by mean concentration (binned)

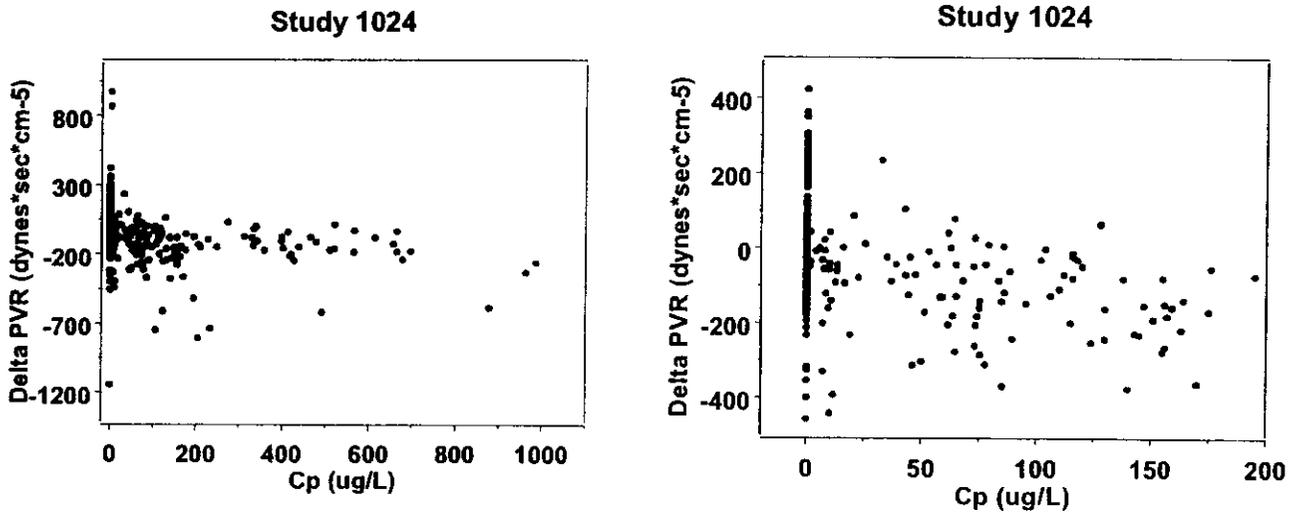
Bin (# patients)	Mean Cp (95 % CI), ug/L	Mean delta PVR (95 % CI), dynes*sec*cm ⁻⁵
1 (276)	0	-2.4 (-17.7, 13.0)
2 (39)	13.3 (9.8, 16.7)	-20.4 (-104.8, 63.9)
3 (39)	65.5 (61.0, 70.1)	-117.5 (-155.0, -80.0)
4 (39)	138.6 (129.2, 147.9)	-200.8 (-262.7, -138.8)
5 (38)	473.0 (408.5, 537.4)	-166.0 (-219.9, -112.1)

Figure 1. PVR mean change from baseline in study 1024 by binned mean concentration (linear scale)



Examining all of the concentration data together also suggests that there is a concentration - delta PVR relationship that follows an E_{max} model and is not flat (See figure 2).

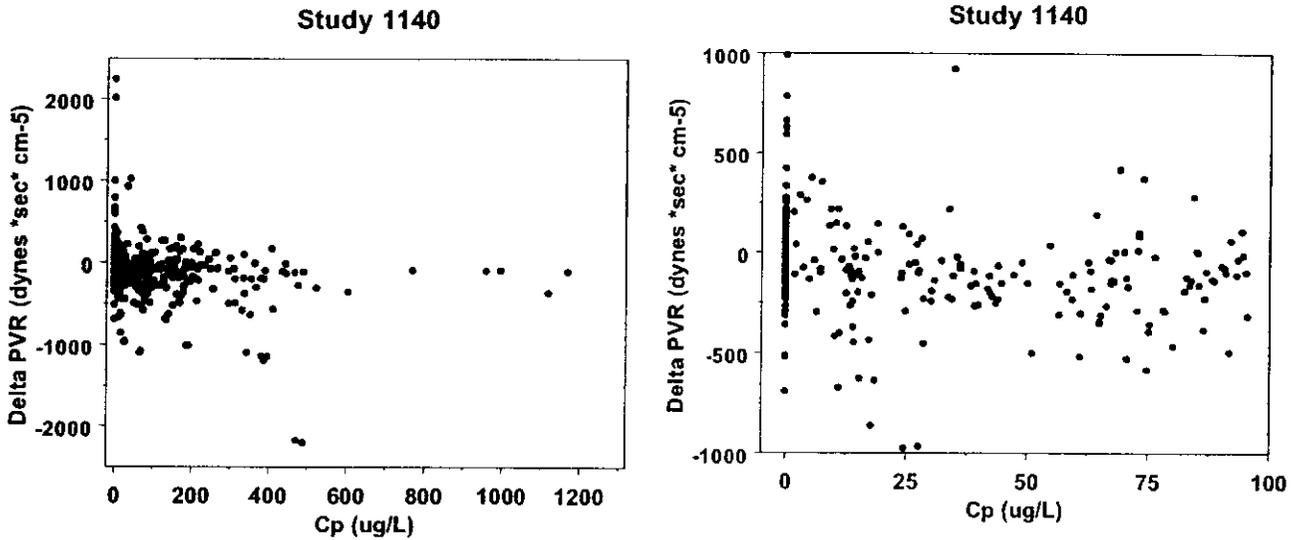
Figure 2. PVR mean change from baseline in study 1024 by concentration (x-axis blown up on right)



2.2.2.2 Study 1140

Figure 3 shows that there is a concentration – change in PVR relationship in the pivotal trial. Again, the effect seems to reach a plateau around 100 ug/L.

Figure 3. PVR change from baseline in study 1140 by concentration (X- and Y-axis blown up on right)



2.2.3 Dose PVR data

2.2.3.1 Study 1140

Table 3 and Figure 4 show that there is a dose PVR relationship. Mean delta PVR data do not suggest that the plateau has been reached.

Figure 4. PVR change from baseline in study 1140 by dose (Y-axis blown up on right)

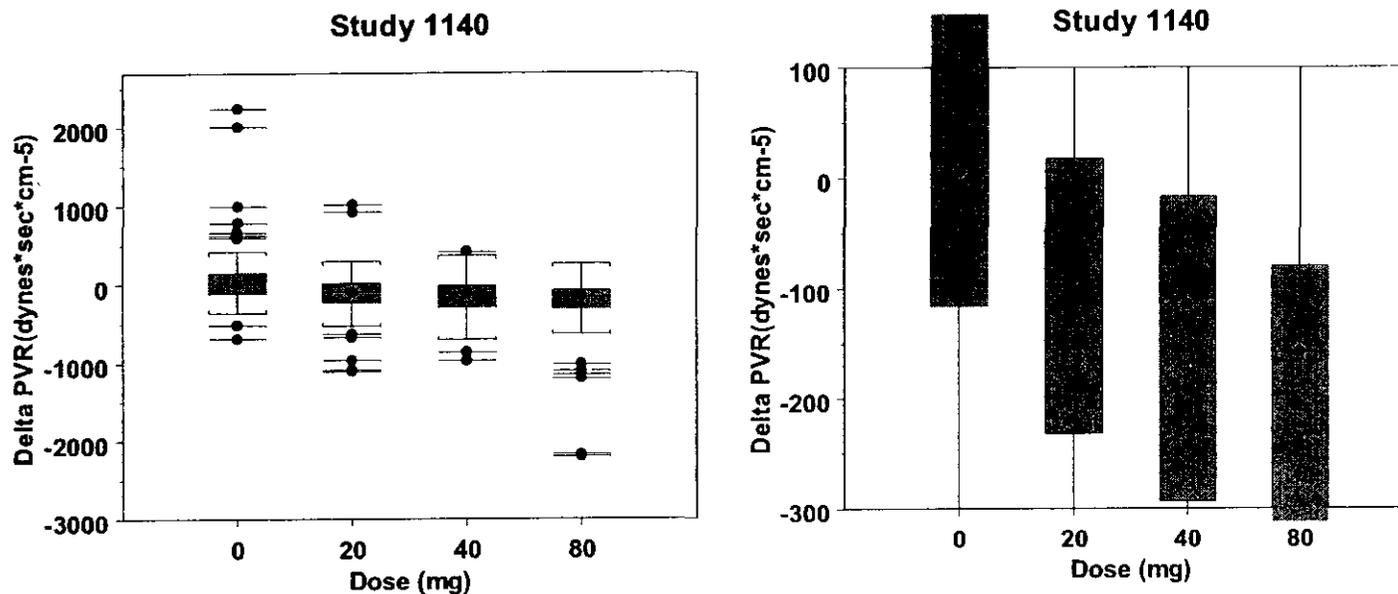


Table 3. PVR change from baseline at week 12 in study 1140 by dose

	0 mg	20 mg	40 mg	80 mg
Sponsor (LOCF)	49	-122	-143	-261
Reviewer PVR	60 ± 398	-115 ± 310	-148 ± 258	-262 ± 398
Reviewer Cp (ug/L)	0	55 ± 62	102 ± 80	251 ± 226
Sponsor PVRI (LOCF)	113	-220	-241	-456

PVR in dynes*sec*cm⁻⁵

PVRI in dynes*sec*cm⁻⁵/m²

Mean ± SD

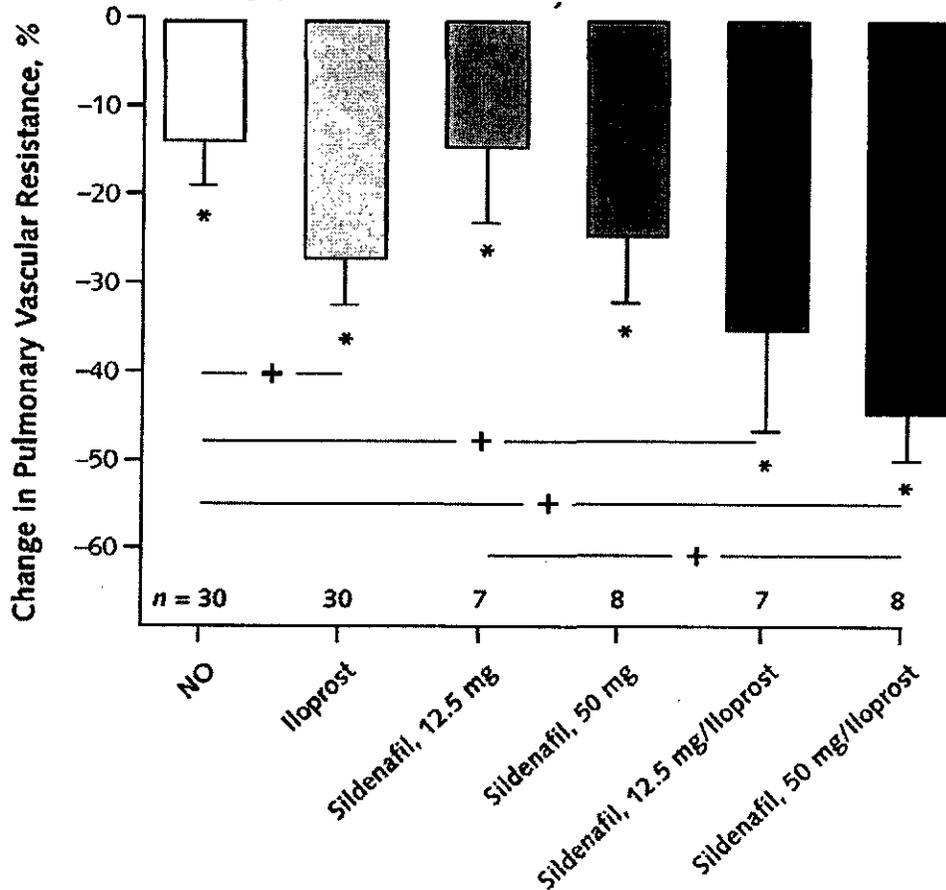
There is a slight discrepancy between the reviewer's calculated delta and the sponsor's because the sponsor used last observation carried forward. The mean concentrations in Table 3 probably resemble a concentration between the mean and the trough for each dose since concentrations were collected at various time points, but more times closer to trough compose the mean concentration.

2.2.3.2 Literature data

A review of the literature found an article that supports a dose response relationship between sildenafil and change in PVR.

Figure 6 is from a study conducted by Ghofrani et al in 30 patients with severe pulmonary HTN (16 with PAH, 1 with aplasia of the left pulmonary artery and 13 with chronic thromboembolic pulmonary HTN). Approximately 7-8 patients were randomized to receive each sildenafil treatment. For the sildenafil only arm, blood and hemodynamic sampling occurred at 15, 30, 60, 90 and 120 minutes. Change in PVR decreased by 15% and 24%, for sildenafil 12.5 mg and 50 mg, respectively (statistically significant). The vasodilatory response was evident at 15 minutes and reached a plateau after 45 to 60 minutes.

Figure 5. PVR Change from baseline



2.2.4 6MWD

The clinical pharmacology review already highlights that there is no concentration - 6MWD relationship. Although no difference in dose response was seen in the ITT population, there was some evidence of response in patients that have a PAH secondary to connective tissue disorder.

Table 4. Week 12 treatment compared to placebo, LOCF

	20 mg	40 mg	80 mg
PPH			
pbo n=39	n=43	n=42	n=46
Mean difference (SE)	40 (13)	48 (14)	62 (13)
99 % CI	(6, 74)	(11, 83)	(27, 96)
CTD			
pbo=21	n=20	n=18	n=19
Mean difference (SE)	55 (16)	49 (16)	28 (20)
99 % CI	(15, 95)	(7, 88)	(-19, 82)

CTD = PAH secondary to connective tissue disease

PPH = primary pulmonary hypertension

2.2.5 Bleeding events

The adverse effect of concern, bleeding events (primarily manifested as epistaxis), was not dose dependent (Table 3). Since 74% of the patients in the pivotal study 1140 were taking vitamin K antagonists, the data were further analyzed by concomitant warfarin use since both S-warfarin and sildenafil are metabolized by CYP2C9. The percent of subjects taking warfarin with bleeding events was 8, 29, 26 and 7 % for placebo, sildenafil 20, 40 and 80 mg TID, respectively. Thus, analysis by dose did not show signs of saturation or dose related bleeding events, although the actual number of events was small. Additionally, the clinical pharmacology review of the drug interaction study with acenocoumarol and phenprocoumon, derivatives of coumadin that are also metabolized by CYP2C9, showed no increase in bleeding time with concomitant sildenafil. On another note, the IC50 for PDE5 inhibition is approximately 47 ug/L while the mean maximum concentration from 20 mg is approximately 100 ug/L. Thus, if bleeding events are related to PDE inhibition, then all doses produced concentrations above the IC50.

**APPEARS THIS WAY
ON ORIGINAL**

Table 5. Bleeding events in study 1140

Adverse event	Placebo N=70	20 mg n=69	40 mg n=67	80 mg n=71	Total N=207
Total patients with bleeding events	11 (16%)	14 (20 %)	12 (18 %)	8 (11 %)	34 (16%)
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 %)
Subjects on warfarin					
	N=37	N=34	N=27	N=28	N=89
Total patients with bleeding events	3 (8.1 %)	10 (29.4 %)	7 (25.9 %)	2 (7.1 %)	19 (21.3 %)
Epistaxis	1 (2.7%)	4 (11.8 %)	3(11.1%)	1 (3.6 %)	8 (9.0 %)
Retinal hemorrhage	0	1 (2.9 %)	2 (7.4 %)	1 (3.6 %)	4 (4.5 %)
Subjects not on warfarin					
	N=19	N=19	N=21	N=19	N=59
Total patients with bleeding events	3 (15.8 %)	3 (15.8 %)	3 (14.3 %)	3 (15.8 %)	9 (15.3 %)
Epistaxis	0	2 (10.5 %)	1 (4.8 %)	2 (10.5 %)	5 (8.5 %)
Retinal hemorrhage	0	0	0	0	0

3. Can sildenafil be administered less frequently than TID?

3.1 Summary

It is most likely that sildenafil cannot be administered less frequently than TID for the treatment of PAH. From the NDA, the EC50 from study 1024 is around 17 ug/L, while the mean minimum concentration from the 20 mg TID dose is around 30 ug/L. Outside literature on PVR time course suggests that administering the drug less frequent than TID is not an option. The literature suggests that the effect on PVR starts to decrease after two hours. Although metabolite was not measured in these studies, the hemodynamic decrease in PVR effect after two hours suggest that any hemodynamic contribution to duration of effect past 8 hours from an active metabolite is unlikely.

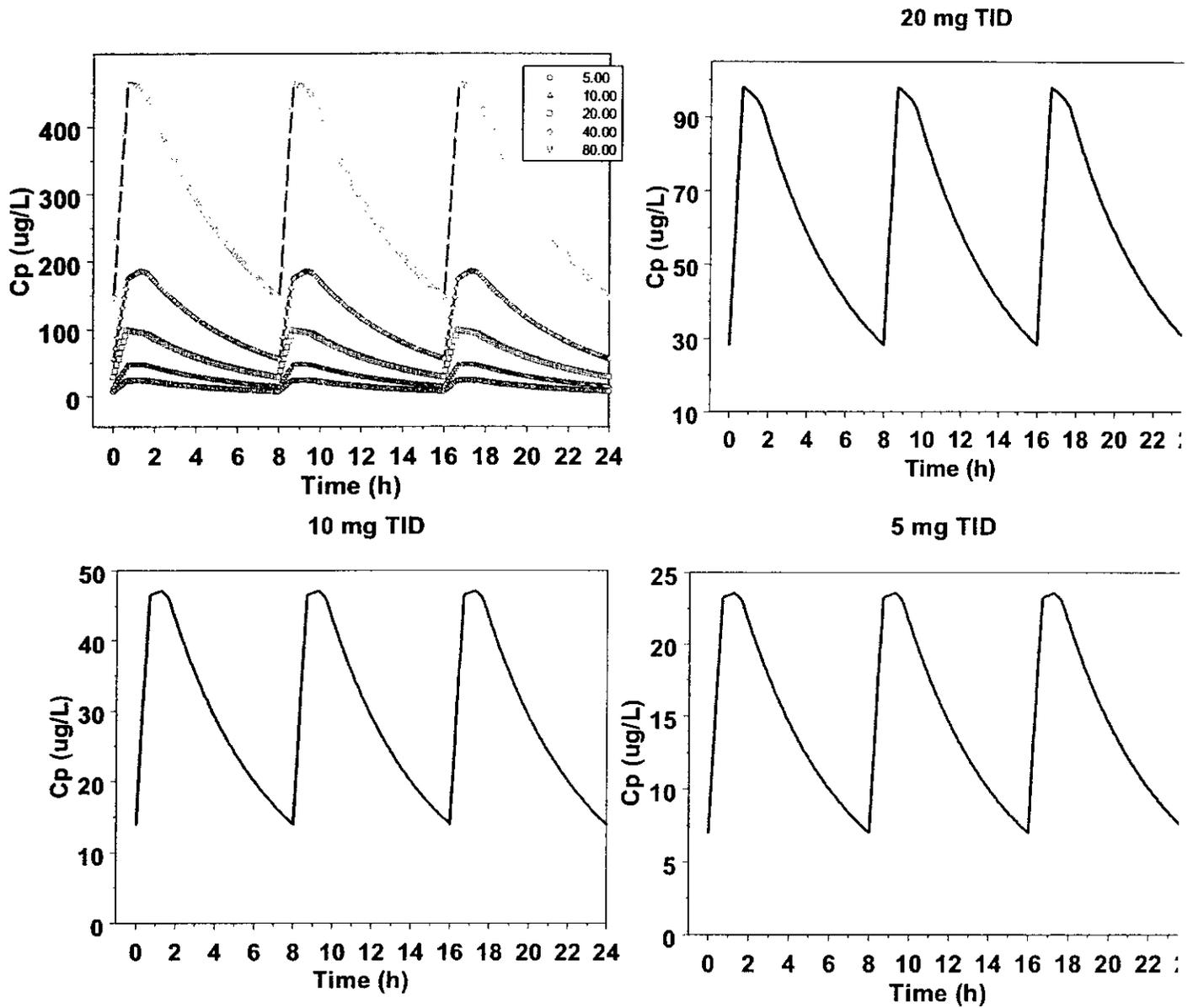
3.1.1 Data analysis

3.1.1.1. Concentration time data from study 1140

Data from study 1140 were used to simulate steady state concentration time data for various TID doses of sildenafil (Figure 6).

**APPEARS THIS WAY
ON ORIGINAL**

Figure 6. Steady state concentration time data for 5, 10, 20, 40, and 80 mg TID and 5, 10 and 20 mg TID



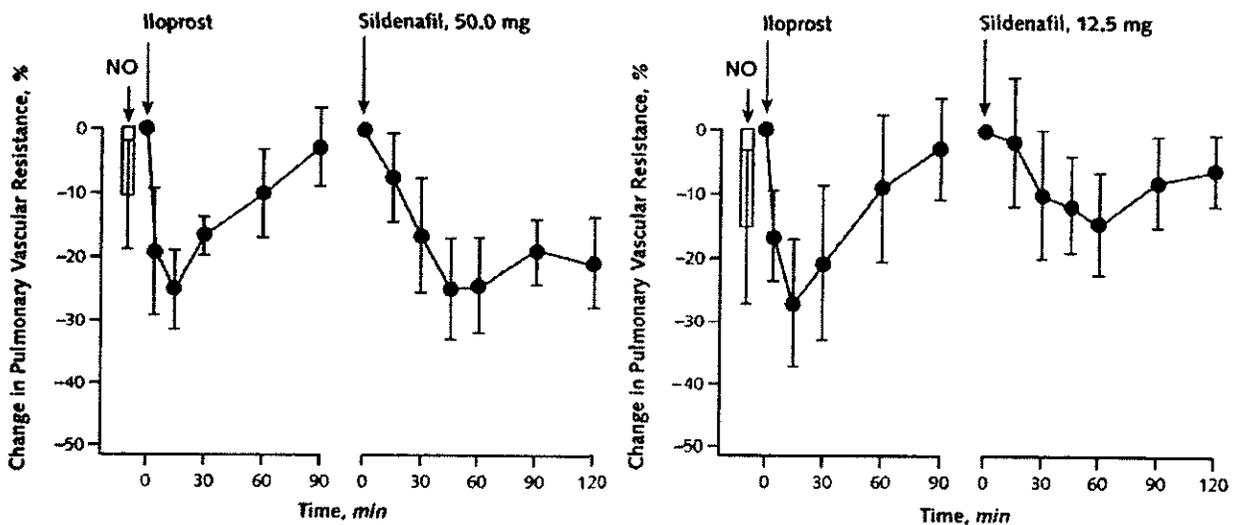
Neither study provides enough information on the time course of concentration effect. Unfortunately, the only study conducted by the sponsor that provides insight on the concentration effect on PVR is study 1024. Study 1140 obtained most concentration and PD measurements around trough. Thus, the better of the two models, data wise, would be that for study 1024. If one believes the population PK/PD model developed by the sponsor for study 1024, then the EC50 is about 3 ug/L. This suggests, based on simulations that a lower dose can

be given three times a day. However, because of the inherent problems with the modeling and the big discrepancies between the two models (EC50 of 16 ug/L with study 1140), which have not been satisfactorily explained, it is difficult to believe that 3 ug/L is the true EC50.

3.1.1.2. Time course of PVR effect data from literature

The data in Figure 8 from Ghofrani et al suggests that the effects on PVR are still sustained after 120 minutes, however the peak effect was reached around 60 minutes. The change in PVR effect starts to lessen after 120 minutes with the 12.5 mg dose. These data are limited by the short duration of data collection, but they suggest that effect on PVR would be diminished by 8 hours, especially for the 12.5 mg dose.

Figure 7. Time course of PVR change from 12.5 and 50 mg of sildenafil



This is the only data on the time course of effect on PVR. Based on this limited data, administering sildenafil less frequently than TID is unlikely. Since duration of effect seems to decrease, it is also unlikely that the active metabolite is contributing to the effect past eight hours.

4. Other review issues

4.1 Summary

There is a discrepancy between the two population PK/PD models developed by the sponsor (an EC50 of 3 ug/L and 16 ug/L). The explanations for these discrepancies are unsatisfactory (different patient populations and outliers included in analysis). However, the reviewer believes that the study design in study 1024 allows for better model development and thus better estimates than the design of study 1140. On another note, the sponsor modeled drug effect in

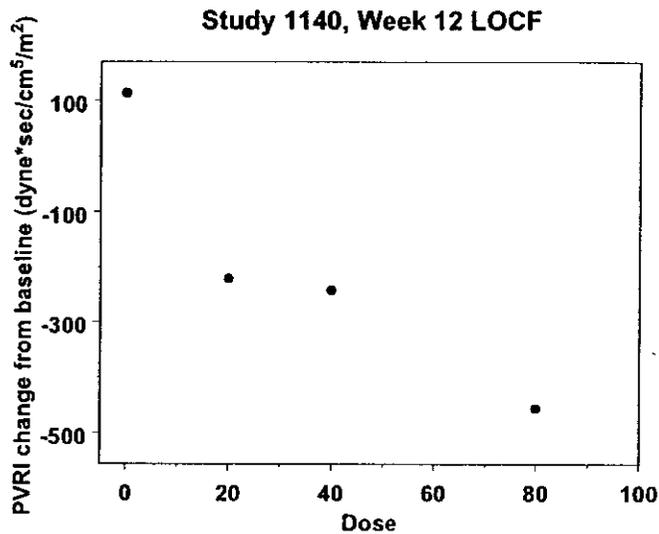
both studies without accounting for the placebo effect. However, when we correctly accounted for the drug effect by including the placebo effect, we did not find a large difference in model parameters.

4.2. Sponsor's Population PK/PD Model

There is a large discrepancy between the EC50 and Emax estimates for the sponsor's two population PK/PD (PVR or PVRI) models. In study 1024 sildenafil EC50 for PVR was 16 ug/L (SE 43%). In study 1140 sildenafil EC50 for PVRI was approximately 3 ug/L.

The sponsor was asked to explain the potential reasons for the discrepancy between the low EC50 (2.92 ug/L) values derived using the concentration-PVRI relationship (model 217) and the non-saturating dose response.

Figure 8. PVRI mean change from baseline by dose



Data obtained from page 62 of study 1140 clinical report.

The sponsor cites that the low EC50 in study 1140 could be due to a few outlier patients and the different EC50s could be due to the differences in patient populations between the two studies. This is difficult to believe, however the sponsor will redo the analysis with the outlier patients removed and submit the results to the Agency.

4.3 Population PK/PD model did not account for placebo effect

Additionally, careful review of the sponsor's model shows that active treatment and placebo effect were modeled separately. In other words, the placebo effect was not accounted for when modeling the effect of active treatment.

The sponsor confirmed our supposition during a teleconference call on May 13, 2005. Despite the inherent problem with the modeling method, when we modeled the data by accounting for a placebo effect, there was not much difference in the final model parameter estimates.

4.3.1. Details

The pharmacodynamic models used to describe the concentration-PVRI relationship for the studies 1024 and 1140 are models 2133 and 217, respectively.

- a. The equations for PLA and ACT do not account for placebo effect when estimating the drug effect. For example, consider the run217 model (study 1140):

$$\begin{aligned} \text{BASE} &= \text{BLA} * \text{ISA} + 0.01 \\ \text{EMAX} &= \text{EMA} * \text{ISA} + 0.01 \\ \text{P50} &= \text{EC50} * \text{ISA} + 0.01 \\ \text{INT} &= \text{BLP} * \text{ISP} + 0.01 \\ \text{SLOP} &= \text{SL} * \text{ISP} + 0.01 \end{aligned}$$

$$\text{ACT} = \text{BASE} * (1 - \text{EMAX} * \text{CONC} / (\text{P50} + \text{CONC})) \quad (1)$$

$$\text{PLA} = \text{INT} + (\text{SLOP} * \text{TIME}) \quad (2)$$

$$\text{F} = \text{PLA} + \text{ACT} \quad (3)$$

Consider a patient receiving the active drug. The equations 1, 2 and 3 can be represented as:

$$\begin{aligned} \text{ACT} &= \text{BLA} * (1 - \text{EMA} * \text{CONC} / (\text{EC50} + \text{CONC})) \\ \text{PLA} &= 0 \text{ (as it is } 0 + (0 * \text{TIME})) \\ \text{F} &= 0 + \text{ACT} \end{aligned}$$

Hence, our interpretation is that the model does not account for placebo effect when estimating the drug effect. A similar derivation for the model2133 (study 1024) showed that the placebo effect, in fact, uses the same parameters as the drug effect, as shown below:

$$\begin{aligned} \text{BASE} &= \text{BLP} * \text{ISP} + \text{BLA} * \text{ISA} \\ \text{EMAX} &= \text{EMP} * \text{ISP} + \text{EMA} * \text{ISA} \\ \text{P50} &= \text{TE50} * \text{ISP} + \text{EC50} * \text{ISA} \end{aligned}$$

$$\text{PLA} = \text{BASE} * (1 - \text{EMAX} * \text{TIME} / (\text{P50} + \text{TIME})) \quad (4)$$

$$\text{ACT} = \text{BASE} * (1 - \text{EMAX} * \text{CONC} / (\text{P50} + \text{CONC})) \quad (5)$$

$$\text{F} = \text{PLA} + \text{ACT} \quad (6)$$

Consider a patient receiving the active drug. The equations 4, 5 and 6 can be represented as:

$$\text{PLA} = \text{BLA} * (1 - \text{EMA} * \text{TIME} / (\text{EC50} + \text{TIME}))$$

$$ACT = BLA * (1 - EMA * CONC) / (EC50 + TIME)$$

The parameters EMA and EC50 are used for both the placebo and drug effects.

Similarly, the parameters for PLA are different for patients who receive placebo (i.e., they will be EMP and TE50).

Reference

Ghofrani HA et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; 136: 515-522.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Jogarao Gobburu
6/1/05 07:01:43 PM
BIOPHARMACEUTICS

Patrick Marroum
6/2/05 10:43:15 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	21-845	N000
Submission Dates:	12/2, 12/28, 2004, 2/16, 4/7, 4/8, 4/11 2005	
Brand Name:	Revatio	
Generic Name:	Sildenafil citrate	
Dosage Form & Strength:	Tablets 20, — mg	
Indication:	Pulmonary Arterial Hypertension	
Category:	6P	
Applicant:	Pfizer Inc.	
Submission:	Original NDA	
Divisions:	DPEI and Cardio-Renal Drug Products, HFD-110	
Primary Reviewers:	Elena V. Mishina, Ph.D.	
Team Leader:	Patrick Marroum, Ph.D.	

Table of Contents

1	EXECUTIVE SUMMARY	7
1.1	RECOMMENDATIONS:	7
1.2	COMMENTS:	7
1.3	SUMMARY OF OCPB FINDINGS	9
1.3.1	Background.....	9
1.3.2	Current Submission.....	9
2	QUESTION BASED REVIEW	13
2.1	GENERAL ATTRIBUTES.....	13
2.2	GENERAL CLINICAL PHARMACOLOGY	14
2.3	INTRINSIC FACTORS	25
2.4	EXTRINSIC FACTORS	27
2.5	GENERAL BIOPHARMACEUTICS	29
2.6	ANALYTICAL SECTION.....	29
2.7	REFERENCES	30
3	DETAILED LABELING RECOMMENDATIONS	31
4	APPENDICES	32
4.1	OCPB PROPOSED LABEL.....	32
4.2	SPONSOR'S PROPOSED LABEL	33
4.3	INDIVIDUAL STUDY REVIEWS.....	44
4.3.1	<i>A DOUBLE BLIND, TWO WAY CROSSOVER, PLACEBO CONTROLLED STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY AND TOLERATION OF SILDENAFIL IN HEALTHY YOUNG WOMEN AND TO INVESTIGATE THE EFFECT OF SILDENAFIL ON THE PHARMACOKINETICS OF ORAL CONTRACEPTIVE STEROIDS (A148 -236)</i>	44
4.3.2	<i>THE EFFECT OF SILDENAFIL ON THE PHARMACOKINETICS OF ATORVASTATIN IN HEALTHY MALE SUBJECTS (258-002):</i>	51
4.3.3	<i>PHASE I OPEN STUDY TO ASSESS THE POTENTIAL INTERACTION BETWEEN ORALLY ADMINISTERED SILDENAFIL (VIAGRA) AND PHENPROCOUMON IN HEALTHY MALE VOLUNTEERS" (1053):</i>	56
4.3.4	<i>PHASE I OPEN STUDY TO ASSESS THE POTENTIAL INTERACTION BETWEEN ORALLY ADMINISTERED SILDENAFIL (VIAGRA) AND ACENOCOUMAROL IN HEALTHY MALE VOLUNTEERS" (1054):</i>	61
4.3.5	<i>A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO INVESTIGATE THE MUTUAL PHARMACOKINETIC INTERACTIONS BETWEEN BOSENTAN AND SILDENAFIL. (A148 -1149)</i>	66
4.3.6	<i>EFFICACY AND TOLERATION OF INTRAVENOUS SILDENAFIL IN SUBJECTS WITH PULMONARY HYPERTENSION. A Population Pharmacodynamic/Pharmacokinetic Analysis of Sildenafil Pulmonary & Systemic Hemodynamic Data (A148 1024)</i>	77
4.3.7	<i>A MULTINATIONAL, MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF 20, 40, AND 80MG TID SILDENAFIL IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION IN SUBJECTS AGED 18 YEARS AND OVER. Population Pharmacokinetic/Pharmacodynamic Report for Sildenafil Phase 3 Data (Protocol A148 1140) in Patients with Pulmonary Arterial Hypertension (PAH)</i>	100
4.4	BIOPHARMACEUTICS	119
4.5	FILING AND REVIEW FORM	121

List of Tables

Table 1: Listing of Clinical Pharmacology PAH and Post-Marketing Studies	9
Table 2: PK/PD parameters reported by the sponsor.....	22
Table 3: Mean sildenafil pharmacokinetic parameters in healthy subjects and PAH patients	23
Table 4: Ratio between metabolite and parent drug based on raw data.....	24
Table 5: Assay Characteristics for Sildenafil and UK-103,320.....	45
Table 6: Assay Characteristics for Ethinylloestradiol and Levonorgestrel.....	45
Table 7: Demographic Characteristics.....	46
Table 8: Sildenafil Pharmacokinetic Parameters	46
Table 9: Ethinylloestradiol pharmacokinetic parameters.....	48
Table 10: Levonorgestrel Pharmacokinetic parameters.....	49
Table 11: Sildenafil PK parameters by treatment group.....	50
Table 12: Assay Characteristics for Sildenafil and UK-103,320.....	52
Table 13: Assay Characteristics for Atorvastatin	52
Table 14: Demographic Characteristics.....	53
Table 15: Atorvastatin Pharmacokinetics	54
Table 16: Sildenafil Pharmacokinetics	55
Table 17: Prothrombin time assay characteristics	57
Table 18: Pharmacodynamic parameters (arithmetic means \pm s. d.)	59
Table 19: Prothrombin time assay characteristics	62
Table 20: Pharmacodynamic parameters (arithmetic means \pm s. d.)	64
Table 21: Study Medications	67
Table 22: Dosing & Treatment Schedule.....	67
Table 23: Assay Characteristics for Sildenafil and UK-103,320.....	68
Table 24: Assay Characteristics for Bosentan and its Metabolites.....	68
Table 25: Assay Characteristics for Cortisol and 6- β -hydroxycortisol	68
Table 26: Demographic Characteristics.....	69
Table 27: Pharmacokinetic parameters of sildenafil.....	70
Table 28: Comparison of Sildenafil Parameters	70
Table 29: Bosentan Pharmacokinetic Parameters.....	73
Table 30: Comparison of Bosentan Parameters.....	74
Table 31: Mean Changes in Vital Signs on Day 16.....	75
Table 32: Test Drugs.....	78
Table 33: Assay Characteristics for Sildenafil and UK-103,320.....	79
Table 34: Parameters of the Final Model.....	82
Table 35: NONMEM parameters estimates for PVR	85
Table 36: NONMEM parameter estimates for systolic PAP	87
Table 37: NONMEM parameter estimates for diastolic pulmonary artery pressure	89
Table 38: NONMEM parameter estimates for systolic blood pressure	91
Table 39: NONMEM estimated parameters for DBP.....	94
Table 40: NONMEM parameter estimation for MAP	96
Table 41: PK parameters of sildenafil	97
Table 42: Sponsor's results	98
Table 43: Results from final sponsor's Runs.....	99
Table 44: Study flow chart.....	101
Table 45: Study medication	102

Table 46: Assay Characteristics for Sildenafil and UK-103,320..... 102
 Table 47: Continuous demographic data 103
 Table 48: Categorical demographic data 103
 Table 49: Laboratory parameters 104
 Table 50: Pharmacokinetic Parameters..... 106
 Table 51: 6MWD t-Test assuming unequal variances..... 108
 Table 52: PVRi Versus Sildenafil..... 110
 Table 53: PVRi t-Test two-sample assuming unequal variances..... 111
 Table 54: Sildenafil Pharmacodynamic Parameters: 6-MWD Versus PVRi..... 114
 Table 55: Differences between tablet formulations used for PAH and MED indications..... 119

List of Figures

Figure 1: 6 Minute walk distance vs. maximal sildenafil plasma concentrations	15
Figure 2: Mean 6MWD vs. sildenafil dose.....	16
Figure 3: PVRi vs. sildenafil plasma concentrations	16
Figure 4: Effect of coadministration of calcium channel blockers on PVRi	17
Figure 5: Effect of covariates on 6MWD baseline	17
Figure 6: Mean and SD PVRi vs. sildenafil dose on Week 12.....	18
Figure 7: 6-MWD vs. PVRi.....	18
Figure 8: 6MWD vs PVRi by dose group (GRP = 0, 20, 40 and 80 mg of sildenafil TID). Baseline, OCC1, data on Week 12, OCC4. The lines are the results of linear regression. ..	19
Figure 9: The relationship between sildenafil dose, PVRi and 6MWD	20
Figure 10: Time course of 6MWD, baseline visit (left) and visit week 12 (right)	20
Figure 11: Time course of PVRi, baseline visit (left) and visit week 12 (right).....	21
Figure 12: Important covariates on CL (CYP3A4 substrates and beta-blockers)	27
Figure 13: Mean sildenafil plasma concentrations on Day 1 and Day 11.	47
Figure 14: Mean sildenafil metabolite plasma concentrations on Day 1 and Day 11.	47
Figure 15: Mean ethinylestradiol plasma concentrations vs. time.....	48
Figure 16: Mean levonorgestrel plasma concentration vs. time	49
Figure 17: Mean atorvastatin plasma concentrations vs. time after the 10 mg dose of atorvastatin administered with placebo or with sildenafil.	54
Figure 18: Mean sildenafil plasma concentrations.	54
Figure 19: Mean sildenafil metabolite plasma concentrations vs. time.....	55
Figure 20: Mean INR values (\pm s. d.) obtained for the whole study period (Days 1 -16).....	58
Figure 21: Mean INR values (\pm s. d.) obtained for the 48-hour periods (two 24-hour dosage intervals each) of the test situation (Days 15 -16) and the reference situation (Days 13 -14)	58
Figure 22: Mean INR values (\pm s. d.) obtained for the whole study period (Days 1 -16)	63
Figure 23: Mean INR values (\pm s. d.) obtained for the 48-hour periods (two 24-hour dosage intervals each) of the test situation (Days 15 -16) and the reference situation (Days 13 -14)	63
Figure 24: Mean Plasma Sildenafil Concentrations, Day 6, Group A vs. Group C.	71
Figure 25: Mean Plasma Sildenafil Concentrations, Day 16.....	71
Figure 26: Mean Plasma Sildenafil Concentrations, Day 6 vs. Day 16, Group C.....	71
Figure 27: Mean Trough Plasma Sildenafil Concentrations, Group A vs. Group C.	72
Figure 28: Mean Plasma Concentrations of UK-103,320, Group A vs. Group C, Day 16.	72
Figure 29: Mean Plasma Concentrations of UK-103,320, Day 6 vs. Day 16, Group A.....	72
Figure 30: Mean Plasma Concentrations of UK-103,320, Day 6 vs. Day 16, Group C.....	73
Figure 31: Mean Plasma Bosentan Concentrations, Group B vs. Group C, Day 16.	74
Figure 32: Mean pulmonary artery pressure vs. time (placebo) or sildenafil concentration	83
Figure 33: Predicted vs. observed mean PAP of sildenafil (left and placebo (right)).....	83
Figure 34: Mean and SE of Emax values for PAP.....	84
Figure 35: PVR vs. time for placebo (left) and vs. sildenafil concentrations (right).....	85
Figure 36: Predicted vs. observed PVR for sildenafil (left and placebo (right)	86
Figure 37: PVR estimations vs. subgroup	86
Figure 38: Systolic PAP vs. time for placebo (left) and vs. sildenafil concentration (right).....	87

Figure 39: Predicted vs. observed systolic PAP for sildenafil (left) and placebo (right)	88
Figure 40: Slope/Emax Systolic Pulmonary Artery Pressure vs. Group	88
Figure 41: Diastolic pulmonary artery pressure versus time after placebo (left) or sildenafil concentration (right).....	89
Figure 42: Predicted vs. observed diastolic PAP for sildenafil (left and placebo (right)	90
Figure 43: Emax for diastolic PAP vs. group of treatment.....	90
Figure 44: Systolic BP vs. time for placebo (left) and vs. sildenafil concentration(right)	91
Figure 45: Predicted vs. observed systolic SBP for sildenafil (left and placebo (right).....	92
Figure 46: Slope/Emax systolic blood pressure vs. treatment group.....	92
Figure 47: EC50 and 90% CI for systolic PAP and systolic BP.....	93
Figure 48: DBP vs. time for placebo (left) and vs. sildenafil concentration (right)	94
Figure 49: Predicted vs. Observed DBP after active treatment (left) and placebo (right).....	95
Figure 50: Emax and 90% CIs vs. the different group of patients.....	95
Figure 51: MAP vs. time for placebo (left) and vs. sildenafil concentration(right)	96
Figure 52: Predicted vs. observed diastolic MAP for sildenafil (left and placebo (right).....	97
Figure 53: Sildenafil plasma concentrations vs. time	98
Figure 54: Predicted vs. observed sildenafil plasma concentrations	98
Figure 55: Important covariates on CL (CYP3A4 substrates and beta-blockers)	105
Figure 56: Predicted vs. Observed sildenafil plasma concentrations	106
Figure 57: 6 Minute walk time vs. maximal sildenafil plasma concentrations	107
Figure 58: Mean 6MWD vs. sildenafil dose.....	108
Figure 59: PVRi vs. sildenafil plasma concentrations.....	109
Figure 60: Predicted vs. observed PVRi.....	109
Figure 61: Predicted and observed PVRi vs. sildenafil plasma concentrations.....	111
Figure 62: Mean and SD PVRi vs. sildenafil dose on Week 12.....	111
Figure 63: 6-MWD Versus PVRi	112
Figure 64: 6MWD vs PVRi by dose group (GRP = 0, 20, 40 and 80 mg of sildenafil TID). Baseline, OCC1, data on Week 12, OCC4.	113
Figure 65: Population predicted vs. observed 6MWD.....	115
Figure 66: Effect of covariates.....	115
Figure 67: The relationship between sildenafil dose, PVRi and 6MWD	116
Figure 68: Comparison of the Dissolution Profiles of 100 mg Viagra ® Tablets and 20 mg Sildenafil Citrate Tablets in 0.01 M Hydrochloric Acid, Baskets Rotating at 100 rpm	120
Figure 69: Comparison of the Dissolution Profiles of 100 mg Viagra Tablets — in 0.01 M Hydrochloric Acid, Baskets Rotating at 100 rpm	120

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-845 and finds the clinical pharmacology and biopharmaceutics sections acceptable.

A 20 mg tablet has been developed for the PAH indication. These tablets are manufactured from — which is qualitatively and quantitatively similar to the commercial Viagra® formulation. The minor differences in the tablet presentations for each indication are a change in tablet shape and the color of the film coat which are Level I changes. The in vitro dissolution method and specifications for sildenafil citrate tablets, 20 mg, are identical to the same of VIAGRA tablets and are shown below.

Condition	Recommendation
Dissolution Medium	0.01N HCL
Basket Speed USP Apparatus I	100 rpm
Volume	900 mL
Specifications	— in 15 minutes

1.2 COMMENTS:

Issue not addressed by the sponsor:

1. The pharmacometrics review will address whether there is an exposure-response relationship and whether the 20 mg is the most adequate dose to be used in PAH patients.

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

Date _____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on April 29, 2005

Attendees: Drs. Mehta, Lasor, Sahajwala, Stockbridge, Marroum, Mishina, Gordon, Marciniak, Parekh, Men.

cc list: NDA 21-742, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

**APPEARS THIS WAY
ON ORIGINAL**

1.3 Summary of OCBP Findings

1.3.1 Background

Pfizer Inc. is seeking approval of sildenafil citrate immediate release tablets 20,mg for the treatment of pulmonary arterial hypertension (PAH).

Sildenafil is a selective inhibitor of phosphodiesterase 5 (PDE5), and acts on the nitric oxide /cyclic guanosine monophosphate pathway.

The pathogenesis of PAH involves vasoconstriction, vascular remodeling, and thrombosis in situ. There is a progressive increase in pulmonary vascular resistance and pressure, right ventricular hypertrophy, and ultimately right ventricular failure. In patients with hypertrophied pulmonary arteries and pulmonary arterial hypertension, inhibition of PDE5 located in the smooth muscle of the pulmonary vasculature could lead to selective vasodilation of the pulmonary vascular bed.

1.3.2 Current Submission

Item 6 of NDA 21-845 contains 15 post-marketing study reports and 3 new PAH studies including population PK and PK-PD analyses and sildenafil-bosentan interaction study. This review focused on studies involving drug-drug interaction studies (5 total: sildenafil with oral contraceptives, atorvastatin, phenprocoumon, acenocoumarol and bosentan), a population PK and PK/PD studies in PAH patients (one pivotal study and one hemodynamics study). The remaining submitted studies were not reviewed because they have been reviewed over the post-marketing period and their results are already included in the Package Insert.

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

Study Number (148-)	PAH Submission
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

Pharmacokinetics

Healthy Subjects

The sponsor referenced the original NDA 20-845, VIAGRA (sildenafil citrate) for MED patients regarding the pharmacokinetics of sildenafil in healthy subjects. In the original NDA, in addition to the traditional studies, a population PK approach was used to describe the pharmacokinetics of sildenafil and its active metabolite (1).

PAH Patients

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, the increase of the average steady state concentrations in patients with pulmonary arterial hypertension compared to healthy volunteers was about 30%. The trough levels of sildenafil in pulmonary arterial hypertension patients were twice higher compared to healthy volunteers at all doses, both findings indicating a lower clearance and/or a higher oral bioavailability of sildenafil in PAH patients.

The pharmacokinetics of sildenafil in PAH patients was described with the same structural population model as it was for the healthy subjects and MED patients. The population PK modeling confirmed the differences in the sildenafil PK between healthy volunteers and patients with PAH. However, the covariates which were significant in healthy subjects did not appear to matter in PAH patients. Concomitant administration of CYP3A4 substrates and beta-blockers had the most influence on clearance. Both drug classes reduced the apparent clearance of sildenafil by 22.3 and 37.4% respectively. The reduction of the apparent clearance due to CYP3A4 substrates and beta-blockers resulted in 43 and 66% increase of sildenafil exposure, respectively compared to patients not receiving these concomitant medications, however, these differences in kinetics do not require the dose adjustment.

Absorption and Distribution:

In healthy subjects, sildenafil is rapidly absorbed with T_{max} observed within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When sildenafil is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism

Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite (UK-103,320) results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. The ratio of metabolite to sildenafil calculated from the raw data was about 40% in healthy volunteers. Therefore, the metabolite's pharmacologic effect is about 20% that of sildenafil. In patients with pulmonary arterial hypertension, the ratio of metabolite to sildenafil plasma levels was about 72% (20 mg TID, at

steady state). The contribution of metabolite to the pharmacological effect of sildenafil would therefore increase to about 36%. The potential impact on efficacy is not known.

Excretion

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

No additional data in PAH patients was submitted.

Special populations

See the original NDA for the data in healthy subjects and MED patients. No additional data in PAH patients was submitted.

PK/PD drug-drug interaction information

In addition to the previously know drug interaction studies described in the NDA 20-895, this submission included studies with the drugs which could be possibly used as comedications in PAH therapy: atorvastatin, anti-coagulants (phenprocoumon and acenocoumarol), bosentan. The interaction study of sildenafil and oral contraceptives was performed because the majority of PAH patients are females.

Bosentan is a CYP3A4 inducer and the main metabolic pathway of sildenafil occurs through CYP3A4.

Effect of bosentan on sildenafil kinetics:

In the presence of bosentan (125 mg BID), mean sildenafil C_{max} and AUC_t were 55% and 63% lower compared to placebo.

Effect of sildenafil on bosentan kinetics:

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, and sildenafil and oral contraceptives given at high therapeutic doses.

There was no difference between the treatment groups in the pharmacodynamic interaction studies with anti-coagulants (for both phenprocoumon and acenocoumarol), however, these drugs are not approved in the US. In the clinical study, an increased incidence of bleeding was observed when sildenafil was coadministered with warfarin. Warfarin and sildenafil share a common pathway; therefore, it is likely that warfarin may interact with sildenafil. This interaction has not been characterized. The Agency recommends to the sponsor to perform a study to rule out any pharmacokinetic and/or pharmacodynamic interaction of sildenafil with warfarin.

Exposure-Response Relationships

There was no correlation between the main clinical endpoint, 6 minutes walk distance (6MWD) 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. When the model included the covariates, the slope was estimated even more shallow, indicating that per each 1000 dyne*sec*cm-5/m²

decrease of PVRi the increase in 6MWD was only by 6 m. The estimated EC50 values of 2.92 ng/mL showed that a low dose of sildenafil was needed to lower PVRi. The lowest studied dose in this study was 20 mg TID. The sponsor reported that the coadministration of sildenafil with calcium channel blockers decreased PVRi baseline values by 23%; however, the lumping of all calcium channel blockers in one group may lead to a wrong conclusion due to a various kinetic and metabolic properties of these drugs.

When compared to placebo, each of sildenafil treatment group had an increase in 6MWD by 50, 42, and 54 m (mean values) and the difference between the placebo and the treatment groups was significant.

The sponsor's proposal to use PVRi measurement as a surrogate marker for the sildenafil efficacy is not supported by this study probably due to high variability in the data and not a wide enough dose range. Moreover, the surrogate marker is defined as a measurement which is easy to perform and which can be a good predictor of a clinical outcome. According to the population modeling results performed in this study, pulmonary vascular resistance was not strongly correlated with a clinical outcome, moreover, its can be assessed only by an invasive method.

Factors influencing the drug effect

The baseline of PVRi decreased with age. The baseline measurements were smaller for older patients. The addition of the oxygen therapy decreased baseline as well. The patients on active treatment had lower baseline PVRi values when receiving calcium channel blockers.

Dosage recommendation based on the PK/PD results:

The dose of 20 mg TID is supported by the results of the PK/PD study.

Biopharmaceutics

The proposed commercial tablet formulation for the PAH indication and the formulation used in the PAH clinical studies is directly analogous to the commercial formulation of Viagra. A 20 mg tablet has been developed for the PAH indication. These tablets are manufactured from which is qualitatively and quantitatively similar to the commercial Viagra ® formulation. The minor differences in the tablet presentations for each indication are a change in tablet shape and the color of the film coat. Since these are Level I changes and in vitro dissolution testing confirmed that the dissolution profiles were the same for the sildenafil citrate tablet for PAH and sildenafil citrate tablet for MED, the waiver for the 20 mg tablet of REVATIO can be granted to the sponsor.

Issue not addressed by the sponsor:

1. The pharmacometrics review will address whether there is an exposure-response relationship and whether the 20 mg is the most adequate dose to be used in PAH patients.

**APPEARS THIS WAY
ON ORIGINAL**

2 QUESTION BASED REVIEW

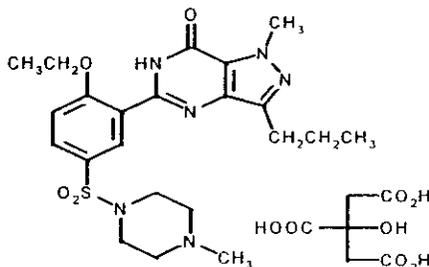
2.1 General Attributes

History of Sildenafil Development and Current Marketing Status

Sildenafil citrate is approved for the treatment of male erectile dysfunction (MED) as VIAGRA and is now being proposed for the oral treatment of pulmonary arterial hypertension (PAH) as REVATIO™.

Highlights of chemistry and physical-chemical properties of the drug substance and product

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7. REVATIO (sildenafil citrate) is formulated as white, film-coated round tablets equivalent to 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin.

What are the proposed mechanisms of action and therapeutic indication?

Sildenafil citrate is a selective inhibitor of phosphodiesterase (PDE) 5, and acts on the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway. Since PDE5 is located in the smooth muscle of the pulmonary vasculature, in patients with hypertrophied pulmonary arteries and pulmonary arterial hypertension, inhibition of PDE5 could lead to selective vasodilation of the pulmonary vascular bed.

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease. The pathogenesis of PAH involves vasoconstriction, vascular remodeling, and thrombosis in situ. There is a progressive increase in pulmonary vascular resistance and pressure, right ventricular hypertrophy, and ultimately right ventricular failure. Patients may therefore present with increasing levels of fatigue, dyspnoea, dizziness, syncope, ankle swelling, or chest pain.

In many patients, the course of PAH is one of steady deterioration and reduced life expectancy. For PAH, the US National Institutes of Health Registry showed survival rates for untreated patients of 68%, 48%, and 34% after 1, 3, and 5 years from diagnosis, respectively. There is no known cure for PAH. Treatments are aimed at relieving clinical symptoms, improving exercise tolerance, and increasing survival time. The only approved oral drug for PAH is bosentan which has potential concerns for serious liver injury, and damage to a fetus.

What are the proposed dosages and route of administration?

The recommended dose of REVATIO is 20 mg three times a day. REVATIO tablets should be taken approximately 6-8 hours apart, with or without food.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In the original NDA 20-895, VIAGRA, the sponsor conducted thirty eight clinical pharmacology studies which examined the safety, toleration, pharmacokinetics, pharmacodynamics, bioavailability, bioequivalence, effect of food and drug interactions of sildenafil, and pharmacokinetic characteristics in special patient populations. Studies were also performed to further define the effect of sildenafil on visual function. An early study assessed the effects of intravenous (IV) sildenafil and 2 studies used iv formulations to define clearance, steady state volume of distribution, absolute bioavailability and the rates and routes of metabolism. Many of these studies are resubmitted with this submission as "original MED studies". Fifteen clinical pharmacology studies were conducted post approval of sildenafil in MED and are also included in this submission.

One new drug interaction study was conducted specifically for the PAH development program. In addition, a population PK and PK/PD data analysis for the hemodynamics Phase 2 study and pivotal Phase 3 study was performed by the sponsor using the data obtained from PAH patients. Since the composition of the tablets developed for the original MED indication and new PAH indication is identical (apart from the shape and color), no new bioequivalence studies have been conducted for the formulation used in the PAH studies.

Totally, 16 drug-drug interaction studies and 2 efficacy studies and their population data analysis, which were applicable for the treatment of PAH, were included in this submission.

Was there a reasonable basis for selecting the response endpoints and were they measured properly to assess efficacy and safety in the clinical pharmacology studies?

Yes.

The primary response endpoint measured in clinical studies was the increase of 6 minute walk distance (6MWD). In the hemodynamic study, the decrease of pulmonary vascular resistance (PVR), diastolic, systolic, and mean pulmonary arterial pressure, increase of cardiac output, pulmonary capillary wedge pressure, decrease of systolic, diastolic and mean systemic arterial blood pressure and other parameters were measured.

The efficacy and safety endpoints were measured properly.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes.

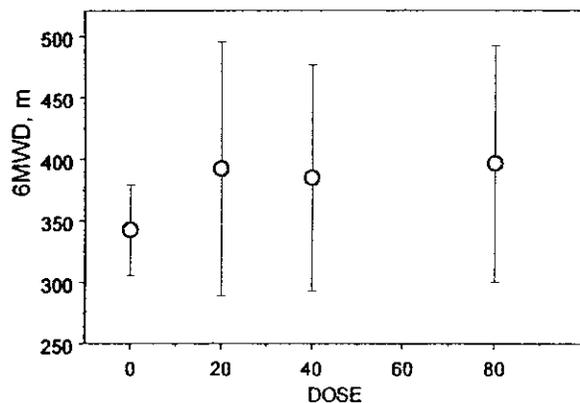


Figure 2: Mean 6MWD vs. sildenafil dose

PVRi vs. sildenafil plasma concentrations

The sildenafil plasma concentrations measured during right heart catheterization at week 12 versus PVRi are shown in Figure 3.

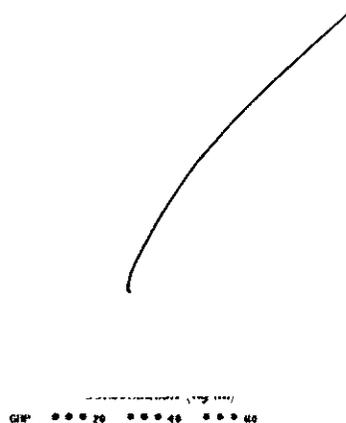


Figure 3: PVRi vs. sildenafil plasma concentrations

An additive linear model best described the placebo PVRi data. For the active treatment data, a proportional inhibitory Emax model provided the best fit.

What factors influence the drug effect?

The investigated covariates were: age, gender, race, duration of disease, etiology of pulmonary arterial hypertension and concomitant medications. The concomitant medications were lumped in the groups: beta-blockers, ACE inhibitors, CYP3A4 substrates CYP3A4 inducers, CYP3A4 inhibitors, CYP2C9 substrates, CYP2C9 inhibitors, digoxin, calcium channel blockers, and diuretics. This way of grouping the drugs might result in misleading conclusions due to a fact that the drugs belonging to same class may have different kinetic and metabolic properties. Thus the effect of the comedications with sildenafil might be different from one drug to the other. Weight related covariates were not included because PVRi is already normalized for body

surface area. The smoking status was not tested due to just a few smokers in the PAH patient population.

The baseline of PVRi decreased with age (about 130 dyne*sec*cm⁻⁵/m² per 10 years of age). Patients on active treatment had 23% lower baseline PVRi values when receiving calcium channel blockers.

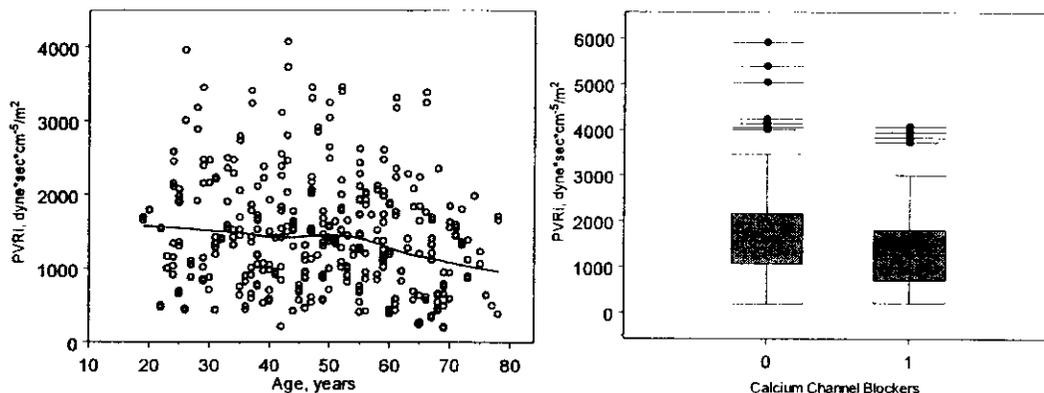


Figure 4: Effect of age and coadministration of calcium channel blockers on PVRi

The effect of covariates on the baseline 6MWD is shown below (Figure 5). The baseline measurements were smaller for older patients with decrease by 20m per 10 years of age. The addition of the oxygen therapy decreased the baseline values by 14%.

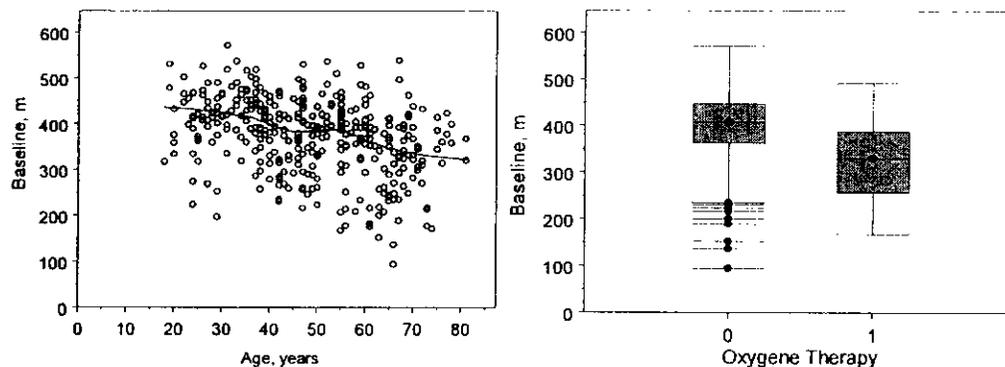


Figure 5: Effect of covariates on 6MWD baseline

What was the relationship between PVRi and sildenafil dose?

Mean and SD of PVRi vs. dose of sildenafil data are plotted below (Figure 6) using the data obtained at Week 12 of sildenafil TID dosing. On average, the decrease of PVRi in the dosing groups of 20, 40, and 80 mg of sildenafil were by 475, 619, and 778 dyne*sec*cm⁻⁵/m² in comparison with the placebo group. The difference between the placebo and treatment groups was statistically significant.

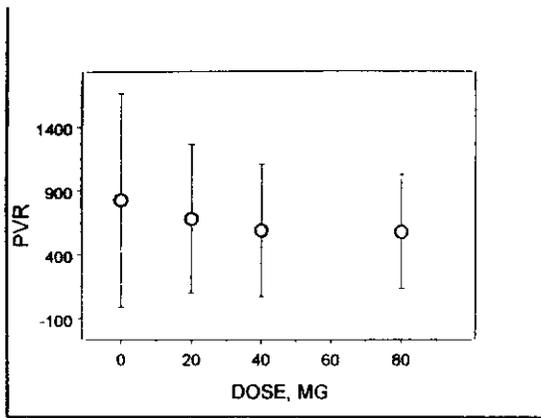


Figure 6: Mean and SD PVRi vs. sildenafil dose on Week 12

6 Minute Walk Distance vs. Pulmonary Vascular Resistance

The sponsor attempted to correlate both responses (6MWD and PVRi). The plot of 6MWD vs. PVRi is shown below (Figure 7).

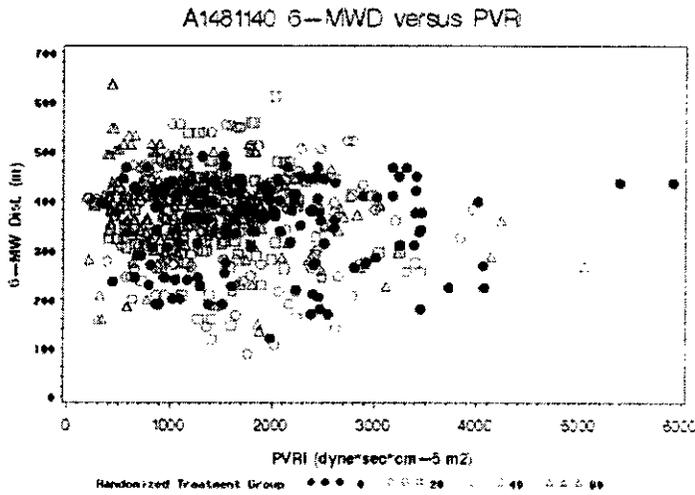


Figure 7: 6-MWD vs. PVRi

Reviewer's plot subdivided by the treatment group and occasion (baseline vs. week 12 of treatment) is shown below (Figure 8).

APPEARS THIS WAY
ON ORIGINAL

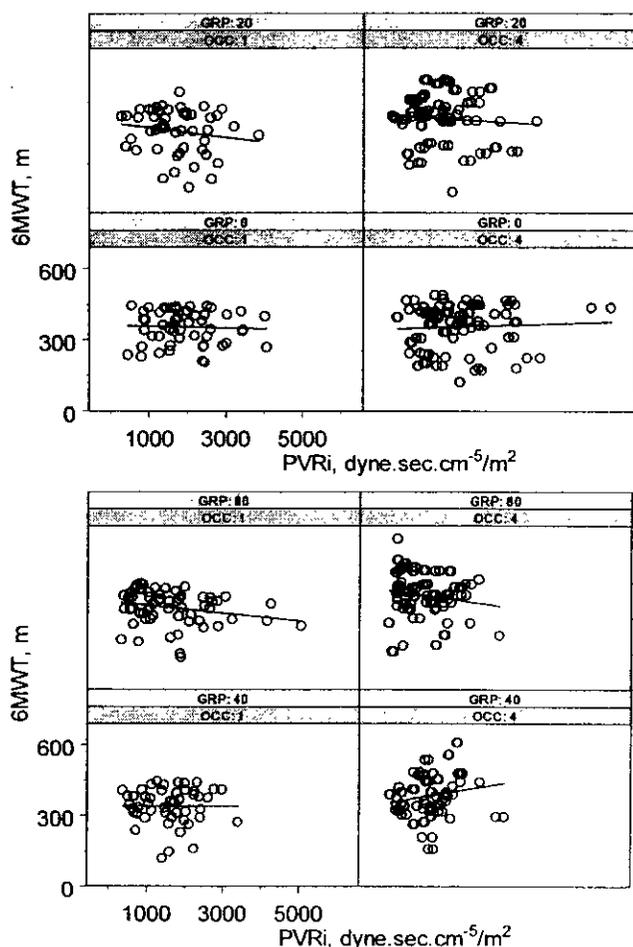


Figure 8: 6MWD vs PVRi by dose group (GRP = 0, 20, 40 and 80 mg of sildenafil TID). Baseline, OCC1, data on Week 12, OCC4. The lines are the results of linear regression.

There is a slight trend in the increase in 6MWD distance comparing to placebo and treatment groups as well as baseline and week 12 measurements. In addition, the placebo group showed a flat response (slope=0) and the slope increased with increasing dose, however, this was not true in the group receiving 40 mg dose of sildenafil. In general, the data does not show a strong correlation. The model proposed by the sponsor described the decrease of the baseline 6MWD measurements with the increases in PVRi. The final model equation was

$$\text{RESPONSE} = \text{BASELINE} - (\text{SLOPE} * \text{PVRi}).$$

The slope predicted by this model was $0.006 \text{ m/dyne} * \text{sec} * \text{cm}^{-5} / \text{m}^2$. This means that for a decrease of 100 units for PVRi, the distance for 6 minute walk would increase by 6 m. The estimation of the slope was very poor. The baseline predictions were 181 meters.

The average 6MW distance was 348 m (placebo), 392 m (20 mg), 384 m (40 mg) and 396 (80 mg). The parameters predicted by the model did not describe the pharmacodynamic response properly.

The relationship between sildenafil dose, PVRi and 6MWD is shown in Figure 9.

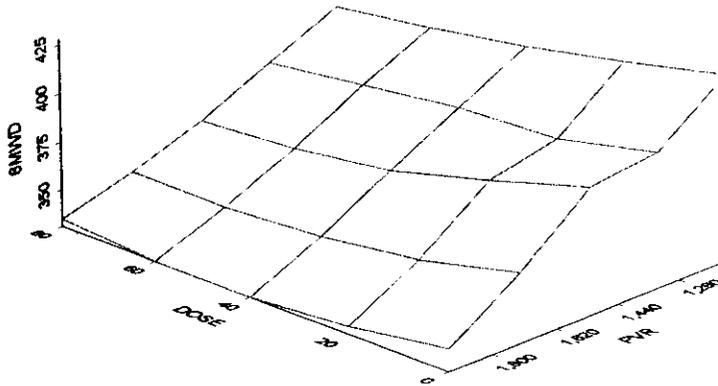


Figure 9: The relationship between sildenafil dose, PVRi and 6MWD

This plot points out that the dose-response relationship between 6MWD, PVRi and sildenafil dose is weak.

Was the time course of effect studied?

No.

The data set included the data obtained at baseline visit and visits week 4, 8, and 12 but only the pharmacodynamic data obtained on week 12 were used for the data analyses.

The distance of 6 minute walk vs. time at the baseline visit (Occasion 1) and after the last dose of sildenafil (Occasion 4) is shown in Figure 10.

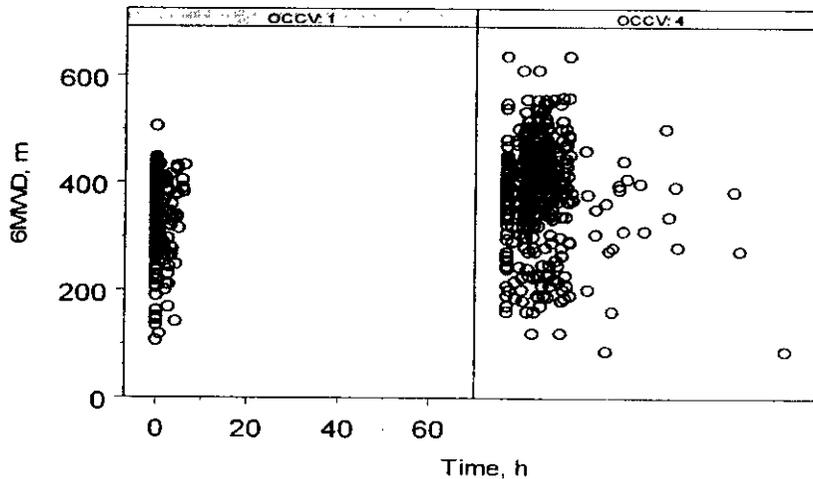


Figure 10: Time course of 6MWD, baseline visit (left) and visit week 12 (right)

This plot shows that the walking distance was longer at week 12 of treatment, there is no correlation between time after dose and 6MWD.

The PVRi values vs. the time at baseline visit (Occasion 1) and after the last dose of sildenafil (Occasion 4) are shown in Figure 11.

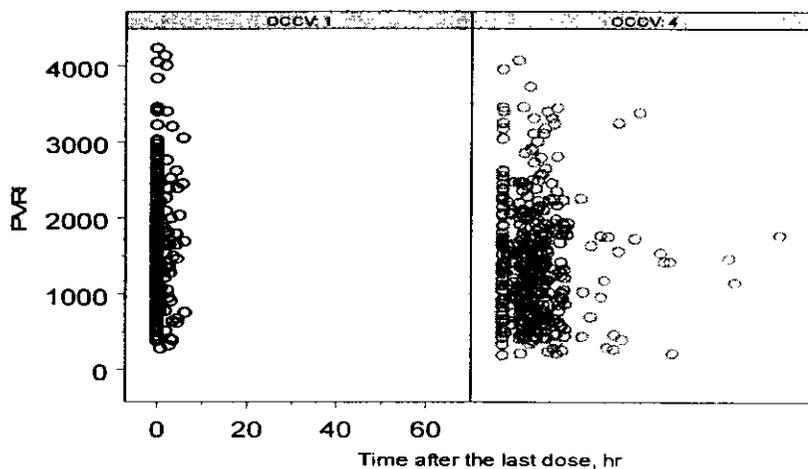


Figure 11: Time course of PVRi, baseline visit (left) and visit week 12 (right)

There is a tendency to have lower PVRi measurements at week 12 of treatment compared to the baseline and there is no correlation between the time after the dose of sildenafil and PVRi.

Were the models proposed by the sponsor acceptable?

Yes.

The model describing the relationship between PVRi and sildenafil plasma concentrations showed that this relationship has a very shallow slope. When the model included the covariates, the slope was estimated even more shallow, indicating that per each 1000 $\text{dyne}\cdot\text{sec}\cdot\text{cm}^{-5}/\text{m}^2$ decrease of PVRi the increase in 6MWD was only by 6 m. The estimated EC50 values of 2.92 ng/mL showed that a low dose of sildenafil was needed to lower PVRi. The lowest studied dose in this study was 20 mg TID. The sponsor reported that the coadministration of sildenafil with calcium channel blockers decreased PVRi baseline values by 23%; however, the lumping of all calcium channel blockers in one group may lead to a wrong conclusion due to a various kinetic and metabolic properties of these drugs.

When compared to placebo, each of sildenafil treatment group had an increase in 6MWD by 50, 42, and 54 m (mean values) and the difference between the placebo and the treatment groups was significant.

Is the use of PVRi as a surrogate marker for the sildenafil efficacy justifiable?

The sponsor's proposal to use PVRi measurement as a surrogate marker for the sildenafil efficacy is not supported by this study probably due to high variability in the data and not a wide enough dose range tested. Moreover, the surrogate marker is defined as a measurement which is easy to perform and which can be a good predictor of a clinical outcome. According to the population modeling results performed in this study, pulmonary vascular resistance was not strongly correlated with a clinical outcome, moreover, its can be assessed only by an invasive method.

Does sildenafil have higher selectivity to the pulmonary vascular bed compared to the

systemic hemodynamic parameters?

The higher selectivity of sildenafil to the pulmonary vascular bed was not fully proven by the sponsor. The sponsor's conclusions were based on a pilot PK/PD study after intravenous infusion of sildenafil. The following measurements were obtained:

- Sildenafil plasma concentrations;
- The pulmonary hemodynamic endpoints: mean pulmonary artery pressure (mean PAP); pulmonary vascular resistance (PVR); systolic pulmonary artery pressure (systolic PAP); diastolic pulmonary artery pressure (diastolic PAP);
- The systemic hemodynamic endpoints: mean arterial pressure (MAP); systolic blood pressure (SBP); diastolic blood pressure (DBP).

The PK/PD relationships were evaluated using a population approach. The Emax and linear models were investigated to each of the relationship between the pharmacodynamic parameter and sildenafil plasma concentrations and for the placebo effect. The estimated EC50 values were compared pairwise for each of the effects (systolic, diastolic, mean pressure).

Table 2: PK/PD parameters reported by the sponsor

Parameter	Systolic PAP (SE,%)	SBP (SE,%)	Mean PAP (SE,%)	MAP (SE,%)	Diastolic PAP (SE,%)	DBP (SE,%)
Baseline, mmHg	52.7	123	17.8	43.9	13.4	66.9
Emax, mmHg	20.9 (2.2)	24.0 (4.7)	5.8 (1.0)	0.105 (16.6)	8.7 (2.8)	0.49 (0.07)
EC50, ng/mL	14.5 (6.7)	53.5 (36.0)	13.7 (8.8)	23.7 (58)	21.4 (8.2)	21.2 (9.4)

Sildenafil reduced both pulmonary and systemic blood pressure after IV administration in patients with pulmonary hypertension. The relative change from baseline for pulmonary and systemic hemodynamic parameters was in most cases similar, except for the systolic pulmonary artery pressure, where sildenafil administration led to a larger relative reduction than for the systolic systemic blood pressure. The plasma concentrations of sildenafil required to reduce systolic pulmonary blood pressure were lower compared to the plasma concentrations required to lower systolic blood pressure.

The systemic pharmacodynamic parameters for sildenafil were poorly estimated probably due to the fact that the effect vs. sildenafil plasma concentrations was evaluated only over a time frame of 2 hours after the start of infusion.

Therefore, the hypothesis regarding the higher selectivity of sildenafil to the pulmonary vascular bed was not fully supported by this study.

Is the dose and dosing regimen selected by the sponsor acceptable?

Yes.

The proposed dosage regimen (20 mg TID) is acceptable because 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. Therefore, the sponsor's proposal to market only 20 mg tablet of sildenafil for the treatment of PAH is acceptable.

What undesirable effects of sildenafil are dose limiting?

When administered with alpha-blockers, the additive effect on the lowering of blood pressure may lead to symptomatic hypotension. The following adverse events were considered treatment related: hot flushes, nausea and headache. Each of these events may have a dose limiting effect.

Do plasma concentrations of sildenafil differ in healthy subjects, PAH and MED patients?

The comparison of the plasma concentrations of sildenafil based on raw data in healthy subjects and PAH patients is shown in Table 3.

Table 3: Mean sildenafil pharmacokinetic parameters in healthy subjects and PAH patients

	20 mg TID	40 mg TID	80 mg TID
Mean Cmax (ng/ml)			
Healthy Volunteers	113	248	527
PH Patients	107	206	503
Mean Average Steady State Concentration (ng/ml)			
Healthy Volunteers	40.3	93	228
PH Patients	59.6	116	291
Mean Cmin (ng/ml)			
Healthy Volunteers	14.1	28.2	69
PH Patients	28.2	56.0	145.9

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, the increase in the average steady state concentrations in patients with pulmonary arterial hypertension compared to healthy volunteers was about 30%. The sildenafil trough plasma concentrations in pulmonary arterial hypertension patients were twice higher compared to healthy volunteers at all doses, both findings indicating a lower clearance and/or a higher oral bioavailability of sildenafil in PAH patients. The Cmax was slightly lower in PAH patients, most likely because about 40% of the patients had a meal within 2 hours pre-dose while the reference data was from a fasted healthy volunteer study.

Was metabolism of sildenafil affected by PAH?

Yes.

The ratio of metabolite to sildenafil has been calculated by the sponsor from the raw data. In healthy volunteers, the ratio is about 40%. Since the metabolite is about 50% as potent as sildenafil with regard to PDE5 inhibition, the overall contribution of the metabolite to the pharmacological effect of sildenafil was estimated to be about 20%. In patients with pulmonary arterial hypertension, the ratio of metabolite to sildenafil plasma levels was about 72% at steady state at the proposed dose of 20 mg TID. The contribution of metabolite to the pharmacological effect of sildenafil would therefore increase to about 36%. The potential impact on efficacy is not known. Descriptive statistics of the ratios are shown in Table 4.

Table 4: Ratio between metabolite and parent drug based on raw data

	20 mg TID	
	Baseline	Week 12
MEAN	0.72	0.72
STD	0.53	0.56
CV%	74.0	77.5
MIN	0.12	0.09
MAX	3.76	5.31
N	189	329

As the patients randomized to 80 mg TID received 40 mg TID for the first week, they were included in the 40 mg group.

Was the pharmacokinetics of sildenafil different in PAH patients vs. MED patients?

Yes.

After a single dose of sildenafil in MED patients, the population typical values (mean \pm SE) were 58.5 ± 1.4 L/h for apparent clearance and 310 ± 6.92 L for apparent volume of distribution. The corresponding values for patients with pulmonary arterial hypertension were 73.6 ± 5.59 L/h for apparent clearance and 294 ± 17.2 L for apparent volume of distribution. In MED patients, the mean sildenafil exposure was similar to healthy volunteers, while PAH patients had higher average steady state and trough concentrations. The sponsor explained that the higher typical value of the apparent clearance in PAH patients were the result of the change in dosing regimen and the higher oral bioavailability of sildenafil at higher doses.

Were covariates influencing the pharmacokinetics of sildenafil different in PAH patients vs. MED patients?

Yes. The covariate model was different for both populations.

In patients with PAH, the only statistically significant covariates ($p < 0.001$) were co-administration of CYP3A4 substrates and beta-blockers. The sponsor reported that both concomitant medication classes reduced CL/F by 22.3% and 37.4% respectively. On most occasions, beta-blockers were given together with CYP3A4 substrates, therefore, the "beta-blocker" effect on CL/F was actually due to the combination of beta-blockers and CYP3A4 substrates. There were only 19 patients (1-4 per drug) out of 206 who received 1 of the nine different beta-blockers. The CYP3A4 substrates were compounded out of 36 different drugs administered to 194 patients at least once at baseline or week 12. From these compounds lidocaine, warfarin, omeprazole and amlodipine were received by 49, 31, 18, and 14 patients respectively, and all other drugs were received by 1-7 patients. It is impossible to conclude on the effect of the CYP3A4 substrates as well as beta-blockers on the apparent clearance of sildenafil because of the difference in the pharmacokinetic and metabolic properties of the listed drugs. Better model which would consider the effect of the individual drugs (for example, warfarin) is needed to describe the covariate effects in PAH patients.

In MED patients, beta-blockers had no impact on sildenafil clearance, but they did reduce the clearance of UK-103,320, the main metabolite of sildenafil. In MED patients, Age, AST (SGOT) concentration and co-administration with CYP3A4 inhibitors significantly influenced CL/F of sildenafil ($p < 0.001$). The extent of these linear relationships (extrapolated from population average values) were, for age, a 4% decrease in CL/F for every decade increase, for AST a 6% decrease in CL/F for every 10 unit increase and for CYP3A4 inhibitors, a 14% decrease in CL/F

following co-administration. Only weight was found to significantly ($p < 0.001$) influence V/F (a 6% increase in V/F for every 10 kg increase).

The covariates associated to demographics and hepatic function had only a moderate impact on sildenafil pharmacokinetics in MED patients. The strongest covariate effect was due to CYP3A4 inhibitors. Compared to MED patients, patients with pulmonary arterial hypertension received far more concomitant medications on a chronic basis, a large number of them being metabolized by CYP3A4. The effect of CYP3A4 substrates and beta-blockers on sildenafil pharmacokinetics in patients with pulmonary arterial hypertension was much larger than any covariate effect observed in MED patients and probably masked any other effects like demographic or hepatic function parameters.

2.3 Intrinsic Factors

What is the inter-and intra-subject variability of the PK parameters in PAH patients, and what are the major causes of variability?

Sildenafil is a moderately variable drug. The typical population value of sildenafil pharmacokinetic parameters in patients with PAH (mean and 90% CI) was 73.6 L/h (64.8 -82.2 L/h) for apparent clearance, 294.0 L (266.0-321.0 L) for apparent volume of distribution and 0.67 hours (0.60 -0.78 hours) for the duration of zero order input. The increase of oral bioavailability at 80 mg TID compared to the lower doses (20 and 40 mg) was 43% (27-60%). The inter-subject variability of the apparent clearance, the apparent volume of distribution and oral bioavailability was 31.5%, 23.9% and 40.1%. The inter-occasion variability of the oral bioavailability was 36.7%.

What intrinsic factors influence exposure?

Although age, weight, body mass index, body surface area, history of alcohol intake, history of smoking, gender, study center, patient group, serum creatinine, urea, glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin were evaluated as covariates in the model, none of these factor were included as a significant covariate in the final population PK and PK/PD models, except for age on baseline measurement of PVRi.

What is the impact of any differences in exposure on efficacy or safety responses?

The difference in the increase of 6 minute walk distance for the sildenafil doses of 20, 40, and 80 mg TID was not significant. The relationship between the safety measurements and drug exposure were not assessed in this submission.

Elderly

Age appears not to be a clinically relevant covariate for sildenafil pharmacokinetics and pharmacodynamics in PAH patients.

Pediatric Patients

No studies were conducted in pediatric subjects. Currently, sildenafil for the treatment of PAH in pediatric patients is being developed

Gender

Gender did not have any effect on the sildenafil pharmacokinetics and pharmacodynamics in PAH patients.

Race

Race was not studied as a covariate since not enough non-White PAH patients were enrolled in the pharmacokinetic study.

Renal impairment

Renal impairment did not have any effect on the sildenafil pharmacokinetics and pharmacodynamics in PAH patients (30 patients used in the covariate analysis out of 206 had creatinine clearance below 50 mL/min).

Hepatic impairment

Hepatic impairment did not have any effect on the sildenafil pharmacokinetics and pharmacodynamics in PAH patients (82 patients used in the covariate analysis had bilirubin level above normal value of 1.1 mg/dL).

Is there a need for dose adjustments in any special patient's populations?

No.

There was no statistical difference between the increases of 6MWD (efficacy endpoint) when sildenafil was administered at doses from 20 to 80 mg TID. In PAH patients, sildenafil was well tolerated at doses up to 80 mg TID, and the incidence and severity of most adverse events was similar across all three dose groups. Based on the efficacy results of study A1481140, the recommended dose of sildenafil to treat pulmonary arterial hypertension was 20 mg TID and the dose adjustment for the special populations is not necessary.

1. The mean average steady state concentration of sildenafil at 80 mg TID was about 5-fold higher compared to the mean average steady state concentration at 20 mg TID. The increase of sildenafil exposure observed in specifically designed clinical pharmacology studies was less than 5-fold.
2. Compared to healthy young volunteers, sildenafil AUC increased in elderly subjects by 84%, in subjects with severe renal impairment by ~ 100%, in subjects with stable hepatic cirrhosis by 85%.
3. The accumulation index of sildenafil for TID dosing was in
 - a. healthy volunteers: 13 -24%,
 - b. elderly -30%,
 - c. renal impairment: mild -36%, moderate -19%, severe -32%,
 - d. hepatic cirrhosis: 37%.
4. Therefore, the safety window for the subpopulations can be expected to be sufficient after chronic dosing of 20 mg TID.
5. No covariates related to demographics, hepatic or renal function had a statistically significant impact on sildenafil pharmacokinetics in PAH patients.

What pharmacogenetics information is there in the application and is it important or not?

Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The collection of the pharmacogenomic information would not be of importance for this drug and it was not performed for this application.

2.4 Extrinsic Factors

What extrinsic factors influence sildenafil exposure and/or response?

The effects of demographics and concomitant medications were evaluated by the sponsor in the PK/PD model. Although the demographic factors were not significant covariates for sildenafil in PAH patients, the coadministration of CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers were the only factors with a statistically significant impact on sildenafil pharmacokinetics. The exposure to sildenafil in patients on concomitant CYP3A4 substrates and CYP3A4 substrates plus beta-blockers was 43% and 66% higher, respectively, compared to patients not receiving these drug classes.

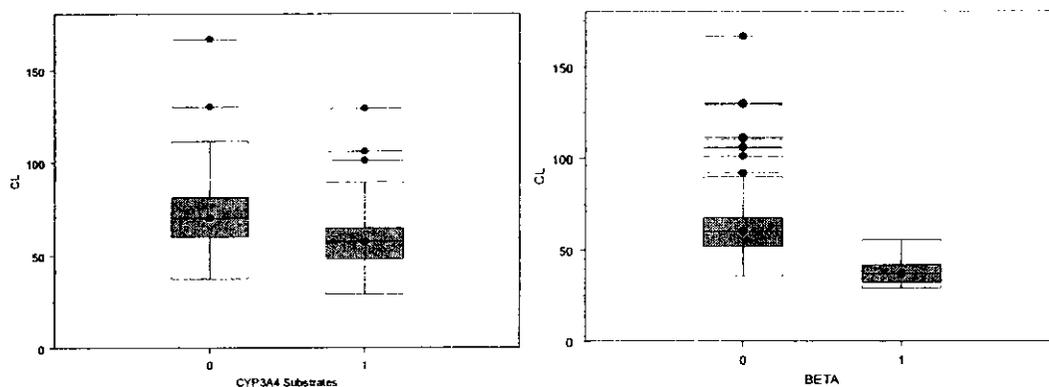


Figure 12: Important covariates on CL (CYP3A4 substrates and beta-blockers)

Clearance of sildenafil decreased in patients who received CYP3A4 substrates (by 22.3%) or beta-blockers (by 37.4%).

Drug-drug interactions

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes.

Effects of other drugs on sildenafil

Sildenafil metabolism is principally mediated by the CYP3A4 (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

Effects of sildenafil on the other drugs

In vitro studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ($IC_{50} > 150 \mu M$). Given sildenafil peak plasma concentrations of

approximately 1 μ M after recommended doses, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes.

Were studies with medications that are likely to be administered for treatment of PAH performed in vivo?

Yes. In addition to the previously reported drug-drug interaction studies for VIAGRA, the sponsor performed new studies with the following drugs: bosentan, atorvastatin, anti-coagulants (phenprocoumon and acenocoumarol), and oral contraceptives. Apart from bosentan, (CYP3A4 inducer), no clinically relevant PK/PD interactions were observed between sildenafil (up to 100 mg dose) and the listed above medications (given at high therapeutic doses).

Sildenafil kinetics: In the presence of bosentan (125 mg BID), mean sildenafil C_{max} and AUC_t were 55% and 63% lower compared to placebo.

Bosentan kinetics: 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.

In the pivotal clinical study A148-1140, PAH patients received large number of comedications. The effect of these comedications was assessed using covariate model. Since the concomitant medications were grouped as beta-blocker, digoxin, calcium channel blockers, ACE inhibitors and diuretics and the effect of each separate drug cannot be ruled out, the results of the covariate effect of comedications evaluated for both PK and PK/PD models are not acceptable (see above).

Was the additive effect of sildenafil and anticoagulants on bleeding time assessed in vivo?

Sildenafil has no effect on bleeding time when taken alone or with aspirin. There was no difference between the treatment groups in the pharmacodynamic interaction studies with anti-coagulants (for both phenprocoumon and acenocoumarol). These drugs are the derivatives of coumarin (warfarin) and although they are used in Europe, they are not approved in the US. In the clinical study, an increased incidence of bleeding was observed when sildenafil was coadministered with warfarin. Warfarin and sildenafil share CYP 2C19, 2C9, and 3A4 pathways; therefore, it is likely that warfarin may interact with sildenafil. This interaction has not been characterized. The Agency recommends to the sponsor to perform a study to rule out any pharmacokinetic and/or pharmacodynamic interaction of sildenafil with warfarin.

Is sildenafil a substrate and/or an inhibitor of P-glycoprotein transport processes?

There is no interaction between sildenafil and digoxin, therefore, sildenafil is not an inhibitor of PgP. However, it is not know, if it is a PgP substrate.

Is there a need for dose adjustments when sildenafil is coadministered with the other drugs?

Most of the other concomitant medications (except for the protease inhibitors) have less than 5-fold increase of sildenafil exposure: cimetidine increased sildenafil AUC by 56%; erythromycin increased sildenafil AUC 2.8 fold; CYP3A4 substrates alone or in combination with beta-blockers increased sildenafil AUC by 43 and 66%.

Protease inhibitors are contraindicated with sildenafil: saquinavir increased sildenafil AUC 3.1 and ritonavir increased sildenafil AUC 11 fold.

The same recommendations as for MED patients apply also for PAH patients.

2.5 General Biopharmaceutics

Was there an impact of food on the bioavailability of sildenafil?

Yes.

When sildenafil is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29%. In PAH patients, sildenafil may be administered with or without food.

Was the sildenafil tablet formulation for PAH equivalent to the previously approved drug strengths?

The proposed commercial tablet formulation for the PAH indication and the formulation used in the PAH clinical studies is directly analogous to the commercial formulation of Viagra (sildenafil citrate, 50 and 100 mg). A 20 mg tablet has been developed for the PAH indication. The tablets are manufactured from _____ which is qualitatively and quantitatively similar to the commercial Viagra ® formulation. The minor differences in the tablet presentations for each indication are change of tablet shape and color of the film coat. Since these are Level I changes and in vitro dissolution testing confirmed that the dissolution profiles were the same for the sildenafil citrate tablet for PAH and sildenafil citrate tablet for MED, the waiver for the 20 mg tablet of REVATIO has been granted to the sponsor.

Are the sponsor proposed dissolution medium and specifications acceptable?

Yes.

The in vitro dissolution method for sildenafil citrate tablets, 20 mg, employs basket apparatus and it is identical to the dissolution method and specification for Viagra.

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Basket Speed	100 rpm
USP Apparatus I	
Volume	900 mL
Specifications	— in 15 minutes

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The plasma concentration data for sildenafil and desmethylsildenafil were mostly generated by a validated _____ method. _____ The quantitation limits for sildenafil and desmethylsildenafil was _____. No interferences by endogenous compounds and other potential co-administered compounds were observed in the assay. A single laboratory, _____, was responsible for all the assays. Additionally, a validated _____

sample preparation was used in one study, A1481024. The quantitation limit for sildenafil and desmethylsildenafil was —. All bioanalytical methods were validated and met the acceptance criteria of the bioanalytical method validation guidance. The assay validation reports were provided for each of the studies.

Which metabolite has been selected for analysis and why?

The desmethylsildenafil (metabolite of sildenafil) has about 50% of activity of the parent drug. Its exposure accounted for about 40% of sildenafil in healthy subjects and about 70% in PAH patients. Although plasma concentrations of desmethylsildenafil were measured in all studies, only pharmacokinetic studies considered the evaluation of the parameters of this metabolite in the present submission. The impact of the active metabolite on the pharmacodynamic effect was not assessed in PAH patients.

Were the validation characteristics of the assay acceptable?

Yes.

All assays have their validation reports, see individual study reviews.

What is the overall conclusion regarding NDA 21-845?

Overall the clinical pharmacology and biopharmaceutics section is acceptable.

2.7 References

1. Milligan PA, Marshall SF, Karlsson MO, A population pharmacokinetic analysis of sildenafil citrate in patients with erectile dysfunction. Br J Clin Pharmacol, 2002. 53: p. 45S-52S.

**APPEARS THIS WAY
ON ORIGINAL**

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The Agency considered that the information provided in the original NDA 21-845 sildenafil citrate tablets was appropriate to evaluate the pharmacokinetic and pharmacodynamics of this drug for the use in PAH therapy.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

CLINICAL PHARMACOLOGY Section should be read as follows:

Pharmacokinetics:

~

DOSE AND ADMINISTRATION Section,

**APPEARS THIS WAY
ON ORIGINAL**

4 APPENDICES

4.1 OCPB Proposed Label

APPEARS THIS WAY
ON ORIGINAL

11 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.3 Individual Study Reviews

4.3.1 A DOUBLE BLIND, TWO WAY CROSSOVER, PLACEBO CONTROLLED STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY AND TOLERATION OF SILDENAFIL IN HEALTHY YOUNG WOMEN AND TO INVESTIGATE THE EFFECT OF SILDENAFIL ON THE PHARMACOKINETICS OF ORAL CONTRACEPTIVE STEROIDS (A148 -236)

DRUG STUDIED: Sildenafil Citrate
INVESTIGATOR(S) AND STUDY SITE: _____
Study Dates: 04 June 1997 to 26 August 1997
Phase of Development: Phase 1

OBJECTIVES:

To investigate the pharmacokinetics of sildenafil in healthy female subjects and the effect of sildenafil compared with placebo on the pharmacokinetics of the oral contraceptive [Microgynon 30 (Schering H. C)] components ethinylloestradiol (EE) and levonorgestrel (LN).

To evaluate the safety and toleration of sildenafil in healthy female subjects.

STUDY DESIGN: This was a double blind, two way crossover, placebo controlled study.

Evaluation Groups:

	Sildenafil	Sildenafil & Microgynon	Double blind placebo	Double blind placebo & Microgynon
Entered Study	16	16	16	16
Completed Study	15	16	16	16
Evaluated for Pharmacokinetics	16	16	16	16
Assessed for Safety:				
Adverse Events	15	16	16	16
Laboratory Tests	15	16	16	16

Diagnoses and Criteria for Inclusion of Subjects: Healthy female volunteers who have been surgically sterilized and are between 18 and 45 years of age (actual range 30 to 42 years).

DRUG ADMINISTRATION:

Dosage Form

Oral 50mg sildenafil citrate tablets (FID No. S00504AA, Lot No. N6058).

Oral placebo tablets (FID No. S0437AE, Lot No. 4469-104).

Oral contraceptives (Microgynon: 30 mg ethinylloestradiol and 150 m g levonorgestrel; Lot No. 64023)

Dosing

Doses were taken orally. Sildenafil 50mg/placebo once daily from Day 1 to Day 11 inclusive. Oral contraceptive (Microgynon 30) taken at the same time as sildenafil/placebo on Days 2 to 11 inclusive.

Duration

11 days (11 days exposure to sildenafil/placebo and 10 days total exposure to oral contraceptive (Microgynon 30).

Pharmacokinetic Evaluations: On Days 1 and 11, blood samples were taken at specified time and up to 24 hours post-dose for measurement of plasma sildenafil and metabolite(UK -- 103,320) concentrations. On Day 11 only, blood samples were also taken at these times for measurement of plasma, ethinyloestradiol (EE) and levonorgestrel (LN) concentrations.

ANALYTICAL METHODS:

Plasma samples were analyzed for sildenafil and UK-103,320 using a previously validated high pressure liquid chromatography with ultraviolet detection method. The calibration range for both sildenafil and UK --103 320 was _____

Table 5: Assay Characteristics for Sildenafil and UK-103,320

Parameter	Measure		Reviewer Comment
	Sildenafil	UK-103,320	
Linearity	/		Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

EE and LN were analyzed using gas chromatography/mass spectrometry _____
 . The two compounds were assayed separately using _____

Table 6: Assay Characteristics for Ethinyloestradiol and Levonorgestrel

Parameter	Measure		Reviewer Comment
	Ethinyloestradiol	Levonorgestrel	
Linearity	/		Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

Statistical Methods:

The pharmacokinetic parameters AUC, AUCt, Cmax, Tmax, t_{1/2} and kel for sildenafil and UK-103,320 (on Days 1 and 11), and AUCt, Cmax and Tmax for EE and LN (on Day 11) were tabulated and summary statistics reported. For sildenafil and UK-103,320, predicted and observed accumulation ratios were derived; geometric means and 95% confidence intervals (CIs) for the geometric means (derived by back-transformation of log-transformed data) were calculated. This was obtained from the analysis of variance (ANOVA), performed on natural log transformed AUC and/or AUCt, allowing for variation due to sequence, subject within sequence

and day. For EE and LN, the natural log transformed AUCt and Cmax and untransformed Tmax (Day 11) were subjected to ANOVA, allowing for variation due to sequence, subject within sequence, treatment and period. 95% CIs were calculated for the difference in treatment means. For AUCt and Cmax, these differences and CIs were back-transformed (exponentiated) to give adjusted geometric means and 95% CIs for the ratio of means (sildenafil and Microgynon 30/placebo and Microgynon 30) on the original scale.

Pharmacokinetic Results:

Demographics is shown in Table 7.

Table 7: Demographic Characteristics

	SILDENAFIL -> DOUBLE BLIND PLACEBO	DOUBLE BLIND PLACEBO -> SILDENAFIL
	FEMALE	FEMALE
NUMBER OF SUBJECTS	9	8
Age (years):		
< 18	0	0
18 - 25	0	0
26 - 35	3	3
36 - 45	5	5
>= 46	0	0
Mean	37.5	37.4
SD	4.5	4.2
Range	31-42	30-41
Race:		
White	7	4
Other	1	0
Weight (kg):		
Mean	65.3	63.5
SD	5.0	4.2
Range	58-74	52-75
N	8	8
Height (cm):		
Mean	163.4	162.4
SD	6.7	6.2
Range	155-172	155-171
N	8	8

Pharmacokinetic parameters are shown in Table 8.

Table 8: Sildenafil Pharmacokinetic Parameters

	AUC (ng.h/ml)*	AUC _t (ng.h/ml)*	C _{max} (ng/ml)*	T _{max} (h) ^b	k _e (/h) ^c	t _{1/2} (h) ^c
Sildenafil (Day 1)	292	284	77.0	1.38	0.190	3.654
Sildenafil & Microgynon 30 ^x (Day 11)	398	384	93.1	1.50	0.163	4.249
		Mean ^a	95% CI			
Predicted Accumulation Ratio		1.03	1.022, 1.038			
Observed Accumulation Ratio		1.352	1.199, 1.524			

For sildenafil, C_{max} was greater on Day 11 (sildenafil plus Microgynon 30) than on Day 1 (sildenafil alone). The ratio of Day 11 to Day 1 mean was 1.28. Values for T_{max} were similar on Days 1 and 11. The mean elimination rate was slightly lower on Day 11 than on Day 1. This decrease in k_{el} corresponded to a small increase in harmonic mean t_{1/2} from 3.92h to 4.56h. Data for UK-103,320 showed a similar pattern to that of sildenafil.

For both sildenafil and UK-103,320 plasma concentrations, the observed accumulation ratio after treatment with sildenafil plus oral contraceptive (Microgynon 30) for 10 days [sildenafil: 1.181 (95% CI: 1.032, 1.352); UK-103,320: 1.352 (95% CI: 1.199, 1.524)] was slightly greater than the predicted accumulation ratio as assessed after a single dose of sildenafil [sildenafil: 1.02 (95% CI: 1.017, 1.024); UK-103,320: 1.03 (95% CI: 1.022, 1.038)].

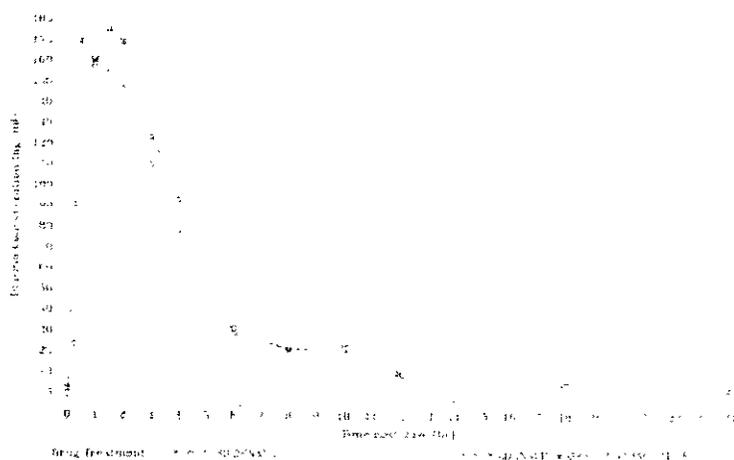


Figure 13: Mean sildenafil plasma concentrations on Day 1 and Day 11.

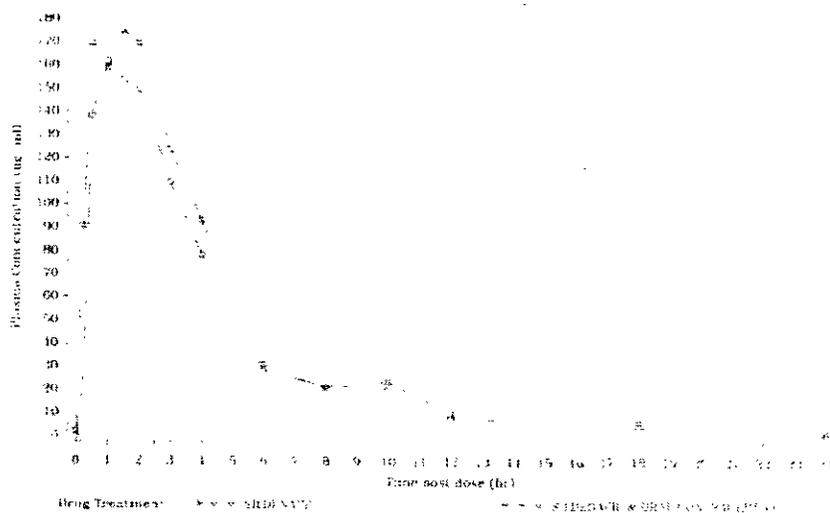


Figure 14: Mean sildenafil metabolite plasma concentrations on Day 1 and Day 11.

Pharmacokinetic parameters for ethinyloestradiol are shown in Table 9.

BEST POSSIBLE COPY

Table 9: Ethinylestradiol pharmacokinetic parameters

	AUC _t (pg.h/ml)*	C _{max} (pg/ml)*	T _{max} (h)*
Sildenafil & Microgynon 30* (Day 11)	631	91.1	1.38
Double blind placebo & Microgynon 30* (Day 11)	596	78.0	1.34
Comparison between Sildenafil & OC and Placebo & OC: Difference or Ratio ^c (95% CIs)	106% (93.6, 120)	117% (102, 134)	0.03 (-0.36, 0.42)

For the treatment effect of sildenafil on the AUCt of the EE component of Microgynon 30, the ratio of the adjusted geometric means for sildenafil and placebo was 106.0%. The 95% CI was 93.6% to 120.1% and included 100%.

For the treatment effect of sildenafil on Cmax of EE, the ratio of the adjusted geometric means for sildenafil and placebo was 116.9%. The 95% CI was 102.3% to 133.5% and did not include 100%.

Mean plasma concentrations for EE on Day 11 for the sildenafil & Microgynon 30 and placebo & Microgynon 30 treatments are shown in Figure 15.

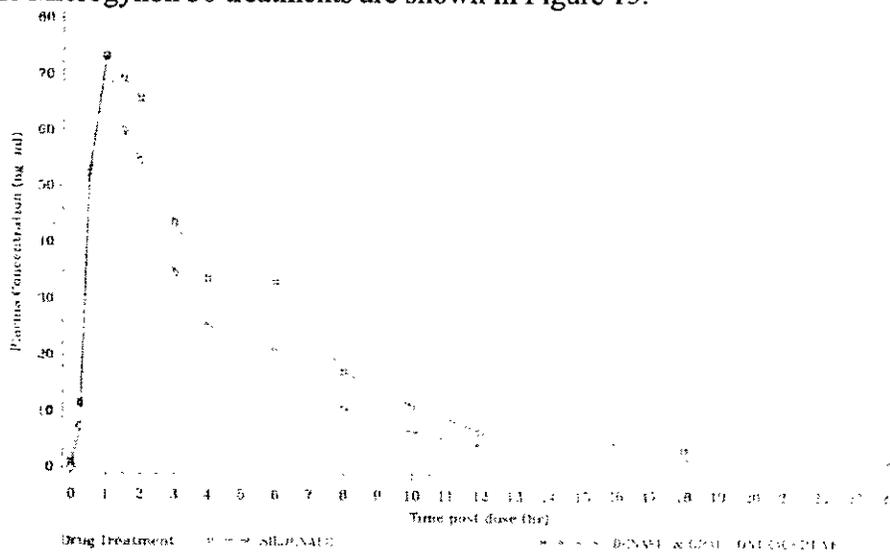


Figure 15: Mean ethinylestradiol plasma concentrations vs. time

Pharmacokinetic parameters for levonorgestrel are shown in Table 10.

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Table 10: Levonorgestrel Pharmacokinetic parameters

	AUC _t (ng.h/ml) ^a	C _{max} (ng/ml) ^a	T _{max} (h) ^b
Sildenafil & Microgynon 30 [®] (Day 11)	76.3	6.04	1.41
Double blind placebo & Microgynon 30 [®] (Day 11)	75.4	6.50	1.50
Comparison between Sildenafil & OC and Placebo & OC: Difference or Ratio ^c (95% CIs)	101% (95.2, 108)	92.9% (82.7, 104)	-0.09 (-0.53, 0.34)

For the treatment effect of sildenafil on the AUC_t of the LN component of Microgynon 30, the ratio of the adjusted geometric means for sildenafil and placebo was 101.2%. The 95% CI was 95.2% to 107.6% and included 100%.

For the treatment effect of sildenafil on the C_{max} of the LN component of Microgynon 30, the ratio of the adjusted geometric means for sildenafil and placebo was 92.9%. The 95% CI was 82.7% to 104.3% and included 100%.

For the treatment effect of sildenafil on the T_{max} of the LN component of Microgynon 30, the difference between the adjusted means for sildenafil and placebo was -0.09 hours. The 95% CI was -0.53 to 0.34 and included zero.

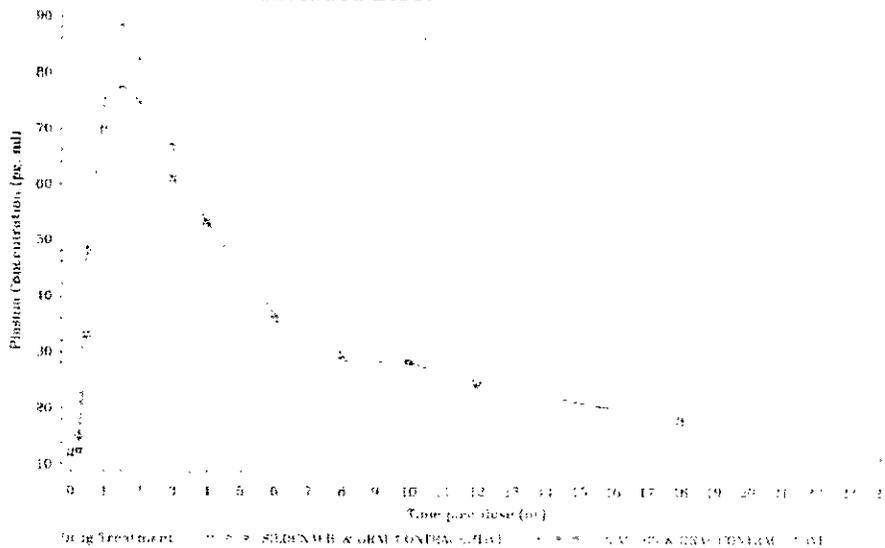


Figure 16: Mean levonorgestrel plasma concentration vs. time

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Table 11: Sildenafil PK parameters by treatment group

	Sildenafil & Microgynon 30*	Double blind placebo & Microgynon 30†	Comparison Difference or Ratio (95% CIs)
Ethinylloestradiol			
AUC, (pg.h/ml)	631	596	106 (93.6, 120)*
C _{max} (pg/ml)	91.1	78.0	117 (102, 134)*
T _{max} (h)	1.38	1.34	0.03 (-0.36, 0.42)
Levonorgestrel			
AUC, (ng.h/ml)	76.3	75.4	101 (95.2, 108)*
C _{max} (ng/ml)	6.04	6.50	92.9 (82.7, 104)*
T _{max} (h)	1.41	1.50	-0.09 (-0.53, 0.34)

*The ratio and corresponding confidence limits for the geometric means are back transformed from the log scale. Geometric means were used for AUC, and C_{max}. Arithmetic means were used for T_{max}.

Sponsor's Conclusions:

In normal healthy female volunteers the combination of sildenafil and oral contraceptive led to a slight increase in C_{max}, slightly lower k_{el} and similar T_{max} for sildenafil on Day 11 (sildenafil plus Microgynon 30 a) compared with Day 1 (sildenafil alone). Data for the metabolite UK-103,320 showed a similar pattern to that for sildenafil.

And slight increases in mean accumulation ratios of sildenafil and its metabolite UK-103,320 were not considered clinically significant. Sildenafil caused a small, clinically insignificant, increase in the maximum plasma concentration of EE, but had no effect on LN pharmacokinetics.

COMMENTS:

1. This study showed that in normal healthy female volunteers, the combination of sildenafil and oral contraceptive led to a slight increase in C_{max}, slightly lower k_{el} and similar T_{max} for sildenafil on Day 11 (plus Microgynon 30 a) compared with Day 1 (sildenafil alone). Data for UK-103,320 showed a similar pattern to that of sildenafil.
2. For both sildenafil and UK-103,320 plasma concentrations, the observed accumulation after treatment with sildenafil plus oral contraceptive (Microgynon 30) for 10 days was slightly greater than the predicted accumulation ratio as assessed after a single dose of sildenafil alone. The slight increases in mean accumulation ratios of sildenafil and its metabolite UK-103,320 were not considered clinically significant.
3. Sildenafil caused a small clinically insignificant increase in the plasma concentration of ethinylloestradiol, but had no effect on levonorgestrel pharmacokinetics.
4. There is no pharmacokinetic interaction between sildenafil and oral contraceptives; therefore, no dosing adjustment is warranted.

4.3.2 THE EFFECT OF SILDENAFIL ON THE PHARMACOKINETICS OF ATORVASTATIN IN HEALTHY MALE SUBJECTS (258-002):

DRUG STUDIED: Sildenafil Citrate

INVESTIGATOR:

Study Dates: 23 March 1999 – 06 June 1999

Phase of Development: Phase I

OBJECTIVE:

To investigate the pharmacokinetic interaction between sildenafil (a single 100 mg dose) and atorvastatin (10 mg daily for 7 days) in healthy male subjects.

STUDY DESIGN: This was a randomized, open-label, multiple-dose two-way crossover study with a seven day washout between treatment periods. Subjects were assigned to one of two treatment sequences as outlined below.

Study Day	Period I			Period II	
	1	2-7	8	16-21	22
Sequence 1	Sildenafil	Atorvastatin	Atorvastatin + Sildenafil	Atorvastatin	Atorvastatin + Placebo
Sequence 2	Sildenafil	Atorvastatin	Atorvastatin + Placebo	Atorvastatin	Atorvastatin + Sildenafil

Sildenafil = 100 mg once daily; Atorvastatin = 10 mg once daily

Evaluation Groups:

	S	A I	A+S I	A+P I	A II	A+S II	A+P II
Treated	24	24	12	12	24	12	12
Completed Study	24	24	12	12	24	12	12
Evaluated for Pharmacokinetics	24	24	12	12	24	12	12
Assessed for Safety:							
Adverse Events	24	24	12	12	24	12	12

Laboratory Tests were performed at screening and on day 0 (LFTs) only.
 S=sildenafil on day 1; A I=atorvastatin on days 2-7; A+S I=atorvastatin and sildenafil on day 8; A+P I=atorvastatin and placebo on day 8; A II=atorvastatin on days 16-21; A+S II=atorvastatin and sildenafil on day 22; A+P II=atorvastatin and placebo on day 22.

SUBJECTS: Healthy male volunteers between 40 and 64 years of age (actual range 40 to 62 years).

DOSAGE FORMS

Sildenafil 100 mg tablets (FID # QC3210, Lot # N8048-G2),
 Atorvastatin 10 mg tablets (Warner-Lambert, Lot # ED-O-106-299) and
 Placebo (FID # QC3222, Lot # N8067-G2).

DRUG ADMINISTRATION: Sildenafil (100 mg QD) only was administered on day 1, followed by atorvastatin (10 mg QD) only on days 2-7. Atorvastatin (10 mg QD) and sildenafil (100 mg QD), or atorvastatin (10 mg QD) and placebo were administered on day 8. There was a 7-day washout period from days 9-15. Atorvastatin (10 mg QD) was administered on days 16-21,

followed by atorvastatin (10 mg QD) and placebo or atorvastatin (10 mg QD) and sildenafil (100 mg QD) on day 22.

Pharmacokinetic Evaluations: Plasma samples for analysis of atorvastatin and sildenafil pharmacokinetics were collected in heparinized tubes at the following times: 0 (just prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after drug administration on days 8 and 22. On day 1, plasma samples were collected at the aforementioned times for analysis of sildenafil pharmacokinetics.

ANALYTICAL METHODS:

Plasma samples were analyzed for sildenafil and UK-103,320 using a previously validated high pressure liquid chromatography with ultraviolet detection method. The calibration range for both sildenafil and UK --103 320 was

Table 12: Assay Characteristics for Sildenafil and UK-103,320

Parameter	Measure		Reviewer Comment
	Sildenafil	UK-103,320	
Linearity	/		Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

Plasma samples were assayed for atorvastatin equivalents using an enzyme (HMG-CoA reductase) inhibition assay. The assay had a linear range of 0.36 to 16 ng/ml with a lower limit of quantitation of 0.36 ng/ml.

Table 13: Assay Characteristics for Atorvastatin

Parameter	Measure	Reviewer Comment
Linearity	/	Satisfactory
Precision (CV%)		Satisfactory
Accuracy Between day		Satisfactory
LLOQ		Satisfactory
Specificity		Satisfactory

Statistical Methods:

The primary statistical analysis compared atorvastatin pharmacokinetic parameters determined after co-administration of atorvastatin and sildenafil (A+ S) with parameters determined after co-administration of atorvastatin and placebo (A+ P). Secondary statistical analyses compared sildenafil and UK-103,320 pharmacokinetic parameters determined after co-administration of atorvastatin and sildenafil (A+S) with parameters determined after sildenafil given alone (S) on Day 1. The natural log transformed atorvastatin AUC0-24 and Cmax and untransformed Tmax and half-life were analyzed (ANOVA). The statistical model included terms for sequence (I or II), subjects nested within sequence (i. e., subject (sequence)), treatment and period (I or II). The

sequence effect was tested using the subject (sequence) mean square from the ANOVA as an error term. All other main effects were tested against the residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least squares means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed). Ninety percent (90%) confidence intervals were determined for the treatment differences. For AUC₀₋₂₄ and C_{max}, the anti-log was taken on the confidence limits to obtain the corresponding confidence limits for the ratio of the treatment means.

The co-administration of atorvastatin and placebo (A+ P) was used as the reference in the treatment comparisons. Sildenafil alone (S) was used as the reference in these comparisons.

All statistical tests were conducted at the 0.05 level of significance.

Results:

All twenty-four subjects received sildenafil on day 1 (S) and atorvastatin alone on days 2-7 (A I) and 16-21 (A II) (Table 1). Twelve subjects received atorvastatin and sildenafil on day 8 (A+ S I) and atorvastatin and placebo on day 22 (A+ P II). The remaining 12 subjects received atorvastatin and placebo on day 8 (A+ P I) and atorvastatin and sildenafil on day 22 (A+ S II). All twenty-four subjects completed the study and were included in the pharmacokinetic and safety analyses.

Demographics is shown in Table 14.

Table 14: Demographic Characteristics

Number of Subjects	12	12
Age (years):		
18-44	4	5
45-64	8	7
Mean	48.6	47.6
SD	5.8	6.5
Range	40-59	40-62
Race:		
WHITE	10	9
BLACK	0	2
HISPANIC	2	1
Weight (kg):		
Mean	77.3	82.7
SD	7.7	5.9
Range	67-88	69-89
N	12	12
Height (cm):		
Mean	174.8	183.6
SD	6.2	8.2
Range	159-182	159-196
N	12	12

Pharmacokinetic parameters of atorvastatin are shown in

Table 15: Atorvastatin Pharmacokinetics

Pharmacokinetic Parameter	Comparison	Adjusted Geometric Means	Ratio (A+S)/(A+P)	90% Confidence Interval	
AUC ₀₋₂₄ (ng•hr/ml)	Atorvastatin & Sildenafil	105	111%	104%	117%
	Atorvastatin & Placebo	94.6			
C _{max} (ng/ml)	Atorvastatin & Sildenafil	8.54	112%	100%	124%
	Atorvastatin & Placebo	7.66			
Pharmacokinetic Parameter	Comparison	Adjusted Arithmetic Means	Difference (A+S) – (A+P)	P-value	
T _{max} (hr)	Atorvastatin & Sildenafil	2.2	0.2	0.716	
	Atorvastatin & Placebo	2.0			
T _{1/2} (hr)	Atorvastatin & Sildenafil	11.5	1.0	0.183	
	Atorvastatin & Placebo	10.4			

None of the sequence effects were statistically significant (p>0.537).

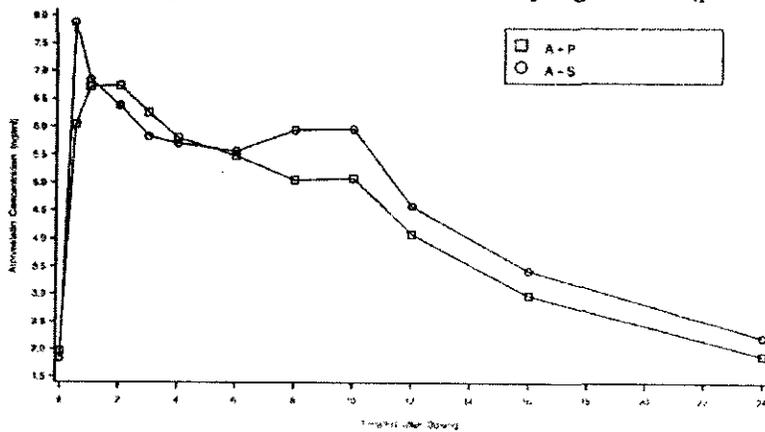


Figure 17: Mean atorvastatin plasma concentrations vs. time after the 10 mg dose of atorvastatin administered with placebo or with sildenafil.

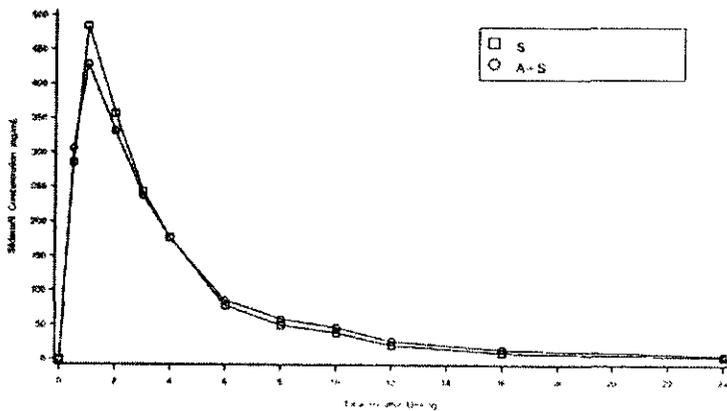


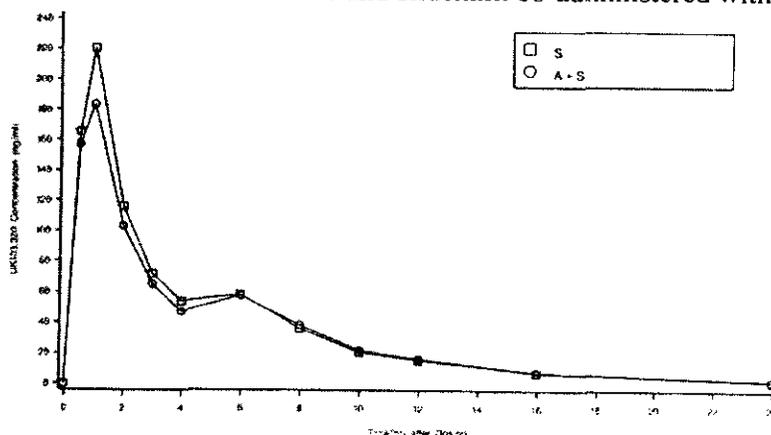
Figure 18: Mean sildenafil plasma concentrations.

Pharmacokinetic parameters for ethinylloestradiol are shown in Figure 18.

Table 16: Sildenafil Pharmacokinetics

Pharmacokinetic Parameter	Comparison	Adjusted Geometric Means	Ratio (A+S)/S	90% Confidence Interval	
AUC ₀₋₂₄ (ng•hr/ml)	Atorvastatin & Sildenafil Sildenafil	1696 1701	100%	92%	109%
C _{max} (ng/ml)	Atorvastatin & Sildenafil Sildenafil	410 456	90%	80%	101%
Pharmacokinetic Parameter	Comparison	Adjusted Arithmetic Means	Difference (A+S) - S	P-value	
T _{max} (hr)	Atorvastatin & Sildenafil Sildenafil	1.1 1.1	0.0	0.770	
T _{1/2} (hr)	Atorvastatin & Sildenafil Sildenafil	4.6 4.1	0.5	0.096	

Mean C_{max}, T_{max}, AUC₀₋₂₄ and half-life values of sildenafil metabolite, UK-103,320, were similar after sildenafil alone and sildenafil co-administered with atorvastatin.

**Figure 19: Mean sildenafil metabolite plasma concentrations vs. time****Sponsor's Conclusions:**

Mean C_{max}, T_{max}, AUC 0-24 and half-life values of atorvastatin were similar following co-administration of sildenafil and atorvastatin, or placebo and atorvastatin. In addition, mean C_{max}, T_{max}, AUC 0-24 and half-life values of sildenafil were similar after sildenafil alone and sildenafil co-administered with atorvastatin. Thus, sildenafil had no effect on the pharmacokinetics of atorvastatin, and atorvastatin did not significantly affect the pharmacokinetics of sildenafil. Also, atorvastatin pharmacokinetics were not affected by the administration sequence (atorvastatin and sildenafil followed by atorvastatin and placebo or vice versa).

COMMENTS:

1. The co-administration of sildenafil and atorvastatin did not alter significantly the pharmacokinetics of either sildenafil or atorvastatin. No dose adjustment is necessary.

4.3.3 PHASE I OPEN STUDY TO ASSESS THE POTENTIAL INTERACTION BETWEEN ORALLY ADMINISTERED SILDENAFIL (VIAGRA) AND PHENPROCOUMON IN HEALTHY MALE VOLUNTEERS" (1053):

DRUG STUDIED: Sildenafil

INVESTIGATOR: —

STUDY SITES:

Clinical Part:

Central Laboratory:

Study Dates: 26 September 2000 – 06 December 2000

Phase of Development: Phase 1

OBJECTIVE:

To determine and compare pharmacodynamic parameters AUC, C_{max}, and T_{max} of 3 mg phenprocoumon tablets given either alone or in combination with 100 mg sildenafil film coated tablets. The pharmacodynamic target parameter was the International Normalization Ratio (INR), for standardized assessment of the prothrombin time (PT) in anticoagulant therapy.

STUDY DESIGN:

An open, non-randomized, multiple dose pharmacodynamic interaction study. Fifteen subjects were enrolled to ensure that twelve subjects would complete the study.

Subjects were hospitalized on Day 0 until after the discharge examination which was performed on Days 18 or 20 when INR was < 2 and prothrombin time (Quick Test) reached at least 70% after the last phenprocoumon dose.

On Days 1 through 16, 3 mg of phenprocoumon were administered once daily after an overnight fast of at least 8 hours. If the INR was stable on Days 10 -12, phenprocoumon dosing was continued for Days 13 -16. Sildenafil was co-administered once daily on Days 15 -16 at 100 mg doses (test situation).

SUBJECTS:

Healthy male volunteers, 24 to 48 years old, a weight between 67 -88 kg and a height of 169 - 189 cm.

DOSAGE FORMS & TREATMENTS

Sildenafil (Viagra) 100 mg tablets, batch no.: 0022303, Pfizer, Ltd.

Phenprocoumon (Marcoumar) 3 mg tablet, batch no.: B1039, Roche Pharma.

The drugs were administered after an overnight fasting period in the morning of each study day at 07: 02 clock time with two-minutes intervals between individual dosages.

PHARMACODYNAMICS

Blood samples were drawn at the following time points: upon admission (Day 0); pre-dose on Days 1 to 12; at 0h (just prior to dosing), 1h, 2h, 4h, 8h, 12h and 24h after study drug administrations on Days 13 -16. Further blood sampling occurred at approximately 30, 48 and 72

hours after the last study drug administration until INR was less than 2 and prothrombin time (Quick Test) reached at least 70%.

Parameters

From plasma INR the following pharmacodynamic parameters were determined:

AUC_{0-t} [INR* h]: area under the INR-time-curve during a 24-hour dosage interval, calculated by the linear trapezoidal rule based on INR following drug administration up to the last measured INR at time point t

C_{max} [INR]: maximum during a 24-hour dosage interval

T_{max} [h]: time after first drug administration of a 24-hour dosage interval to reach C_{max}

ANALYTICAL METHODS:

Analytical measurements of prothrombin times and calculation of INR values were carried out. Prothrombin time was determined by single measurement for each sample. Analysis of prothrombin time was based upon

Table 17: Prothrombin time assay characteristics

Limit of quantitation: /

Reference values: /

Performance characteristics of the test [3.9, Data evaluation]:

- Coefficient of Variation (CV)*: /
- Accuracy: /
- (Relative Deviation (RD))*: /

These characteristics are acceptable.

STATISTICAL METHODS:

90% Confidence intervals using paired t-tests were calculated for the geometric mean ratios test/reference for AUC_{0-t} and C_{max} (ln-transformed values). The equivalence of the situations was concluded if the 90% confidence interval was in the range of 0.80 -1.25 for the AUC-ratio as well as for the ratio of C_{max}.

RESULTS:

Mean INR (\pm s. d.) for the whole study period (Days 1 -16) as well as separately for the test and reference situation are plotted below. From the mean INR plots no relevant difference between the test and the reference situation was observed.

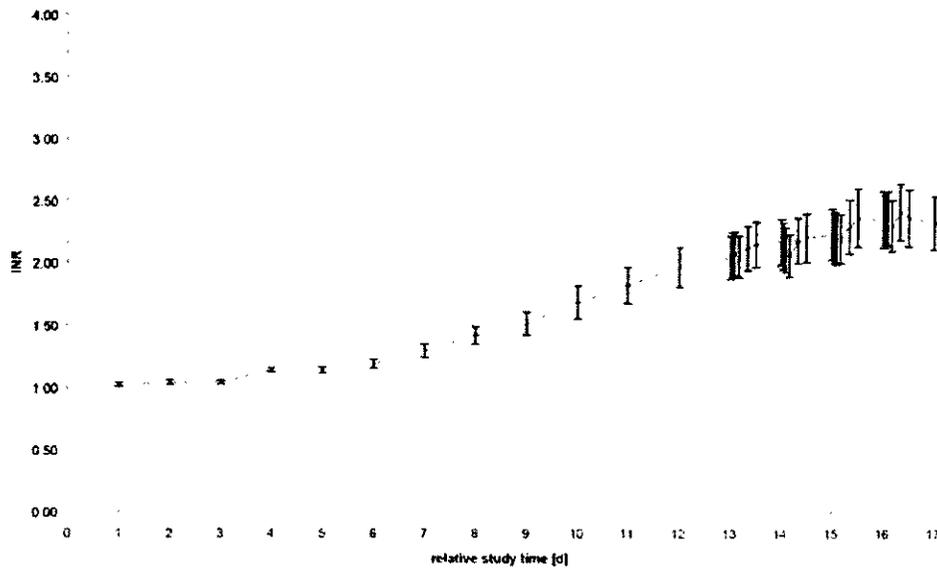


Figure 20: Mean INR values (\pm s. d.) obtained for the whole study period (Days 1 -16)

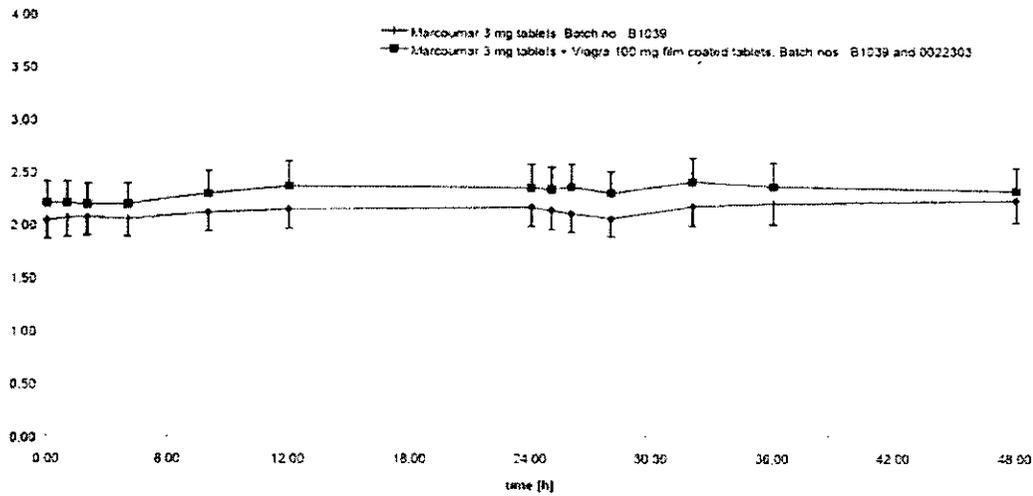


Figure 21: Mean INR values (\pm s. d.) obtained for the 48-hour periods (two 24-hour dosage intervals each) of the test situation (Days 15 -16) and the reference situation (Days 13 -14)

The pharmacodynamic parameters are compared in Table 2.

Table 18: Pharmacodynamic parameters (arithmetic means \pm s. d.)

Preparations	AUC _{0-t} [INR*h]	C _{max} [INR]	t _{max} [h]
Test Situation (Mean of Days 15 + 16): Marcoumar [®] 3 mg tablets+ Viagra [®] 100 mg film coated tablets	55.80 \pm 19.08	2.42 \pm 0.84	10.62 \pm 4.99
Reference Situation (Mean of Days 13 + 14): Marcoumar [®] 3 mg tablets	51.52 \pm 15.97	2.23 \pm 0.71	13.08 \pm 7.27
Test Situation (Days 15): Marcoumar [®] 3 mg tablets+ Viagra [®] 100 mg film coated tablets	55.28 \pm 19.12	2.40 \pm 0.85	14.77 \pm 8.70
Test Situation (Days 16): Marcoumar [®] 3 mg tablets+ Viagra [®] 100 mg film coated tablets	56.32 \pm 19.09	2.43 \pm 0.83	6.47 \pm 6.55
Reference Situation (Day 13): Marcoumar [®] 3 mg tablets	50.89 \pm 15.46	2.19 \pm 0.67	13.23 \pm 9.54
Reference Situation (Day 14): Marcoumar [®] 3 mg tablets	52.15 \pm 16.50	2.27 \pm 0.74	12.92 \pm 9.95

The observed confidence intervals including pertaining point estimators (geometric mean ratios) were as follows:

Test Situation (Mean of Days 15 -16) vs. Reference Situation (Mean of Days 13 -14)

AUC_{0-t}: 104.1% -110.3% (point estimator: 1.07)
 C_{max}: 104.5% -110.3% (point estimator: 1.07)
 T_{max}: -6.0 -1.0 (point estimator: -3.0 [h])

Statistical evaluation of pharmacodynamic effects observed within treatment periods Days 13 -14 and Days 15 -16 generated the following 90% confidence intervals including point estimators:

Test Situation (Day 15) vs. Test Situation (Day 16)

AUC_{0-t}: 96.3% -99.8% (point estimator: 0.98)
 C_{max}: 96.5% -100.7% (point estimator: 0.99)
 T_{max}: 2.0 -14.0 (point estimator: 8.0 [h])

Reference Situation (Day 13) vs. Reference Situation (Day 14)

AUC_{0-t}: 96.6% -99.5% (point estimator: 0.98)
 C_{max}: 95.4% -98.9% (point estimator: 0.97)
 T_{max}: -7.0 -8.0 (point estimator: 0.0 [h])

The equivalence, in terms of pharmacodynamic non-interaction, between the test and reference situation was demonstrated.

COMMENTS:

1. Based on the assumption that sildenafil might affect the anticoagulant activity, pharmacodynamic interaction between study drugs was assessed. The equivalence or pharmacodynamic non-interaction between test and reference was demonstrated. Maximum therapeutic doses of sildenafil (100 mg) did not influence the steady state pharmacodynamic response (INR) upon once daily 3 mg phenprocoumon doses.

**APPEARS THIS WAY
ON ORIGINAL**

4.3.4 PHASE I OPEN STUDY TO ASSESS THE POTENTIAL INTERACTION BETWEEN ORALLY ADMINISTERED SILDENAFIL (VIAGRA) AND ACENOCOUMAROL IN HEALTHY MALE VOLUNTEERS" (1054):

DRUG STUDIED: Viagra 100 mg film coated tablets, Batch No.: 0022303
Sintram 4 mg tablets, Batch No.: T9105

INVESTIGATOR: _____

STUDY SITES:

Clinical Part:

Central Laboratory: _____

Study Dates: 22 November 2000 – 17 January 2001

Phase of Development: Phase I

OBJECTIVE:

To determine and compare the pharmacodynamic parameters AUC, C_{max}, and T_{max} of 3 mg acenocoumarol tablets given either alone or in combination with 100 mg sildenafil film coated tablets. The pharmacodynamic target parameter was the International Normalization Ratio (INR), for standardized assessment of the prothrombin time (PT) in anticoagulant therapy.

STUDY DESIGN:

An open, non-randomized, multiple dose pharmacodynamic interaction study. Nineteen subjects were enrolled to ensure that fifteen subjects would complete the study.

Subjects were hospitalized on Day 0 until after the discharge examination which was performed on Days 16, 19 or 20 when INR was < 2 and prothrombin time (Quick Test) reached at least 70% after the last acenocoumarol dose.

On Days 1 through 16, 4 mg of acenocoumarol were administered once daily after an overnight fast of at least 8 hours. If the INR was stable on Days 10 -12, acenocoumarol dosing was continued for Days 13 -16. Sildenafil was co-administered once daily on Days 15 -16 at 100 mg doses (test situation).

SUBJECTS:

Healthy male volunteers, aged between 28 and 54 years, weighted between 68 – 91 kg and with the height of 165 – 192 cm.

DOSAGE FORMS & TREATMENTS

Sildenafil (Viagra) 100 mg tablets, batch no.: 0022303, Pfizer, Ltd.

Acenocoumarol (Sintram) 4 mg tablet, batch no.: T9105, Novartis Pharma.

The drugs were administered after an overnight fasting period in the morning of each study day at 07: 02 clock time with two-minutes intervals between individual dosages.

PHARMACODYNAMICS

Blood samples were drawn at the following time points: upon admission (Day 0); pre-dose on Days 1 to 12; at 0h (just prior to dosing), 1h, 2h, 4h, 8h, 12h and 24h after study drug

administrations on Days 13 -16. Further blood sampling occurred at approximately 24, 48, 72 and 96 hours after the last study drug administration until the INR was less than 2 and the prothrombin time (Quick Test) reached at least 70%.

Parameters

From plasma INR the following pharmacodynamic parameters were determined:

AUC_{0-t} [INR* h]: area under the INR-time-curve during a 24-hour dosage interval, calculated by the linear trapezoidal rule based on INR following drug administration up to the last measured INR at time point t

C_{max} [INR]: maximum during a 24-hour dosage interval

T_{max} [h]: time after first drug administration of a 24-hour dosage interval to reach C_{max}

ANALYTICAL METHODS:

Analytical measurements of prothrombin times and calculation of INR values were carried out. Prothrombin time was determined by single measurement for each sample. Analysis of prothrombin time was based upon

Table 19: Prothrombin time assay characteristics

Limit of quantitation:

Reference values:

Performance characteristics of the test [3.9, Data evaluation]:

- Coefficient of Variation: (CV)*:

- Accuracy:

(Relative Deviation (RD))*:

These characteristics are acceptable.

STATISTICAL METHODS:

90% Confidence intervals using paired t-tests were calculated for the geometric mean ratios test/reference for AUC_{0-t} and C_{max} (ln-transformed values). The equivalence of the situations was concluded if the 90% confidence interval was in the range of 0.80 -1.25 for the AUC-ratio as well as for the ratio of C_{max}.

RESULTS:

Mean INR (\pm s. d.) for the whole study period (Days 1 -16) as well as separately for the test and reference situation are plotted below. From mean INR plots no relevant difference between the test and the reference situation was observed.

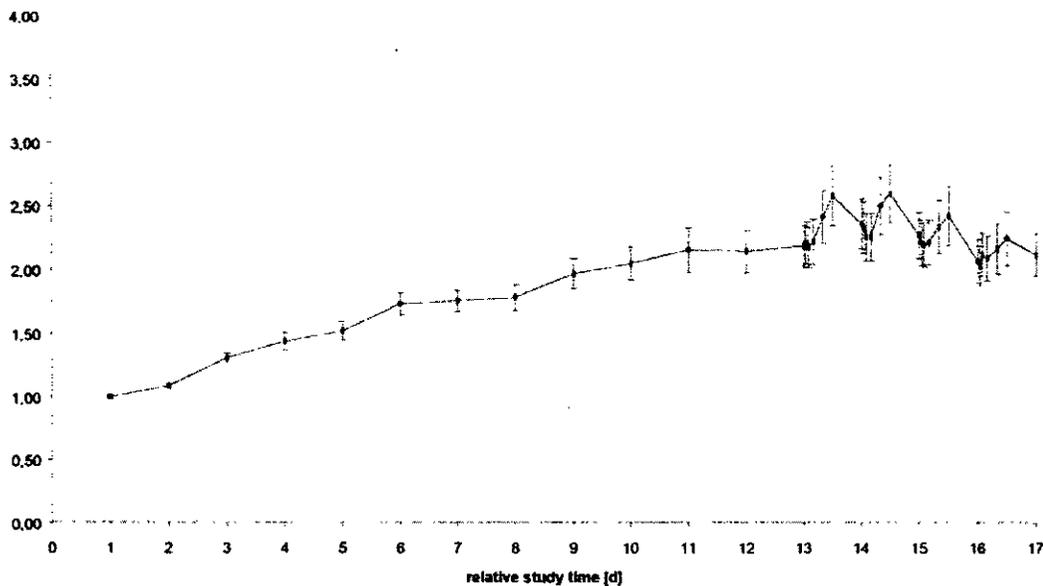


Figure 22: Mean INR values (± s. d.) obtained for the whole study period (Days 1 -16)

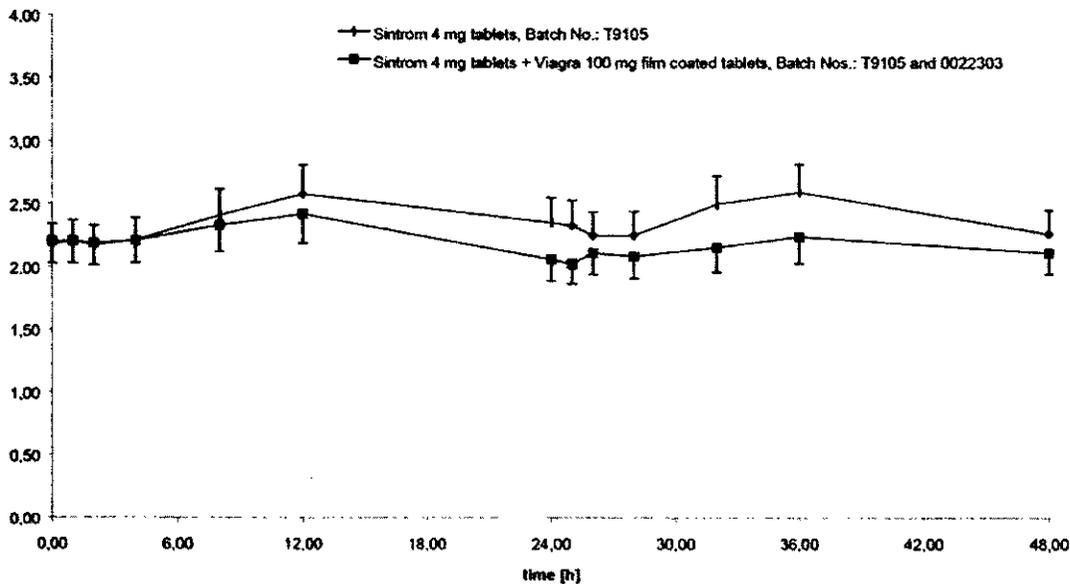


Figure 23: Mean INR values (± s. d.) obtained for the 48-hour periods (two 24-hour dosage intervals each) of the test situation (Days 15 -16) and the reference situation (Days 13 -14)

The pharmacodynamic parameters are compared in Table 2.

APPEARS THIS WAY
ON ORIGINAL

Table 20: Pharmacodynamic parameters (arithmetic means \pm s. d.)

Preparations	AUC _{0-t} [INR* <i>h</i>]	C _{max} [INR]	t _{max} [h]
Test Situation (Mean of Days 15 + 16): Sintrom [®] 4 mg tablets and Viagra [®] 100 mg film coated tablets	52.94 \pm 15.95	2.36 \pm 0.75	8.83 \pm 5.06
Reference Situation (Mean of Days 13 + 14): Sintrom [®] 4 mg tablets	57.72 \pm 17.01	2.60 \pm 0.81	10.04 \pm 3.57
Test Situation (Day 15): Sintrom [®] 4 mg tablets and Viagra [®] 100 mg film coated tablets	54.24 \pm 16.52	2.44 \pm 0.79	7.33 \pm 5.61
Test Situation (Day 16): Sintrom [®] 4 mg tablets and Viagra [®] 100 mg film coated tablets	51.63 \pm 15.44	2.29 \pm 0.71	10.33 \pm 5.71
Reference Situation (Day 13): Sintrom [®] 4 mg tablets	57.72 \pm 17.00	2.58 \pm 0.81	9.75 \pm 4.47
Reference Situation (Day 14): Sintrom [®] 4 mg tablets	57.92 \pm 17.12	2.61 \pm 0.82	10.33 \pm 3.60

The observed confidence intervals including pertaining point estimators (geometric mean ratios) were as follows:

Test Situation (Mean of Days 15 -16) vs. Reference Situation (Mean of Days 13 -14)

AUC_{0-t}: 88.8% -94.8% (point estimator: 0.92)
 C_{max}: 87.7% -94.8% (point estimator: 0.91)
 T_{max}: -3.0 -0.5 (point estimator: -1.0 [h])

Statistical evaluation of pharmacodynamic effects observed within treatment periods Days 13 - 14 and Days 15 -16 generated the following 90% confidence intervals including point estimators:

Test Situation (Day 15) vs. Test Situation (Day 16)

AUC_{0-t}: 102.6% -107.1% (point estimator: 1.05)
 C_{max}: 103.1% -109.1% (point estimator: 1.06)
 T_{max}: -6.0 -0.0 (point estimator: -2.0 [h])

Reference Situation (Day 13) vs. Reference Situation (Day 14)

AUC_{0-t}: 97.0% -101.6% (point estimator: 0.99)
 C_{max}: 95.4% -102.5% (point estimator: 0.99)
 T_{max}: -2.0 -2.0 (point estimator: 0.0 [h])

The equivalence, in terms of pharmacodynamic non-interaction, between the test and reference situation was demonstrated.

COMMENTS:

1. This study was performed to assess a pharmacodynamic interaction between sildenafil and acecoumarol based on the assumption that sildenafil might have an effect on the anticoagulant activity of the other drugs. The equivalence between test and reference was demonstrated. Maximum therapeutic doses of sildenafil (100 mg) did not influence the steady state pharmacodynamic response (INR) upon once daily 4 mg acenocoumarol doses.

**APPEARS THIS WAY
ON ORIGINAL**

4.3.5 A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO INVESTIGATE THE MUTUAL PHARMACOKINETIC INTERACTIONS BETWEEN BOSENTAN AND SILDENAFIL. (A148 -1149)

DRUG STUDIED:	Sildenafil Citrate
INVESTIGATOR AND STUDY SITE:	—
Safety data analysis:	—
Assay of sildenafil:	—
Assay of bosentan:	—
Assay of cortisol:	—
Study Dates:	9/10/2003 to 1/5/2004
Phase of Development:	Phase 1

OBJECTIVES:

To investigate the impact of bosentan on the pharmacokinetics of sildenafil
 To investigate the impact of sildenafil on the pharmacokinetics of bosentan
 To investigate the safety and tolerability of the co-administration of bosentan and sildenafil

STUDY DESIGN:

This was a randomized, double blind (third party open), placebo controlled, parallel group study in healthy male volunteers. Subjects were screened in the three weeks prior to study start. The subjects were randomly assigned to one of three treatment groups:

- Group A: sildenafil plus bosentan placebo,
- Group B: bosentan plus sildenafil placebo,
- Group C: sildenafil plus bosentan.

Each subject attended the unit on three occasions: at screening, for the main dosing and assessment part of the study (Day – 2 to Day 18) and for the follow-up visit. Due to the frequent dosing of sildenafil and bosentan, the subjects were required to reside in the unit from the evening of Day – 2 to the morning of Day 18.

SUBJECTS:

Healthy male volunteers who are between 18 and 45 years of age.

DRUG ADMINISTRATION & TREATMENTS:

Any prescribed or over the counter drug (except paracetamol) were not allowed three weeks prior and throughout the study. The consumption of grapefruit, grapefruit juice, alcohol, caffeine or methylxanthines, and unaccustomed exercise during the 48 hours prior to and throughout the study was not advised.

Table 21: Study Medications

Study drug	Lot number	Formulation identification number
Placebo tablet for sildenafil 20mg	CF-0400702 (03-003584)	F00008AC
Placebo tablet for sildenafil 80mg	CF-0370702 (03-000452)	F00010AC
Sildenafil 20mg tablet	CF-0350702 (03-004257)	F00012AE
Sildenafil 80mg tablet	CF-0481002 (03-004376)	F00016AE
Placebo tablet for bosentan 125mg	C0020001 (03-004505)	-
Bosentan 125mg tablet	F1034A001 (03-004504)	-

Table 22: Dosing & Treatment Schedule

Study day	Group A sildenafil plus bosentan placebo	Group B bosentan plus sildenafil placebo	Group C sildenafil plus bosentan
Days 1 to 3	sildenafil 20mg TID	sildenafil placebo TID	sildenafil 20mg TID
Days 4 and 5	sildenafil 80mg TID	sildenafil placebo TID	sildenafil 80mg TID
Day 6	sildenafil 80mg single morning dose	sildenafil placebo single morning dose	sildenafil 80mg single morning dose
Days 7 to 10	bosentan placebo BID	bosentan 125 mg BID	bosentan 125 mg BID
Day 11 to 13	sildenafil 20mg TID bosentan placebo BID	sildenafil placebo TID bosentan 125 mg BID	sildenafil 20mg TID bosentan 125 mg BID
Day 14 - 15	sildenafil 80mg TID bosentan placebo BID	sildenafil placebo TID bosentan 125 mg BID	sildenafil 80mg TID bosentan 125 mg BID
Day 16	sildenafil 80mg single morning dose bosentan placebo BID	sildenafil placebo single morning dose bosentan 125 mg BID	sildenafil 80mg single morning dose bosentan 125 mg BID
Day 17	bosentan placebo single morning dose	bosentan 125 mg single morning dose	bosentan 125 mg single morning dose

PHARMACOKINETICS**Blood Sampling****Sildenafil**

Day 1: time 0 (baseline, pre morning dose) and just before the second daily dose.

Days 2 to 5: just before the second daily sildenafil/placebo dose.

Day 6: time 0 (pre morning dose) and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6 and 8 hours after the morning dose (just before the second daily dose).

Day 11 to 15: just before the second daily sildenafil/placebo dose

Day 16: time 0 (pre morning dose) and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (just before the evening dose of bosentan/placebo on Day 16), 16, 18, 24 (just before the morning dose of bosentan/placebo on Day 17) and 36 hours after the morning dose of Day 16.

Bosentan

Day 7 to 9: pre morning dose.

Day 10: time 0 (pre morning dose) and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours (just before the evening dose of bosentan/placebo).

Day 11 to 15: pre morning dose.

Day 16: time 0 (pre morning dose) and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours (just before the evening dose of bosentan/placebo).

ANALYTICAL METHODS:

Plasma samples were analyzed for sildenafil and UK-103,320 using a previously validated high pressure liquid chromatography with ultraviolet detection method. The calibration range for both sildenafil and UK -103 320 was

Table 23: Assay Characteristics for Sildenafil and UK-103,320

Parameter	Measure		Reviewer Comment
	Sildenafil	UK-103,320	
Linearity	/		Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

The bosentan plasma samples were assayed for bosentan and its metabolites Ro 47-8634, Ro 48-5033 and Ro 64-1056 using a previously validated method.

Table 24: Assay Characteristics for Bosentan and its Metabolites

Parameter	Measure				Reviewer Comment
	Bosentan	Ro 48-5033	Ro 47-8634	Ro 64-1056	
Linearity	/				Satisfactory
Precision (CV%)					Satisfactory
Accuracy Between day					Satisfactory
LLOQ					Satisfactory
Specificity					Satisfactory

PHARMACODYNAMICS

The cortisol metabolic index was determined as a measure of CYP-3A4 induction. The urine samples were assayed for 6- β -hydroxycortisol and cortisol using a previously validated method

Table 25: Assay Characteristics for Cortisol and 6- β -hydroxycortisol

Parameter	Measure		Reviewer Comment
	Cortisol	6- β -hydroxycortisol	
Linearity	/		Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

Chromatograms were shown for each method.

Statistical Methods:

The sildenafil and UK-103,320 plasma pharmacokinetic parameters AUC_t, AUC, C_{max}, C_{avss}, T_{max}, t_{1/2}, and k_{el} were summarized by day and treatment group. The bosentan, Ro 47-8634, Ro 48-5033 and Ro 64-1056 plasma pharmacokinetic parameters AUC_t, C_{max}, C_{avss} and T_{max} were also summarized by day and treatment group. The two main comparisons of interest (ANOVA) were

1. Sildenafil + bosentan (Day 16 – Day 6) vs. sildenafil + bosentan placebo (Day 16 – Day 6)

2. Sildenafil + bosentan (Day 16 – Day 10) vs. bosentan + sildenafil placebo (Day 16 – Day 10).

The differences between treatment means, standard errors associated with these differences and corresponding 90% confidence intervals (CIs) were presented. For both AUC_t and C_{max}, the ratio of the anti-logged treatment means and the corresponding anti-logged CIs were shown.

The urine concentrations of cortisol and 6-β-hydroxycortisol and the ratio of 6-β-hydroxycortisol to cortisol were listed and summarized by treatment group on the day prior to treatment (Day – 1) and Days 6 and 16. The within group differences were also provided between Day 6 and – 1 and Day 16 and – 1.

Blood pressure and pulse rate data were summarized by the mean baseline and the mean changes from baseline at each measured time post dose, for each treatment group.

Pharmacokinetic Results:

Fifty-five healthy subjects were screened and assigned to study treatment. Demographics are shown in Table 26.

Table 26: Demographic Characteristics

	Sildenafil + Bosentan Placebo	Bosentan + Sildenafil Placebo	Sildenafil + Bosentan
	MALE	MALE	MALE
Number of Subjects	18	18	19
Age (years):			
< 18	0	0	0
18-44	18	18	19
45-64	0	0	0
>= 65	0	0	0
Mean	26.4	26.8	26.4
SD	5.8	5.9	5.7
Range	20-40	18-37	18-39
Race:			
WHITE	18	18	18
BLACK	0	0	1
Weight (kg):			
Mean	75.7	76.8	73.4
SD	9.9	6.9	7.9
Range	59.3-99.7	67.0-91.4	61.7-91.6
N	18	18	19
Height (cm):			
Mean	179.6	178.1	176.7
SD	5.6	6.5	7.3
Range	171.0-190.0	169.0-194.0	163.0-198.0
N	18	18	19

Sildenafil Pharmacokinetics

All comparisons for sildenafil pharmacokinetic parameters were based on within subject differences between Day 6 and Day 16.

In the presence of bosentan, mean sildenafil C_{max} and AUC_t were 55% and 63% lower, respectively, compared to placebo. In the sildenafil and bosentan treatment group mean sildenafil C_{max} and AUC_t were 55% and 60% lower between Days 6 and 16. The differences in T_{max} were not significant in each group. In the sildenafil and bosentan placebo group, the differences in parameters between Days 6 and 16 were not significant. Pharmacokinetic parameters of sildenafil are shown in Table 27.

Table 27: Pharmacokinetic parameters of sildenafil

Parameter	Group A (sildenafil plus bosentan placebo)				Group C (sildenafil plus bosentan)			
	N	Day 6	N	Day 16	N	Day 6	N	Day 16
AUC _t (ng.h/ml) ^a	17	1719.7 (30)	17	1846.5 (28.7)	16	1607.5 (45)	17	634.2 (35)
AUC (ng.h/ml) ^a		NC	16	2211.1 (31.5)		NC	16	698.8 (38)
C _{max} (ng/ml) ^a	17	580.3 (45)	17	585.2 (27.2)	17	611.0 (44)	17	274.9 (58)
C _{avss} (ng/ml) ^a	17	215.0 (30)	17	230.7 (28.8)	16	201.3 (45)	17	79.3 (35)
T _{max} (h) ^b	17	1.24 (70)	17	1.25 (72.1)	17	0.88 (68)	17	0.99 (50)
T _{1/2} (h) ^b		NC	16	4.46 (28.2)		NC	16	4.29 (80)
K _d (/h) ^c		NC	16	0.16		NC	16	0.16

Table 28: Comparison of Sildenafil Parameters

Parameter	Comparison	Ratio of Geometric Means (%)	90% Confidence Limits on Ratio of Means	
			Lower (%)	Upper (%)
AUC _t (ng.h/ml)	sil + bos (Day 16/Day 6)	37.4	32.3	43.2
	sil + bos pbo (Day 16/Day 6)			
	sil + bos (Day 16/Day 6)	40.1	36.2	44.5
	sil + bos pbo (Day 16/Day 6)	107.4	97.1	118.8
C _{max} (ng/ml)	sil + bos (Day 16/Day 6)	44.6	33.4	59.7
	sil + bos pbo (Day 16/Day 6)			
	sil + bos (Day 16/Day 6)	45.0	36.6	55.3
	sil + bos pbo (Day 16/Day 6)	100.8	82.1	123.9
Parameter	Comparison	Difference Between Means	90% Confidence Limits on Difference Between Means	
			Lower	Upper
T _{max} (h)	sil + bos (Day 16-Day 6) - sil + bos pbo (Day 16-Day 6)	0.09	-0.53	0.70
	sil + bos (Day 16-Day 6)	0.10	-0.33	0.54
	sil + bos pbo (Day 16-Day 6)	0.01	-0.42	0.45

Figures 1 and 2 below show the comparison of plasma sildenafil concentrations on Day 6 and 16 (Group A vs. Group C).

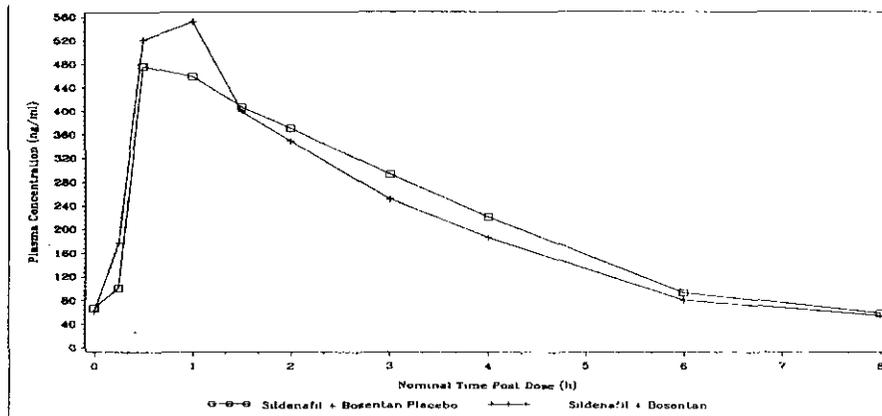


Figure 24: Mean Plasma Sildenafil Concentrations, Day 6, Group A vs. Group C.

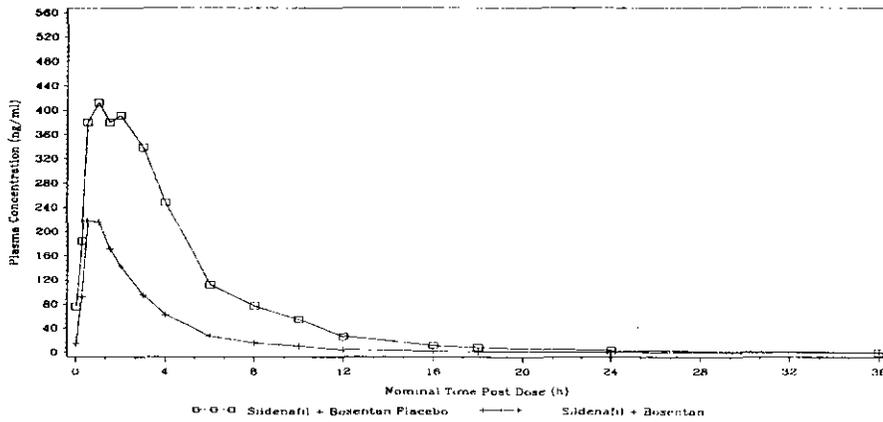


Figure 25: Mean Plasma Sildenafil Concentrations, Day 16

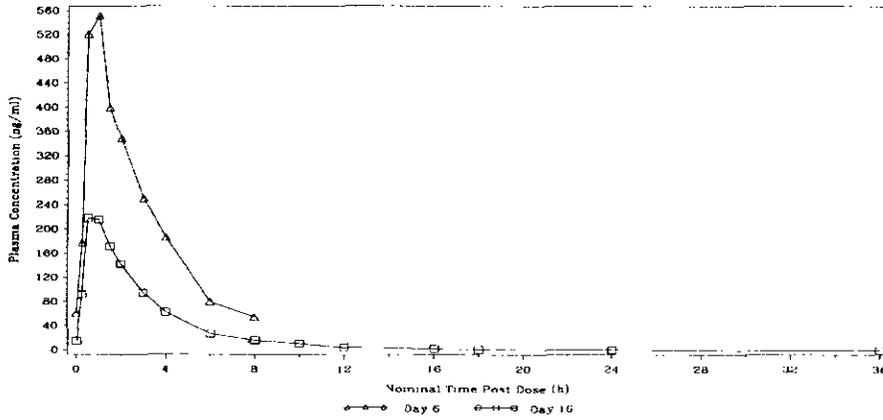


Figure 26: Mean Plasma Sildenafil Concentrations, Day 6 vs. Day 16, Group C

Figure 3 compares sildenafil plasma profiles on Day 6 and 16 for Group C.

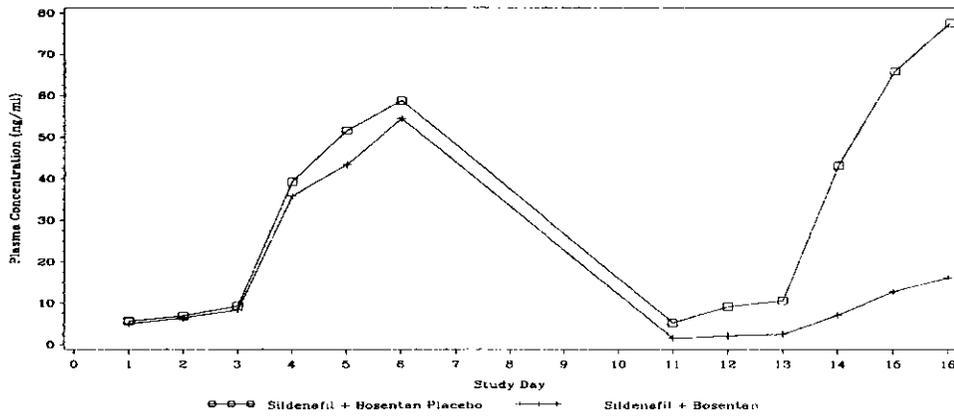


Figure 27: Mean Trough Plasma Sildenafil Concentrations, Group A vs. Group C.

Figure 28 below shows the comparison of mean plasma concentrations of sildenafil metabolite in the group who received only sildenafil (circles) vs. the group who received both sildenafil and bosentan (squares).

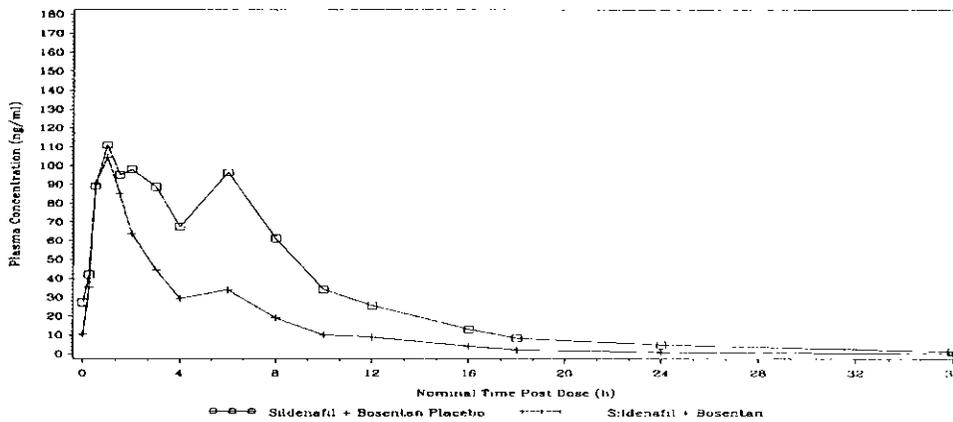


Figure 28: Mean Plasma Concentrations of UK-103,320, Group A vs. Group C, Day 16.

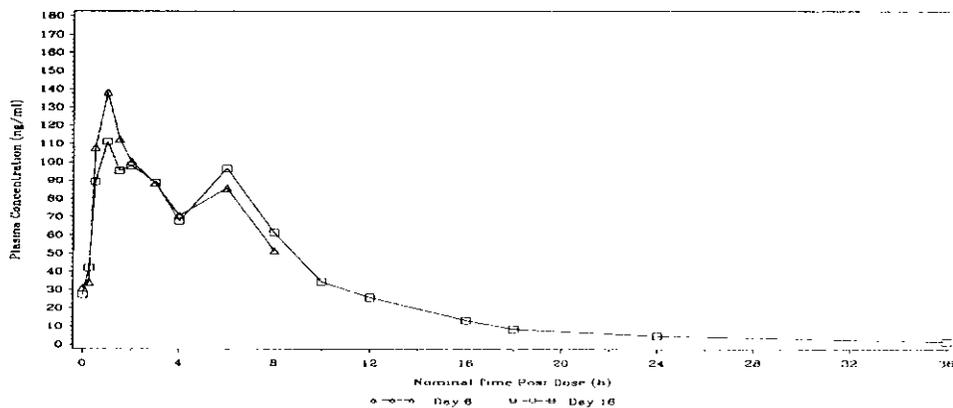


Figure 29: Mean Plasma Concentrations of UK-103,320, Day 6 vs. Day 16, Group A.

There were no changes in the sildenafil metabolite kinetics in the sildenafil + bosentan placebo group (Figure 6). Due to the enzyme induction caused by bosentan, the AUCt of UK-103,320 showed an increase during the co-administration with bosentan (Figure 7). The sponsor has not performed a formal statistical analysis on the UK-103,320 data.

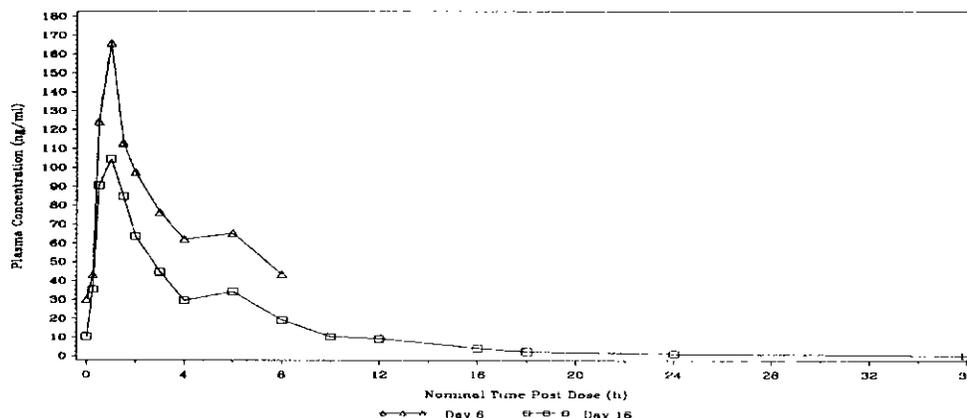


Figure 30: Mean Plasma Concentrations of UK-103,320, Day 6 vs. Day 16, Group C.

Bosentan Pharmacokinetic Parameters

All comparisons for bosentan pharmacokinetic parameters were based on within subject comparisons between Day 10 and Day 16.

In the presence of sildenafil, mean bosentan C_{max} and AUC_t were 42% and 50% higher compared to placebo. In the sildenafil and bosentan treatment group, mean C_{max} and AUC_t were 21% and 30% higher on Day 16 compared to Day 10. In the sildenafil placebo and bosentan treatment group mean C_{max} and AUC_t were 15% and 13% lower, on Day 16 compared to Day 10.

Table 29: Bosentan Pharmacokinetic Parameters

Parameter	Group B (bosentan plus sildenafil placebo)				Group C (sildenafil plus bosentan)			
	N	Day 10	N	Day 16	N	Day 10	N	Day 16
AUC _t (ng.h/ml) ^a	18	5203.5 (27)	17	4355.3 (22)	17	5337.2 (29)	17	6924.6 (32)
C _{max} (ng/ml) ^a	18	1111.3 (34)	17	912.0 (31)	17	1278.7 (37)	17	1546.8 (34)
C _{avss} (ng/ml) ^a	18	433.8 (26)	17	363.0 (22)	17	444.8 (29)	17	577.3 (32)
T _{max} (h) ^b	18	2.94 (32)	17	2.82 (31)	17	2.71 (31)	17	2.85 (38)

Table 30: Comparison of Bosentan Parameters

Parameter	Comparison	Ratio of Geometric Means (%)	90% Confidence Limits on Ratio of Means	
			Lower (%)	Upper (%)
AUC _t (ng·h/ml)	sil + bos (Day 16/Day 6)	149.8	128.7	174.5
	bos + sil pbo (Day 16/Day 10)			
	sil + bos (Day 16 / Day 10)	129.7	116.5	144.5
	bos + sil pbo (Day 16 Day 10)	86.6	77.8	96.4
C _{max} (ng/ml)	sil + bos (Day 16/Day 6)	142.0	115.4	174.8
	bos + sil pbo (Day 16/Day 10)			
	sil + bos (Day 16 / Day 10)	121.0	104.4	140.1
	bos + sil pbo (Day 16/Day 10)	85.2	73.5	98.6

Parameter	Comparison	Difference Between Means	90% Confidence Limits on Difference Between Means	
			Lower	Upper
T _{max} (h)	sil - bos (Day 16-Day 6) - bos + sil pbo (Day 16-Day 10)	0.26	-0.47	1.00
	sil - bos (Day 16-Day 10)	0.15	-0.37	0.67
	bos + sil pbo (Day 16-Day 10)	-0.12	-0.64	0.40

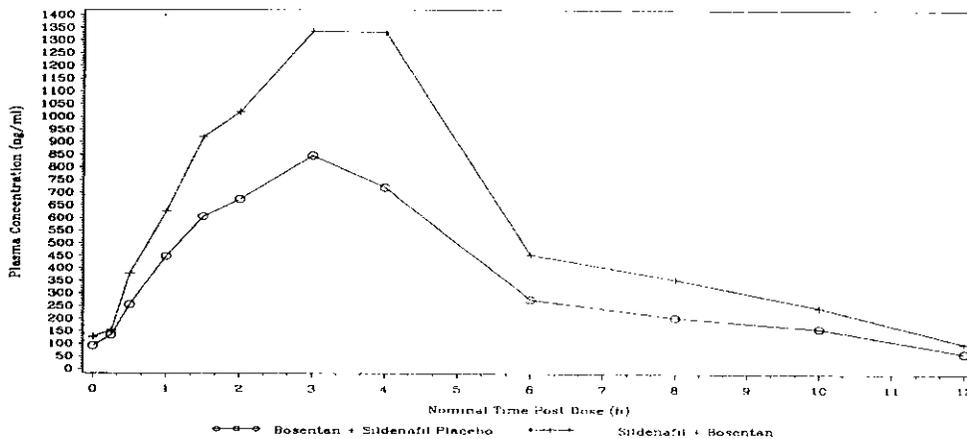


Figure 31: Mean Plasma Bosentan Concentrations, Group B vs. Group C, Day 16.

The sponsor has not performed a formal statistical analysis on the metabolites of bosentan. There were no major changes of the ratios of AUC_t metabolites/bosentan observed during the co-administration of sildenafil.

PHARMACODYNAMIC RESULTS

In Group A the 6-β-hydroxycortisol/cortisol ratio between Day - 1 and Day 16 decreased by 1.14, in Groups B and C it increased by 3.39 and 2.98, respectively.

Group	N	Day -1	N	Day 16	N	Difference (Day16- Day -1)
Group A (sildenafil plus bosentan placebo)	13	5.47 (33)	14	4.48 (31)	12	-1.14 (-163)
Group B (bosentan plus sildenafil placebo)	15	6.27 (37)	15	9.58 (37)	13	3.39 (64)
Group C (sildenafil plus bosentan)	13	6.36 (38)	12	8.65 (36)	10	2.98 (48)

Effect on Blood Pressure and Heart Rate:

The sponsor presented the mean changes in standing and supine systolic and diastolic blood pressure and heart rate from each of the treatment group. The changes were more pronounced in the Group C with combined treatment (Table 31), however, these changes were not considered to be clinically significant.

Table 31: Mean Changes in Vital Signs on Day 16

POSITION	TIME POST DOSE (Hrs)	Group A: Sildenafil 80mg OD + Bosentan Placebo BID			Group B: Sildenafil Placebo OD + Bosentan 125mg BID			Group C: Sildenafil 80mg OD + Bosentan 125mg BID		
		MEAN	SD	N	MEAN	SD	N	MEAN	SD	N
Standing Systolic BP (mmHg)										
	0	-7.3	9.5	17	-5.6	11.3	17	-5.7	15.1	16
	1	-3.3	14.6	17	-4.8	9.2	17	-7.6	13.6	17
	2	-11.4	12.9	17	-6.2	12.4	17	-6.3	14.8	17
	3	-6.1	8.5	17	-5.7	18.3	17	-5.5	13.1	17
	4	-7.1	10.6	17	-4.5	13.7	17	-4.6	12.1	17
	6	-2.9	9.3	17	1.7	12.3	17	5.1	12.9	17
	8	-4.0	12.8	17	-6.8	13.3	17	-0.7	13.8	17
Standing Diastolic BP (mmHg)										
	0	-5.9	6.9	17	-4.3	6.3	17	-6.8	10.0	16
	1	-5.5	6.2	17	-4.1	8.7	17	-8.9	7.7	17
	2	-9.2	5.1	17	-5.4	6.2	17	-7.9	12.2	17
	3	-4.2	7.4	17	-3.7	8.8	17	-7.2	7.2	17
	4	-4.2	7.8	17	-5.5	7.3	17	-7.5	7.7	17
	6	-4.4	7.5	17	-5.4	6.7	17	-4.5	10.3	17
	8	-5.5	8.7	17	-4.1	5.7	17	-5.7	6.0	17
Standing Heart Rate (bpm)										
	0	7.8	9.9	17	7.8	8.4	17	6.3	8.9	16
	1	6.2	12.5	17	3.4	10.6	17	5.4	12.7	17
	2	5.3	13.2	17	7.2	13.9	17	11.1	15.8	17
	3	2.6	11.8	17	3.0	11.3	17	4.6	11.8	17
	4	3.7	9.9	17	2.7	6.5	17	2.4	10.4	17
	6	16.3	12.3	17	13.5	7.6	17	13.3	11.7	17
	8	8.1	10.9	17	6.0	12.5	17	3.6	7.4	17
Supine Systolic BP (mmHg)										
	0	-7.0	8.1	17	-9.0	7.2	17	-6.6	12.2	17
	1	-4.6	8.6	17	-7.6	7.1	17	-8.7	9.2	17
	2	-9.0	6.9	17	-8.0	7.6	17	-10.1	8.9	17
	3	-8.3	5.4	17	-7.0	10.1	17	-10.7	12.8	17
	4	-6.6	6.6	17	-8.0	9.8	17	-5.9	12.0	17
	6	-4.4	8.4	17	-2.0	12.4	17	-0.3	9.6	17
	8	-2.9	9.2	17	-5.5	7.4	17	-1.3	7.7	17
Supine Diastolic BP (mmHg)										
	0	-7.6	4.0	17	-7.9	4.7	17	-7.6	5.5	17
	1	-7.3	4.6	17	-6.5	6.5	17	-8.7	4.8	17
	2	-8.0	4.9	17	-5.2	6.3	17	-8.7	5.5	17
	3	-6.6	5.0	17	-5.8	5.2	17	-10.0	8.9	17
	4	-5.1	7.7	17	-5.6	5.5	17	-7.6	5.8	17
	6	-8.4	4.8	17	-6.5	5.3	17	-7.8	7.6	17
	8	-6.7	6.6	17	-4.1	5.5	17	-6.2	6.3	17
Supine Heart Rate (bpm)										
	0	9.2	9.4	17	5.5	7.5	17	6.7	7.1	17
	1	6.3	7.9	17	7.2	8.9	17	5.3	7.2	17
	2	4.9	8.1	17	5.0	7.6	17	4.4	7.3	17
	3	6.6	9.8	17	4.2	7.3	17	4.7	6.2	17
	4	5.9	8.0	17	2.9	6.6	17	7.3	5.9	17
	6	14.7	9.4	17	12.5	7.6	17	15.6	7.2	17
	8	9.5	8.3	17	5.8	6.7	17	10.7	6.4	17

Sponsor's Conclusions:

- In the presence of bosentan, mean sildenafil C_{max} and AUC_t were 55% and 63% lower compared to placebo. In the sildenafil and bosentan treatment group, mean sildenafil C_{max} and AUC_t decreased by 55% and 60% on Day 16 compared to Day 6. In the sildenafil and bosentan placebo treatment group, mean sildenafil C_{max} and AUC_t were similar on Day 6 and Day 16.

2. In the presence of sildenafil, mean bosentan C_{max} and AUC_t increased by 42% and 50% compared to placebo. In the sildenafil and bosentan treatment group, mean C_{max} and AUC_t increased by 21% and 30% from Day 10 to Day 16. In the sildenafil placebo and bosentan treatment group, mean C_{max} and AUC_t decreased by 15% and 13% from Day 10 to Day 16.
3. The mean 6-β-hydroxycortisol/cortisol ratio between Day – 1 and Day 16 was lower in Group A by 1.14 and higher in Groups B and C by 3.39 and 2.98, respectively.

COMMENTS

1. The study was well designed and was able to determine whether there is an interaction between sildenafil and bosentan.
2. Sildenafil kinetics: In the presence of bosentan, mean sildenafil C_{max} and AUC_t were 55% and 63% lower compared to placebo. In the sildenafil and bosentan treatment group, mean sildenafil C_{max} and AUC_t decreased by 55% and 60% on Day 16 compared to Day 6. In the sildenafil and bosentan placebo treatment group, mean sildenafil C_{max} and AUC_t were similar on Day 6 and Day 16.
3. Bosentan kinetics: 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. In the sildenafil and bosentan treatment group, mean C_{max} and AUC_t increased by 21% and 30% from Day 10 to Day 16. In the sildenafil placebo and bosentan treatment group, mean C_{max} and AUC_t decreased by 15% and 13% from Day 10 to Day 16.
4. The higher mean 6-β-hydroxycortisol/cortisol ratio between Day – 1 and Day 16 in Groups B and C (3.39 and 2.98) in comparison with Group A (1.14) confirmed that in presence of bosentan CYP3A4 was induced.
5. The decreases in blood pressure and increase in heart rate were slightly higher in the group of healthy subjects receiving the combination of sildenafil and bosentan and it was not unexpected for these drugs. The sponsor considered these changes to be clinically insignificant.
6. The sponsor mentioned in the Package Insert regarding the alteration of plasma levels of both drugs when sildenafil is coadministered with bosentan however, the recommendations are not definite.
7. There is no need for the dose adjustment when sildenafil and bosentan are coadministered.

4.3.6 EFFICACY AND TOLERATION OF INTRAVENOUS SILDENAFIL IN SUBJECTS WITH PULMONARY HYPERTENSION. A Population Pharmacodynamic/Pharmacokinetic Analysis of Sildenafil Pulmonary & Systemic Hemodynamic Data (A148 1024)

DRUG STUDIED: Sildenafil Citrate
INVESTIGATORS AND STUDY SITES: Multicenter
Study Dates: 1/7/2000-29/1/2002
Population Data Analysis Report: 10/22/2004
Phase of Development: Phase 2a

OBJECTIVES

Primary:

To assess the effect of IV sildenafil on PVR in subjects with pulmonary hypertension. The study hypothesis was that intravenous (IV) sildenafil may decrease PAP and PVR in a similar or greater proportion of subjects compared to placebo.

Secondary:

To observe the effect of IV sildenafil on systolic, diastolic and mean PAP (sPAP, dPAP and mPAP); cardiac output (CO); pulmonary capillary wedge pressure (PCWP); systolic, diastolic and mean systemic arterial blood pressure (sBP, dBP and mBP); systemic venous pressure (SVP); mixed venous oxygen saturation (mVO₂); and systemic vascular resistance (SVR) in comparison to NO and placebo. In addition, arterial partial pressure of oxygen and carbon dioxide (PaO₂ and PaCO₂ respectively) and saturation of oxygen (SpO₂) were observed.

To assess the safety and tolerance of IV sildenafil in subjects with pulmonary hypertension.

To assess the optimal infusion dose of sildenafil to reduce PVR

To assess the clinical viability of sildenafil in the management of subjects with pulmonary hypertension

To assess the feasibility of conducting this protocol methodology in subjects with hypoxic pulmonary hypertension (referred to in the protocol as: chronic obstructive pulmonary disease).

STUDY DESIGN:

This study was a pilot, multi-centre study to assess the safety, efficacy and toleration of IV sildenafil in subjects with pulmonary hypertension. Subjects were stratified into one of three groups prior to randomization according to type of pulmonary hypertension [pulmonary arterial hypertension (primary and secondary) (Group 1a), pulmonary venous hypertension due to congestive heart failure (Group 1b), and hypoxic pulmonary hypertension (Group 2)]. The ratio of Group 1 subjects receiving sildenafil versus placebo was three to one. All subjects in Group 2 received sildenafil.

The treatment phase was carried out in the cardiac catheterization laboratory at each centre. A 7F triple lumen flow directed thermal dilution catheter was inserted through the right internal jugular, brachial or femoral vein into the pulmonary artery under fluoroscopic control. An arterial line (appropriate site decided by the investigator) was

installed to measure blood pressure continuously throughout the treatment phase, and to facilitate periodic assessment of PaO₂ and PaCO₂. SpO₂ was measured and a peripheral venous cannula was inserted for infusion of study drug. Once the catheter was inserted baseline haemodynamic measurements were performed, these were repeated three times over half an hour to ensure stability of the data.

The haemodynamic parameters measured throughout the treatment phase were:

- pulmonary artery pressure (PAP, systolic, diastolic and mean)
- systemic arterial blood pressure (systolic, diastolic and mean)
- pulmonary capillary wedge pressure
- systemic venous pressure
- mixed venous oxygen saturation
- heart rate
- cardiac output.

Pulmonary and systemic vascular resistance (PVR and SVR) were calculated.

After the initial baseline (Baseline 1) assessment the subjects who received NO were given 40ppm of NO by inhalation for five minutes. When the value of PAP returned to a re-established baseline (Baseline 2) (\pm 5% Baseline 1) haemodynamic measurements were conducted followed by the step infusion of study drug.

The infusion was administered at a controlled rate to maintain plasma concentrations of 100, 300 and 500ng/ml in the original part of the protocol. For the extension phase the infusion was administered at a controlled rate to maintain plasma concentrations of 10, 50 and 100ng/ml.

Haemodynamic measurements at each plasma level were performed after 10 minutes of every maintenance step of the infusion.

Blood samples (5ml) were withdrawn from the pulmonary artery to measure plasma levels of study drug at times coinciding with the haemodynamic measurements during the maintenance steps of the infusion.

NO or study drug was discontinued if mBP fell by 10% or more than the baseline reading, and in Group 2 only if PaO₂ fell by more than 10mm/Hg from the baseline reading or the subject developed shortness of breath.

INVESTIGATIONAL PRODUCTS

Sildenafil formulation identification number (FID) S00027CA, Lot 7057-132 and 4687-196 were supplied in 50ml vials of 1mg/ml. Placebo FID S00781AA, Lot 7057-133 and 4687-195 were supplied as 50ml vials of 5% mannitol solution. The batches of study drug provided in Table 32.

Table 32: Test Drugs

<u>Drug</u>	<u>Lot Number</u>	<u>FID Number</u>	<u>Potency</u>	<u>Formulation</u>
Sildenafil Citrate	7057-132	S00027CA	1mg/ml	Solution
Mannitol (Placebo)	7057-133	S00781AA	5%	Solution
Sildenafil Citrate	4687-196	S00027CA	1mg/ml	Solution
Mannitol (Placebo)	4687-195	S00781AA	5%	Solution

SUBJECTS:

Male or female subjects (aged 18 years or over) with pulmonary hypertension with mean pulmonary artery pressure = 25mmHg at rest.

PHARMACOKINETICS

Blood Sampling

During sildenafil infusion, blood samples (5ml to provide a minimum plasma volume of 3ml) is taken in parallel to the haemodynamic measurements, starting at pre-infusion for the 1st sample. The sampling is carried out from pulmonary blood. During infusion, sampling is performed at the three maintenance levels of the step infusion.

Plasma concentrations of sildenafil and the metabolite UK -103,320 was measured by a pre-validated analytical method. Only samples taken from the patients on active treatment were analyzed.

ANALYTICAL METHODS:

Plasma samples were analyzed for sildenafil and UK-103,320 using a previously validated high pressure liquid chromatography with ultraviolet detection method. The calibration range for both sildenafil and UK -103 320 was

Table 33: Assay Characteristics for Sildenafil and UK-103,320

Parameter	Measure		Reviewer Comment
	Sildenafil	UK-103,320	
Linearity			Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

Chromatograms were shown for each method.

**APPEARS THIS WAY
ON ORIGINAL**

A POPULATION PHARMACODYNAMIC/PHARMACOKINETIC ANALYSIS OF SILDENAFIL PULMONARY & SYSTEMIC HEMODYNAMIC DATA

SUBJECTS:

The original protocol included 30 patients and was extended later. The final data set available for the population PK/PD analysis included data from 85 patients. The patient groups are shown in Table 1.

	Original Study		Study Extension			
	Sildenafil with NO	Placebo with NO	Sildenafil with NO	Placebo with NO	Sildenafil without NO	Placebo without NO
Group 1a - pulmonary arterial hypertension (primary and secondary)	12	3	9	3	14	4
Group 1b - pulmonary venous hypertension due to congestive heart failure	10	3	9	3	6	3
Group 2 - hypoxic pulmonary hypertension	6					

DATA

The SAS programs were used to create the NONMEM data sets from the original data sets and details on the data sets. Criteria for exclusion of data points are acceptable.

METHODOLOGY

Formal population PK/PD analysis was performed using the non-linear mixed effects modeling approach. The UNIX system utilized a SUN Sparcf77 compiler while the DOS setup used the Compaq Fortran 6.5 compiler.

The statistical package Splus 6 (Insightful Inc.) installed in a PC platform under Windows 2000 was used for the exploratory analysis and Xpose, version 3.031 (University of Uppsala, Sweden) as well as SAS version 8 in a PC platform under Windows 2000 were used to assist in the model building.

Covariate Model Building

The general approach for the covariate analysis was similar for PK/PD analyses and the investigation of the impact of covariates on sildenafil clearance in patients with pulmonary hypertension.

The following covariates were investigated on the appropriate PK/PD parameters: age, weight, body mass index, body surface area, history of alcohol intake, history of smoking, gender, study center, patient group, serum creatinine, urea, glomerular filtration rate (calculated with Cockcroft and Gault equation), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin.

Comedications were tested for their potential impact on the relationship between sildenafil exposure and pulmonary and systemic hemodynamic parameters. Comedications given to less than 4 patients were not included in the analysis.

The covariate effects were evaluated through a stepwise, automated covariate model-building algorithm. An exponential model was used for all continuous covariates if deemed appropriate. The forward inclusion criteria of a drop in objective function value OFV (for one degree of freedom) by at least 3.84 ($p=0.05$) and a backward elimination criterion of a change of 10.83 ($p=0.001$) were employed. For the covariate center (eight categories), there are seven degrees of freedom, thus the appropriate criteria for forward and backward consideration, were 14.07 and 24.32 changes in OFV, respectively.

Endpoints:

The pulmonary hemodynamic endpoints:

- Mean pulmonary artery pressure (mean PAP)
- Pulmonary vascular resistance (PVR)
- Systolic pulmonary artery pressure (systolic PAP)
- Diastolic pulmonary artery pressure (diastolic PAP)

The systemic hemodynamic endpoints:

- Mean arterial pressure (MAP)
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)

Structural Models

The structural models were built in three steps: modeling of the placebo data, modeling of the active treatment data and combined modeling of active treatment and placebo data. The baseline data did not change sufficiently over time to build a separate baseline model. Therefore, both active treatment and placebo data were modeled as change from baseline. Emax and linear models were investigated. Additive or proportional changes from baseline were explored. The combined model was additive (Placebo + Active).

Estimation Methods

The sponsor used the first-order conditional estimation method or ln-additive models for residual variability and first-order conditional estimation method with interaction (FOCEI) with proportional, additive + proportional and exponential models for residual variability.

Covariate Modeling

Men and women were equally represented in the data set. Race was not investigated because the majority of the subjects were Caucasian. Smokers represented about 13% of the patients, 42% never smoked and 45% were ex-smokers. Groups 1A, 1B and Group 2 had 53%, 40% and 7% of all patients.

Loop diuretics and oral anticoagulants were the most frequently administered comedications in this patient population.

Statistical Models

The data supported the estimation of inter-subject variability terms on baseline for active treatment and placebo, but not on Emax or slope. An additive model was used for all endpoints.

The following models for residual variability were used in the PK/PD analyses:

- Mean PAP: additive

- PVR: combined additive/proportional
- Diastolic PAP: proportional
- MAP: additive
- SBP: proportional for active treatment, additive for placebo
- DBP: additive

Internal Validation

The model diagnostics included objective function value changes (for p values see above), goodness of fit plots and precision of parameter estimates. The 90% confidence intervals of the parameters of each final model were obtained by bootstrapping (100 replicates for each endpoint). The 5% and 95% percentiles of the bootstrap distribution were used as lower and upper boundaries of the 90% confidence interval. The bias of the PK/PD parameter estimates was calculated by subtracting the population mean from the bootstrap mean.

As the current data set was relatively small, contained a lot of subgroups and included the data of only one study, no formal model validation was done at this point in time.

Modeling of Sildenafil Clearance

Due to the nature of the data, only a limited pharmacokinetic evaluation could be done. Sildenafil clearance was estimated from steady state concentrations. An exponential model was used for inter-subject variability, an additive model for residual variability.

RESULTS:

Mean Pulmonary Artery Pressure

Structural Models:

Placebo = Baseline $-(E_{max} * Time / (TE_{50} + Time))$

Treatment = Baseline $-(E_{max} * Concentration / (EC_{50} + Concentration))$

Observation = placebo + treatment.

The sponsor's model could not properly estimate the E_{max} and TE_{50} values for placebo treatment. The covariates were only tested on placebo baseline and on all parameters estimated for active treatment. The intermediate model included the effect of patient group on the baseline of active treatment and penicillins, oral anticoagulants as well as loop diuretics on E_{max} . From the bootstrap results, the effect of patient group was not important. Parameters of the final model for PAP are shown in Table 34.

Table 34: Parameters of the Final Model

Parameter	Population Mean	± SE of estimate
Baseline Placebo mmHg	20.9	1.25
inter-subject variability,%	5.2	
E_{max} Placebo, mmHg	-0.95	1.47
TE_{50} , h	0.681	0.79
Baseline Active Treatment, mmHg	17.8	0.654
inter-subject variability,%	5.2	
E_{max} Active Treatment	5.81	1.04

Loop Diuretics on Emax	0.645	0.27
Anticoagulants on Emax	-0.375	0.109
EC50, ng/mL	13.7	8.83
Residual Variability, %	3.02	

Figure 1 shows the observed values of mean pulmonary artery pressure, the population mean predictions and the individual predictions versus time (placebo) and sildenafil plasma concentrations (active treatment).

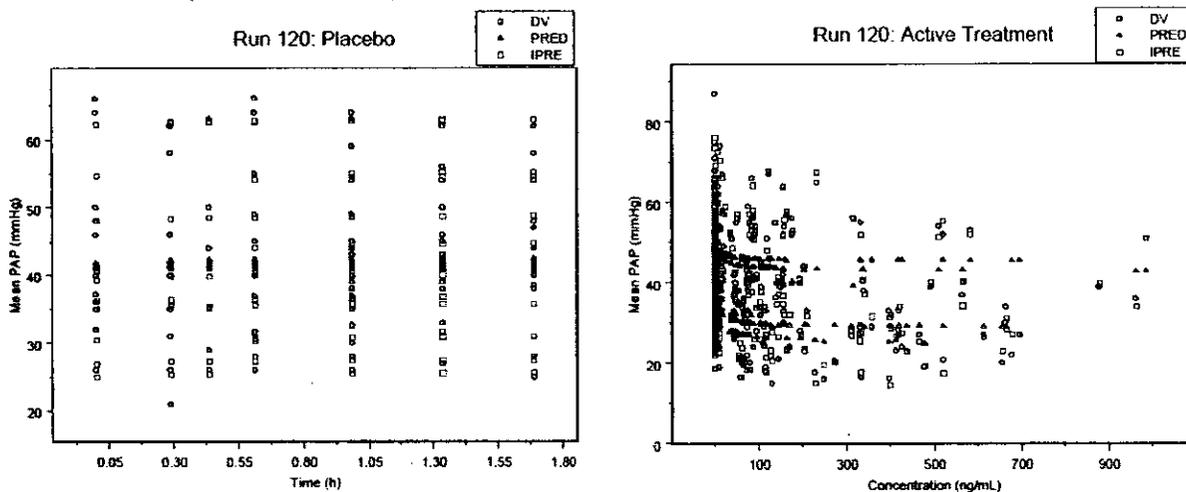


Figure 32: Mean pulmonary artery pressure vs. time (placebo) or sildenafil concentration

Goodness of fit plots were satisfactory for the active treatment.

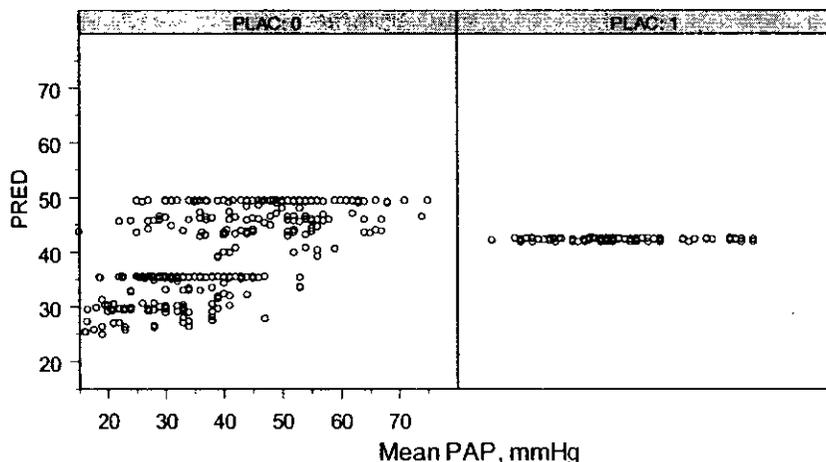


Figure 33: Predicted vs. observed mean PAP of sildenafil (left and placebo (right))

The Emax values estimated for placebo and active treatment and in patients using anticoagulants and loop diuretics compared below.

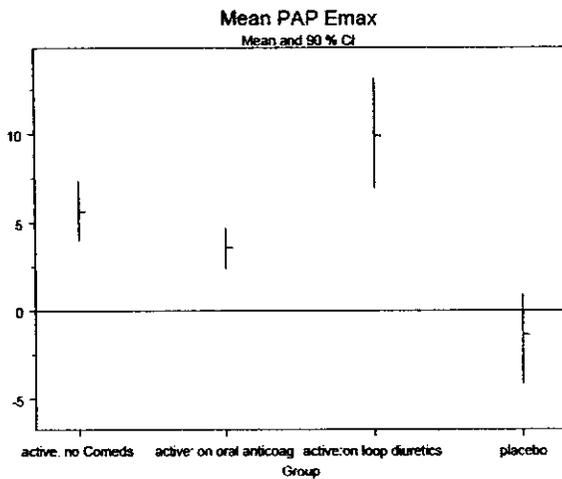


Figure 34: Mean and SE of Emax values for PAP

Treatment with sildenafil affected most patients who were simultaneously taking loop diuretics.

Pulmonary Vascular Resistance

Structural Models:

Placebo = Baseline * (1 - Emax * Time / (TE50 + Time))

Treatment = Baseline * (1 - Emax * Concentration / (EC50 + Concentration))

The sponsor's model did not properly estimate the Emax and TE50 values for placebo treatment, and the covariates were only tested on placebo baseline and on all parameters estimated for active treatment. The model resulting from the automated covariate search included patient group on the baseline of active treatment, smoking history on the maximum treatment effect and since PVR and not PVRi (PVR normalized for body surface area) was used, body surface area appeared as a covariate on baseline for both, active treatment and placebo. The bootstrap results showed that bias were significant for Emax of both placebo and sildenafil.

The parameters for the final model are shown in Table 35.

**APPEARS THIS WAY
ON ORIGINAL**

Table 35: NONMEM parameters estimates for PVR

Run No	219			
Objective Function Value	588			
Residual Variability (CV %) +/- SE (%)	12.4		30	
Residual Variability (SD) +/- SE (%)	354		22.2	
	Placebo		Active Treatment	
Baseline (dyne*sec*cm-5) +/- SE (%)	111	11.1	73.8	15.3
Intersubject Variability of Baseline (SD) +/- SE (%)	87	19.9	162	31.2
Emax (% change from BL) +/- SE (%)	-79	54.0	99.9	8.8
EC50 (ng/ml) +/- SE (%)			17.6	30.8
TE50 (h) +/- SE (%)	2.71	97.8		
Pat Group 1A on BL Active +/- SE (%)			1.7	27.6
Pat Group 2 on BL Active +/- SE (%)			0.6	48.9
BSA on BL Active +/- SE (%)			-3.7	19.0
BSA on BL Placebo +/- SE (%)	-6.25	8.32		
Smoking on Emax: Non-Smokers +/- SE (%)			-0.527	10.9
Smoking on Emax: Ex-Smokers +/- SE (%)			-0.684	7.7

Figure below shows the population and individual predicted and observed PVR data vs. time for placebo and sildenafil treatments.

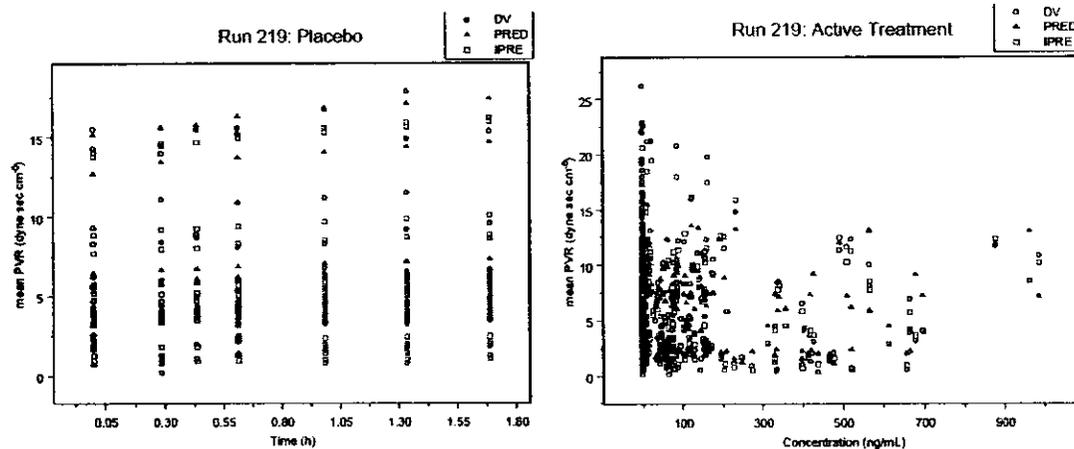


Figure 35: PVR vs. time for placebo (left) and vs. sildenafil concentrations (right)

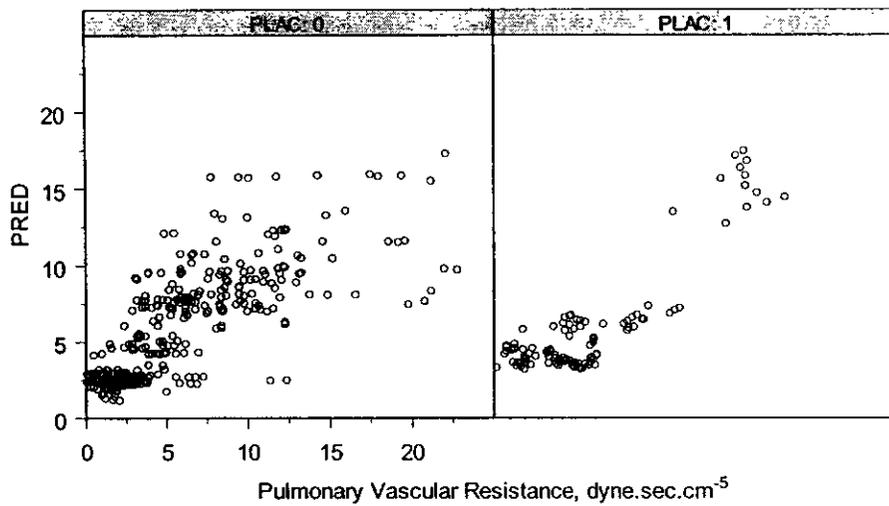


Figure 36: Predicted vs. observed PVR for sildenafil (left) and placebo (right)

The goodness of fit plots were satisfactory.

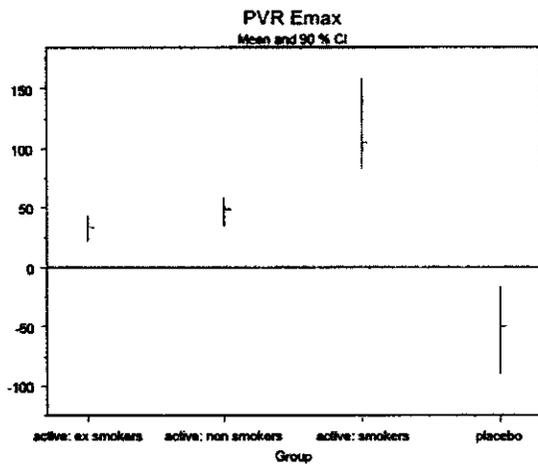


Figure 37: PVR estimations vs. subgroup

The maximum change from the baseline PVR values was significantly larger in patients receiving sildenafil, and from this group of patients the larger response was in the subgroup of smokers.

Systolic Pulmonary Artery Pressure

Structural Models:

$$\text{Placebo} = \text{Intercept} + \text{Slope} * \text{Time}$$

$$\text{Treatment} = \text{Baseline} - (\text{Emax} * \text{Concentration} / (\text{EC50} + \text{Concentration}))$$

$$\text{Observation} = \text{placebo} + \text{treatment.}$$

The sponsor' model did not properly estimate the slope for the placebo treatment, and the covariates were only tested on the placebo intercept and on all parameters estimated for the active treatment.

The parameters of the final model are shown in Table 36.

Table 36: NONMEM parameter estimates for systolic PAP

Run No	327			
Objective Function Value	2200			
Residual Variability (SD) +/- SE (%)	4.5		13.7	
	Placebo		Active Treatment	
Intercept/Baseline (mmHg) +/- SE (%)	69.0	6.5	52.7	3.7
Intersubject Variability of Intercept/Baseline (SD) +/- SE (%)	19.5	39.6	17.3	21.9
Slope/Emax (mmHg) +/- SE (%)	-0.289	284.8	20.9	10.6
EC50 (ng/ml) +/- SE (%)			14.5	41.9
Pat Group 1A on BL +/- SE (%)			0.552	16.3
Smoking on Emax: non-smokers +/- SE (%)			-0.522	13.9
Smoking on Emax: ex-smokers +/- SE (%)			-0.614	11.3

The goodness of fit is shown in Figure 38.

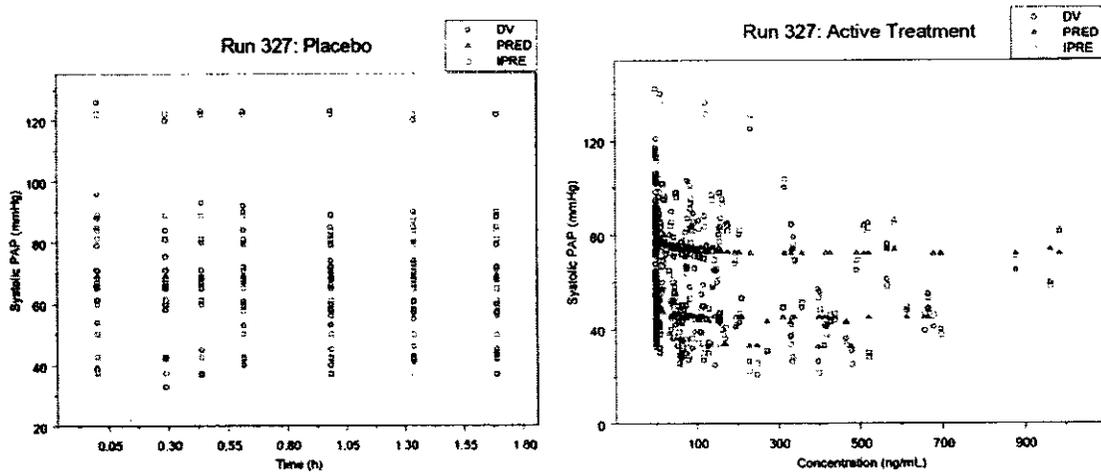


Figure 38: Systolic PAP vs. time for placebo (left) and vs. sildenafil concentration (right)

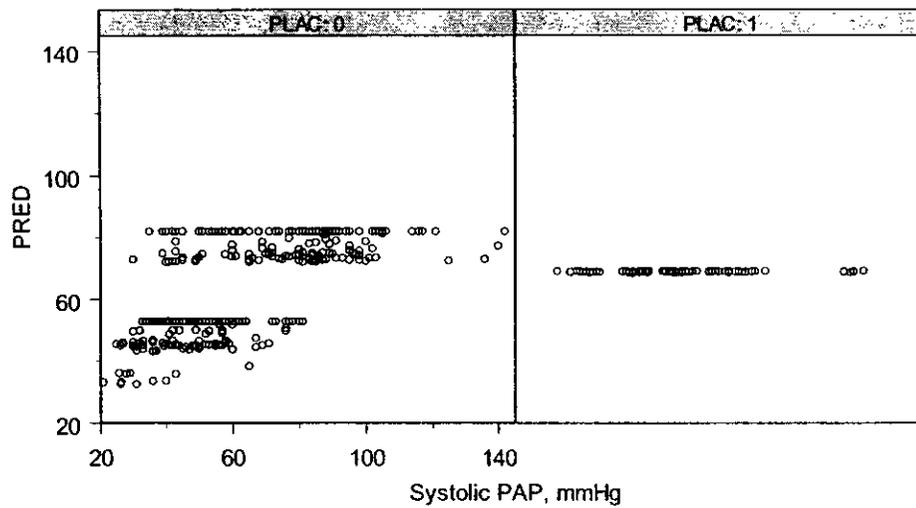


Figure 39: Predicted vs. observed systolic PAP for sildenafil (left) and placebo (right)

The model predicted systolic PAP satisfactorily.

The comparison of the parameters (slope for placebo and Emax for sildenafil) estimated for systolic pulmonary pressure are shown in Figure 40.

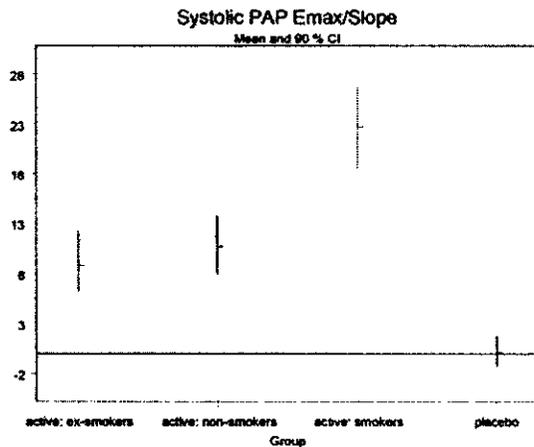


Figure 40: Slope/Emax Systolic Pulmonary Artery Pressure vs. Group

In the group of smokers, the effect of sildenafil on systolic pulmonary artery pressure was the largest.

Diastolic Pulmonary Artery Pressure

Structural Models:

Placebo = Baseline - (Emax * Time/(TE50 + Time))

Treatment = Baseline - (Emax * Concentration/(EC50 + Concentration))

Observation = placebo + treatment.

The sponsor's model did not properly estimate the Emax and TE50 values for placebo treatment, and covariates were only tested on placebo baseline and on all parameters estimated for active treatment. The impact of smoking history on Emax was confirmed by the bootstrap. The parameter estimates for the final model are shown in Table 37.

Table 37: NONMEM parameter estimates for diastolic pulmonary artery pressure

Run No	426			
Objective Function Value	1743			
Residual Variability (CV%) +/- SE (%)	12.3		15.7	
	Placebo		Active Treatment	
Baseline (mmHg) +/- SE (%)	12.6	8.0	13.4	4.1
Intersubject Variability of Baseline (SD) +/- SE (%)	4.17	32.0	4.11	20.3
Emax (mmHg) +/- SE (%)	-1.280	81.3	8.74	23.8
TE50 (h)/EC50 (ng/ml) +/- SE (%)	0.60	91.5	21.4	38.2
Smoking on Emax: non-smokers +/- SE (%)			-0.440	34.1
Smoking on Emax: ex-smokers +/- SE (%)			-0.571	19.8

The goodness of fit is shown in Figure 41 and Figure 42.

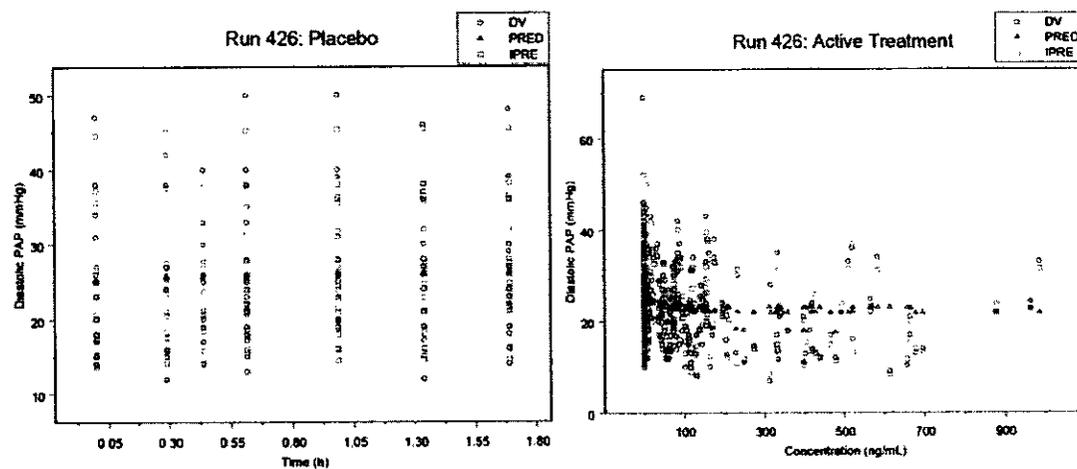


Figure 41: Diastolic pulmonary artery pressure versus time after placebo (left) or sildenafil concentration (right)

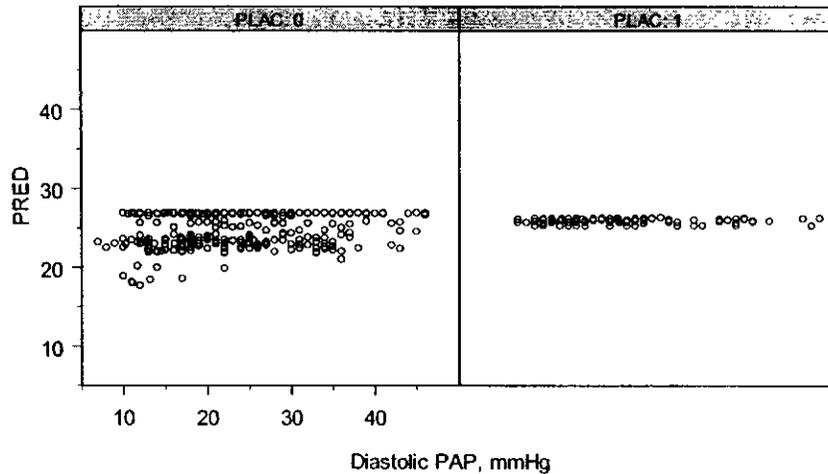


Figure 42: Predicted vs. observed diastolic PAP for sildenafil (left and placebo (right)

The model predicted diastolic pulmonary pressure poorly.

The comparison of the maximal change from the baseline for the diastolic PAP between subgroups is shown in Figure 43. The lines are the 90% confidence intervals for the parameters. In smokers, sildenafil has the largest effect on diastolic PAP.

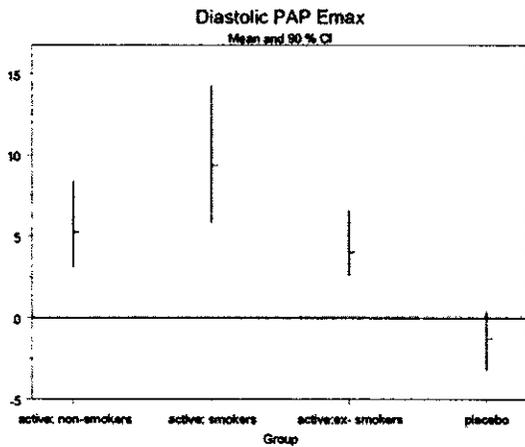


Figure 43: Emax for diastolic PAP vs. group of treatment

Systolic Blood Pressure

Structural Models:

Placebo = Intercept + Slope * Time

Treatment = Baseline - (Emax * Concentration/(EC50 + Concentration))

Observation = placebo + treatment.

Covariates were only tested on placebo intercept and on all parameters estimated for active treatment. The bootstrap supported the inclusion of smoking status as covariate on the Emax of the active treatment.

Table 38: NONMEM parameter estimates for systolic blood pressure

Run No	532			
Objective Function Value	2429			
	Placebo		Active Treatment	
Intercept/Baseline (mmHg) +/- SE (%)	121.0	3.8	123	2.5
Intersubject Variability of Intercept/Baseline (SD) +/- SE (%)	21	20.2	23	21.5
Slope/Emax Smokers (mmHg/h, mmHg) +/- SE (%)	0.751	119.8	24.0	19.7
EC50 (ng/ml) +/- SE (%)			53.5	67.3
Fact. Emax non-Smokers +/- SE (%)			-0.661	14.7
Fact. Emax ex-Smokers +/- SE (%)			-0.605	13.9
Residual Variability (SD/CV%) +/- SE (%)	-5.35	9.9	4.9	4.7

The goodness of fit is shown in Figure 44 and Figure 45.

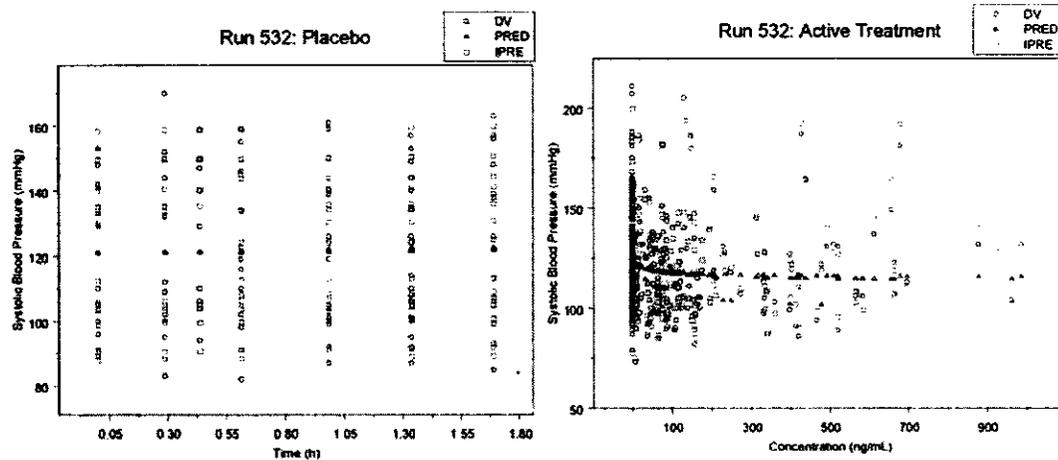


Figure 44: Systolic BP vs. time for placebo (left) and vs. sildenafil concentration(right)

**APPEARS THIS WAY
ON ORIGINAL**

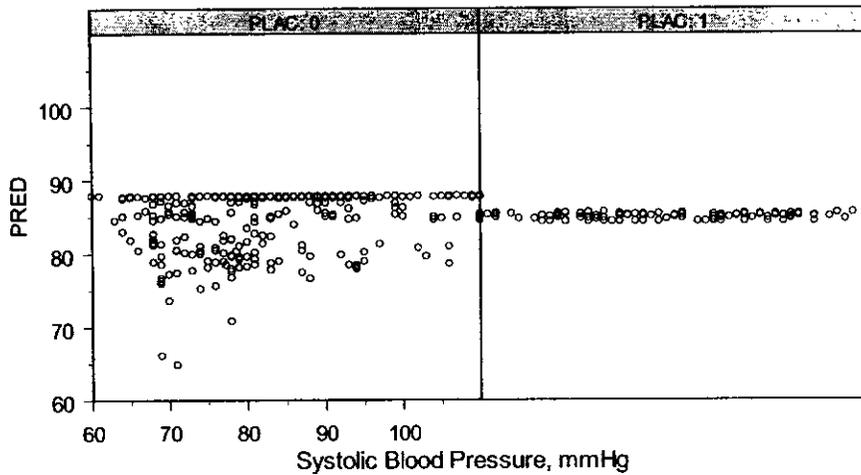


Figure 45: Predicted vs. observed systolic SBP for sildenafil (left and placebo (right)
 The model predicted systolic BP poorly.

The slope/ E_{max} systolic blood pressure vs. treatment group is compared in Figure 46. The lines are the 90% confidence intervals for the parameters.

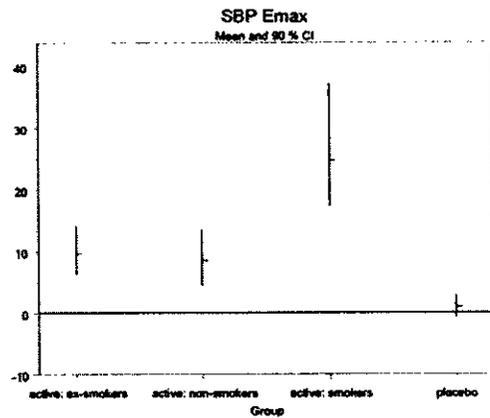


Figure 46: Slope/ E_{max} systolic blood pressure vs. treatment group

In smokers, sildenafil has the largest effect on systolic blood pressure. After the treatment with sildenafil, both systolic pulmonary artery pressure and systolic blood pressure decreased in comparison with the baseline parameters. EC_{50} and the corresponding 90% confidence intervals for systolic pulmonary artery pressure and systolic blood pressure are shown in Figure 47.

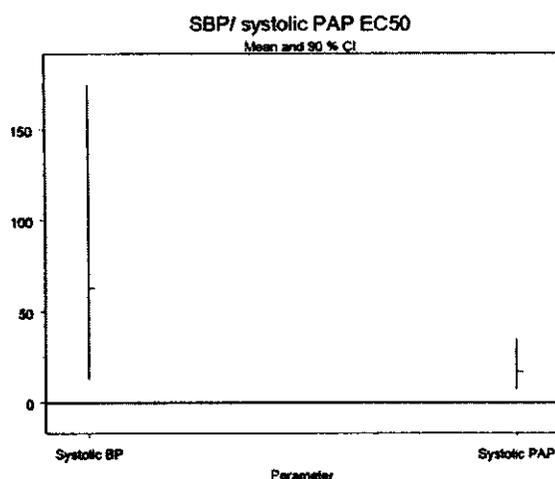


Figure 47: EC50 and 90% CI for systolic PAP and systolic BP

The means of the EC50 obtained from the bootstrap of the final population PK/PD model of the systolic pulmonary artery pressure and the systolic blood pressure were quite different, indicating that higher plasma concentrations of sildenafil were required to have an impact on systolic blood pressure compared to systolic pulmonary artery pressure. However, the difference was not statistically significant, the 90% confidence intervals overlap.

Diastolic Blood Pressure

Structural Models:

Placebo = Baseline * (1 - Emax * Time / (TE50 + Time))

Treatment = Baseline * (1 - Emax * Concentration / (EC50 + Concentration))

Observation = placebo + treatment.

Covariates were only tested on placebo baseline and on all the parameters estimated for the active treatment. The model resulting from the automated covariate search included smoking history on the maximum treatment effect and age on EC50 as significant covariates. The bootstrap analysis supported the inclusion of smoking status as a covariate on Emax and age on EC50 of active treatment.

The parameters estimated by the sponsor are in Table 39.

Table 39: NONMEM estimated parameters for DBP

Run No	627			
Objective Function Value	1977			
Residual Variability (SD) +/- SE (%)	3.69		8.4	
	Placebo		Active Treatment	
Baseline (mmHg) +/- SE (%)	32.4	3.0	34.4	2.2
Intersubject Variability of Baseline (SD) +/- SE (%)	4.74	33.6	6.0	20.5
Emax (%) +/- SE (%) (Smokers for Active Treatment)	-5.2	72.4	49.3	13.7
TE50 (h)/EC50 (ng/ml) +/- SE (%)	0.145	FIX	21.2	44.1
Age on EC50 +/- SE (%)			-6.99	41.5
Smoking on Emax: non-smokers +/- SE (%)			-0.54	15.1
Smoking on Emax: ex-smokers +/- SE (%)			-0.51	16.3

Goodness of fit from the final model (sponsor) is shown in Figure 48 and Figure 49.

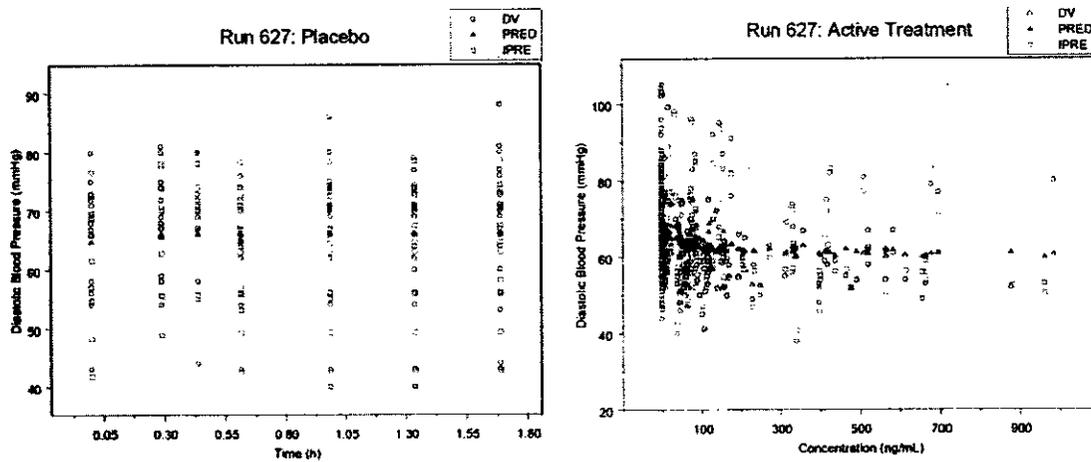


Figure 48: DBP vs. time for placebo (left) and vs. sildenafil concentration (right)

APPEARS THIS WAY
ON ORIGINAL

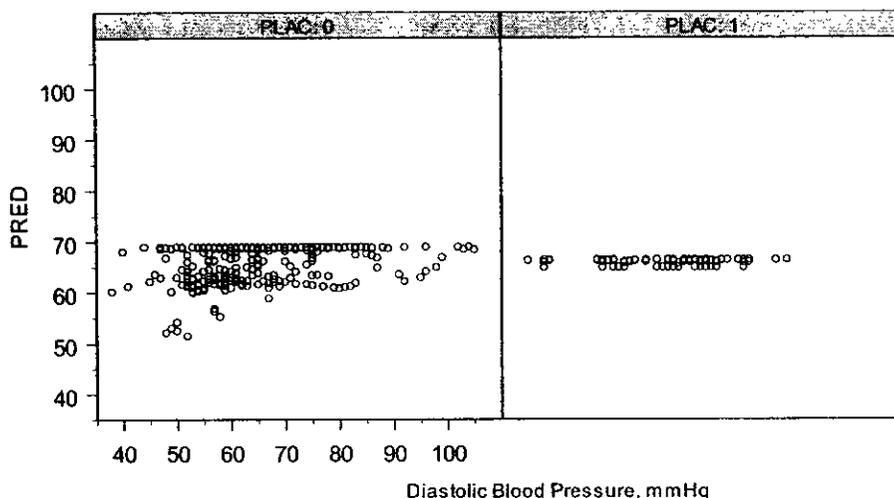


Figure 49: Predicted vs. Observed DBP after active treatment (left) and placebo (right)

The model predicts the data for both placebo and active treatment poorly. The maximum change in DBP from baseline vs. the various group of patients is shown in Figure 50.

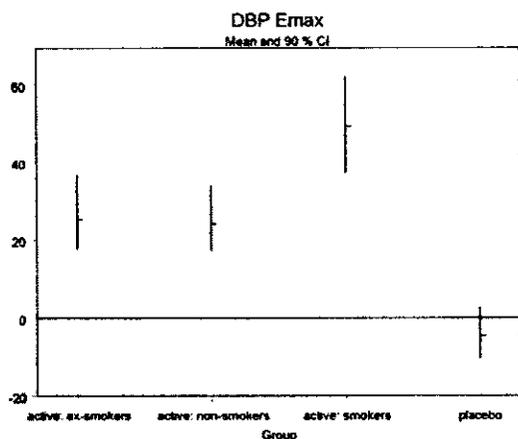


Figure 50: Emax and 90% CIs vs. the different group of patients.

In smokers, the effect of sildenafil in lowering diastolic blood pressure was the largest. The sildenafil selectivity for pulmonary blood vessels in comparison with peripheral vascular bed was not confirmed for the DBP because the EC50 values for both effects are very similar.

Mean Arterial Pressure

Structural Models:

$$\text{Placebo} = \text{Baseline} * (1 - \text{Emax} * \text{Time} / (\text{TE50} + \text{Time}))$$

$$\text{Treatment} = \text{Baseline} * (1 - \text{Emax} * \text{Concentration} / (\text{EC50} + \text{Concentration}))$$

$$\text{Observation} = \text{placebo} + \text{treatment.}$$

The effect of the covariates on the placebo baseline and on all parameters estimated for the active treatment were tested. The model resulting from the automated covariate search included the NO treatment and SGPT on the maximum treatment effect as significant covariates. The bootstrap results supported the inclusion of the NO treatment and SGPT on the Emax as covariates. Table 40 lists the parameter estimations.

Table 40: NONMEM parameter estimation for MAP

	Active Treatment		Placebo	
Baseline				
Population mean (mmHg)	43.9		42.2	
Bootstrap mean (mmHg)	44.0		42.4	
90 % CI	42.5	- 45.5	40.3	- 44.3
Inter-subject variability of Baseline				
Estimate (SD)	7.6		6.3	
Emax	Patients with NO Treatment			
Population mean (%)	10.5		-4.2	
Bootstrap mean (%)	10.8		-4.1	
90 % CI	8.5	- 13.6	-15.3	8.1
Emax	Patients without NO Treatment			
Population mean (%)	3.8			
Bootstrap mean (%)	4.0			
90 % CI	-0.16	- 8.4		
Impact of GPT on Emax				
Population mean (factor)	-1.1			
Bootstrap mean (factor)	-1.0			
90 % CI	-1.7	- -0.12		
EC50				
Population mean (ng/mL)	23.7			
Bootstrap mean (ng/ml)	28.4			
90 % CI	12.9	- 56.6		

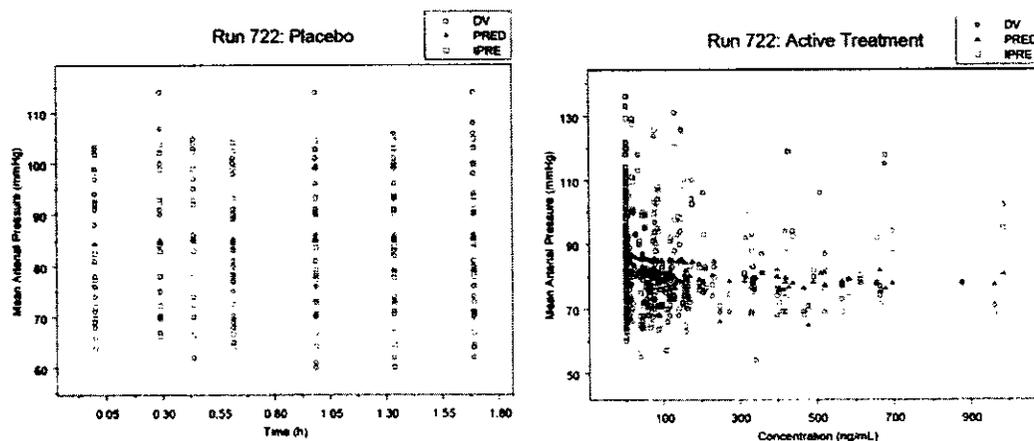


Figure 51: MAP vs. time for placebo (left) and vs. sildenafil concentration(right)

Goodness of fit is shown in Figure 51 and Figure 52.

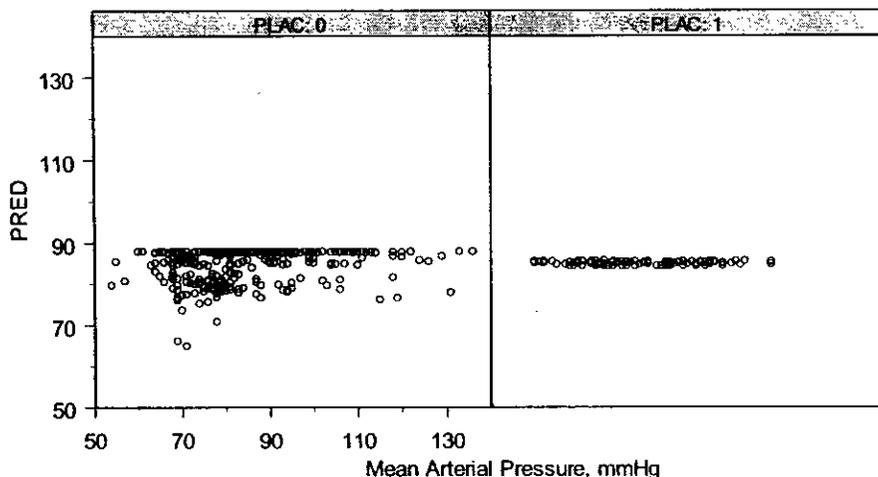


Figure 52: Predicted vs. observed diastolic MAP for sildenafil (left and placebo (right)

The model predicted mean arterial pressure poorly.

PHARMACOKINETICS

Structural Models

Only a simple model estimating systemic clearance could be fitted:

$$C_{avss} = R_0/CL$$

C_{avss} = average steady state concentration

R_0 = infusion rate

The estimated parameters are shown in Table 41

Table 41: PK parameters of sildenafil

Run No	802	
Objective Function Value	1404	
Residual Variability (SD) +/- SE (%)	37.7	40.8
	Active Treatment	
Clearance (l/h) +/- SE (%)	24.7	4.1
Intersubject Variability of Clearance (CV %) +/- SE (%)	24.4	32.0

The model resulting from the automated covariate search included smoking history as a significant covariate on clearance.

The estimate of systemic sildenafil clearance in patients with pulmonary hypertension in this study was comparable to the value found in healthy volunteers.

Sildenafil plasma concentrations vs. time are shown in Figure 53.

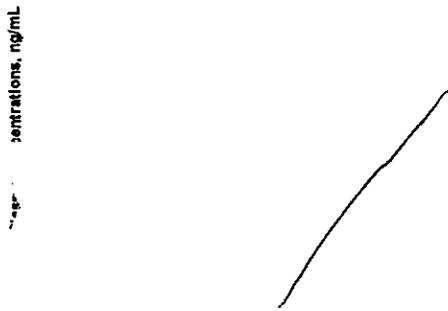


Figure 53: Sildenafil plasma concentrations vs. time

Goodness of fit is shown in Figure 54 below.

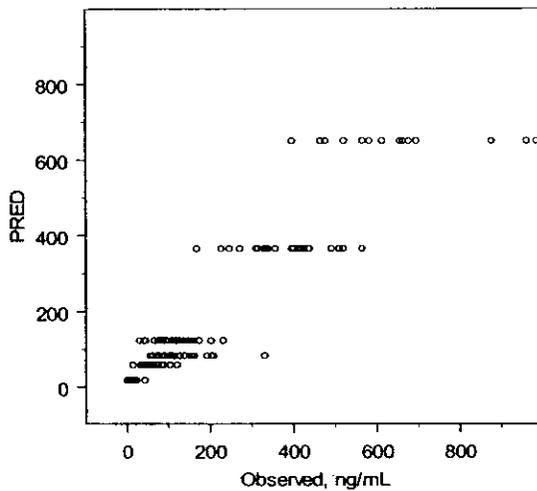


Figure 54: Predicted vs. observed sildenafil plasma concentrations

The model predicted the observed sildenafil plasma concentrations reasonably well.

SUMMARY:

There are some discrepancies in the summary pharmacodynamic parameters reported by the sponsor and the same parameters found in the final runs. The sponsor's summary results reported in Table 42 and the same results reported in the NONMEM runs are shown in Table 40.

Table 42: Sponsor's results

Parameter	Sys PAP (SE,%)	Sys BP (SE,%)	Mean PAP (SE,%)	MAP (SE,%)	Dia PAP (SE,%)	Dia BP (SE,%)
Baseline, mmHg	68.6	123	42.3	86.4	26	66.9

E _{max} , mmHg	10.3 (9.2)	9.96 (28.4)	6.5 (12.1)	20.3 (16.6)	4.9 (12.3)	23.7% (14.7)
EC ₅₀ , ng/mL	16.3 (37.7)	53.4 (111.8)	19.9 (51.8)	25 (58)	26 (37.9)	35.8 (49.7)

Table 43: Results from final sponsor's Runs

Parameter	Sys PAP (SE)	Sys BP (SE)	Mean PAP (SE)	MAP (SE)	Dia PAP (SE)	Dia BP (SE)
Baseline, mmHg	52.7	123	17.8	43.9	13.4	34.4 +32.4
E _{max} , mmHg	20.9 (2.2)	24.0 (4.7)	5.8 (1.0)	0.105 (16.6)	8.7 (2.8)	15.9 (0.07)
EC ₅₀ , ng/mL	14.5 (6.7)	53.5 (36.0)	13.7 (8.8)	23.7 (58)	21.4 (8.2)	21.2 (9.4)

The sponsor concluded that sildenafil generally led to a small reduction in systemic blood pressure and a larger reduction in pulmonary blood pressure. In this study population of patients with pulmonary but not suffering from hypertension, sildenafil showed selectivity for the pulmonary vasculature. The largest lowering of pulmonary pressure by sildenafil was achieved in smokers.

COMMENTS

1. The study showed that sildenafil reduced both pulmonary and systemic blood pressure after IV administration in patients with pulmonary hypertension. The relative change from baseline for pulmonary and systemic hemodynamic parameters was in most cases similar, except for the systolic pulmonary artery pressure, where sildenafil led to a larger relative reduction than for the systolic systemic blood pressure. The plasma concentrations of sildenafil required to reduce systolic pulmonary blood pressure were lower compared to the plasma concentrations required to lower systolic blood pressure.
2. The fact that the effect vs. sildenafil plasma concentrations was evaluated over a time frame of 2 hours after the start of infusion, may have been a reason for the poor estimation of systemic pharmacodynamic parameters for sildenafil.
3. The proposed model poorly estimated all the parameters for the systemic blood pressure.
4. From all pulmonary and systemic blood pressure parameters only systolic pulmonary pressure was reduced more effectively than systolic pressure.
5. The comparison of the diastolic pulmonary and diastolic systemic blood pressure is the most valuable comparison from the clinical point of view.

4.3.7 A MULTINATIONAL, MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF 20, 40, AND 80MG TID SILDENAFIL IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION IN SUBJECTS AGED 18 YEARS AND OVER. Population Pharmacokinetic/Pharmacodynamic Report for Sildenafil Phase 3 Data (Protocol A148 1140) in Patients with Pulmonary Arterial Hypertension (PAH).

DRUG STUDIED:	Sildenafil Citrate
INVESTIGATORs AND STUDY SITES:	Multicenter
Study Dates:	10/02/2002-11/21/2003
Population Data Analysis Report:	10/22/2004
Phase of Development:	Phase 3

OBJECTIVES

Primary:

To evaluate the effect of three doses of oral sildenafil (20, 40, and 80mg three times a day) on exercise capacity, as measured by the 6-Minute Walk test, after 12 weeks of treatment in subjects with PAH who were aged 18 years and over.

Secondary:

To assess the safety and tolerability of three doses of oral sildenafil during a 12 week treatment period.

To investigate the plasma concentration-effect relationship.

To determine the population pharmacokinetic parameters.

STUDY DESIGN:

This was a multinational, multi-centre, double-blind, double-dummy, parallel group study with three dose levels (20, 40 and 80 mg TID of sildenafil) and placebo. Two hundred and forty evaluable subjects were required (60 per study arm). The study consisted of five visits, one telephone call to the subject and a follow-up visit for those subjects who did not enter the extension study A1481142. Study flow chart is shown in Table 44. Subjects were assigned to treatment groups using a central randomization scheme across all centers. Randomization to treatment arms was stratified according to baseline walking distance (< 325m, = 325m) and etiology (Primary pulmonary hypertension (PPH), PAH secondary to connective tissue disease, PAH with surgical repair), to ensure a balance in these factors across treatment groups. Eligible subjects were randomly assigned to treatment groups (placebo, sildenafil 20mg, sildenafil 40mg, or sildenafil 80mg) in a 1: 1: 1: 1 ratio. Subjects who were randomized to sildenafil 80mg received 40mg for the first seven days and then underwent an up-titration to 80mg. Subjects randomized to placebo, sildenafil 20mg or sildenafil 40mg underwent a dummy up-titration after seven days. Study drug was taken three times a day, at least six hours apart.

Blood Sampling for Pharmacokinetics

At the baseline visit as well as at the Week 12 visit, blood samples were collected in the three time intervals: 15 minutes to 3 hours, > 3 to 6 hours, and > 6 to 8 hours after the

first dose. At the Week 8 visit, two samples were collected, (one upon arrival of the other close to the end of the dosing interval but at least 30 minutes apart). The two PK samples were additionally taken during the haemodynamic assessments at the visit on Week 12.

Table 44: Study flow chart

	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 (if approved)				X			
Inclusion/exclusion criteria	X	X					
Demography	X						
Diagnosis	X						
Functional classification*	X	X		X	X	X	X
Medical history	X						
Safety							
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	

INVESTIGATIONAL PRODUCTS

Sildenafil formulation identification numbers (FID) and drug lot numbers are provided in Table 32.

APPEARS THIS WAY
ON ORIGINAL

Table 45: Study medication

Drug Lot Number (Formulation Identification Number)					
Placebo			Sildenafil		
20mg	40mg	80mg	20mg	40mg	80mg
261 (F00008AC)	255 (F00009AC)	258 (F00010AC)	8978-107 (F00012AE)	336 (F00014AC)	337 (F00016AC)
8978-108 (F00008AC)	259 (F00009AC)	260 (F00010AC)	335 (F00012AE)	8978-086 (F00014AC)	676 (F00016AD)
	8978-062 (F00009AB)	674 (F00010AC)			
		8978-061 (F00010AB)			

SUBJECTS:

Male or female subjects aged 18 and over who had any of the following conditions:

Primary pulmonary hypertension (PPH);

PAH with connective tissue disease and/or with surgical repair;

Subjects with a mean PAP (pulmonary artery pressure) = 25mmHg and a pulmonary artery wedge pressure (PAWP) of < 15mmHg at rest, assessed via right heart catheterization within 21 days prior to randomization.

Subjects who underwent right heart catheterization.

ANALYTICAL METHODS:

Plasma samples were analyzed for sildenafil and UK-103,320 using a previously validated high pressure liquid chromatography with ultraviolet detection method. The calibration range for both sildenafil and UK -103 320 was

Table 46: Assay Characteristics for Sildenafil and UK-103,320

Parameter	Measure		Reviewer Comment
	Sildenafil	UK-103,320	
Linearity			Satisfactory
Precision (CV%)			Satisfactory
Accuracy Between day			Satisfactory
LLOQ			Satisfactory
Specificity			Satisfactory

Chromatograms were shown.

Population Pharmacokinetic/Pharmacodynamic Report for Sildenafil Phase 3 Data (Protocol A148 1140) in Patients with Pulmonary Arterial Hypertension (PAH)

OBJECTIVES

To investigate the pharmacokinetics of sildenafil in subjects with pulmonary arterial hypertension after oral TID dosing.

To investigate the relationship between exposure to sildenafil and 6-minute walking distance.

To investigate the relationship between exposure to sildenafil, the index of pulmonary vascular resistance (PVRi) and 6-minute walking distance.

SUBJECT'S DEMOGRAPHICS:

A total of 206 patient's data were included in the PK and PK/PD data analysis. Summary of demographic parameters for data used for the PK data analysis is shown below.

Table 47: Continuous demographic data

	Age (years)	Weight (kg)	BSA (m ²)	BMI (kg/m ²)
MEAN	48.8	72.0	1.8	26.7
STD	14.7	17.0	0.2	5.8
CV%	30.2	23.0	12.3	21.6
MEDIAN	48.5	70.0	1.8	26.1
MIN	19.0	41.0	1.3	15.8
MAX	81.0	122.0	2.4	44.2
N	206	206	206	206

Table 48: Categorical demographic data

Variable	Category	Frequency (n)	Percent
Dose Randomised	20 mg	69	33.5
	40 mg	66	32.0
	80 mg	71	34.5
Food Intake ¹⁾	0-1 h pre-dose	51	24.76
	>1 - 2 h pre-dose	34	16.5
	> 2 h pre-dose	53	25.7
	post-dose	68	33.0
Gender	Males	55	26.7
	Females	151	73.3
Race ²⁾	White	174	84.5
	Black	5	2.4
	Asian	17	8.3
	Other	10	4.9
Aetiology ³⁾	Primary PH	132	64.0
	CTD	62	30.1
	Surgical Repair	12	5.8

Table 49: Laboratory parameters

	Creatinine Clearance (ml/min)	Albumin (g/dl)	Bilirubin (mg/dl)	Aspartate Aminotransferase /AST (U/l)	Alanine Aminotransferase /ALT (U/l)	Alkaline Phosphatase (U/l)
MEAN	79.7	4.1	0.859	28	24	98
STD	28.6	0.4	0.678	18	20	44
CV%	35.9	10.3	79.0	63.0	81.0	46.0
MEDIAN	74.5	4.2	0.642	24	19	89
MIN	23.0	2.5	0.117	4	4	16
MAX	173.9	5.2	7.7	168	206	333
N	364	366	356	355	362	361

The demographics for the data used for PVRi vs. sildenafil exposure and for 6MWD vs. PVRi was similar.

DATA

The SAS programs were used to create the NONMEM data sets from the original data sets and details on the data sets. Criteria for exclusion of data points are acceptable.

METHODOLOGY

The software package NONMEM, version V, level 1.1 installed in a DOS platform was used in the analysis, employing the Compaq FORTRAN compiler version 6.6.

The statistical package Splus Version 6.0 Professional installed in PC platform under Windows 2000 was used for the exploratory analysis and Xpose, version 3.010 was used to assist in the model building. Additional graphical and statistical analyses were done using SAS 8.02 under Windows 2000/Windows XP professional.

Covariate Model Building

The general approach for the covariate analysis was similar for all analyses.

The following covariates were investigated on the appropriate PK and PD parameters: age, weight, body mass index, body surface area, history of alcohol intake, history of smoking, gender, study center, patient group, serum creatinine, urea, glomerular filtration rate (calculated with Cockcroft and Gault equation), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin.

The comedications were tested for their potential impact on the relationship between sildenafil exposure and pulmonary and systemic hemodynamic parameters.

The covariate effects were evaluated through a stepwise, automated covariate model-building algorithm. An exponential model was used for all continuous covariates if deemed appropriate. The forward inclusion criteria of a drop in objective function value (OFV) for one degree of freedom by at least 3.84 ($p=0.05$) and a backward elimination criterion of a change of 10.83 ($p=0.001$) were employed. For the covariate center (eight categories), there are seven degrees of freedom, thus the appropriate criteria for forward and backward consideration, were 14.07 and 24.32 changes in OFV, respectively.

Estimation Methods

The first order conditional estimation method (FOCE) with additive or ln-additive models for residual variability and first-order conditional with interaction (FOCEI) with proportional, additive + proportional and exponential models for residual variability.

Internal Validation

The model diagnostics included objective function value changes (for p values see above), goodness of fit plots and precision of parameter estimates. The 90% confidence intervals of the parameters of each final model were obtained by bootstrapping (100 replicates for each endpoint). The 5% and 95% percentiles of the bootstrap distribution were used as lower and upper boundaries of the 90% confidence interval. The bias of the PK/PD parameter estimates was calculated by subtracting the population mean from the bootstrap mean.

As the current data set was relatively small, contained a lot of subgroups and included the data of only one study, no formal model validation was done at this point in time.

RESULTS:

Pharmacokinetics

A one-compartment model with zero order input provided the best fit of sildenafil plasma concentrations in patients with PAH. The same model was used previously for the MED patients and healthy subjects (NDA 20-895). The model included the impact of food on sildenafil absorption. In healthy volunteers, sildenafil plasma levels increase slightly more than proportionally to the doses at chronic doses > 50 mg TID, therefore, the oral bioavailability was included as an additional parameter for the dose of 80 mg TID. Including of the inter-occasion variability significantly improved the fit.

Covariates tested: weight, gender, age, liver function tests, concomitant medications and race and the etiology of pulmonary arterial hypertension. The only covariates reaching the pre-specified statistical significance criteria and remaining in the model were CYP 3A4 substrates and beta-blockers on CL/F.

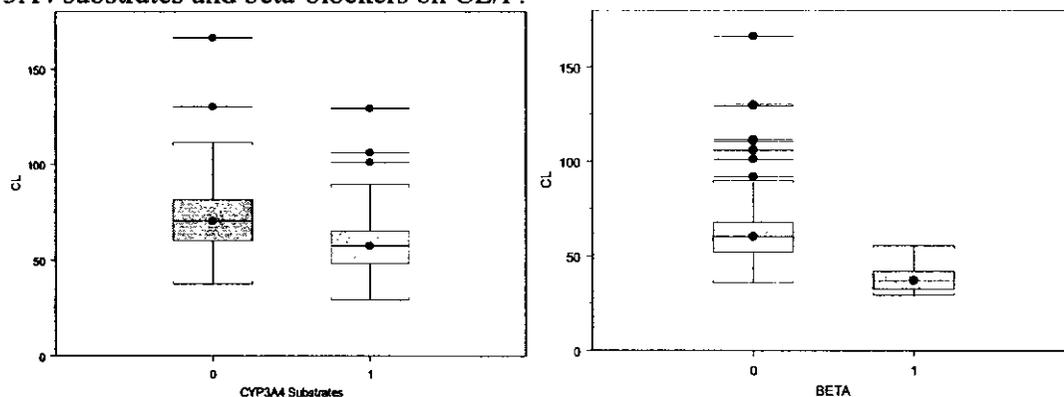


Figure 55: Important covariates on CL (CYP3A4 substrates and beta-blockers)

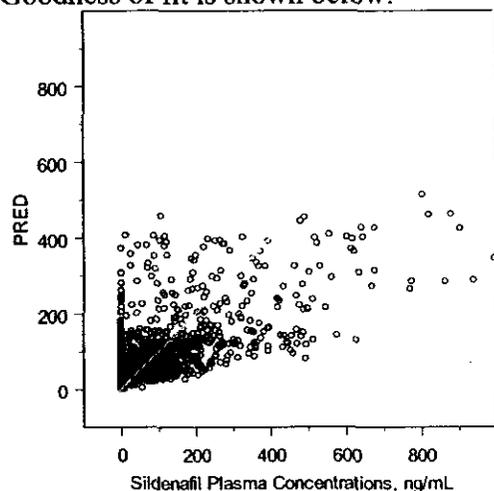
Clearance of sildenafil decreased in patients who received CYP3A4 substrates (by 22.3%) or beta-blockers (by 37.4%).

The final model parameters are shown in Table 50.

Table 50: Pharmacokinetic Parameters

Run No	24	
Objective Function Value	9801	
Residual Variability (CV %) +/- SE (%)	44.6	2.7
D1 (h) +/- SE (%)	0.67	0.13
Impact of food intake on D1, Food intake 0-1h pre-dose (+/- SE (%))	0.9	22.1
Impact of food intake on D1, Food intake > 1h-2h pre-dose (+/- SE (%))	1.43	23.0
CL/F (l/h) +/- SE (%)	73.6	7.6
Intersubject Variability of CL/F (CV %) +/- SE (%)	31.5	35.6
Impact of CYP3A4 Substrates on CL/F (+/- SE (%))	-0.223	25.4
Impact of Beta Blockers on CL/F (+/- SE (%))	-0.374	22.4
Increase of F for 80 mg TID +/- SE (%)	0.43	23.1
Intersubject Variability of F (CV %) +/- SE (%)	40.1	27.4
Interoccasion Variability of F (CV %) +/- SE (%)	36.7	20.9
V/F (l) +/- SE (%)	294	5.9
Intersubject Variability of V/F (CV %) +/- SE (%)	23.9	69.4

Goodness of fit is shown below.

**Figure 56: Predicted vs. Observed sildenafil plasma concentrations**

The population predictions of the plasma sildenafil concentrations were satisfactory. The bootstrap (1000 replicates) results confirmed the model predicted parameters. Biases were small and 90% CI calculated for all parameters included zero.

Dose adjustment based on PK:

The mean average steady state concentration of sildenafil at 80 mg TID was about 5-fold higher compared to the mean average steady state concentration at 20 mg TID. The increase of sildenafil exposure observed in specifically designed clinical pharmacology studies was less than 5-fold.

• Compared to healthy young volunteers, sildenafil AUC increased in elderly subjects (aged = 65 years) by 84%, in subjects with severe renal impairment by ~ 100% and in subjects with stable hepatic cirrhosis (Child-Pugh A or B) by 85%.

All these studies used single doses of sildenafil, and the accumulation index (based on the mean half-life of the respective subject groups) was calculated for TID dosing:

Healthy volunteers: 13-24%

Elderly subjects: 30%

Subjects with renal impairment mild: 36%,
 moderate: 19%
 severe: 32% •

Subjects with hepatic cirrhosis: 37%.

Therefore, the safety window for the subpopulations can be expected to be sufficient after chronic dosing of 20 mg TID. The 20 mg TID is proposed without adjustments.

Pharmacodynamics

6MWD vs. sildenafil plasma concentrations

The plots of 6 Minute walk time vs. sildenafil plasma concentrations show that there is no correlation between these parameters. The sponsor explored these relationships for C_{max}, C_{avss} and C_{min}. The example of 6MWD vs. C_{max} is shown in Figure 57.

A1481140: 6—Minute Walking Distance vs Sildenafil Exposure

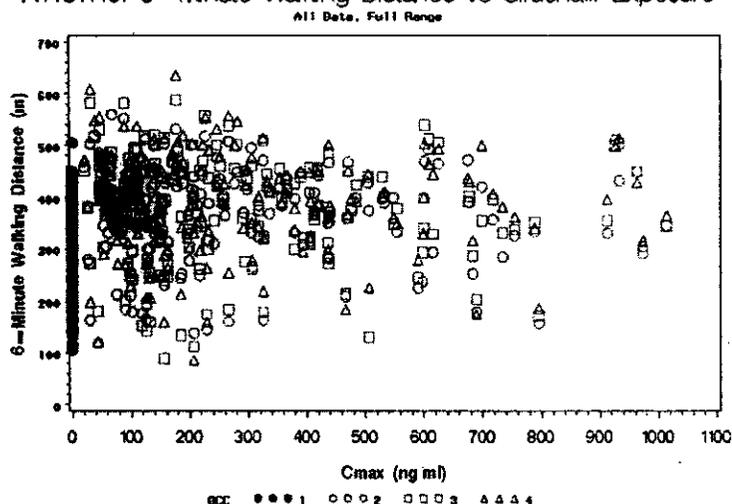


Figure 57: 6 Minute walk time vs. maximal sildenafil plasma concentrations

The attempts to describe this relationship through modeling were not successful. The reviewer plotted the mean (and SD) values of 6MWD vs. dose for each of treatment group at Week 12 (Figure 58).

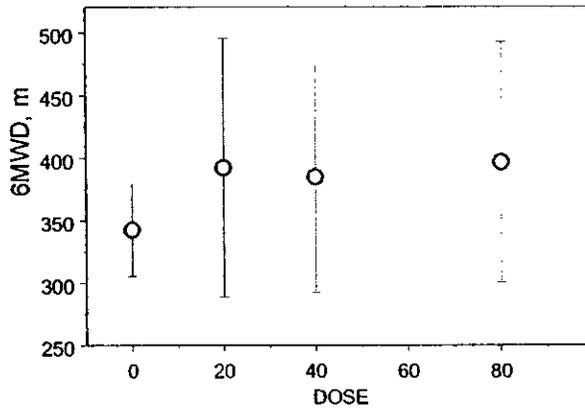


Figure 58: Mean 6MWD vs. sildenafil dose

The mean values of walking distance increased with administration of sildenafil, and the difference between the placebo group and 20 mg dose treatment was significant (Table 51).

Table 51: 6MWD t-Test assuming unequal variances

6 Minutes Walk Distance	20 mg dose	placebo
Mean, m	392.30	354.59
Variance	10761.87	7755.92
Observations	95	148
Hypothesized Mean Difference	0	
df	177	
t Stat	2.929	
P(T<=t) one-tail	0.00192	
t Critical one-tail	1.653	
P(T<=t) two-tail	0.00384	
t Critical two-tail	1.973	

PVRi vs. sildenafil plasma concentrations

The sildenafil plasma concentrations measured during right heart catheterization at week 12 versus PVRi are shown in Figure 59.

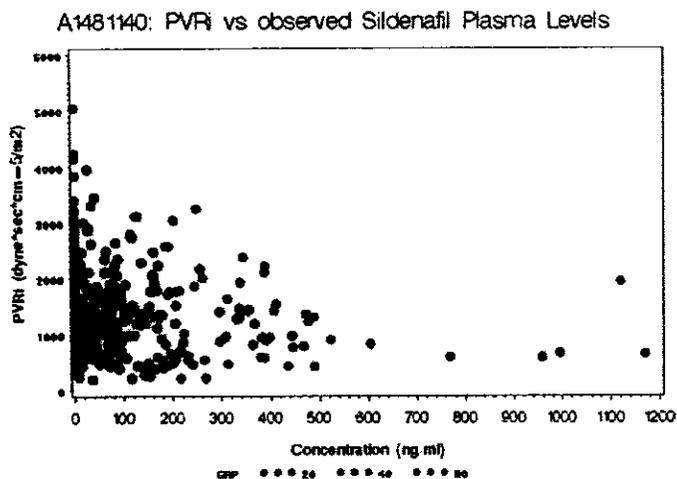


Figure 59: PVRi vs. sildenafil plasma concentrations

An additive linear model best described the placebo PVRi data. Intersubject variability was estimated for both intercept and slope. For the active treatment data, a proportional inhibitory Emax model provided the best fit. Intersubject variability was obtained for baseline and Emax, but not for EC50.

The investigated covariates: age, gender, race, duration of disease, etiology of pulmonary arterial hypertension and concomitant medications. Weight related covariates were not included because PVRi is already normalized for body surface area. The smoking status was not tested due to just a few smokers in PAH patient population.

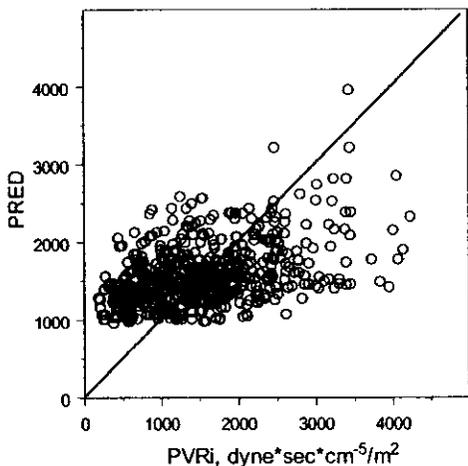


Figure 60: Predicted vs. observed PVRi

The final run was bootstrapped (1000 replicates). All covariates included in the final model were supported by the bootstrap. The goodness of fit is shown in Figure 60. The model predicted PVRi values with a moderate precision. The population pharmacodynamic parameter estimates are shown in Table 52.

Table 52: PVRi versus sildenafil plasma concentrations

Run No	217	
Objective Function Value	7716	
Residual Variability (SD) +/- SE (%)	123	24.4
	Placebo	Active Treatment
Baseline (dyne*sec*cm ⁻⁵ /m ²) +/- SE (%)	872	4.5
Intersubject Variability of Baseline (SD) +/- SE (%)	779	11.9
E _{max} (% change from BL) +/- SE (%)	19.5	13.0
Intersubject Variability of E _{max} (SD) +/- SE (%)	0.23	25.2
EC50 (ng/ml) +/- SE (%)	2.92	102.7
Age on Baseline	-0.714	26.6
CA Blockers on Baseline	-0.226	23.5
Intercept (dyne*sec*cm ⁻⁵ /m ²) +/- SE (%)	797	7.3
Intersubject Variability of Intercept (SD) +/- SE (%)	753	19.8
Slope (dyne*sec*cm ⁻⁵ /m ² /h) +/- SE (%)	0.0261	179
Intersubject Variability of Slope (SD) +/- SE (%)	0.35	61
Age on Intercept +/- SE (%)	-0.943	22.6
Oxygen on Intercept +/- SE (%)	0.491	41.5

For the active treatment model, the standard errors of the bootstrap and the bias of the bootstrap mean to the parameter estimates were low, except for EC50 values. The 90% confidence interval for the slope included zero. The baseline PVRi tended to decrease with age. Placebo patients who received oxygen had higher baseline PVRi values than patients not requiring oxygen. Patients on active treatment had lower baseline PVRi values when receiving calcium channel blockers.

The predicted and observed PVRi vs. sildenafil plasma concentrations are shown in Figure 61. The model predicted the observed values satisfactorily. Even though the relationship between PVRi and sildenafil plasma concentration was very shallow, nevertheless, it was quantifiable.

APPEARS THIS WAY
ON ORIGINAL

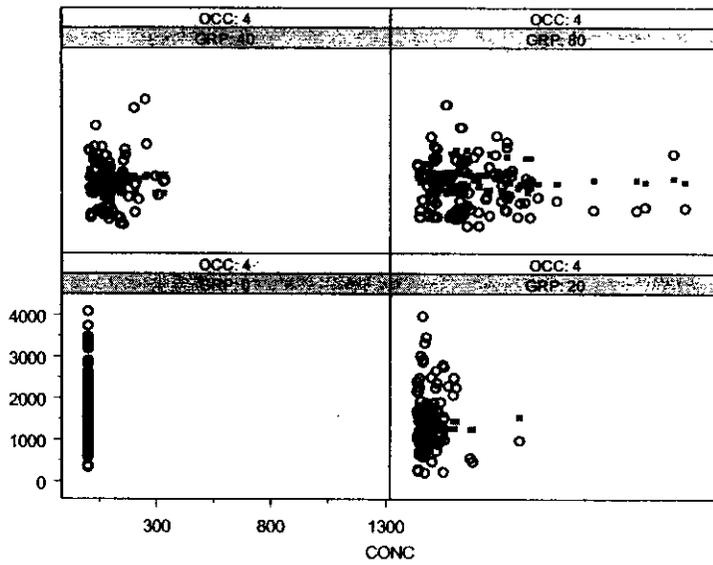


Figure 61: Predicted and observed PVRi vs. sildenafil plasma concentrations

Mean and SD of PVRi vs. dose of sildenafil data are plotted below (Figure 62s) using the data obtained at Week 12 of sildenafil TID dosing.

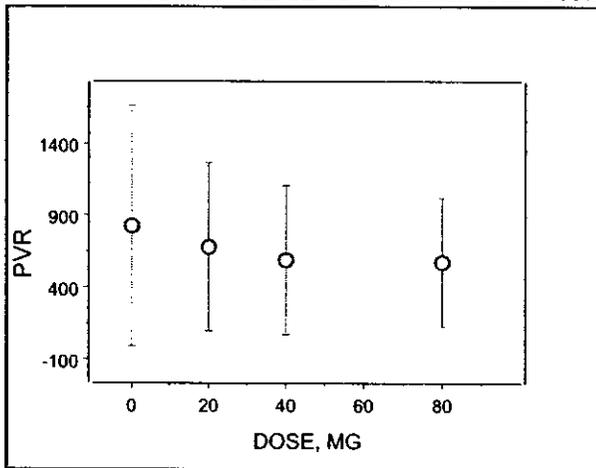


Figure 62: Mean and SD PVRi vs. sildenafil dose on Week 12

On average, the decrease of PVRi in the dosing groups of 20, 40, and 80 mg of sildenafil were by 475, 619, and 778 $\text{dyne}\cdot\text{sec}\cdot\text{cm}^{-5}/\text{m}^2$ in comparison with the placebo group. The difference between placebo and 20 mg dose treatment was statistically significant. Results of t-test is shown in

Table 53: PVRi t-Test two-sample assuming unequal variances

<i>PVRi</i>	<i>placebo</i>	<i>20 mg dose</i>
Mean, $\text{dyne}\cdot\text{sec}\cdot\text{cm}^{-5}/\text{m}^2$	1925.25	1446.242105
Variance	899225.0323	603673.7386
Observations	148	95
Hypothesized Mean Difference	0	
df	227	

t Stat	4.2963
P(T<=t) one-tail	1.2878E-05
t Critical one-tail	1.6515
P(T<=t) two-tail	2.57559E-05
t Critical two-tail	1.9704

6 Minute Walk Distance vs. Pulmonary Vascular Resistance

The sponsor attempted to correlate both responses (6MWD and PVRi). The plot of 6MWD vs. PVRi is shown below.

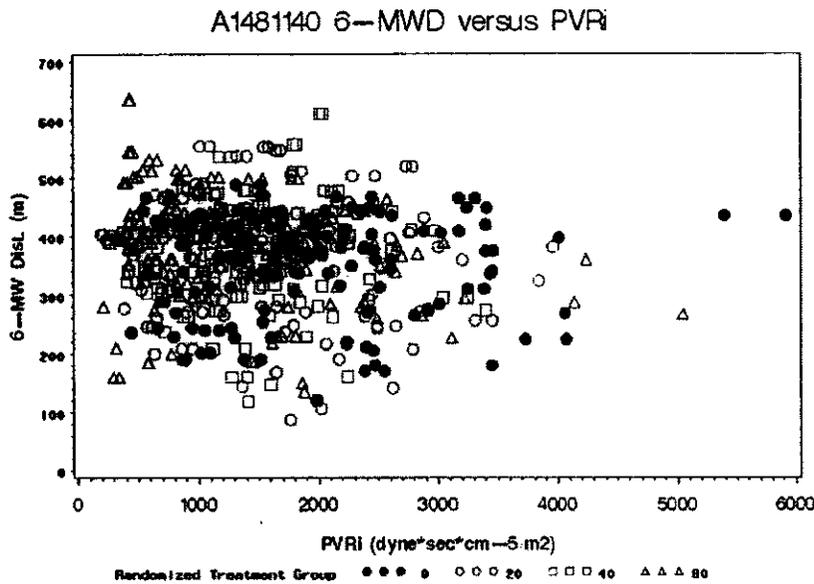


Figure 63: 6-MWD Versus PVRi

Reviewer's plot conditioned by treatment group and occasion (baseline vs. week 12 of treatment) is shown below:

**APPEARS THIS WAY
ON ORIGINAL**

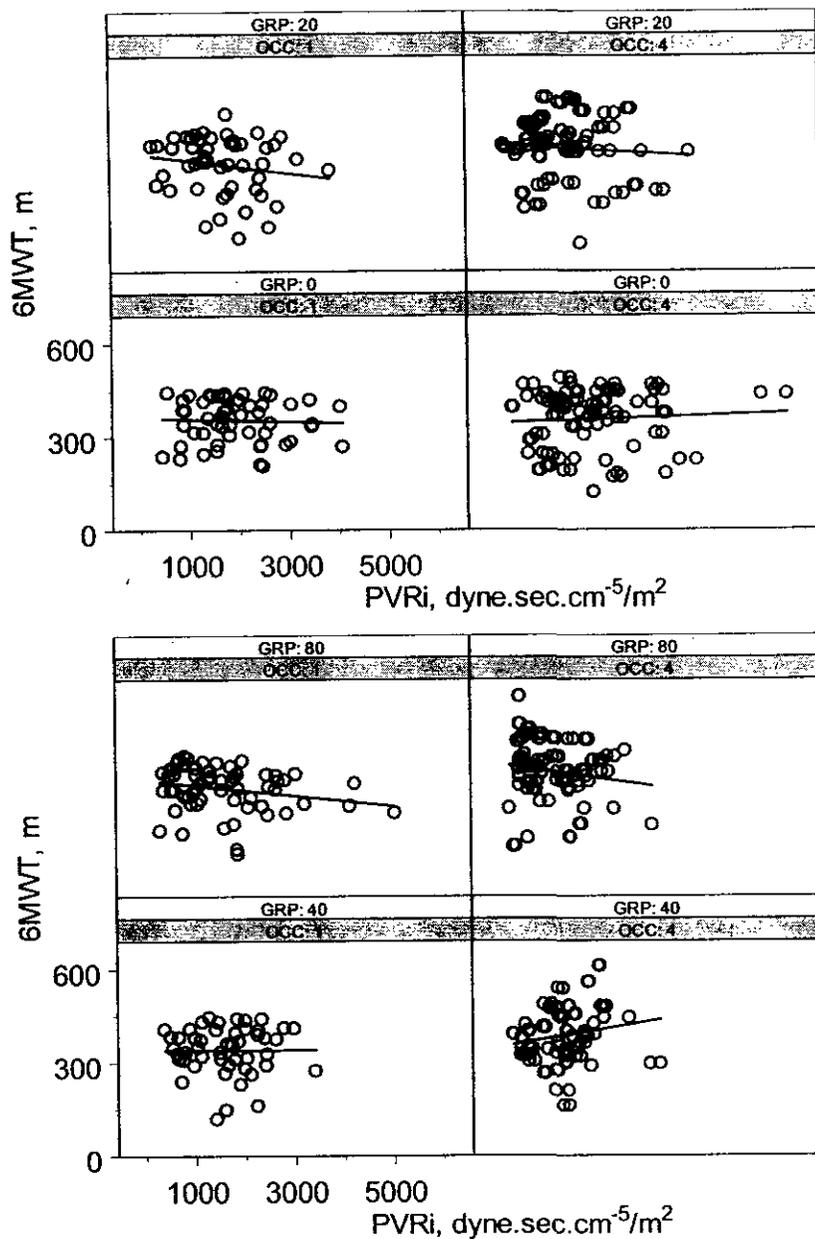


Figure 64: 6MWD vs PVRi by dose group (GRP = 0, 20, 40 and 80 mg of sildenafil TID). Baseline, OCC1, data on Week 12, OCC4.

There is a slight trend in the increase in 6MWD distance comparing to placebo and treatment groups as well as baseline and week 12 measurements. In addition, the placebo group showed a flat response (slope=0) and the slope increased with increasing dose, however, this was not true in the group receiving 80 mg dose of sildenafil. The lines are the result of linear regression obtained by Splus.

The sponsor described 6-MWD versus PVRi data after chronic dosing of sildenafil TID or placebo with an additive linear model (as structural model). The covariates were tested using an automatic approach. The final model parameters are shown in Table 54.

Table 54: Sildenafil Pharmacodynamic Parameters: 6-MWD Versus PVRi.

Run No	315	
Objective Function Value	5319	
Residual Variability (SD) +/- SE (%)	34	17.7
Intercept (m) +/- SE (%)	181	3.9
Intersubject Variability of Intercept (SD) +/- SE (%)	74	11.0
Age on Intercept +/- SE (%)	-0.33	21.5
Oxygen on Intercept +/- SE (%)	-0.14	23.5
20 mg TID on Intercept +/- SE (%)	0.121	20.7
40 mg TID on Intercept +/- SE (%)	0.137	22.9
80 mg TID on Intercept +/- SE (%)	0.133	23.4
Slope (m/dyne*sec*cm ⁻⁵ /m ²) +/- SE (%)	0.006	125.2

The bootstrap analysis confirmed the effect of covariates. Covariates reaching the pre-specified statistical significance criteria ($p < 0.01$ for forward inclusion and $p < 0.001$ for backward deletion) and remaining in the model were age on both intercept and slope, oxygen therapy and dose on intercept.

Although the 90% CI for the slope still included zero and the standard error of the slope was large, the 90% CIs for all the remaining parameters did not include zero. The standard error and bias were reasonable. The placebo group was used as the reference to estimate the effect of the different dose groups. The effect of all three doses on the intercept compared to placebo was well estimated. It was about the same magnitude for all three dose groups.

The goodness of fit is shown in Figure 65. The model predicted the observed 6MWD reasonably.

APPEARS THIS WAY
ON ORIGINAL

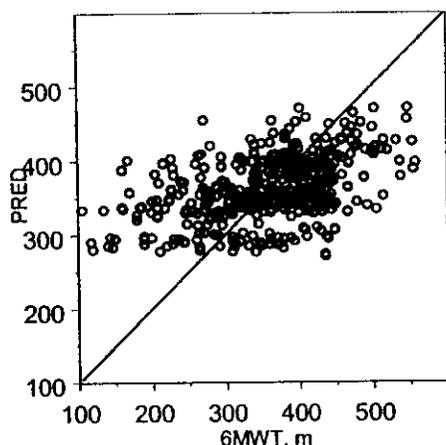


Figure 65: Population predicted vs. observed 6MWD

The proposed by the sponsor model described the decrease of the baseline 6MWD measurements with the increases in PVRi. The final model equation was

$$\text{RESPONSE} = \text{BASELINE} - (\text{SLOPE} * \text{PVRi}).$$

The slope predicted by this model was $0.006 \text{ m/dyne} \cdot \text{sec} \cdot \text{cm}^{-5} / \text{m}^2$. This means that for a decrease of 1000 units for PVRi, the distance for 6 minute walk would be 6 m. The estimation of the slope was very poor. The baseline predictions were 181 meters. The average 6MW distance was 348 m (placebo), 392 m (20 mg), 384 m(40 mg) and 396 (80 mg). The parameters predicted by the model do not describe the pharmacodynamic response properly.

The effect of covariates on the baseline 6MWD is shown below (Figure 66). The baseline measurements were smaller for older patients. The addition of the oxygen therapy decreased baseline as well.

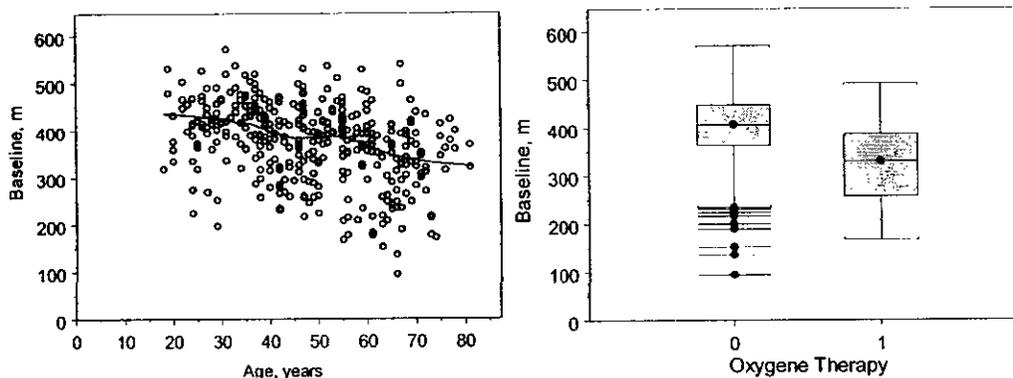


Figure 66: Effect of covariates on the baseline 6MWD

The relationship between sildenafil dose, PVRi and 6MWD is shown in Figure 67. This plot points out that the dose-response relationship between 6MWD, PVRi and sildenafil dose is weak.

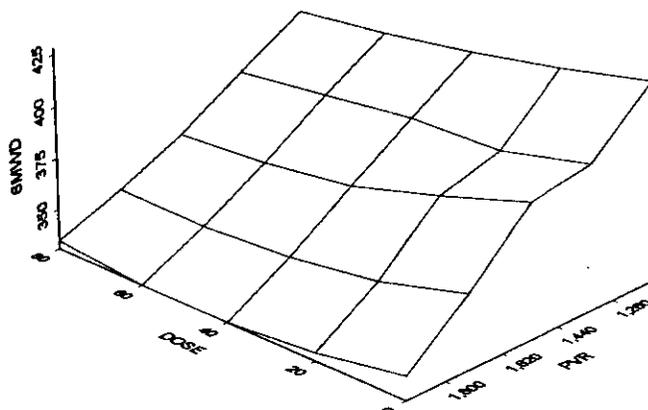


Figure 67: The relationship between sildenafil dose, PVRi and 6MWD

SPONSOR'S CONCLUSIONS

Pharmacokinetics

1. Compared to healthy volunteers, sildenafil average steady state levels were 20-50% higher in patients with pulmonary arterial hypertension. The trough levels were 100% higher, indicating a lower clearance and/or a higher oral bioavailability of sildenafil in the patient population.
2. As in healthy volunteers and ED patients, food delayed the absorption of sildenafil in patients with pulmonary arterial hypertension. This effect has no clinical relevance for the treatment of pulmonary arterial hypertension with sildenafil.
3. There was a more than dose proportional increase of sildenafil exposure after 80 mg TID compared to 20 and 40 mg TID, similar to the findings in healthy volunteers after chronic TID dosing.
4. The only covariates reaching statistical significance in patients with pulmonary arterial hypertension were CYP3A4 substrates and beta-blockers. Both drug classes reduced the apparent clearance of sildenafil by 22.3 and 37.4% respectively. The reduction of the apparent clearance due to CYP3A4 substrates and beta-blockers resulted in 43 and 66% increase of sildenafil exposure, respectively compared to patients not receiving these concomitant medications.
5. Based on the population pharmacokinetic evaluation of study A148 1140, no dose adjustments are required for most subpopulations.
6. Though the number of patients receiving CYP3A4 inducers in A148 1140 was small, the impact of strong inducers on sildenafil pharmacokinetics was obvious and substantial. Therefore, in the presence of potent inducers of CYP3A4 like carbamazepine,

primidone, presumably phenytoin, pyrazinamide and rifampicin, patients should be monitored for response.

Pharmacodynamics:

1. After 12 weeks of chronic administration, sildenafil reduced PVRi by 19.5% of the baseline. The EC50 was 2.92 ng/ml. Covariates reaching statistical significance were
 - a. Age on Baseline for active treatment and on the intercept for the patients on placebo. Older patients tended to have lower baseline PVRi values.
 - b. Calcium channel blockers on the baseline PVRi of patients on active treatment: The baseline PVRi of patients on active treatment receiving calcium channel blockers was 23% lower compared to patients not on calcium channel blockers
 - c. Oxygen therapy on the intercept of PVRi of patients on placebo: The intercept of patients on placebo on oxygen therapy was 49.1% higher than the intercept of placebo patients not receiving oxygen.
2. The concentration -effect relationship between the sildenafil plasma concentrations and the 6-minute walking distance was flat, supporting the clinical evidence for a lack of dose response.
3. The low EC50 values required to lower PVRi in combination with the good efficacy results of the 20 mg TID dose and the flat dose-and concentration -effect relationship between 6-MWD indicate that the in vitro data for PDE5 inhibition in human corpus cavernosum did not fully predict the effect of sildenafil on human pulmonary vessels in vivo and the steady state exposure of sildenafil to reduce pulmonary vascular resistance and to achieve improvement of the 6-MWD is similar.
4. PVRi could potentially be of use as a surrogate marker for the 6-MWD. Using placebo and active treatment data, the 6-MWD decreased by 23.5 m/1000 dyne * sec* cm-5/m2 of PVRi. However, the slope reflected the difference between placebo and active treatment. The PVRi/6-MWD relationship was flat at doses > 20 mg TID.
5. Covariates reaching statistical significance were age, oxygen and dose on the intercept. The 6-MWD decreased with age. Patients requiring oxygen had a 14% lower intercept of 6-MWD compared to patients not requiring oxygen. The intercept of 6-MWD of patients on active treatment was, independent of the administered dose, about 13% higher compared to patients on placebo.
6. The recommended dose of 20 mg TID is fully supported by the results of these analyses.

COMMENTS

1. The population PK and PK/PD modeling performed by the sponsor confirmed the differences in the sildenafil PK between healthy volunteers and patients with PAH. However, dose adjustment is not necessary because:
 - In patients with pulmonary arterial hypertension the effect of concomitant medications appeared to mask the effects of any other covariates like age, hepatic function, body weight, which are known to have an impact on sildenafil pharmacokinetics.
 - There was a 5-fold difference of sildenafil exposure between the recommended dose of 20 mg TID and the well-tolerated top dose of 80 mg TID in A148 1140.
 - The increase in sildenafil exposure due to age, renal and hepatic impairment or concomitant medications (including erythromycin and saquinavir) was less than 5 fold.
 - Ritonavir (500 mg BID) caused an 11-fold increase in sildenafil exposure. A similar result can be expected for other potent CYP3A4 inhibitors like ketoconazole or itraconazole. Therefore, the concomitant administration of sildenafil and potent CYP3A4 inhibitors is not recommended.
2. The relationship between 6MWD and sildenafil exposure cannot be ruled out in this study. Although the mean values show an increase in 6MWD in patients receiving sildenafil compared to the placebo group, the difference was statistically significant.
3. The model describing the relationship between PVRi and sildenafil plasma concentrations showed that this relationship was weak although quantifiable. Coadministration of calcium channel blockers decreased PVRi baseline values by 23%. The estimated EC50 values of 2.92 ng/mL showed that a low dose of sildenafil was needed to lower PVRi. The lowest studied dose in this study was 20 mg TID.
4. The relationship between 6MWD and PVRi was weak. When the model included the covariates, the slope was very shallow, indicating that per each 1000 dyne*sec*cm⁻⁵/m² decrease of PVRi the increase in 6MWD was only 6 m. When compared to placebo, each of sildenafil treatment group had an increase in 6MWD by 50, 42, and 54 m (mean values) and the difference between groups was significant. The sponsor's proposal to use PVRi measurement as a surrogate marker for the sildenafil efficacy is not supported by this study probably due to high variability in data and not wide enough dose range.
5. The dose of 20 mg TID is supported by the results of this study.

4.4 Biopharmaceutics

The proposed commercial tablet formulation for the PAH indication and the formulation used in the PAH clinical studies are directly analogous to the commercial formulation of Viagra. A 20 mg tablet has been developed for the PAH indication. The tablets are manufactured from — which is qualitatively and quantitatively similar to the commercial Viagra ® formulation. Based on previous data showing no impact of formulation changes on bioequivalence, the pharmacokinetic data generated for the male erectile dysfunction (MED) indication are equally applicable for the PAH formulation, given the equivalence of the 2 formulations.

The same — formulation is used to produce the appropriately weighted tablets for both the PAH and MED indications. The minor differences in the tablet presentations for each indication are shown in Table 55.

Table 55: Differences between tablet formulations used for PAH and MED indications

Indication	Tablet strengths ^a	Tablet shape	Tablet colour
PAH	20,	Round normal convex	White film coat ^b
MED	25, 50 and 100 mg	Diamond	Blue film coat

These minor differences in the tablet presentations for each indication are change of tablet shape and color of the film coat.

In Vitro Dissolution Profile of Sildenafil

The in vitro dissolution method for sildenafil citrate tablets, 20 mg, employs the basket apparatus with the baskets rotating at 100 rpm in 900 ml of hydrochloric acid (0.01 M) held at 37°C ± 0.5°C. Aliquots of the dissolution medium are analyzed using a UV spectrophotometric procedure.

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Basket Speed	100 rpm
USP Apparatus I	
Volume	900 mL
Specifications	— in 15 minutes

100 mg Viagra ® Tablets Versus 20 mg Sildenafil Citrate Tablets used for PAH Studies

The method and specification requirement for sildenafil citrate tablets are the same as those developed for Viagra tablets. Since the highest tablet dose developed for Viagra was 100 mg the dissolution medium and test conditions were considered applicable to lower tablet strengths, i.e. sink conditions are met. Sildenafil citrate tablets gave comparable dissolution profiles to those obtained for the Viagra tablets. Comparative dissolution profiles for the 20 mg sildenafil citrate tablets and 100 mg Viagra tablets (batch N60601) which was one of the formulations studied in Study 148-226 are provided in Figure 68.

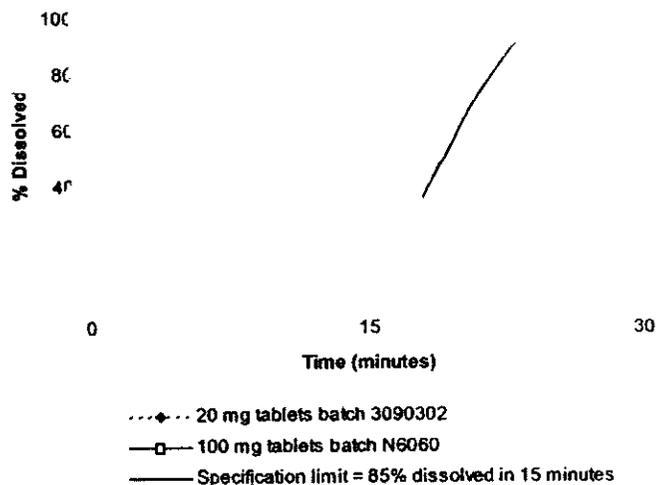


Figure 68: Comparison of the Dissolution Profiles of 100 mg Viagra® Tablets and 20 mg Sildenafil Citrate Tablets in 0.01 M Hydrochloric Acid, Baskets Rotating at 100 rpm

The final commercial film-coated tablet formulation developed for MED differed slightly from the tablet formulation used in Study 148-226 in that a clear film-coat was applied to the tablets. This difference was considered insignificant; equivalence of the final commercial tablet to the tablets studied in 148-226 was subsequently confirmed by in vitro dissolution testing. Figure 69 shows dissolution profiles for batches of 100 mg Viagra tablets with and without a clear film-coat: Batch N6060 does not have a clear film-coat and Batch N7053 does have a clear film-coat.

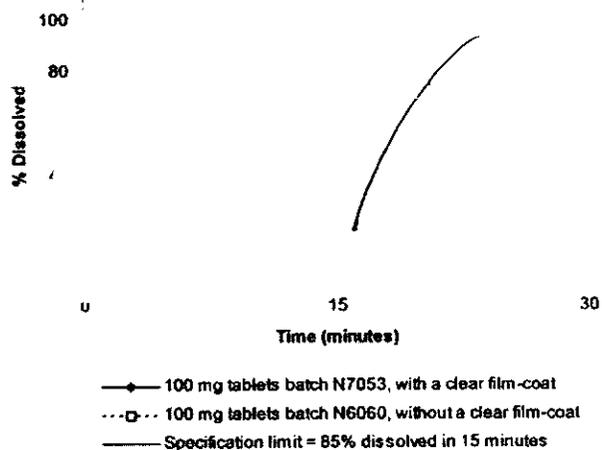


Figure 69: Comparison of the Dissolution Profiles of 100 mg Viagra Tablets with and without a clear film-coat in 0.01 M Hydrochloric Acid, Baskets Rotating at 100 rpm

In vitro dissolution testing confirmed that the dissolution profiles were the same for the sildenafil citrate tablet for PAH and sildenafil citrate tablet for MED.

4.5 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-845	Brand Name	none	
OCPB Division (I, II, III)	DIV-1	Generic Name	Sildenafil	
Medical Division	CARDIORENAL	Drug Class		
OCPB Reviewer	ELENA MISHINA	Indication(s)	PAH	
OCPB Team Leader	P. Marroum	Dosage Form	Tablets 20,	
		Dosing Regimen		
Date of Submission	December 3, 2004	Route of Administration	oral	
Estimated Due Date of OCPB Review	April 30, 2005	Sponsor	Pfizer Pharmaceuticals	
PDUFA Due Date	June 3, 2005	Priority Classification	P	
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting /non-fasting single dose:				
fasting /non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	14		
In-vivo effects of primary drug:	X	14		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	X	2		
Data rich:				
Data sparse:	X	2		

II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability - solution as reference:			
alternate formulation as reference:			
Bioequivalence studies - traditional design; single /multi dose:			
replicate design; single /multi dose:			
Food-drug interaction studies:			
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References	x		
Electrophysiology Study			
Pharmacodynamic studies	x		
Total Number of Studies Reviewed	7		
Filability and QBR comments			
	X if yes	Comments	
Application filable ?	X		
Comments sent to firm ?			
QBR questions (key issues to be considered)			
Other comments or information not included above			
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

CC: NDA 21-845, HFD-850(Lee), HFD-860 (Marroum, Mehta, Mishina), Biopharm (CDER)

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

/s/

Elena Mishina
5/20/05 04:43:21 PM
BIOPHARMACEUTICS

Patrick Marroum
5/20/05 04:56:46 PM
BIOPHARMACEUTICS