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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Revatio™/Sildenafil citrate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00430716

PROTOCOL NO.: A1481244

PROTOCOL TITLE: A Multinational, Multicentre, Randomized, Parallel Group, Double-Blind Study to Assess the Efficacy and Safety of 1 mg, 5 mg and 20 mg TID of Oral Sildenafil in the Treatment of Subjects Aged 18 Years and Over With Pulmonary Arterial Hypertension (PAH)

Study Center(s): A total of 34 centers took part in the study, including 9 in USA, 5 in India, 2 each in Brazil, China, Italy, Netherlands, Philippines, Thailand and United Kingdom and 1 each in Poland, Greece, Latvia, Malaysia, Romania, and Russian Federation,.

Study Initiation Date and Primary Completion or Completion Dates: 08 April 2008 to 25 May 2010. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objective(s):

Primary: To demonstrate a dose response for 1 mg, 5 mg and 20 mg three times a day (TID) oral sildenafil for the treatment of subjects with PAH

Secondary:

- To assess the safety and tolerability of sildenafil (1 mg, 5 mg and 20 mg TID) after 12 weeks of treatment in subjects with PAH.
- To evaluate the effects of sildenafil (1 mg, 5 mg and 20 mg TID) on biomarkers of progression of PAH as measured by B-type natriuretic peptide (BNP)/pro BNP levels and tricuspid annular plane systolic excursion (TAPSE).
- To determine the population PK parameters, and assess potential relationship of 6-minute walk distance (6MWD), BNP/pro BNP, TAPSE, Pulmonary Vascular Resistance Index (PVRI) and sildenafil exposure.

METHODS

Study Design: This was a multi-national, multi-center, randomized, double-blind, parallel group study to assess the efficacy and safety of 1 mg, 5 mg and 20 mg TID oral sildenafil in the treatment of PAH in subjects aged 18 years and over. At the baseline visit, subjects were randomized to receive 1 of the 3 doses of sildenafil during a 12-week dose response treatment phase. The double-blind phase consisted of 4 clinic visits (Weeks 1, 4, 8 and 12) during which efficacy and safety data were collected. Subjects who withdrew during the course of the study were followed up for safety assessments 30 days after the last treatment date. Those subjects who completed the 12 week double-blind treatment phase of the study were rolled over to receive sildenafil 20 mg TID for further 12 weeks (open-label extension phase) and attend a follow-up visit 30 days after the last treatment date.

Number of Subjects (Planned and Analyzed): Approximately 219 subjects were planned to be randomized (73 per study arm) to ensure that there were 210 evaluable subjects. Of the total planned, 169 subjects were screened and 130 subjects were assigned to study treatment. The study was terminated prematurely based on the recommendations made by the Data Monitoring Committee (DMC).

Diagnosis and Main Criteria for Inclusion: Subjects aged ≥18 years with idiopathic PAH (IPAH), PAH associated with connective tissue disease (CTD-APAH), or PAH associated with congenital heart disease with surgical repair (at least 5 years previously) whose baseline 6MWD was ≥100 m and ≤450 m and whose pulmonary artery pressure (PAP) was of ≥25 mmHg and pulmonary artery wedge pressure (PAWP) was of ≤15 mmHg at rest via right heart catheterization performed within 12 weeks prior to randomization. All women of childbearing potential had to use adequate contraception.

Study Treatment: Subjects were randomized to 1 of the 3 treatment groups: 1 mg sildenafil, 5 mg sildenafil or 20 mg sildenafil TID in a 1:1:1 ratio. For the double-blind phase, subject received sildenafil 1 mg, 5 mg or 20 mg tablets and for the open-label extension phase, all subjects received sildenafil 20 mg tablets at least 4 to 6 hours apart with or without food for 12 weeks. For Weeks 1, 4 and 8 visits, subjects were instructed to take their morning dose approximately 4 to 6 hours prior to the scheduled morning appointment time to facilitate the 6-minute walk test (6MWT) at trough levels of sildenafil. At baseline and Week 12 visits, subjects were given their morning dose in the clinic to facilitate PK sample collection.

During the 12 week open label extension phase, all subjects who completed the 12 week double blind treatment phase, received open label sildenafil 20 mg TID. For Weeks 12, 16 and 20 visits, subjects were instructed to take 1 tablet TID at least 4 to 6 hours apart with or without food. For Week 16 and Week 20 visits, subjects were instructed to take their morning dose approximately 4 to 6 hours prior to the scheduled morning appointment time to facilitate the 6MWT at trough levels of sildenafil.

Efficacy Evaluations:

- Primary endpoint was change from baseline in the total distance walked during the 6MWT at Week 12.

- Secondary endpoints included the change from baseline at Week 12 in mean PAP, BNP and pro-BNP levels, TAPSE index, BORG dyspnea score and pulmonary hypertension criteria for functional capacity and therapeutic class; time from randomization to the first occurrence of clinical worsening during the 12 week treatment phase of the study.

- Tertiary endpoints included change from baseline at Week 12 in chronic use of background therapy for PAH and hemodynamic parameters including cardiac output (CO), pulmonary vascular resistance (PVR), PVR index (PVRI), pulmonary capillary wedge pressure (PCWP), systolic, diastolic and mean systemic arterial pressure, systolic and diastolic pulmonary arterial pressure (sPAP, dPAP), heart rate, right atrial pressure (RAP), systemic vascular resistance (SVR) and SVR index (SVRI).

Pharmacokinetic Evaluations: Plasma concentrations for sildenafil, and desmethyl sildenafil (UK-103,320) at the designated time points were determined.

Safety Evaluations: Safety was determined using the following assessments: monitoring of adverse events (AEs) and serious adverse events (SAEs) and laboratory tests [hemoglobin, hematocrit, mean corpuscular volume, red blood cell (RBC) count, white blood cell (WBC) count (including differentials in absolute), and platelets, total bilirubin, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase, albumin, total protein, blood urea nitrogen, creatinine, sodium, and potassium] at screening, baseline, Week 4, Week 8 and Week 12. Other safety assessments included vital sign measurements, physical examinations, electrocardiogram (ECG), ocular safety and AEs secondary to excessive pharmacological effects of sildenafil in case of overdose.

Statistical Methods:

Efficacy Population:

Intent to treat (ITT) Population (Full Analysis Set): The ITT population included all subjects who were randomized to study treatment and received at least 1 dose of study drug.

Per Protocol (PP) Population: The PP population included subjects who satisfied the ITT criteria and in addition had:

- Taken 100%±20% of specified dosage of drug for the duration of double blind therapy. This was based on the recorded treatment information where complete missed doses were recorded on the CRF.

- Not violated any of the inclusion/exclusion criteria that could affect the efficacy assessments.

- Not deviated from the protocol with regard to concomitant medication use that could affect the primary efficacy assessment.

- A baseline assessment and a 12 week 6MWT performed at trough levels of sildenafil (to allow for a 30 minute window around the protocol criteria) and prior to the next dose. The Week 12 6MWT was also required to be within the Week 12 window (adjusted to greater than 2 hours post dose) and prior to the next dose.

Safety Population: The safety population consisted of all randomized subjects who had taken at least 1 dose of study drug and was therefore the same as the ITT population.

Analysis of Primary Efficacy Endpoint: The primary analysis was based on the ITT population and the primary endpoint change in 6MWT distance at Week 12. An analysis of variance (ANOVA) model followed by the Williams trend test (one-sided, at the 2.5% level of significance) were used. Missing values were replaced according to the last observation carried forward (LOCF) approach. The Williams trend test firstly determined if there was a significant downward trend in response for the descending doses, and then subsequently determined the highest dose that was statistically inferior to 20 mg (known to be an effective dose of sildenafil). To support the interpretation of the primary analysis, an identical analysis as described above, based upon the PP population, was conducted. The baseline value was taken as the average of the screening and baseline readings for the ITT population. For the PP analysis of the primary endpoint the average of readings recorded in the baseline window (Day -5 to 1) was used. A sensitivity analysis was performed using a nonparametric Williams test. Two further analyses were conducted in which missing data at Week 12 were imputed under missing at random (MAR) and informative missing assumptions. Estimates of the 20 mg vs 5 mg and 20 mg vs 1 mg contrasts at Week 12 were produced with nominal 97.5% one-sided CI. The purpose of these analyses was to check the robustness of the estimates of effect size obtained from the LOCF.

Changes from Week 12 (LOCF) at Week 24 (LOCF) were modeled by analysis of covariance (ANCOVA) with randomized treatment, baseline walk, etiology (as stratification factors) and Week 12 (LOCF) included in the model. Treatment group differences were estimated and presented (95% CI) in a pair-wise manner. For the analysis of the open label phase, baseline was taken to be Week 12 (LOCF) and changes to Week 24 (LOCF) were analyzed provided there was a non-missing post-Week 12 assessment.

Analysis of Secondary Efficacy Endpoints: The covariates for each analysis were baseline walking distance and etiology. All analyses were performed on the ITT population alone. Missing Week 12 data were replaced according to the LOCF approach. All secondary endpoints were summarized using descriptive statistics.

Analysis of Tertiary Efficacy Endpoints: The following summaries of changes in chronic use of background therapy for PAH (anticoagulants, oxygen, diuretics, calcium channel blockers, cardiac glycosides) were presented by treatment group:

- The percentage of subjects with additions (from baseline) in 1 or more classes of drug used as background therapy;

- The percentage of subjects with discontinuations (from baseline) in 1 or more classes of drug used as background therapy.

Any drugs that started and stopped on the same day and took place on the same day as a subject's right heart catheterization were not classified as additions or discontinuations. The number of subjects who were treatment naïve to the background therapies, individually and overall, at baseline was also recorded. Descriptive summaries were produced for the change from baseline in the additional hemodynamic parameters.

No formal analyses were planned for safety data. These data were explored through standard descriptive statistics of the sponsor.

RESULTS

Subject Disposition and Demography: One hundred sixty nine subjects were screened, 130 subjects were randomized to 3 treatment groups. Disposition of subjects is presented in Table 1.

Table 1 Subject Disposition and Subjects Analyzed

		Sildenafil		
Number of Subjects		**1 mg**	**5 mg**	**20 mg**
Screened	169			
Assigned to Treatment		42	43	45
Treated		41	43	45
Completed		27	31	32
Discontinued		14	12	13
Double blind phase				
Entered		41	43	45
Completed		36	38	39
Discontinued		5	5	6
Open label phase				
Entered		36	38	39
Completed		27	31	32
Discontinued		9	7	7
Analyzed for Efficacy				
ITT population		41	43	45
PP population		29	31	33
Analyzed for Safety				
Adverse Events		41	43	45
Laboratory Data		41	40	44
Safety population		41	43	45

FAS: Full Analysis Set; ITT: Intent-to-treat; PP: Per Protocol

A summary of subject demographics and baseline characteristics are presented in Table 2.

Table 2: Summary of Demographic Characteristics

Characteristics	Sildenafil 1 mg	Sildenafil 5 mg	Sildenafil 20 mg
N	**41**	**43**	**45**
Age (years)			
Mean (SD)	42.5 (16.5)	44.4 (17.4)	46.4 (17.7)
Sex (N)			
Female	28	33	26
Male	13	10	19
Race			
White	11	11	14
Black	2	2	1
Asian	27	30	30
Other	1	0	0
BMI (kg/m^2)			
Mean (SD)	24.3 (5.6)	24.3 (6.6)	23.8 (6.2)
Range	15.6-35.8	13.3-42.1	15.6-38.6
Height (cm)			
Mean (SD)	159.0 (11.3)	160.2 (10.7)	160.7 (8.7)
Range	130.0-181.6	129.0-189.0	147.0-181.0
Weight (kg)			
Mean (SD)	61.7 (17.0)	63.1 (19.7)	61.4 (15.7)
Range	32.0-117.0	26.5-126.1	35.0-100.0
WHO Classification of Pulmonary Hypertension:			
Class I	0	1 (2.3)	3 (6.7)
Class II	25 (61.0)	22 (51.2)	27 (60.0)
Class III	16 (39.0)	16 (37.2)	13 (28.9)
Class IV	0	1 (2.3)	0
Baseline Six Minute Walk			
Mean (SD)	347.5 (67.3)	347.7 (73.4)	340.4 (76.3)
Range	167.5-441.5	109.0-455.0	114.0-429.0
n (%)	41 (100.0)	40 (93.0)	42 (93.3)
Baseline mPAP (mmHg)			
Mean (SD)	57.2 (21.9)	55.4 (19.7)	51.1 (21.4)
Range	25.0-110.0	26.3-117.0	25.0-106.0
N	33 (80.5)	33 (76.7)	34 (75.6)
Baseline PVRI (wood units*m*2)			
Mean (SD)	25.4 (15.6)	20.6 (11.0)	18.4 (13.1)
Range	4.6-69.3	4.7-60.4	2.4-44.3
n (%)	33 (80.5)	32 (74.4)	32 (71.1)
Baseline Cardiac Index (l/min/m*2)			
Mean (SD)	2.1 (0.7)	2.3 (0.6)	2.8 (1.2)
Range	1.0-3.5	1.0-3.8	1.1-5.9
n (%)	33 (80.5)	32 (74.4)	32 (71.1)
Baseline RAP (mmHg)			
Mean (SD)	10.5 (5.1)	10.1 (6.1)	8.4 (4.7)
Range	4.0-20.0	2.0-23.0	2.0-27.0
n (%)	33 (80.5)	33 (76.7)	34 (75.6)

mPAP: mean pulmonary arterial pressure; PVRI: pulmonary vascular resistance index; RAP: right atrial pressure; SD: Standard Deviation
n=number of subjects evaluable at the given parameter

Efficacy Results: The primary efficacy endpoint, 6MWD was assessed in the ITT and PP populations. The change from baseline in total distance walked during a 6MWT from baseline to Week 12 (ITT, LOCF population) is presented in Table 3. There was an increase in total distance walked in each treatment group at Week 12 (LOCF). The increase was clinically significant in the 5 and 20 mg groups (mean changes of 41 meters [95% CI: 25.16, 56.34] and 38 meters [95% CI: 23.77, 52.94], respectively) but smaller and not clinically significant in the 1 mg group (mean change of 14 meters [95% CI: 0.41, 28.00]).

Table 3: Change from Baseline in Total Distance Walked During a 6MWT at Week 12 (ITT, LOCF)

Treatment	Sildenafil 1 mg	Sildenafil 5 mg	Sildenafil 20 mg
Number of subjects (N)	**41**	**40**	**42**
Baseline			
Mean (SD)	347.50 (67.29)	347.73 (73.42)	340.38 (76.31)
95% CI	326.26, 368.74	324.25, 371.20	316.60, 364.16
Week 12 (LOCF)			
Mean (SD)	361.71 (76.33)	388.48 (82.30)	378.74 (77.95)
95% CI	337.61, 385.80	362.16, 414.79	354.45, 403.03
Change from baseline			
Mean (SD)	14.21 (43.70)	40.75 (48.75)	38.36 (46.81)
95% CI	0.41, 28.00	25.16, 56.34	23.77, 52.94

6MWT: 6-Minute Walk Test, ITT: Intent To Treat, LOCF: Last Observation Carried Forward, SD: Standard Deviation, CI: Confidence Interval

The results from the PP population were comparable to the ITT population. Analysis of change from baseline in 6MWT at Week 12 (LOCF) as determined from Williams Trend Test (WTT) for ITT population demonstrated that there was a statistically significant ($p = 0.011$) downward trend observed when sildenafil 1 mg was compared to sildenafil 20 mg but no statistically significant downward trend between sildenafil 5 mg and 20 mg ($p = 0.545$). Non parametric WTT analysis demonstrated that sildenafil 1 mg was the highest dose that was statistically inferior ($p = 0.006$) to 20 mg (known to be an effective dose of sildenafil). There was some evidence of treatment effect modification at Week 12 by baseline walking distance and etiology. Following 24 weeks of treatment including 12 weeks of open label phase when all the subjects were administered sildenafil 20 mg dose, the increase in 6MWT observed at the end of the double blind phase was maintained in the sildenafil 5 mg group (mean change of 50 meters) but a larger increase was observed in the sildenafil 1 mg and 20 mg groups (mean change of 47 and 70 meters, respectively). The results showed that the sildenafil 20 mg dose maintains the treatment effect regardless of prior low dose treatment, but prior low dose treatment did not achieve the increase in 6MWT noted for the group continuously receiving 20 mg initially when assessed at 24 weeks.

There was a decrease in mean PAP score from baseline in each of the treatment groups but none of the decreases were statistically significant. The majority of subjects in each treatment group remained in the same functional class from baseline to Week 12 (LOCF). The odds ratio analysis demonstrated that the sildenafil 20 mg group did not have a higher efficiency than the 1 mg and 5 mg groups in relation to changes in functional class. A total of 4 subjects (1 subject each in the sildenafil 1 mg and 5 mg groups, and 2 subjects in the sildenafil 20 mg group) reported events defined as clinical worsening. Decreases in BNP and

pro-BNP were observed in all 3 treatment groups at Week 12 and Week 12 (LOCF). Mean increase in TAPSE index and mean decreases in BORG scores were observed for each treatment group at Week 12 (LOCF) (0.14, 0.17 and 0.04 cm for the sildenafil 1 mg, 5 mg and 20 mg groups, respectively). A small number of subjects had change of background therapies during the study. A total of 10 subjects (4 subjects each in the sildenafil 1 mg and 5 mg groups and 2 subjects in the sildenafil 20 mg group) had any additions and 8 subjects (3 subjects each in the sildenafil 1 mg and 20 mg groups, and 2 subjects in the sildenafil 5 mg group) had any discontinuations of background therapies in all classes. Changes at Week 12 in additional hemodynamic parameters were generally small, variable between treatment groups and the clinical significance of the changes are difficult to evaluate.

Safety Results: During the double blind phase of the study, a similar number of subjects reported treatment-emergent adverse events (TEAEs) in each treatment group (17 subjects each in the sildenafil 1 mg and 5 mg groups, and 19 subjects in the sildenafil 20 mg group). The numbers of TEAEs reported were also similar (46, 41, and 47 in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively). The majority of TEAEs were mild or moderate in severity; a total of 8 subjects reported severe AEs (3 subjects each in the sildenafil 1 mg and 5 mg groups, and 2 subjects in the sildenafil 20 mg group).

During the open label phase of the study (when all subjects received sildenafil 20 mg), a similar number of subjects reported TEAEs in each treatment group (23 subjects in the sildenafil 1 mg group and 22 subjects each in sildenafil 5 mg and 20 mg groups). The numbers of TEAEs reported were also similar in the sildenafil 5 mg and 20 mg (69 and 74, respectively) but more TEAEs (90) were reported in sildenafil 1 mg group. The majority of TEAEs were mild or moderate; a total of 14 subjects reported severe AEs (5 subjects each in the sildenafil 1 mg and 5 mg group, and 4 subjects in the sildenafil 20 mg group).

The TEAEs (all causalities) reported by ≥2 subjects during the double blind phase and open label phase are presented in Table 4

Table 4. Incidence of TEAEs (All Causalities) Reported by ≥2 Subjects in Any Treatment Group

TEAE	Sildenafil 1 mg N = 41	Sildenafil 5 mg N = 43	Sildenafil 20 mg N = 45
Double blind phase			
Number of TEAEs	46	41	47
Anaemia	1	0	3
Diarrhoea	0	2	1
Fatigue	2	1	0
Oedema peripheral	1	1	2
Nasopharyngitis	2	1	1
Back pain	0	1	2
Myalgia	0	0	2
Dizziness	2	1	1
Headache	1	1	3
Dyspnoea	2	3	3
Epistaxis	0	2	0
Pulmonary fibrosis	0	2	0
Rash	0	1	2
Flushing	0	2	1
Open label phase			
Number of TEAEs	90	69	74
Anaemia	1	1	3
Right ventricular failure	1	0	2
Diarrhoea	1	2	1
Gastrooesophageal reflux disease	0	0	2
Asthenia	1	2	2
Chest pain	0	2	0
Fatigue	3	1	0
Oedema peripheral	1	1	2
Pyrexia	2	2	0
Lower respiratory tract infection	2	0	1
Nasopharyngitis	2	1	3
Urinary tract infection	0	2	1
Blood potassium decreased	2	0	0
Weight decreased	1	2	0
Back pain	1	1	3
Muscle spasms	2	0	1
Myalgia	1	0	2
Pain in extremity	1	1	2
Pain in jaw	2	0	0
Dizziness	3	2	2
Headache	2	3	3
Presyncope	0	2	0
Cough	2	0	1
Dyspnoea	2	4	3
Epistaxis	1	3	0
Pulmonary fibrosis	0	2	0
Rash	0	1	2
Flushing	0	2	1

Medical Dictionary for Regulatory Activities (MedDRA) v13.1 coding dictionary applied.

During the double blind phase, 9, 10 and 14 subjects in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively, reported treatment-related TEAEs. The number of AEs reported was 12, 17 and 24 in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively. Two subjects reported severe treatment-related TEAEs (1 subject each in the sildenafil 1 mg and 5 mg

groups, and no subject in the sildenafil 20 mg group). One subject in the sildenafil 20 mg group reported a SAE.

During the open label phase, 11, 12 and 15 subjects in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively reported treatment-related TEAEs. The number of AEs reported was 19, 27 and 31 in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively. Three subjects reported severe treatment-related TEAEs (1 and 2 subjects in the sildenafil 1 mg and 5 mg groups, respectively and no subject in the sildenafil 20 mg group). Two subjects in the sildenafil 20 mg group reported SAEs.

Five subjects permanently discontinued from the study due to TEAEs. Permanent discontinuations are summarized in Table 5. Three of these subjects permanently discontinued due to SAEs. Two subjects temporarily discontinued due to AEs.

Table 5. Permanent Discontinuations due to Adverse Events

AE	Treatment group	AE Start day	AE Stop day	Severity/ Outcome	Causality	SAE
Right ventricular failure	1 mg	14	>59	Severe/ Still present	Related	No
Acute exacerbation of idiopathic pulmonary fibrosis	5 mg	3	>16	Severe/ Still present	Unrelated	Yes
Drug allergy	20 mg	8	45	Mild/ Resolved	Related	Yes
Skin rash	20 mg	15	>21	Moderate/ Still present	Related	No
Right heart failure	20 mg	35	>64	Severe/ Still present	Unrelated	Yes

AE: Adverse Event; SAE: Serious Adverse Event

Two subjects died during the double blind phase. One subject was randomized to sildenafil 1 mg group and the other was randomized to sildenafil 5 mg group. Neither of the deaths was judged as causally related to study drug by the investigators. No deaths were reported in the open label phase.

A total of 10 subjects (4, 2 and 4 subjects in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively) during the double blind phase and 8 subjects (3, 2 and 3 subjects in the sildenafil 1 mg, 5 mg and 20 mg groups, respectively) during the open label phase reported SAEs. There were no discontinuations due to laboratory test abnormalities.

CONCLUSION(S):

- The study was terminated prematurely based on the recommendations made by the DMC. The number of subjects recruited was lower than planned due to premature termination.
- The study population may have differed from those usually investigated in this indication.

- Sildenafil 20 mg dose was more effective than 1 mg as determined from the primary and other efficacy endpoints.

- There was no obtained difference between the sildenafil 20 mg and 5 mg doses; however the equivalence of the sildenafil 20 mg and 5 mg doses could not be inferred.

- Sildenafil was generally well tolerated; the majority of AEs were mild or moderate.