

Clinical trial protocol

Title

A multinational, multicentre, randomized, double-blind study to assess the efficacy and safety of oral sildenafil 20 mg TID or placebo when added to Bosentan in the treatment of subjects, aged 18 years and above, with pulmonary arterial hypertension (PAH)

Etude internationale, multicentrique, randomisée en double aveugle évaluant l'efficacité et la tolérance du sildenafil oral 20 mg trois fois par jour contre placebo en association avec le bosentan dans le traitement de patients âgés de 18 ans et plus présentant une hypertension artérielle pulmonaire (HTAP)

Inclusion criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

- **1** Subjects aged 18 and above at the time of the screening visit who have any of the following types of pulmonary arterial hypertension and functional class, and for which bosentan therapy is indicated according to national license:

For US subjects only:

- Idiopathic 'Primary' Pulmonary Arterial Hypertension (PAH).
- Pulmonary hypertension secondary to connective tissue disease.
- Pulmonary hypertension with surgical repair (at least 5 years previously) of:-
- Atrial septal defect (ASD).
- Ventricular septal defect (VSD).
- Patent ductus arteriosus (PDA).
- Aorto-pulmonary window.
- Subjects with WHO functional class III / IV prior to initiation of bosentan therapy

For EU subjects only:

- Idiopathic 'Primary' Pulmonary Arterial Hypertension (PAH).
- Pulmonary Hypertension secondary to Scleroderma.
- Subjects with WHO functional class III prior to initiation of bosentan therapy.

For Australian subjects only

- Idiopathic 'Primary' Pulmonary Arterial Hypertension (PAH).
- Pulmonary Hypertension secondary to Scleroderma.
- Subjects with WHO functional class III / IV prior to initiation of bosentan therapy.

For Israeli subjects only

- Idiopathic 'Primary' Pulmonary Arterial Hypertension (PAH).
- Pulmonary Hypertension secondary to Scleroderma or other connective tissue disease.
- Subjects with any WHO functional class prior to initiation of bosentan therapy.

- **2** Subjects must have been treated continually with a stable dose of bosentan (62.5mg bid or 125mg bid) for a minimum of three months prior to randomization.

- **3** Subject with a mean pulmonary artery pressure ≥ 25 mmHg and a pulmonary capillary wedge pressure of < 15 mmHg at rest, via right heart catheterization within 3 years prior to randomization.

- **4** Subjects whose baseline 6-Minute Walk Test distance is ≥ 100 m and ≤ 450 m.

- **5** Subjects who have given written informed consent to participate in the study before being screened for the study.

- **6** All women of childbearing potential must use adequate contraception (i.e. hormonal in conjunction with intrauterine device or barrier methods with spermicide) throughout the study and for the duration of their bosentan therapy or must be celibate or their partner must have had vasectomy. The screening serum pregnancy test must be negative. Women who have been surgically sterilized or are at least two years postmenopausal may be enrolled and do not need to use birth control.

Exclusion criteria:

Subjects presenting with any of the following will not be included in the trial:

- **1** PAH secondary to any aetiology including congenital heart disease other than those specified in the inclusion criteria.
- **2** With the exception of bosentan therapy, subjects who are currently receiving any forms of chronic treatment for PAH such as any formulations of prostacyclin, PDE-5 inhibitors, other endothelin-receptor antagonists, nitrates or nitric oxide donors (e.g. arginine supplements) including nicorandil in any form or any potent CYP3A4 inhibitors (e.g. Cyclosporin A and Glibenclamide). Note: Acute vasodilator response testing with any short acting vasodilators such as prostacyclin or inhaled NO during right heart catheterization is permitted.
- **3** Subjects with significant (i.e. > 2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation. Subjects with previous surgical replacement of a valve may be eligible for entry into the study after consultation with a Pfizer study clinician provided the following conditions are satisfied:
 - That there was no evidence of PAH secondary to valvular disease prior to surgery.
 - The prosthetic valve is functioning normally on echocardiography.
 - The valve replacement occurred at least one year prior to randomization.
- **4** Subjects with acutely decompensated heart failure within 30 days prior to randomization.
- **5** Subjects with LV Ejection Fraction of <45% or LV shortening fraction of <0.2 within three months prior to randomization.
- **6** Subjects who have had a myocardial infarction or stroke within 6 months prior to randomization.
- **7** Subjects who have had a change of dose or class of standard background therapy used for treatment of PAH (i.e. oxygen, calcium channel blockers, digoxin, diuretics) used for the treatment of PAH within 30 days prior to randomization. Note: a change in the dose or oral anticoagulant therapy within this timeframe to maintain the INR within the therapeutic range is acceptable.
- **8** Subjects with congenital heart disease (unless they fulfill inclusion 4.1.1), pulmonary hypertension due to thromboembolism, HIV or schistosomiasis.
- **9** Subjects who have undergone atrial septostomy within six months prior to randomization.
- **10** Subjects with uncontrolled brady- or tachyarrhythmias, placement of pacemakers or implantable defibrillators <60 days prior to randomization.
- **11** Subjects whose 6 Minute Walk Test distance may be limited by conditions other than PAH related dyspnoea or fatigue e.g. claudication from vascular insufficiency or arthritis.
- **12** Pregnant or lactating women.
- **13** Subjects with a history or pulmonary embolism verified by ventilation/perfusion scan, angiogram or spiral chest CT scan.
- **14** Subjects with hypotension defined as systolic arterial pressure <90 mm Hg after sitting for 5 minutes at either screening or baseline.
- **15** Subjects with known hereditary degenerative retinal disorders (such as retinitis pigmentosa) or history of non-arteritic ischemic optic neuropathy (NAION).
- **16** Subjects with history of chronic lung diseases / restrictive lung disease (e.g. COPD or scleroderma) with impairment of lung function as defined by TLC <60% and/or FEV1 ≤80% predicted within 30 days or randomization.
- **17** Subjects who have previously failed on bosentan or sildenafil therapy (defined as those subjects who had no evidence of clinical improvement whilst on the medicines, and no worsening in symptoms or clinical status, on discontinuation of the medicines).
- **18** Subjects at screening with impairment of renal function (serum creatinine > 2.5 X Upper Limits of Normal (ULN)).
- **19** Subjects at screening with severe hepatic impairment (ALT/AST > 3X ULN) or portal pulmonary hypertension.
- **20** Subjects using chronic arginine supplementation including HeartBar.

- **21** Subjects who have received any experimental drug within the past four months prior to randomization. An experimental drug is defined as any drug that does not have regulatory approval for the indication that it is being prescribed for.
- **22** Subjects who have evidence of any drug abuse, including alcohol.
- **23** Subjects who have donated blood during the previous month or intend to donate blood or blood products during the study or for one month following the completion of the study.
- **24** In the opinion of the investigator, a subject who is not likely to complete the study for whatever reason.
- **25** Subjects who have untreated proliferative diabetic retinopathy.
- **26** Subjects with a history of multiple clinically significant allergies (including those with known allergies or intolerances to sildenafil).
- **27** Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

Recruitment:

For FRANCE : four centres with at least five patients per centre

Start of the study

June 2006

End of the study:

December 2008

Trial phase

Phase IV

Drug

Sildenafil (and bosentan)

International multicenter study