ASK1

Inclusion

1) Man or woman age 18 thorough 75 years

2) Diagnosis of one of the following:
   a) IPAH
   b) HPAH
   c) Drug- and toxin-induced PAH
   d) PAH associated with one of the following:
      i) Connective tissue disease
      ii) HIV infection
      iii) Congenital heart defects, repaired greater than 1 year prior to screening (atrial septal
defects, ventricular septal defects, and patent ductus arteriosus)

3) Meet all of the following hemodynamic criteria by means of ascreening RHC :
   a) mPAP of ≥ 25 mmHg
   b) PVR ≥ 400 dyne•sec/cm5
      i) PCWP or LVEDP of ≤ 12 mmHg if PVR ≥ 400 and < 500 dyne•sec/cm5, or PCWP/LVEDP ≤
         15 mmHg if PVR ≥ 500 dyne•sec/cm5

4) Be able to walk a distance of at least 100 m during the screening 6MWT

5) Have WHO Functional Class II or III symptoms at the screening visit, as assessed by the investigator

6) Meet the following criteria determined by PFTs completed no more than 24 weeks prior to screening
   a) Forced expiratory volume in one second (FEV1) ≥ 55% of predicted normal
   b) FEV1:FVC ratio ≥ 0.60

7) Currently on a stable treatment regimen with one or more drugs approved for PAH. Stable therapy is
   defined as ≥ 12 consecutive weeks prior to the screening RHC and at a stable dose for ≥ 8 consecutive
   weeks prior to the screening RHC.

8) If diagnosed with HIV, must have stable disease status.
   a) Stable treatment with HIV medications for at least 8 weeks prior to screening
   b) No active opportunistic infection during the screening period
   c) No hospitalizations due to HIV for at least 4 weeks prior to screening

9) Have documented evidence of the exclusion of CTEPH by a negative or low probability lung
   ventilation/perfusion (V/Q) scan or negative pulmonary arteriogram

10) Women of childbearing potential must have a negative pregnancy test at Screening

11) If engaged in heterosexual activity and of child-bearing potential must agree to use protocol-
specified method(s) of contraception
12) If participating in an exercise program for pulmonary rehabilitation, the program must have been initiated ≥12 weeks prior to screening, and subjects must agree to maintain the current level of rehabilitation for the first 24 weeks of study treatment.

13) If not participating in an exercise training program for pulmonary rehabilitation, must agree not to enroll in an exercise training program for pulmonary rehabilitation during study treatment.

**Exclusion Criteria:**

1) Diagnosis of PAH associated with:
   a) Significant venous or capillary involvement (PCWP > 15 mm Hg)
   b) Pulmonary capillary hemangiomatosis
   c) Portal hypertension
   d) Unrepaired congenital heart defects

2) Pulmonary hypertension (PH) belonging to groups 2 to 5 of the 2013 NICE classification (29019).

3) Evidence of ≥ 3 of the following left ventricular disease/dysfunction risk factors (a-d):
   a) Body mass index (BMI) ≥ 30
   b) History of essential hypertension
   c) Diabetes mellitus – any type
   d) Historical evidence of significant coronary artery disease (CAD) established by any one of the following: MI; percutaneous intervention; angiographic evidence of CAP; positive stress test with imaging; previous coronary artery surgery; chronic stable angina

4) Left ventricular ejection fraction (LVEF) ≤ 40% or clinically significant ischemic, valvular or constrictive heart disease

5) Receiving intravenous inotropes within 4 weeks prior to the screening visit (e.g. dopamine, dobutamine)

6) Receiving treatment with a strong CYP3A4 inhibitor (e.g. protease inhibitors, systemic ketoconazole or systemic itraconazole).

7) Receiving treatment with a strong CYP3A4 inducer (e.g. rifampin).

8) Receiving treatment with a strong OATP1B1/1B3 inhibitor (e.g. cyclosporine).

9) Receiving treatment with a sensitive P-gp substrate (e.g. digoxin).

10) Uncontrolled hypertension (≥180/110 mm Hg) at screening

11) End stage renal disease
12) Severe liver disease (Child-Pugh Class C, with or without cirrhosis)

13) Severe arthritis, musculoskeletal problems, or morbid obesity that, in the opinion of the investigator, is the cause of the subject’s functional limitation and would affect the subject’s ability to perform or complete the 6MWT

14) History of malignancies within the past 5 years

15) Pregnant or breastfeeding; lactating females must agree to discontinue nursing before the study drug is administered

16) Demonstrated noncompliance with previous medical regimens

17) Current alcohol or substance

18) Participation in a clinical study involving another investigational drug or device within 4 weeks before the screening visit.

19) Known hypersensitivity to the study drug, the metabolites, or formulation excipients.