PHocus: A Global Phase 2 Study of Inhaled Mosliciguat in Interstitial Lung Disease-Associated Pulmonary Hypertension (ILD-PH)

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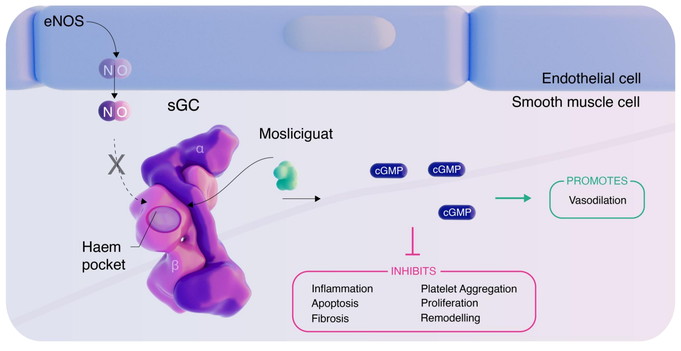
Background

- Pulmonary hypertension (PH) is a debilitating cardiopulmonary condition characterised by pathologic changes to the pulmonary vasculature resulting in right ventricular strain, remodelling, and eventually right heart failure.[1]
  - The key haemodynamic criterion for diagnosis of PH is mean pulmonary arterial pressure >20 mmHg.[2,3]
- The World Symposium on Pulmonary Hypertension has classified PH into 5 groups: pulmonary arterial hypertension (Group 1), PH due to left-sided heart disease (Group 2), PH due to lung disease and/or hypoxia (Group 3), PH due to pulmonary artery obstructions (Group 4), and PH with multifactorial and/or unclear mechanisms (Group 5).[3]
- Interstitial lung disease (ILD)-associated PH (ILD-PH) is part of Group 3 PH.[3]
  - PH accompanying ILD results from loss of small vessels, thickening and obstruction of large vessels, vasoconstriction, and impaired angiogenesis.[4]
  - When present, the PH component of ILD contributes to functional impairment in patients with ILD and is a poor prognostic indicator.[4,5]
  - Treatment of ILD-PH has focused on management of the underlying disease, and effective treatment options for the PH component remain limited.[5]
- Mosliciguat is a novel, investigational, first-in-class, small-molecule soluble guanylate cyclase (sGC) activator with lung-targeted delivery via dry powder inhaler (DPI).[6,7]
- Mosliciguat has a unique mechanism of action, directly binding to the haem pocket of sGC (**Figure 1**).[7]
  - Under oxidative stress, iron in the haem pocket of sGC becomes oxidised, which decreases affinity for nitric oxide (NO).[8] Under these conditions, mosliciguat mimics NO signalling by targeting the NO-insensitive oxidised apoenzyme-sGC, thus restoring activity of NO-insensitive apoenzyme-sGC. By virtue of being an sGC activator, mosliciguat does not require an intact prosthetic haem pocket to increase sGC enzymatic activity.[7]

Figure 1. Proposed Mechanism of Action of Mosliciguat.



Abbreviations: cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; sGC, soluble guanylate cyclase.

- Mosliciguat has shown potent vasodilation in preclinical models of PH, including in experimental conditions of oxidative stress that simulate an environment typically observed in patients with PH, such as impaired NO signalling and NO depletion.[7]
  - Inhaled mosliciguat could have clinical benefits for the treatment of PH, including in patients with high oxidative stress burden.[7]
- The Phase 2 PHocus study is evaluating mosliciguat as a potential treatment for ILD-PH, a condition marked by high mortality and in need of therapeutic options.

Aim

- Evaluate the safety and efficacy of once daily inhaled mosliciguat via DPI in ILD-PH.

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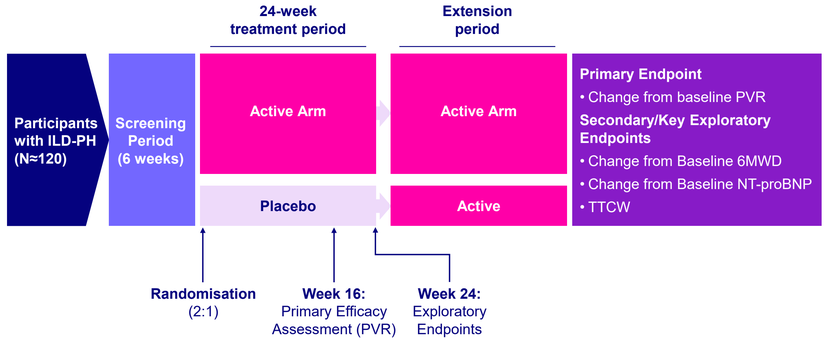
Methods

Study Design

- PHocus (NCT06635850) is a global, multicentre, two-part, randomised, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of once daily inhaled mosliciguat via DPI in adult patients with ILD-PH (**Figure 2**).
  - PHocus comprises two parts: Part 1 (placebo-controlled treatment period), which is a 24-week double-blind treatment period, and Part 2 (extension period), in which all participants may receive mosliciguat either until the participant discontinues or the study ends.
- Approximately 120 adult patients with ILD-PH will be enrolled at approximately 85 sites.

Figure 2. PHocus Study Design.



Abbreviations: 6MWD, 6-minute walk distance; ILD-PH, interstitial lung disease-associated pulmonary hypertension; NT-proBNP, N-terminal probrain natriuretic peptide; PVR, pulmonary vascular resistance; TTCW, time to clinical worsening

Objectives and Endpoints

- The primary endpoint is change from baseline at Week 16 in pulmonary vascular resistance (PVR).
- Secondary, safety, pharmacokinetic, and key exploratory endpoints are listed in **Table 1**.
- Functional improvement and time to clinical worsening (TTCW) will be assessed at 24 weeks.
  - TTCW will be adjudicated by an Independent Event Adjudication Committee.

Table 1. PHocus Objectives and Endpoints.

Primary Objective	Primary Endpoint
Determine the magnitude of reduction in PVR at 16 weeks	Percent change from baseline in PVR assessed at estimated peak exposure at Week 16 by RHC
Secondary Objectives	**Secondary Endpoints**
Determine the improvement in 6MWD at 16 weeks	Change in 6MWD from baseline measured at estimated peak exposure at Week 16 using the 6MWT
Determine change in NT-proBNP at 16 weeks	Change from baseline in NT-proBNP at Week 16
Safety Objectives	**Safety Endpoints**
Evaluate the safety and tolerability of mosliciguat	Incidence and nature of participant TEAEs, SAEs, and AEs leading to discontinuation
Evaluate the effect of mosliciguat on heart rate, systemic BP, and oxygenation	Change over time in heart rate, BP, oxygen saturation by pulse oximetry, and requirement for supplemental oxygen (L/min)
Pharmacokinetic Objectives	**Pharmacokinetic Endpoints**
Understand the PK of mosliciguat in participants with ILD-PH	Plasma PK parameters of mosliciguat (eg, C_{max}, t_{max}, C_{trough}, AUC)
Key Exploratory Objectives	**Key Exploratory Endpoints**
Evaluate TTCW	TTCW will be evaluated over the duration of the study and will be adjudicated by an Independent Event Adjudication Committee
Longitudinal assessments in pulmonary function testing	Change from baseline including, but not limited to, FVC, FEV_1, and DLCO

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; AE, adverse event; AUC, area under the plasma concentration-time curve; BP, blood pressure; C_{max}, maximum plasma concentration; C_{trough}, plasma concentration at the end of the dosage interval; DLCO, diffusion capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD-PH, interstitial lung disease-associated pulmonary hypertension; NT-proBNP, N-terminal probrain natriuretic peptide; PK, pharmacokinetic(s); PVR, pulmonary vascular resistance; RHC, right heart catheterisation; SAE, serious adverse event; TEAE, treatment-emergent adverse event; t_{max}, time to maximum plasma concentration; TTCW, time to clinical worsening.

Patient Population

- Eligible participants are adult patients with ILD-PH diagnosed by right heart catheterisation and with elevated PVR.
  - Diagnosis of ILD will be confirmed by high resolution computed tomography showing diffuse parenchymal disease with evidence of fibrotic component and limited emphysema component.
  - Eligible ILD subgroups include: idiopathic interstitial pneumonia, chronic hypersensitivity pneumonitis, combined pulmonary fibrosis and emphysema, and ILD associated with connective tissue disease.
- **Table 2** provides key inclusion and exclusion criteria for the patient population.

Table 2. PHocus Key Inclusion and Exclusion Criteria.

Key Inclusion Criteria	Key Exclusion Criteria

• Adult between 18 and 85 years of age
• Diagnosis of ILD (confirmed by central read of HRCT scan) showing diffuse parenchymal disease
  ○ Eligible ILD subgroups: IIP, chronic hypersensitivity pneumonitis, CPFE, ILD associated with CTD
• HRCT criteria: diffuse parenchymal disease with evidence of fibrotic component and limited emphysema component
• Confirmed PH by RHC during screening with evidence of elevated PVR
• ILD-PH who meet 1 of the following:
  ○ Naïve to PH-directed therapy
  ○ Previously treated with PH-directed therapy and now off therapy (washout of ≥5 half-lives or 28 days prior to screening RHC procedure [whichever is longer])
• 6MWD ≥100 m
	• Diagnosis of PH Group 1 (eg, PAH), Group 2 (PH related to left-heart dysfunction), Group 4 (eg, CTEPH), or Group 5 (eg, unclassified)
	• Diagnosis of PH Group 3 outside of diseases listed in inclusion criteria
	• Currently on therapy for PH, including but not limited to: prostacyclins (eg, treprostinil), prostacyclin receptor agonists (eg, selexipag), endothelin receptor antagonists (eg, ambrisentan), or activin inhibitors (eg, sotatercept)
	• History of intolerance to or lack of efficacy with mosliciguat or sGC stimulators or activators
	• Evidence of clinically significant left-sided heart disease: PCWP >15 mmHg or LVEF <40%

Abbreviations: 6MWD, 6-minute walk distance; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; HRCT, high resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; ILD-PH, interstitial lung disease-associated pulmonary hypertension; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; sGC, soluble guanylate cyclase.

Study Drug

- Patients will be randomised 2:1 to once daily inhaled mosliciguat or matched placebo and individually titrated to a maximally tolerated dose.

Statistical Analysis

- The Full Analysis Set will include all participants who are randomised and receive ≥1 dose of study drug. It will be the primary analysis set for the primary endpoint and all efficacy analyses (unless otherwise specified).
- The Safety Analysis Set will include all participants who receive ≥1 dose of study drug. It will be used for safety analyses.
- The Pharmacokinetic Analysis Set will include all participants who receive ≥1 dose of study drug and have ≥1 post-treatment measurable plasma concentration of mosliciguat.

Conclusions

- Inhaled mosliciguat is a once daily, sGC activator with targeted delivery to the lungs.[6]
- The phase 2 PHocus study is currently enrolling adult patients with ILD-PH and is designed to generate clinical data to inform the therapeutic potential of inhaled mosliciguat administered via DPI in patients with ILD-PH, a population with high morbidity and mortality for whom therapeutic options are lacking.

References and Notes

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For more information about the Phase 2 PHocus study in ILD-PH: http://phocusstudy.com/