ATMOS, a Proof-of-Concept Trial of Inhaled Mosliciguat in Untreated PAH or CTEPH

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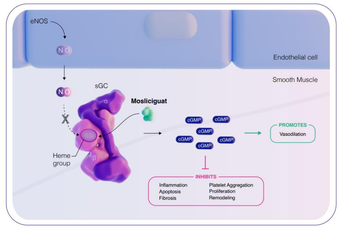
Background

- Pulmonary hypertension (PH) is a debilitating disorder comprising a heterogenous group of progressive conditions with different aetiologies and characterized by progressive right heart failure, functional decline, and increased mortality[1,2]
- Soluble guanylate cyclase (sGC) is a key enzyme in the nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signalling pathway that helps maintain vascular homeostasis. NO binds sGC, triggering cGMP production, which leads to[3-8]:
  - Increased vasodilation
  - Reduced inflammation and apoptosis
  - Reduced platelet aggregation
  - Reversal of vascular remodeling
  - Anti-fibrotic effects
- PH and lung disease conditions can have reduced sGC activity[9,10]
- Mosliciguat is an investigational inhaled sGC activator with targeted delivery to the lungs that aims to restore sGC function, even in the conditions of oxidative stress as seen in PH[11,12]

Figure 1. Mosliciguat Mechanism of Action



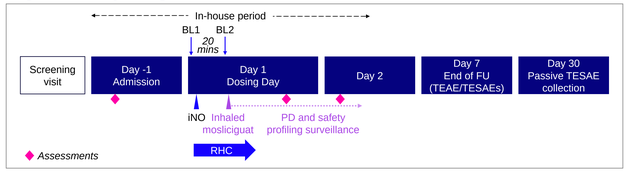
Aims

- The proof-of-concept ATMOS trial evaluated efficacy, safety, tolerability, and pharmacokinetics (PK) of inhaled mosliciguat in participants with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) (World Health Organization PH Groups 1 and 4, respectively), following single-dose administration of mosliciguat[12-14]
- Study objectives were[12,13]:
  - Primary: Peak percent reduction from baseline in pulmonary vascular resistance (PVR) following single dosing by inhalation of mosliciguat, with ≥-20% reduction in PVR defined as clinically meaningful
  - Secondary: safety, tolerability, and incidence of treatment-emergent adverse events (TEAEs)

Methods

- ATMOS (NCT03754660) was a Phase 1b, nonrandomised, open-label, single-dose escalation (5 doses up to 4 mg) trial in patients with untreated PAH or CTEPH conducted at 8 study centres in 4 countries[12,13]
- The trial enrolled participants aged 18 to 80 years with confirmed disease who were untreated or participants pre-treated with phosphodiesterase type 5 inhibitors (PDE5i), endothelin receptor antagonists (ERAs), prostanoids, or sGC stimulators who underwent a drug specific wash-out period at the discretion of the investigator for ≥24 hours prior to Day -1 if medically safe[12,13]

Figure 2. Study Design[12]



Study design: patients inhaled NO (iNO) over 5 min for vasoreactivity testing prior to mosliciguat administration. Right heart catheterization (RHC) assessments of haemodynamics were conducted ≥3 hours up to 5 hours post dose.

Data analysis sets

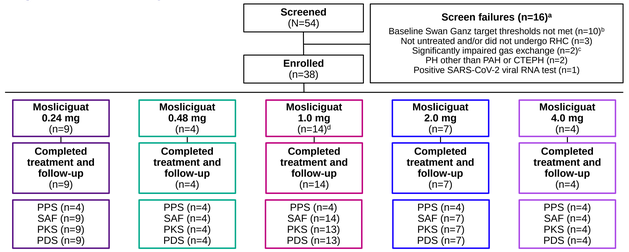
- Safety analysis set (SAF): all participants who received ≥1 dose of mosliciguat
- Per-protocol set (PPS): all participants of the SAF with 1) valid PVR profile based on RHC measurements immediately before start of mosliciguat inhalation until ≤3 hours post administration; 2) mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and PVR ≥ 400 dyn.sec.cm-5 (5 Wood units [WU]) confirmed by RHC before mosliciguat administration; 3) did not respond to iNO (where positive response is defined as reduction of mPAP ≥10 mmHg to reach absolute value of mPAP ≤40 mmHg, with an increased or unchanged cardiac output [CO]); and 4) no important deviation from the protocol or validity finding having an impact on the primary PD variable
- Pharmacokinetics (PK) analysis set (PKS): all participants with 1) ≥1 valid mosliciguat plasma concentration and 2) no validity findings considered to influence PK evaluation
- Pharmacodynamic (PD) analysis set (PDS): all participants with a) ≥1 valid measurement of a PD variable and 2) no deviation from protocol that would interfere with evaluation of PD

Abbreviations

BL, baseline; cGMP, cyclic guanosine monophosphate; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; ERAs, endothelin receptor antagonists; FU, follow up; iNO, inhaled nitric oxide; mPAP, mean pulmonary artery pressure; NO, nitric oxide; PAH, pulmonary arterial hypertension, PAWP, pulmonary artery wedge pressure; PD, pharmacodynamics; PDE5i, phosphodiesterase type 5 inhibitors; PDS, PD analysis set; PH, pulmonary hypertension; PK, pharmacokinetics; PKS, PK analysis set; PPS, per-protocol set; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SAF, safety analysis set; SEM, standard error of the mean; sGC, soluble guanylate cyclase; SVR, systemic vascular resistance; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; WU, Wood units.

Results

Figure 3. Patient Disposition



[a]Participants may have experienced ≥1 reason for screen failure. [b]Participants were eligible to be assigned to study treatment if confirmatory baseline Swan Ganz measurements showed mPAP ≥25 mmHg and PVR ≥240 dyn·sec·cm-5 (3 WU). [c]Significantly impaired gas exchange with decreased oxygen saturation <90% at room air. [d]One patient in the 1.0 mg dosing group was excluded from the PPS, PKS, and PDS secondary to a protocol violation in which the study intervention was not administered to the participant according to the protocol.

- 54 participants were enrolled; 16 were screening failures, 38 were allocated to treatment
- All 38 participants completed the study and were included in the SAF. Thirty-seven participants were included in the PDS and PKS each, and 20 participants were included in the PPS

Table 1. Baseline Demographics and Clinical Characteristics in the PPS (N=20)

Parameter	0.24 mg (n=4)	0.48 mg (n=4)	1.0 mg (n=4)	2.0 mg (n=4)	4.0 mg (n=4)	Total (N=20)
Age (years)						
Median	65.5	68.0	58.0	65.0	62.0	63.5
Min, max	26, 75	54, 76	50, 65	64, 71	53, 76	26, 76
Sex						
Male	1 (25.0%)	0	2 (50.0%)	4 (100.0%)	3 (75.0%)	10 (50.0%)
PH type						
PAH	3 (75.0%)	3 (75.0%)	0	1 (25.0%)	4 (100.0%)	11 (55.0%)
CTEPH	1 (25.0%)	1 (25.0%)	4 (100.0%)	3 (75.0%)	0	9 (45.0%)
Smoking history						
Former smoker	4 (100.0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	2 (50.0%)	10 (50.0%)
Current smoker	0	0	1 (25.0%)	0	2 (50.0%)	3 (15.0%)
Haemodynamic parameters (mean) at baseline[a]						
PVR (dyn*sec*cm-5)	788.3	1055.9	608.9	468.6	714.0	727.1
SVR (dyn*sec*cm-5)	1847.8	2217.2	1911.8	1716.8	1864.1	1895.5
mPAP (mmHg)	42.8	55.0	34.3	33.5	46.0	42.3
CO (L/min)	3.9	3.6	3.8	4.4	4.1	4.0
PAWP (mmHg)	8.8	7.8	6.0	8.0	9.5	8.0

[a]Baseline refers to baseline 2 following completion of iNO challenge.[12]

- Similar demographics were observed for the SAF (data not shown)

Table 2. Primary Endpoint: Peak Percent Reduction From Baseline 2 in PVR[a]

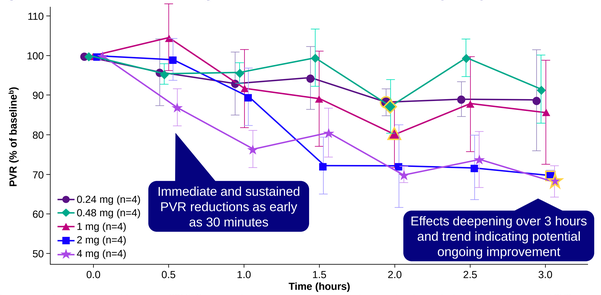
	PPS (N=20)			PDS (N=36[b])		
Dose Group (mg)	n	Mean	*95% CI*	n	Mean	*95% CI*
0.24	4	**-21.0**	*-31.6, -10.4*	8[b]	**-20.8**	*-31.2, -10.5*
0.48	4	**-16.1**	*-32.8, 0.7*	4	**-16.1**	*-32.8, 0.7*
1.00	4	**-25.9**	*-60.3, 8.4*	13	**-31.3**	*-41.6, -20.9*
2.00	4	**-38.1**	*-55.9, -20.3*	7	**-34.3**	*-48.8, -19.9*
4.00	4	**-36.3**	*-48.3, -24.4*	4	**-36.3**	*-48.3, -24.4*

Up to mean -38% PVR reductions

[a]Measured in dyn*sec*cm-5. [b]One patient in the PDS 0.24 mg group did not have a baseline.

- In the PPS, mosliciguat 2.0 and 4.0 mg doses led to mean peak percentage reductions in PVR from baseline of -38.1% and -36.3%, respectively
- Similar effect on PVR was observed in the PDS, which included both participants who were responsive or nonresponsive to iNO, with mean peak percentage reductions from baseline in the 2.0 mg and 4.0 mg dose groups of -34.3% and -36.3%, respectively
- Mosliciguat doses 1.0 mg and above showed mean peak percentage reductions in PVR ≥-25%, exceeding the predefined ≥-20% threshold for the primary outcome

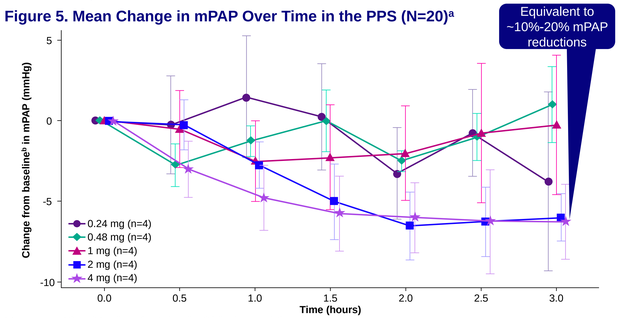
Figure 4. Mean Percent Change in PVR Over Time in the PPS (N=20)[a]



[a]Bars represent standard error of the mean (SEM). Symbols with yellow highlighting indicate time points with greatest observed mean percent PVR reduction for each dose group. [b]Baseline refers to baseline 2 following completion of iNO challenge.

- Reductions in PVR after mosliciguat administration were stable and persisted until end of 3-hour RHC period

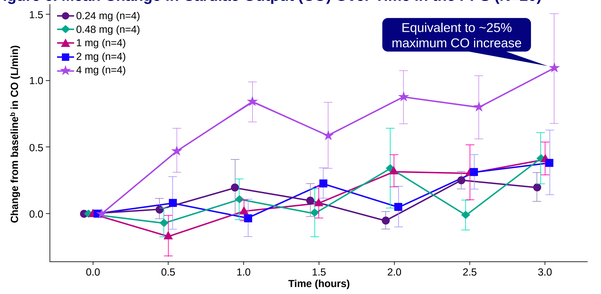
Figure 5. Mean Change in mPAP Over Time in the PPS (N=20)[a]



[a]Bars represent SEM. [b]Baseline refers to baseline 2 following completion of iNO challenge.

- At 1 hour after administration of mosliciguat, reductions in mPAP were -2.8 mmHg and -4.8 mmHg in the 2.0-mg and 4.0-mg dose groups, respectively, reaching -6.0 mmHg and -6.3 mmHg at the end of 3-hour RHC
  - Overall reductions were equivalent to approximately -10% to -20% for the 2.0-mg and 4.0-mg dose groups, with no clear changes observed at lower doses

Figure 6. Mean Change in Cardiac Output (CO) Over Time in the PPS (N=20)[a]



[a]Bars represent SEM. [b]Baseline refers to baseline 2 following completion of iNO challenge.

- CO was increased in the 4.0-mg dose group beginning at 0.5 hours, with a maximum increase from baseline of 1.1 L/min, equivalent to approximately 25% increase from baseline, at 3 hours post dose

Table 3. Overall Summary of Number of Participants With TEAEs in the SAF (N=38)

TEAEs[a]	0.24 mg (n=9)	0.48 mg (n=4)	1.0 mg (n=14)	2.0 mg (n=7)	4.0 mg (n=4)	Total (N=38)
Any TEAE	3 (33.3%)	3 (75.0%)	1 (7.1%)	1 (14.3%)	3 (75.0%)	11 (28.9%)
Maximum intensity for any TEAE						
Mild	3 (33.3%)	2 (50.0%)	1 (7.1%)	0	3 (75.0%)	9 (23.7%)
Moderate	0	1 (25.0%)	0	1 (14.3%)	0	2 (5.3%)
Any drug-related TEAE	2 (22.2%)	1 (25.0%)	0	1 (14.3%)	1 (25.0%)	5 (13.2%)
Maximum intensity for drug-related TEAE						
Mild	2 (22.2%)	1 (25.0%)	0	0	1 (25.0%)	4 (10.5%)
Moderate	0	0	0	1 (14.3%)	0	1 (2.6%)
Any TEAE related to procedures required by the protocol	0	2 (50.0%)	0	0	1 (25.0%)	3 (7.9%)
Any TESAE	1 (11.1%)[b]	0	0	0	0	1 (2.6%)
Study drug related	1 (11.1%)	0	0	0	0	1 (2.6%)
Related to procedures required by the protocol	0	0	0	0	0	0
TEAE with the outcome death	0	0	0	0	0	0

[a]Number (%) of participants with the TEAEs. [b]Participant developed haemoptysis of mild intensity that was upgraded to TESAE due to prolonged hospitalization. The TESAE was reported to be resolved 5 days after occurrence.

- Reported TEAEs (100%) were of mild/moderate intensity, with no dose dependence observed
- The most frequently reported TEAEs were headache (n=3; 7.9%), fatigue (n=2; 5.3%), and decreased oxygen saturation (n=2; 5.3%)
- No systemic TEAEs were observed indicative of reduced safety

Conclusions

- A single dose of inhaled mosliciguat, an investigational first-in-class sGC activator, led to sustained, clinically meaningful reductions of up to -38% in mean peak PVR
- Once-daily dosing via dry powder inhaler was well tolerated, with low rates of TEAEs observed following treatment with mosliciguat (total of 11 participants), with only headache, fatigue, and decreased oxygen saturation reported in more than 1 participant
- The profound effects of mosliciguat on haemodynamic parameters were observed in iNO responsive, and nonresponsive participants, suggesting that the novel mechanism of action of the drug may allow for broader activity across the spectrum of PH
- The proof-of-concept ATMOS study provided evidence supporting further clinical development of the novel inhaled sGC activator mosliciguat, including the potential to improve haemodynamic parameters such as PVR in patients with PH, a favourable safety profile, and lack of clinically relevant systemic side effects
- The global Phase 2 PHocus study of mosliciguat in ~120 patients with PH associated with interstitial lung disease (PH-ILD) is scheduled to initiate by the second half of 2024

References and Notes

References: 1. Humbert M, et al. *Eur Respir J*. 2019;53(1):1801887. 2. Johnson S, et al. *Am J Respir Crit Care Med*. 2023;208(5):528-548. 3. Stasch JP, et al. *Circulation*. 2011;123(20):2263-73. 4. Sandner P, Stasch JP. *Respir Med*. 2017;122(Suppl 1):S1-S9. 5. Dumitrascu R, et al. *Circulation*. 2006;113(2):286-295. 6. Mauersberger C, et al. *Nat Cardiovasc Res*. 2022;1:1174-1186. 7. Beyer C, et al. *Ann Rheum Dis*. 2015;74:1408–1416. 8. Schmidt HH, et al. *Handb Exp Pharmacol*. 2009;(191):v-vi. 9. Dhont S, et al. *ERJ Open Res*. 2022;8(4):00272-2022. 10. Dasgupta A, et al. *Clin Pharmacol Ther*. 2015;97(1):88-102. 11. Becker-Pelster EM, et al. *Respir Res*. 2022;23(1):272. 12. Data on File. Pulmovant. 2024. 13. ClinicalTrials.gov identifier: NCT03754660. Updated September 28, 2023. Accessed July 26, 2024. https://www.clinicaltrials.gov/study/NCT03754660 14. Humbert M, et al. *Eur Respir J*. 2023;61:2200879.

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For more information about the upcoming Phase 2 PHocus study in PH-ILD: clinicaltrials@pulmovant.com

Presenting author disclosures: HAG reports receiving consultant fees from Gossamer Bio, Inc., Aerovate, Altavant, Bayer AG, Attgeno, Janssen/Actelion, MSD/Accelleron, Pfizer, Liquidia, Morphic, and Keros; receiving payment or honoraria for lectures, presentations, or speaking from Bayer AG, Janssen/Actelion, Gossamer Bio, Keros, and MSD/AGossamer; serving as an advisory committee member for Aerovate, Altavant, Bayer AG, Attgeno, Janssen/Actelion, MSD/Accelleron, and Pfizer; serving as a data and safety monitoring board member for Insmed; and spouse employment by Liquidia.

Presented at the 2024 European Respiratory Society (ERS) Congress; September 7-11, 2024; Vienna, Austria, Poster #PA5238