IMPALA: Efficacy Measures in Patients With Autoimmune Pulmonary Alveolar Proteinosis (aPAP) Who Required Whole-Lung Lavage

Badrul Chowdhury, MD, PhD,[1] Jack Bennett, MS,[2] Yoshikazu Inoue, MD, PhD[3]

[1]Savara Inc., Langhorne, PA, USA; [2]PHASTAR, Raleigh, NC, USA; [3]Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka, Japan

OBJECTIVE

To perform post hoc analysis of data from the IMPALA (NCT02702180) trial to evaluate the benefit of continuous (daily) recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) molgramostim nebulizer solution (MOL) 300 µg vs placebo (PBO) among patients with autoimmune pulmonary alveolar proteinosis (aPAP) who required whole-lung lavage (WLL) during the treatment period

CONCLUSIONS

Patients with aPAP treated daily with MOL after undergoing WLL had greater improvements in endpoint measures of gas exchange (Alveolar-arterial oxygen difference [A-aDO$_2$], diffusing capacity of the lungs for carbon monoxide [DLco] corrected for hemoglobin levels) and health status (St. George's Respiratory Questionnaire-Total [SGRQ-T] and -Activity [SGRQ-A]) when compared with PBO-treated controls

Consistency of results across gas exchanges measures and health status measures increases confidence in the improved outcomes observed following WLL

DISCLOSURES

Savara Inc. participated in the trial design; trial research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster. All authors had access to the data; participated in the development, review, and approval of the poster; and agreed to submit this poster to the European Respiratory Society (ERS) International Congress 2022. Savara Inc. funded the research for this trial and provided writing support for this poster. Medical writing assistance, funded by Savara Inc., was provided by Jennifer A Jiménez, PhD, of JB Ashtin.

BC is an employee of Savara Inc. and may hold Savara Inc. stock and/or stock options. **JB** is an employee of PHASTAR and may hold PHASTAR stock and/or stock options. **YI** is a member of the clinical advisory board for Savara Inc. and primary investigator of the IMPALA trial (related to this study); advisory board member for Boehringer Ingelheim, Roche, Taiho Pharmaceutical; and receives guest lecture fees from Boehringer Ingelheim, Shionogi, GSK, and Kyorin Pharmaceutical Co.

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Background

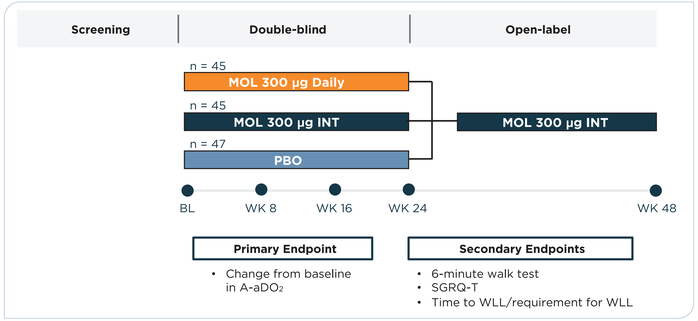
- aPAP is a rare lung disease characterized by the accumulation of lipoproteinaceous surfactant material in the alveoli of the lungs that can lead to respiratory distress, hypoxemia, and increased infection risk[1]
- WLL is the standard treatment for patients with aPAP, a procedure that physically removes lipoproteinaceous material by washing the alveoli with saline[2,3]
- WLL is performed in a limited number of centers as an inpatient procedure requiring general anesthesia and mechanical ventilation
- MOL has demonstrated efficacy for aPAP, but is not yet approved for treating the disease[4]
- There is limited evidence whether the addition of MOL therapy in patients with aPAP who have had WLL provides further benefit beyond that of WLL alone

Methods

Trial Design and Treatment

- IMPALA (NCT02702180) was a Phase 2/3, 24-week, randomized, double-blind (DB), PBO-controlled, multicenter clinical trial that evaluated the efficacy and safety of daily or intermittently inhaled MOL vs PBO in patients with aPAP **(Figure 1)**

Figure 1. MOL-PAP-002 (IMPALA) Trial Design



A-aDO$_2$, alveolar-arterial oxygen difference; INT, intermittent; MOL, molgramostim nebulizer solution; PBO, placebo; SGRQ-T, St. George's Respiratory Questionnaire-Total; WK, week; WLL, whole-lung lavage.

- We performed a post hoc analysis of results from selected outcome measures that showed benefit from IMPALA for all patients in the MOL 300 µg daily group (referred to as MOL group) and PBO group who received WLL **(Table)**

WLL Patient Characteristics

- 84 of 138 (60.9%) patients enrolled in the trial had a history of WLL, 23 (50.0%) and 30 (63.8%) patients in the MOL group and PBO group, respectively
- The number of patients in the DB period requiring WLL was 4 (8.7%) and 6 (12.8%) in the MOL group and PBO group, respectively
- Comparable percentages of WLL procedures were performed in patients before baseline (47.8% [MOL group] and 55.3% [PBO group]), and during the DB period (8.7% [MOL group] and 12.8% [PBO group])
  - The rates of WLL for the DB period were 0.422 in the MOL group, and 0.815 in the PBO group
- All but 1 of the WLL procedures conducted for the MOL group occurred in patients with severe disease
- There were no differences in the timing of WLL between the 2 groups **(Figure 2)**

Table. Summary of Number of Patients With WLL Before BL and Number of WLLs in DB Period

		MOL 300 µg daily (n = 46)	PBO (n =47)
Patients, N (%)	Number of patients with previous WLL	23 (50.0)	30 (63.8)
	Number of patients in DB	46	47
	Number of patients needing WLL in DB	4 (8.7)	6 (12.8)
		MOL 300 µg daily (n = 46)	**PBO (n =47)**
WLLs, N (%) Events[a]/Rate[b]	Number of WLLs before BL	22 (47.8) 103/0.676	26 (55.3) 104/0.829
	Number of WLLs in DB	4 (8.7) 9/0.422	6 (12.8) 17/0.815

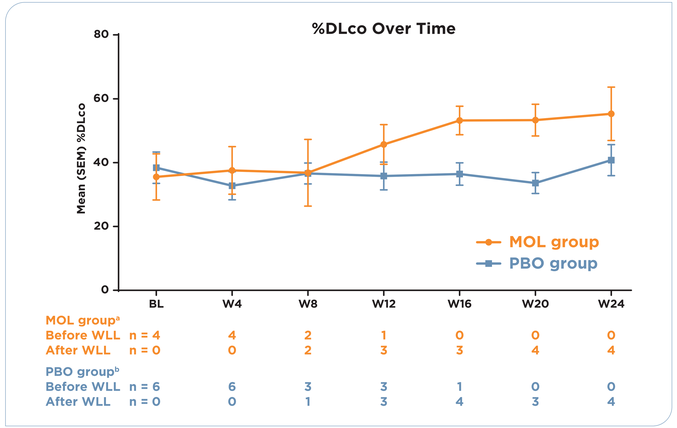
BL, baseline; DB, double-blind period; MOL, molgramostim nebulizer solution; PBO, placebo; WLL, whole-lung lavage.
[a]Number of events (if WLL in both lungs at the same time point then counted as 2).
[b]Number of events per subject year (1 year counted as 365.25 days).

Assessments

- Outcome measures:
  - Alveolar-arterial oxygen difference (A-aDO$_2$)
  - St. George's Respiratory Questionnaire-Total (SGRQ-T) and -Activity (SGRQ-A)
  - Diffusing capacity of the lungs for carbon monoxide (DLco)
- Outcome measures were assessed at 24 weeks and the results were compared with baseline findings

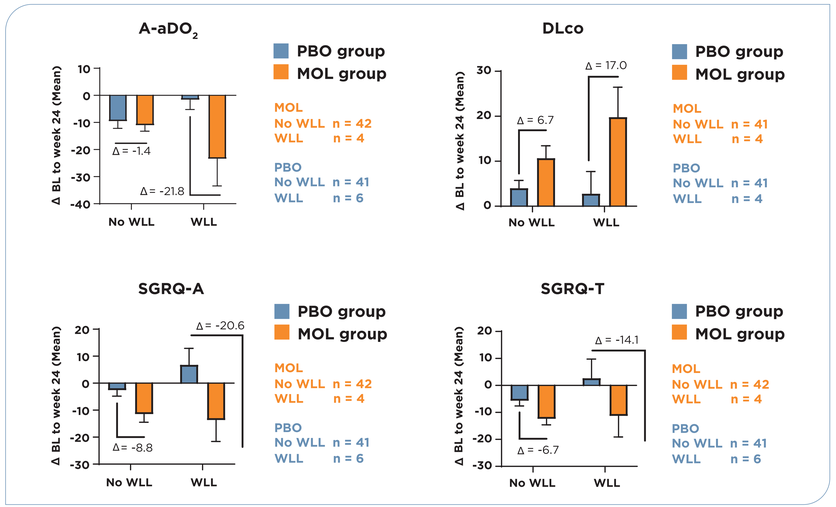
Results

Figure 2. Improvements in DLco in Patients Before and After WLL at Intervals Throughout the IMPALA Trial



BL, baseline; DLco, diffusing capacity of the lungs for carbon monoxide; MOL, molgramostim nebulizer solution; PBO, placebo; W, week; WLL, whole-lung lavage.
[a]Patients who received MOL had a total of 9 WLL events.
[b]Patients who received PBO had a total of 14 WLL events.

Figure 3. Improvements in Efficacy Variables After 24 Weeks Comparing MOL and PBO in Patients With or Without WLL



A-aDO$_2$, alveolar-arterial oxygen difference; BL, baseline; DLco, diffusing capacity of the lungs for carbon monoxide; MOL, molgramostim nebulizer solution; PBO, placebo; SGRQ-A, St. George's Respiratory Questionnaire-Activity; SGRQ-T, St. George's Respiratory Questionnaire-Total; WLL, whole-lung lavage.
Results represent the mean and SEM.

Limitations

- These observations are based on a total of 10 patients who underwent WLL (4 in the MOL group, and 6 in the PBO group); therefore, further study is warranted