Inhaled Molgramostim for the Treatment of Autoimmune Pulmonary Alveolar Proteinosis (PAP): Results from the IMPALA-2 Phase 3 Clinical Trial

Yoshikazu Inoue,[1,2] Francesco Bonella,[3] Tisha Wang,[4] Cormac McCarthy,[5] Bruce C. Trapnell,[6] Brian Robinson,[7] Rosanna Fleming,[7] Yasmine Wasfi,[7] Raymond Pratt[7]

1. NHO Kinki Chuo Chest Medical Center, Osaka, Japan; 2. Osaka Anti-tuberculosis Association Osaka Fukujuji Hospital, Osaka, Japan; 3. Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany; 4. University of California Los Angeles, Los Angeles, CA USA; 5. University College Dublin, St. Vincent's University Hospital, Elm Park, Dublin, Ireland; 6. Cincinnati Children's Hospital, Cincinnati, OH USA; 7. Savara Inc., Langhorne, PA USA

Background and Objective

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) is critical for alveolar macrophage function and alveolar surfactant homeostasis[1,2]
- Autoimmune PAP is a rare lung disease characterized by the accumulation of surfactant in the alveoli leading to respiratory distress, hypoxemia, and increased infection risk[3-5]
- Autoimmune PAP is caused by anti-GM-CSF autoantibodies that block GM-CSF signaling, resulting in impaired surfactant clearance[5]
- Molgramostim inhalation solution (molgramostim) is an inhaled recombinant human GM-CSF that is being studied for the treatment of patients with autoimmune PAP in the IMPALA-2 phase 3 clinical trial

Objective: To evaluate the efficacy and safety of molgramostim for the treatment of patients with autoimmune PAP

Methods

Patients

- Patients were required to have:
  - A positive (abnormal) anti-GM-CSF autoantibody test result
  - Hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO%) ≤70% at the first screening and baseline visits
  - Change in DLCO% of <15% during the screening period to ensure stability of impaired patients

Endpoints

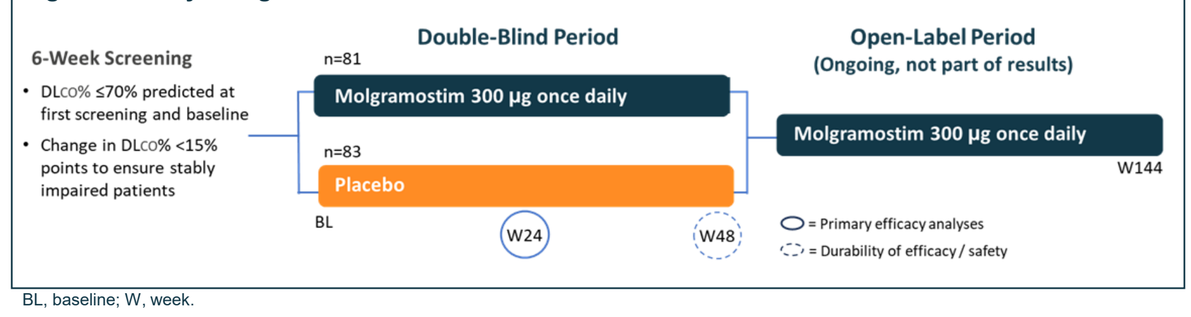
- **Primary endpoint:**
  - Change from baseline in DLCO% at Week 24
- **Secondary endpoints:**

Change from baseline in:
  - DLCO% at Week 48
  - St. George's Respiratory Questionnaire (SGRQ) Total score at Weeks 24 and 48
  - SGRQ Activity score at Weeks 24 and 48
  - Exercise capacity expressed as peak metabolic equivalents (METs) at Weeks 24 and 48
- Safety was assessed by monitoring adverse events (AEs), laboratory assessments, electrocardiograms, vital signs, physical exams and spirometry

Study Design

- IMPALA-2 is a randomized, double-blind, placebo-controlled Phase 3 clinical trial being conducted at 43 clinical sites across 16 countries
- The trial consists of a 48-week double-blind intervention period followed by a 96-week open-label treatment period (**Figure 1**)
- For the double-blind period, patients were randomly assigned, in a 1:1 ratio, to self-administer inhaled molgramostim 300 µg or matching placebo once daily using a proprietary nebulizer (eFlow® Nebulizer System, PARI)

Figure 1. Study Design



BL, baseline; W, week.

This poster reports results from the 48-week, double-blind intervention period, which has been completed. The open-label treatment period is ongoing

Patients

- A total of 164 patients with autoimmune PAP underwent randomization; 81 were assigned to receive molgramostim and 83 to receive placebo
- Baseline demographic and clinical characteristics were similar between treatment groups **(Table 1)**

Table 1. Baseline Demographic and Clinical Characteristics

		Molgramostim n=81	Placebo n=83
Age	Mean (SD)	50.8 (13.0)	48.4 (12.7)
years	Range	20-80	21-79
Sex	Male	44 (54.3)	54 (65.1)
n (%)	Female	37 (45.7)	29 (34.9)
Race	White	38 (46.9)	40 (48.2)
n (%)	Asian	36 (44.4)	37 (44.6)
	Black or African American	3 (3.7)	2 (2.4)
	Other	4 (4.9)	4 (4.8)
DLco%	Mean (SD)	52.6 (11.7)	52.6 (10.4)
	Median	54	55
	Range	25-72	28-71

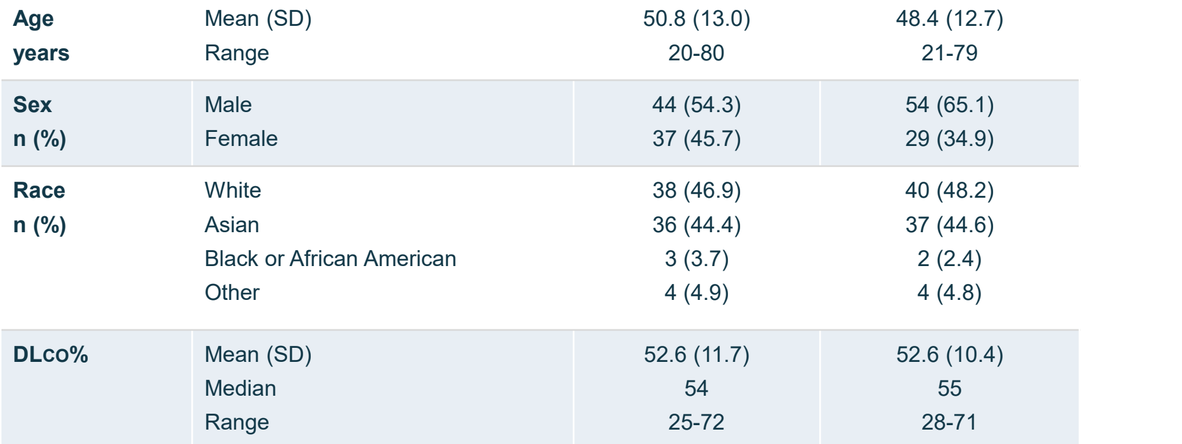
DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; n, number; SD, standard deviation.

Efficacy

Molgramostim Improved Pulmonary Gas Transfer

- The primary endpoint, change from baseline in DLCO% at Week 24, was significantly greater in the molgramostim group compared with the placebo group (difference in least squares mean change 6.0%; P=0.0007) (**Figure 2A**). The significant effect of molgramostim on DLCO% was maintained at Week 48.
- Changes from baseline in disease severity score (**Figure 2B**) support the beneficial effects of molgramostim compared with placebo

Figure 2. Pulmonary Gas Transfer

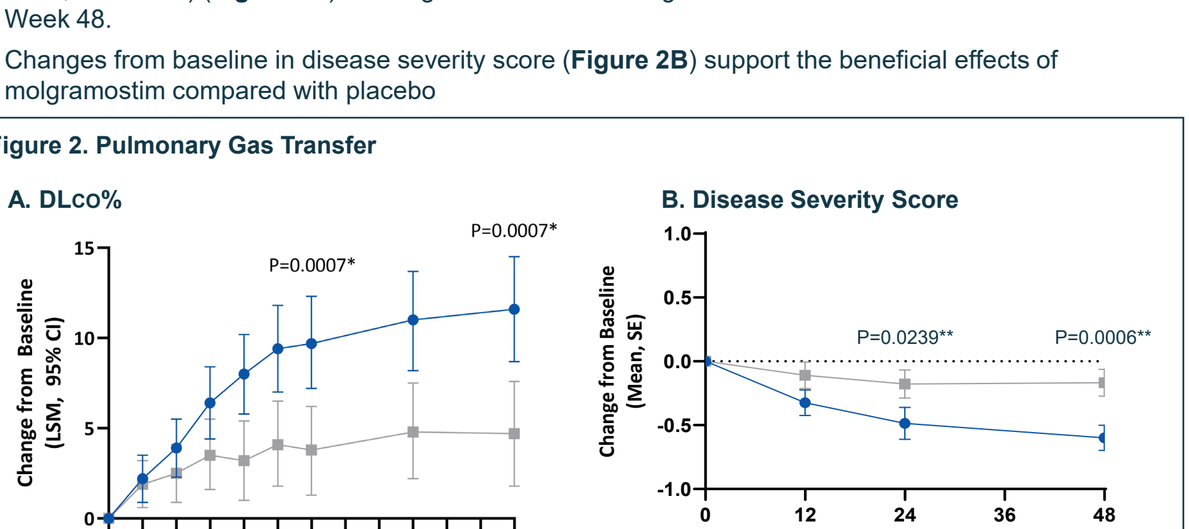


*Statistically significant; **Based on *post-hoc* analysis. CI, confidence interval; DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; LSM, least squares mean; n, number; SE, standard error.

Molgramostim Improved Respiratory Health-Related Quality of Life (HRQoL)

Mean changes from baseline in the SGRQ Total and SGRQ Activity scores were greater in the molgramostim group than the placebo group at Weeks 24 and 48 (**Figure 3**)

Figure 3. HRQoL

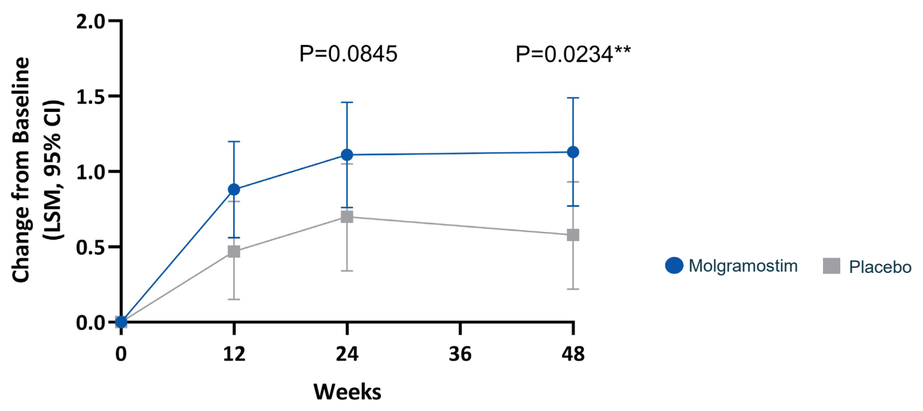


*Statistically significant. **Nominally significant. SGRQ, St. George's Respiratory Questionnaire.

Molgramostim Improved Patient Function

Mean changes in exercise capacity expressed as peak METs from baseline to Weeks 24 and 48 were greater in the molgramostim group compared with the placebo group (**Figure 4**)

Figure 4. Patient Function: Exercise Capacity (Peak METs)

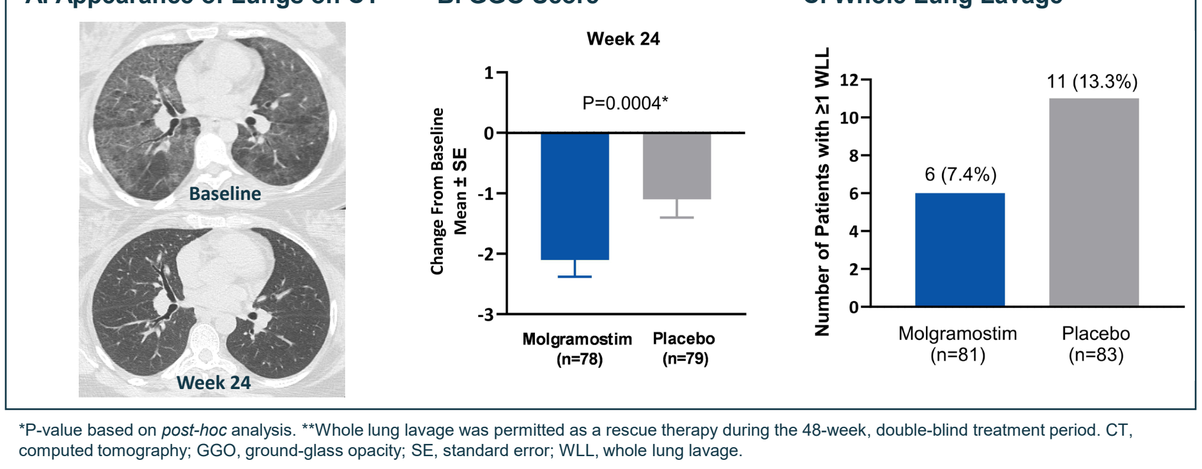


*Nominally significant. CI, confidence interval; LSM, least squares mean; MET, metabolic equivalent. METs = [speed (meters/min) * (0.17 + fractional grade * 0.79) + 3.5]/3.5.

Molgramostim Reduced Surfactant Burden

Molgramostim reduced surfactant burden as shown by representative chest computed tomography (CT) scan images from a patient who responded to molgramostim **(Figure 5A)**, improvement in ground-glass opacity (GGO) score at Week 24 (**Figure 5B**), and the number of patients who underwent ≥1 whole lung lavage over 48 Weeks (**Figure 5C**)

Figure 5. Surfactant Burden



*P-value based on *post-hoc* analysis. **Whole lung lavage was permitted as a rescue therapy during the 48-week, double-blind treatment period. CT, computed tomography; GGO, ground-glass opacity; SE, standard error; WLL, whole lung lavage.

Safety

- No deaths occurred during the 48-week double-blind intervention period
- The proportions of patients experiencing AEs and serious AEs (SAEs) were similar between the molgramostim and placebo groups
- One SAE in the molgramostim group was considered by the investigator to be treatment-related, but did not result in study discontinuation
- Most AEs were mild to moderate in severity and did not result in treatment discontinuation. AEs with notable imbalances in the frequencies between treatment groups were symptomatic COVID-19 infection (22% molgramostim vs. 10% placebo) and diarrhea (11% molgramostim vs. 2% placebo)
- Molgramostim was well tolerated; 98% of patients completed the 48-week double-blind intervention period

CONCLUSIONS

IMPALA-2 achieved statistical significance on its primary endpoint, change from baseline to Week 24 in DLCO%, and multiple secondary endpoints

Molgramostim improved the cardinal manifestations of the disease, reducing surfactant burden, which improved pulmonary gas transfer, HRQoL, and exercise capacity in patients with autoimmune PAP

Molgramostim was well tolerated and demonstrated a favorable benefit/risk profile

DISCLOSURES
- IMPALA-2 clinical trial is sponsored by Savara, Inc.
- YI is a clinical advisory board member for Savara Inc. and an investigator for the IMPALA-2 clinical trial

REFERENCES
1.Dranoff G, et al. *Science* 1994;264:713-716; 2. Trapnell BC, Whitsett JA. *Annu Rev Physiol* 2002;64:775-802; 3. Rosen SH, et al. *N Engl J Med* 1958;258:1123-1142; 4. Seymour JF, Presneill JJ. *Am J Respir Crit Care Med* 2002;166:215-235; 5. Trapnell BC, et al. *Nat Rev Dis Primers* 2019;5:16.

Presented at the 65th Annual Meeting of the Japanese Respiratory Society • Tokyo, Japan • 11–13 April 2025
(Encore of poster presented by Trapnell B, et al. at the European Respiratory Society (ERS) Congress 2024 in Vienna, Austria on September 8, 2024)

SAVARA