Long-Term Efficacy and Safety of Molgramostim in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP): Results from the IMPALA-2 Trial Open-Label Treatment Period

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OBJECTIVE

To report results from the first 48 weeks of the 96-week open-label treatment period in the IMPALA-2 Phase 3 clinical trial

CONCLUSIONS

Long-term treatment with molgramostim continuously improved pulmonary gas transfer and respiratory health-related quality of life (HRQoL) in patients with aPAP

In addition, placebo cross-over patients demonstrated improved pulmonary gas transfer and respiratory HRQoL with molgramostim

Safety and tolerability were consistent with results observed in the double-blind treatment period

DISCLOSURES
- The IMPALA-2 is sponsored by Savara Inc.
- BCT has received financial compensation from Savara Inc. for consultant services.

REFERENCES
1. McCarthy C, et al. *Am J Respir Crit Care Med.* 2022;205:1016-35.
2. Rosen S, et al. *New Engl J Med.* 1958;258:1123-42.
3. Trapnell BC, et al. *Nat Rev Dis Primers.* 2019;5:16.

Presented at the American Thoracic Society (ATS) 2026 International Conference • Orlando, FL USA • 19 May 2026

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Background

- Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease caused by autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF)[1]
- aPAP is characterized by the accumulation of surfactant in the alveoli, leading to respiratory distress, hypoxemia, and increased infection risk[2,3]
- Molgramostim inhalation solution (molgramostim), an investigational recombinant human GM-CSF, is being evaluated for the treatment of aPAP in a Phase 3 clinical trial (IMPALA-2)
- IMPALA-2 is a randomized, double-blind, placebo-controlled trial comprised of a 48-week double-blind treatment (DB) period (completed) followed by a 96-week open-label treatment (OL) period (ongoing) to assess the long-term efficacy and safety of molgramostim
- In the DB period, IMPALA-2 achieved statistical significance on its primary endpoint, change from baseline in hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO%) at Week 24, and multiple secondary endpoints
- Here we report results from the first 48 weeks of the ongoing 96-week OL period

Methods

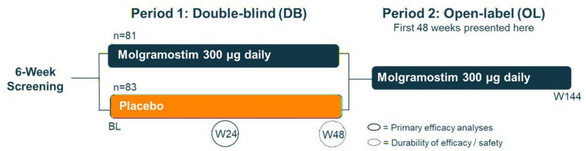
Patients

- Patients were required to have:
  - A positive (abnormal) anti-GM-CSF autoantibody test result
  - DLCO% ≤70% at the first screening and baseline visits
  - Change in DLCO% of <15 percentage points during the screening period to ensure stability of impaired patients

Study Design

- IMPALA-2 is a randomized, DB, placebo-controlled Phase 3 clinical trial being conducted at 43 clinical sites across 16 countries
- The trial consists of a 48-week DB period followed by a 96-week OL period (**Figure 1**)
- During the DB period, patients received inhaled molgramostim 300 µg or placebo once daily using a proprietary nebulizer (eFlow® Nebulizer System, PARI)
- During the OL period, all patients received molgramostim
- Patients who received molgramostim during both DB and OL periods are designated as the MOL-MOL group
- Patients who received placebo during the DB period and crossed over to molgramostim in the OL period are designated as the PBO-MOL group

Figure 1. Study Design



BL, baseline; W, week.

OL Period Efficacy Measures

- Change from baseline in:
  - DLco%
  - St. George's Respiratory Questionnaire (SGRQ) Total score
  - SGRQ Activity score
- Arithmetic mean changes from baseline values for the above measures are presented

Results

Patients

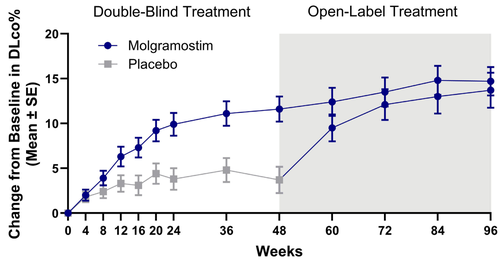
- A total of 164 patients with aPAP underwent randomization; 81 were assigned to receive molgramostim and 83 to receive placebo
- Of 164 patients treated in the DB period, 160 (98%) completed the DB period and continued into the OL period, 79 in the MOL-MOL group and 81 in the PBO-MOL group
- During the OL period through the data cut-off date of July 3, 2025, 9 of 160 patients discontinued study treatment and withdrew from the study (disposition data not shown)

Efficacy

DLco% (Figure 2)

- At Week 48, the mean (standard error [SE]) changes from baseline in DLCO% were 11.6 (1.4) for molgramostim and 3.9 (1.5) for placebo
- During the OL period, MOL-MOL patients continued to show improvement in DLco% through Week 96; the mean increase during Weeks 48-96 was 2.8 (1.2), with an overall mean increase from baseline (Weeks 0-96) of 14.7 (1.6)
- In PBO-MOL patients, DLCO% increased during the OL period through Week 96; the mean increase in DLCO% during Weeks 48-96 was 8.8 (1.6)

Figure 2. DLco%



DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; SE, standard error.

SGRQ Total Score (Figure 3)

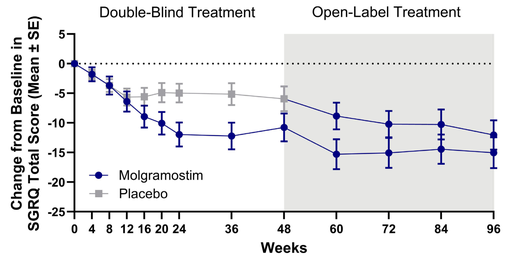
- At Week 48, the mean (SE) changes from baseline in SGRQ Total score were -10.8 (2.3) for molgramostim and -6.1 (2.1) for placebo
- During the OL period, MOL-MOL patients continued to improve through Week 96; the mean change during Weeks 48-96 was -3.8 (1.6), with an overall change from baseline (Weeks 0-96) of -15.0 (2.6)
- In PBO-MOL patients, SGRQ Total score decreased during the OL period through Week 96; the mean change during Weeks 48-96 was -6.5 (1.6)

SGRQ Activity Score (Figure 4)

- At Week 48, the mean (SE) changes from baseline in SGRQ Activity score were -12.8 (3.1) for molgramostim and -7.8 (2.7) for placebo
- During the OL period, MOL-MOL patients continued to show improvement through Week 96; the mean change during Weeks 48-96 was -4.2 (2.5), with an overall change from baseline (Weeks 0-96) of -18.3 (3.4)
- In PBO-MOL patients SGRQ Activity score decreased during the OL period through Week 96; the mean change during Weeks 48-96 was -7.9 (2.0)

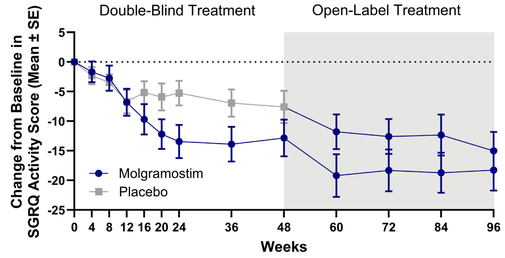
Results

Figure 3. SGRQ Total Score



SGRQ, St. George's Respiratory Questionnaire; SE, standard error.

Figure 4. SGRQ Activity Score



SGRQ, St. George's Respiratory Questionnaire; SE, standard error.

Safety

- The safety and tolerability of molgramostim during the OL period were consistent with the DB period; treatment-emergent adverse events (AEs) are shown in **Table 1**
- The most common AEs (>10% of patients) in MOL-MOL and PBO-MOL groups were nasopharyngitis (24% and 21%), COVID-19 (19% and 14%), cough (17% and 12%), influenza (16% and 10%), upper respiratory tract infection (15% and 14%), alveolar proteinosis (9% and 15%), and dyspnea (6% and 11%)
- There were no study discontinuations due to treatment-related AEs

Table 1. Treatment-emergent AEs during the OL period[a]

	MOL-MOL n=79 n (%)	PBO-MOL n=81 n (%)
Any AE	**72 (91)**	**70 (86)**
Severe AEs[b]	11 (14)	15 (19)
Treatment related	**10 (13)**	**9 (11)**
Serious AEs	**17 (22)**	**23 (28)**
Not treatment related	16 (20)	23 (28)
Treatment related[c]	1 (1)	0
Leading to death[d]	**1 (1)**	**2 (2)**
Leading to drug discontinuation	**1 (1)**	**3 (4)**
Special interest	**12 (15)**	**10 (12)**
Serious special interest[c]	1 (1)	0

[a]Number of patients. Safety data are for all available data through a cut-off date of 03Jul2025.
[b]One patient in the MOL-MOL group was reported with a severe event of cough that was considered treatment-related.
[c]One patient was reported with a moderate event of chest pain that was assessed as treatment-related.
[d]All deaths were assessed as not related to treatment.