Inhaled Molgramostim Improves Pulmonary Gas Exchange and Respiratory Health-Related Quality of Life (HRQoL) in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP): Results from Phase 3 IMPALA-2 Clinical Trial

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OBJECTIVE

Evaluate the efficacy and safety of molgramostim for the treatment of aPAP patients

CONCLUSIONS

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

Molgramostim corrects the underlying pathophysiology in aPAP, improving cardinal manifestations of the disease

It reduces surfactant burden, which improves pulmonary gas exchange, improves exercise capacity, and improves HRQoL in patients with aPAP

Molgramostim is well tolerated and has a favorable benefit/risk profile

DISCLOSURES
- The IMPALA-2 clinical trial is sponsored by Savara, Inc.
- BCT is an advisory board member and consultant to Savara Inc.

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.

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SAVARA

Background

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) is critical for alveolar macrophage function and alveolar surfactant homeostasis[1,2]
- aPAP 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]
- aPAP is caused by anti-GM-CSF autoantibodies that block GM-CSF signaling, resulting in impaired surfactant clearance[5]
- Molgramostim nebulizer solution (molgramostim) is an inhaled recombinant GM-CSF that is being studied for the treatment of patients with aPAP

Methods

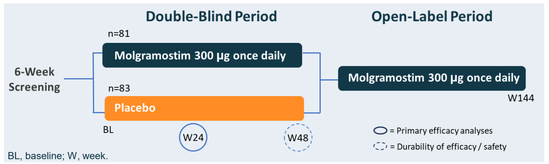
Patients

- 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 ($DLCO\%_{adj}$) ≤70% at the first screening and baseline visits
  - Change in $DLCO\%_{adj}$ of <15 percentage points during the screening period to ensure stability of impaired patients

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. Design



BL, baseline; W, week.

Endpoints

- **Primary endpoint:**
  Change from baseline $DLCO\%_{adj}$ at Week 24
- **Secondary endpoints:**
  Change from baseline in:
  - $DLCO\%_{adj}$ 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)

Results

This poster reports results from the 48-week, double-blind intervention period, which has been completed. The 96-week open-label treatment period is ongoing

Patients

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

Results Cont.

Table 1. Baseline Demographic and Clinical Characteristics

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

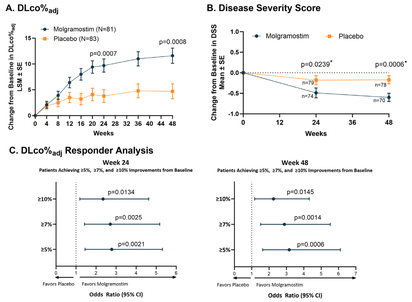
$DLCO\%_{adj}$ hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide.
The top 5 enrolling countries were Japan (n=53), USA (n=23), Turkey (n=18), South Korea (n=16) and Germany (n=10).

Efficacy

Molgramostim Improves Pulmonary Gas Exchange

- The primary endpoint, mean change from baseline in $DLCO\%_{adj}$ 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 $DLCO\%_{adj}$ was maintained at Week 48 (**Figure 2A**)
- Change from baseline in Disease Severity Score (**Figure 2B**) and $DLCO\%_{adj}$ responder analysis (**Figure 2C**) support beneficial effects of molgramostim compared with placebo

Figure 2. $DLCO\%_{adj}$ and Disease Severity Score

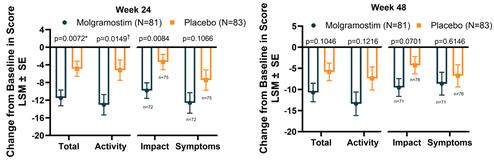


*P-values based on *post-hoc* analysis. CI, confidence interval; $DLCO\%_{adj}$ hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; DSS, disease severity score; LSM, least squares mean; SE, standard error.

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

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

Figure 3. SGRQ Total and Component Scores



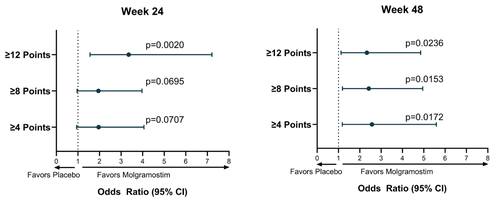
*Statistically significant. †Nominally significant. SGRQ, St. George's Respiratory Questionnaire.

Molgramostim Improves Respiratory HRQoL (Cont.)

Responder analysis supports improvements in SGRQ Total score with molgramostim (**Figure 4**)

Figure 4. SGRQ Total Score Responder Analysis

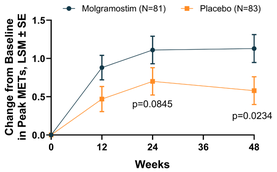
Patients Achieving ≥4-, ≥8-, and ≥12-Point Improvements from Baseline in SGRQ Total Score



Molgramostim Improves Patient Functionality

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 5**)

Figure 5. Exercise Capacity (Peak METs)

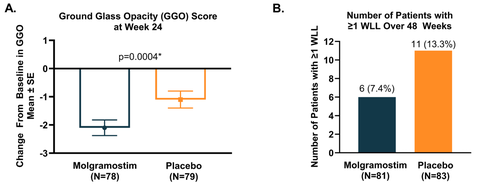


LSM, least squares mean; MET, metabolic equivalent; SE, standard error. METs = [speed (meters/min) * (0.17 + fractional grade * 0.79) + 3.5]/3.5

Molgramostim Reduces Surfactant Burden

Ground glass opacity score at Week 24 improved more in the molgramostim group than in the placebo group (**Figure 6A**) and fewer patients in the molgramostim group underwent ≥1 whole lung lavage (**Figure 6B**) over 48 weeks than in the placebo group

Figure 6. Ground Glass Opacity Score and Whole Lung Lavage



*P-value based on post-hoc analysis. Whole lung lavage was permitted as a rescue therapy during the 48-week, double-blind treatment period. 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 (SAE) 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)
  - Worsening of aPAP (5% molgramostim vs. 14% placebo)
  - Diarrhea (11% molgramostim vs. 2% placebo)
- Molgramostim was well tolerated; 97% of patients completed the 48-week double-blind intervention period. Only 2 adverse events led to discontinuation of molgramostim