Molgramostim Reduces Surfactant Burden and Number of Whole Lung Lavage Procedures in Patients with Autoimmune Pulmonary Alveolar Proteinosis (PAP): Results from the IMPALA-2 Phase 3 Clinical Trial

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OBJECTIVE

To report the effects of molgramostim on surfactant burden as measured by ground-glass opacity (GGO) score and the number of patients who received ≥1 whole lung lavage (WLL) procedure in IMPALA-2

CONCLUSIONS

In autoimmune PAP patients, molgramostim reduced surfactant burden as measured by GGO scores and fewer patients in the molgramostim group required rescue WLL

The observation that molgramostim reduced pulmonary surfactant burden, which drives the clinical manifestations of autoimmune PAP, provides strong support for a beneficial treatment effect of molgramostim

DISCLOSURES
- IMPALA-2 is sponsored by Savara Inc.
- TW has received financial compensation from Partner Therapeutics, Savara, and GSK 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.

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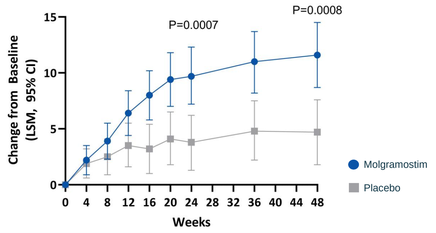
SAVARA

Background

- Autoimmune pulmonary alveolar proteinosis (PAP) is a rare lung disease caused by autoantibodies to granulocyte-macrophage colony stimulating factor (GM-CSF)[1]
- Autoimmune PAP 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 autoimmune PAP in a Phase 3 clinical trial (IMPALA-2)
- 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
- Mean change from baseline in DLCO% at week 24 was significantly greater in the molgramostim group compared with placebo (difference in least-squares mean change of 6.0%; P=0.0007). The significant effect of molgramostim on DLCO% was maintained at week 48 (a secondary endpoint) (**Figure 1**)

Figure 1. Change from baseline in DLCO%



CI, confidence interval; DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; LSM, least-squares mean.

Methods

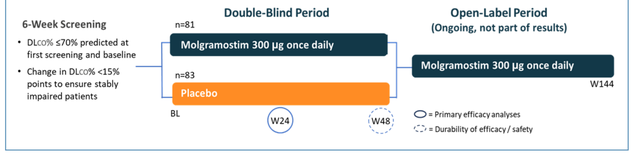
Patients

- 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 percentage points during the screening period to ensure stability of impaired patients

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 2**)
- Patients were randomly assigned to self-administer inhaled molgramostim 300 µg or placebo once daily using a proprietary nebulizer (eFlow® Nebulizer System, PARI)

Figure 2. Study Design



BL, baseline; W, week.

Methods

Exploratory Endpoints

- Exploratory endpoints included:
  - Ground-glass opacity (GGO) score at week 24 and the number of patients who received ≥1 whole lung lavage (WLL) as rescue therapy over the 48-week treatment period
- GGO score was determined from visual inspection of chest computed tomography (CT) scans by two blinded radiologists with expertise in radiological diagnosis of PAP
  - GGO scores range from 0 to 15, with higher scores indicating more of the lung affected by abnormal surfactant accumulation
  - The average total GGO score of the two readers was used in the statistical analysis
- WLL was administered at the discretion of site investigators as rescue therapy during the 48-week intervention period

Results

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 Reduced GGO Score

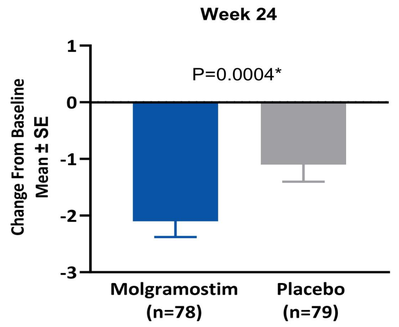
- The mean reduction in GGO score from baseline to week 24 was greater in the molgramostim group (n=78) than in the placebo group (n=79) (-2.1 vs. -1.1; P=0.0004) (**Figure 3**)
- Molgramostim reduced surfactant burden as shown by representative chest CT scan images from a patient who responded to molgramostim (**Figure 4**)

Fewer Molgramostim Patients Underwent WLL Procedures

- In general, WLL is more likely to be performed in patients with greater surfactant burden
- During the double-blind treatment period, 6 patients (7.4%) in the molgramostim group underwent a total of 15 WLLs and 11 patients (13.3%) in the placebo group underwent a total of 24 WLLs (**Figure 5**) (P=NS)

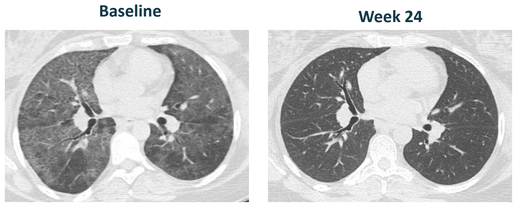
Results

Figure 3. Surfactant Burden as Measured by GGO Score



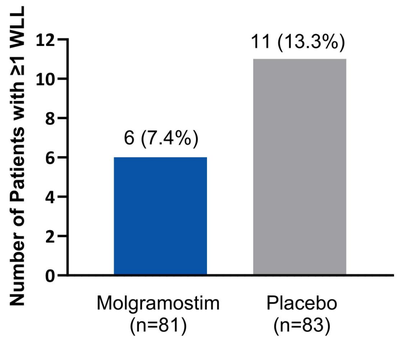
*P-value based on *post-hoc* analysis. GGO, ground-glass opacity; SE, standard error.

Figure 4. Representative CT Scans from Molgramostim Responder



CT, computed tomography.

Figure 5. Number of Patients with ≥1 WLL Procedure Over 48 Weeks



WLL, whole lung lavage.