The Effects of Molgramostim on Respiratory Health-Related Quality of Life and Patient-Reported Outcomes in Patients with Autoimmune Pulmonary Alveolar Proteinosis (PAP)

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OBJECTIVE

To report the effects of molgramostim on respiratory health-related quality of life (HRQoL) and patient-reported outcomes (PROs) in patients with autoimmune PAP from the IMPALA-2 clinical trial

CONCLUSIONS

Molgramostim improved HRQoL as measured by the St. George's Respiratory Questionnaire (SGRQ) and the EuroQol 5 Dimensions, 5 Levels (EQ-5D-5L)

More patients with autoimmune PAP on molgramostim than on placebo reported improvements in breathing problems and physical activity level measured by Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scales

DISCLOSURES
IMPALA-2 is sponsored by Savara Inc.
AA has received financial compensation from Merck, Savara Inc., United Therapeutics, and Lungpacer 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.
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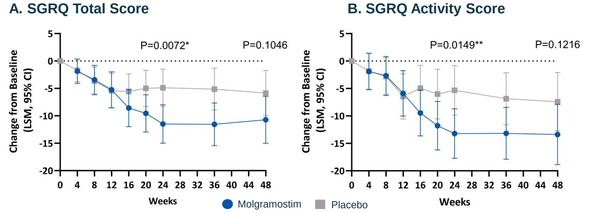
SAVARA

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
- Molgramostim improved respiratory health-related quality of life (HRQoL) as measured by changes from baseline in secondary endpoints of St. George's Respiratory Questionnaire (SGRQ) Total score and SGRQ Activity score compared with placebo (**Figure 1**)

Figure 1.SGRQ Total and SGRQ Activity Scores



*Statistically significant. **P-value ≤0.05, but not statistically significant due to prespecified testing hierarchy. CI, confidence interval; LSM, least-squares mean; SGRQ, St. George's Respiratory Questionnaire. SGRQ scores range from 0 to 100, with higher scores indicating more severe effects on a patient's respiratory health-related quality of life.

Methods

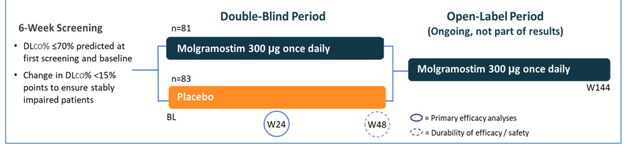
Patients

- 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, double-blind, placebo-controlled Phase 3 clinical trial (**Figure 2**) being conducted at 43 clinical sites across 16 countries
- 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.

HRQoL and PRO Endpoints

Additional HRQoL and PROs exploratory endpoints included changes from baseline in SGRQ Impact and Symptom scores, the EuroQol 5 Dimensions, 5 Levels (EQ-5D-5L), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC) at weeks 24 and 48

Results

Patients

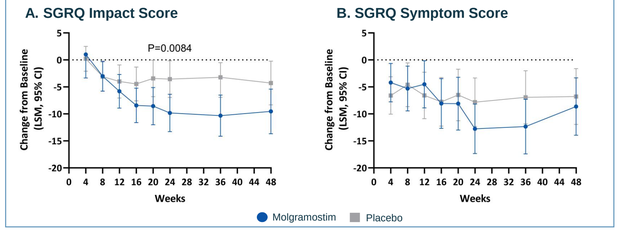
- A total of 164 patients with autoimmune PAP underwent randomization; 81 were assigned to receive molgramostim and 83 to receive placebo
- Baseline demographic and clinical characteristics were similar between treatment groups
- The mean age (±standard deviation [SD]) of patients at screening was 49.6 (12.9) years and 66 (40.2%) patients were female
- Approximately 48% of patients were White, 45% Asian, and 8% Black or other races.
- The mean (SD) DLCO% at randomization was 52.6 (11.0)

HRQoL

HRQoL Measured by SGRQ

- Molgramostim improved respiratory HRQoL as measured by changes in SGRQ Impact score (**Figure 3A**) and SGRQ Symptom score (**Figure 3B**)

Figure 3. SGRQ Impact and Symptom Scores

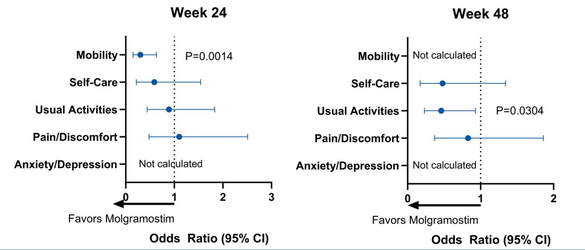


CI, confidence interval; LSM, least-squares mean, SGRQ, St. George's Respiratory Questionnaire. SGRQ scores range from 0 to 100, with higher scores indicating more severe effects on a patient's respiratory health-related quality of life.

HRQoL Measured by EQ-5D-5L

- The EQ-5D-5L is a generic HRQoL instrument comprised of a short descriptive system questionnaire that allows patients to rate their health across 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- Odds ratios of responses on the EQ-5D-5L descriptive system questionnaire numerically favored the molgramostim group on 3 of the 5 dimensions (mobility, self-care, and usual activities) at weeks 24 and 48 (**Figure 4**)

Figure 4. EQ-5D-5L Descriptive System Questionnaire Analysis*



*Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The odds ratios reflect the odds of achieving a higher response rating (a worse condition) for a particular domain. Hence, an odds ratio <1 favors molgramostim.

CI, confidence interval; EQ-5D-5L, EuroQol 5 Dimensions, 5 Levels; Not calculated, not calculated due to the statistical model not achieving convergence.

Patient-Reported Breathing Problems

Severity of Breathing Problems

- At baseline, there were no differences between molgramostim and placebo groups in the severity of breathing problems (data not shown)
- Differences between molgramostim and placebo groups in severity of breathing problems, as assessed by distribution of PGIS categories (None, Mild, Moderate, Severe, and Very Severe), were reported at weeks 24 (P=0.0305) and 48 (P=0.0049) (**Table 1**)

Table 1. PGIS of Overall Breathing Problems

		Molgramostim n=81	Placebo n=83	P-Value
Week 24 n (%)	None	6 (8.1)	2 (2.6)	0.0305
	Mild	33 (44.6)	25 (32.9)	
	Moderate	33 (44.6)	39 (51.3)	
	Severe	2 (2.7)	10 (13.2)	
	Very Severe	0	0	
	n	74	76	
Week 48 n (%)	None	6 (7.8)	5 (6.3)	0.0049
	Mild	41 (53.2)	24 (30.4)	
	Moderate	28 (36.4)	39 (49.4)	
	Severe	2 (2.6)	11 (13.9)	
	Very Severe	0	0	
	n	77	79	

PGIS, Patient Global Impression of Severity.

Change in Breathing Problems

- For overall change (PGIC) in breathing problems, more patients in the molgramostim group than in the placebo group reported being "Much better" at weeks 24 (37.8% vs. 25.0%) and 48 (42.7% vs. 24.1%) (P-values >0.05; data not shown)

Patient-Reported Physical Activity

Severity of Limitations in Daily Physical Activity Due to Breathing Problems

- At baseline, there were no differences between treatment groups in severity of limitations in daily physical activity levels due to breathing problems.
- More molgramostim patients than placebo patients reported daily physical activity were "not at all" or "slightly" limited by breathing problems at weeks 24 and 48 (P-values >0.05; data not shown)

Change in Daily Physical Activity

- More molgramostim patients reported better improvements in overall change in daily physical activity level, as measured by more patients assessing themselves as "Much better" or "A little better" compared with placebo at weeks 24 and 48 (week 24, P=0.0368; week 48, P=0.0193) (**Table 2**)

Table 2. PGIC in Overall Daily Physical Activity

		Molgramostim n=81	Placebo n=83	P-Value
Week 24 n (%)	Much better	28 (37.8)	15 (19.7)	0.0368
	A little better	27 (36.5)	29 (38.2)	
	No change	18 (24.3)	30 (39.5)	
	A little worse	1 (1.4)	2 (2.6)	
	Much worse	0	0	
	n	74	76	
Week 48 n (%)	Much better	33 (44.0)	17 (21.5)	0.0193
	A little better	26 (34.7)	33 (41.8)	
	No change	13 (17.3)	22 (27.8)	
	A little worse	3 (4.0)	4 (5.1)	
	Much worse	0	3 (3.8)	
	n	75	79	

PGIC, Patient Global Impression of Change.