Efficacy of Inhaled Molgramostim According to Severity of Autoimmune Pulmonary Alveolar Proteinosis (PAP)

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OBJECTIVE

To determine the efficacy of molgramostim in patients with autoimmune PAP based on their disease severity at randomization in the IMPALA-2 Phase 3 clinical trial

CONCLUSIONS

Molgramostim significantly improved measures of pulmonary gas transfer, respiratory health-related quality of life (HRQoL), and patient functionality compared with placebo in both subgroups of patients with hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide (DLco%) values of ≤50% or >50% at randomization

Molgramostim was effective in patients with autoimmune PAP regardless of disease severity defined by DLco%

ACKNOWLEDGEMENTS

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- Disclosure: CM is an advisory board member and consultant to Savara Inc.

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1. Rosen SH, et al. *N Engl J Med* 1958;258:1123-114; 2. Seymour JF, Presneill JJ. *Am J Respir Crit Care Med* 2002;166:215-235; 3.Trapnell BC, et al. *Nat Rev Dis Primers* 2019;5:16.

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Background

- 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[1-3]
- Autoimmune PAP is caused by autoantibodies that block granulocyte-macrophage colony stimulating factor (GM-CSF) signaling, resulting in impaired surfactant clearance[3]
- Molgramostim inhalation solution (molgramostim) is a recombinant human GM-CSF that is being studied for the treatment of patients with autoimmune PAP
- The efficacy and safety of molgramostim for the treatment of autoimmune PAP are being evaluated in a randomized, double-blind Phase 3 clinical trial (IMPALA-2)
- IMPALA-2 met its primary endpoint, change in DLco% from baseline to week 24
- Analyses were conducted to determine if the beneficial clinical effects of molgramostim in IMPALA-2 were similar in autoimmune PAP patients based on DLco% (≤50% or >50%) at randomization

Methods

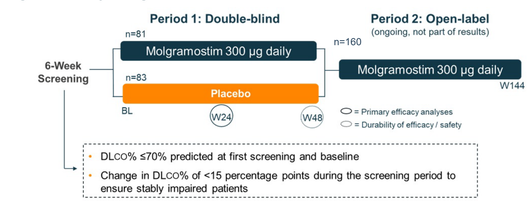
Patients

- Adult patients with autoimmune PAP were required to have:
  - A positive anti-GM-CSF autoantibody test result
  - A DLco% of ≤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, which is currently ongoing (**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; DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; W24, week 24; W48, week 48; W144, week 144.

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

Analyses

- Prespecified analyses were conducted in subgroups of patients with DLco% ≤50% or >50% at randomization using a generalized linear mixed model for repeated measures, with treatment, DLco% subgroup at randomization (≤50% or >50%), region, visit, interactions for treatment-visit, subgroup-visit, and subgroup-treatment-visit, and actual DLco% at baseline as dependent variables

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)**
- More patients in both treatment groups (62%) had a DLco% of >50% at randomization:
  - 31 patients in the molgramostim group and 32 patients in the placebo group had a DLco% of ≤50% at randomization
  - 50 patients in the molgramostim group and 51 patients in the placebo group had a DLco% of >50% at randomization

Table 1. Baseline Demographic and Clinical Characteristics

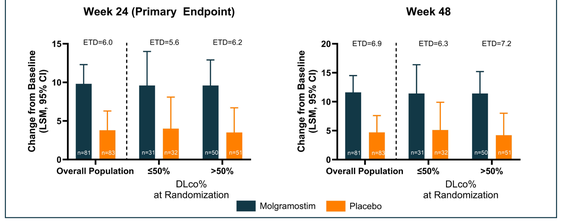
		Molgramostim n=81	Placebo n=83	Total N=164
Age years	Mean (SD)	50.8 (13.0)	48.4 (12.7)	49.6 (12.9)
	Range	20-80	21-79	20-80
Sex n (%)	Male	44 (54.3)	54 (65.1)	98 (59.8)
	Female	37 (45.7)	29 (34.9)	66 (40.2)
Race n (%)	White	38 (46.9)	40 (48.2)	78 (47.6)
	Asian	36 (44.4)	37 (44.6)	73 (44.5)
	Black or African American	3 (3.7)	2 (2.4)	5 (3.0)
	Other	4 (4.9)	4 (4.8)	8 (4.9)
DLco%*	Mean (SD)	52.6 (11.7)	52.6 (10.4)	52.6 (11.0)
	Median	54	55	55
	Range	25-72	28-71	25-72
n (%)	≤50%	31 (38)	32 (39)	63 (38)
	>50%	50 (62)	51 (61)	101 (62)

*Descriptive statistics are for actual DLco% value at baseline for which the DLco% was adjusted for Visit 3/baseline hemoglobin; frequencies are for DLco% stratification at randomization for which the DLco% was adjusted for Visit 2/Screening Visit 2 hemoglobin. DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; n, number; SD, standard deviation.

Molgramostim Improved Pulmonary Gas Transfer (Figure 2)

- In the overall population, the primary endpoint, mean change from baseline in DLco% at week 24, was significantly greater in the molgramostim group compared with the placebo group (estimated treatment difference [ETD] in least squares mean [LSM] change, 6.0%; P=0.0007)
- Similar treatment effects on the primary endpoint were observed in subgroups of patients with a DLco% of ≤50% (ETD in LSM change, 5.6; 95% confidence interval [CI] 0, 11.3) and those with a DLco% of >50% at randomization (ETD in LSM change, 6.2; 95% CI 1.7, 10.6)
- The beneficial effect of molgramostim on DLco% was maintained at week 48 in the overall population (ETD in LSM change, 6.9; P=0.0008) and both subgroups

Figure 2. Effect of Molgramostim on DLco% at 24 and 48 Weeks



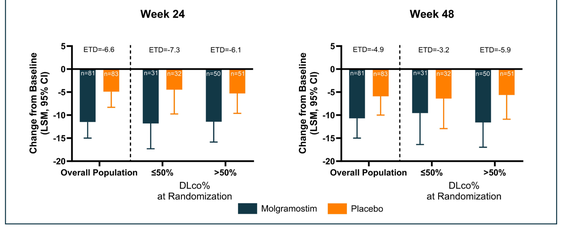
DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; ETD, estimated treatment difference in least-squares mean change; LSM, least-squares mean; n, number.

Molgramostim Improved HRQoL (Figure 3)

SGRQ Total Score

- In the overall population, mean improvement from baseline in SGRQ Total score at week 24 was significantly greater in the molgramostim group compared with the placebo group (ETD in LSM change -6.6; P=0.0072)
- Similar treatment effects were observed at 24 weeks in subgroups of patients with a DLco% of ≤50% (ETD in LSM change, -7.3; 95% CI -14.8, 0.2) and those with a DLco% of >50% at randomization (ETD in LSM change, -6.1; 95% CI -12.3, 0)
- At 48 weeks, the effect of molgramostim on SGRQ Total score was slightly lower in patients with a DLco% of ≤50% and slightly higher in patients with a DLco% of >50% than that of the overall population (ETD in LSM change, -4.9)

Figure 3. Effect of Molgramostim on SGRQ Total Score at 24 and 48 Weeks



DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; ETD, estimated treatment difference in least-squares mean change; LSM, least-squares mean; n, number; SGRQ, St. George's Respiratory Questionnaire.

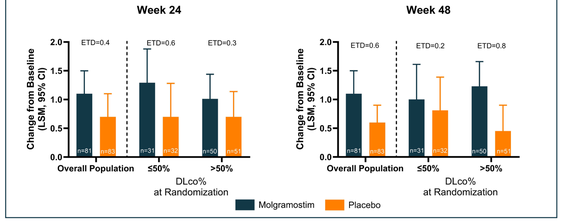
SGRQ Activity Score (data not shown)

- In the overall population, mean improvement from baseline in SGRQ Activity score was greater in the molgramostim group compared with the placebo group at week 24 (ETD in LSM change -7.8; 95% CI -14.1, -1.5)
- Similar treatment effects were observed at 24 weeks in subgroups of patients
- Similar to SGRQ Total score at 48 weeks, the effect of molgramostim on SGRQ Activity score was lower in patients with a DLco% of ≤50% (ETD in LSM change, -4.6) and higher in patients with a DLco% of >50% (ETD in LSM change, -6.9) than that of the overall population (ETD in LSM change, -6.0)

Molgramostim Improved Patient Functionality (Figure 4)

- In the overall population, mean change from baseline in exercise capacity expressed as peak METs was greater in the molgramostim group compared with the placebo group at week 24 (ETD in LSM change, 0.4; 95% CI -0.1, 0.9) and at week 48 (ETD in LSM change, 0.6; 95% CI 0.1, 1.0)
- The effect of molgramostim on mean change from baseline in peak METs was numerically greater compared with placebo in the DLco% ≤50% subgroup and the in the DLco% >50% subgroup at 24 and 48 weeks; the magnitude of effect was generally similar across subgroups at 24 weeks and was smaller in the ≤50% subgroup at 48 weeks

Figure 4. Effect of Molgramostim on peak METs at 24 and 48 Weeks



DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; ETD, estimated treatment difference in least-squares mean; LSM, least-squares mean change; METs, metabolic equivalents; n, number.