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

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CHEST 2025 Annual Meeting, October 21, 2025, Chicago, IL

Financial Disclosures

- Scientific Advisory Board Member: Savara Inc.
- Honoraria and consulting fees: Savara Inc.
- Consulting Fees: Partner Therapeutics
- Consulting Fees: Theravance Inc.

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 DL_{CO}% from baseline to week 24[4]
- This analysis was conducted to determine if the beneficial clinical effects of molgramostim in IMPALA-2 were similar in patients with autoimmune PAP based on disease severity defined by DL_{CO}% (≤50% or >50%) at randomization

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; 4. Trapnell BC, et al. *N Engl J Med* 2025;393:764-773.

Study Design and Analysis

Design

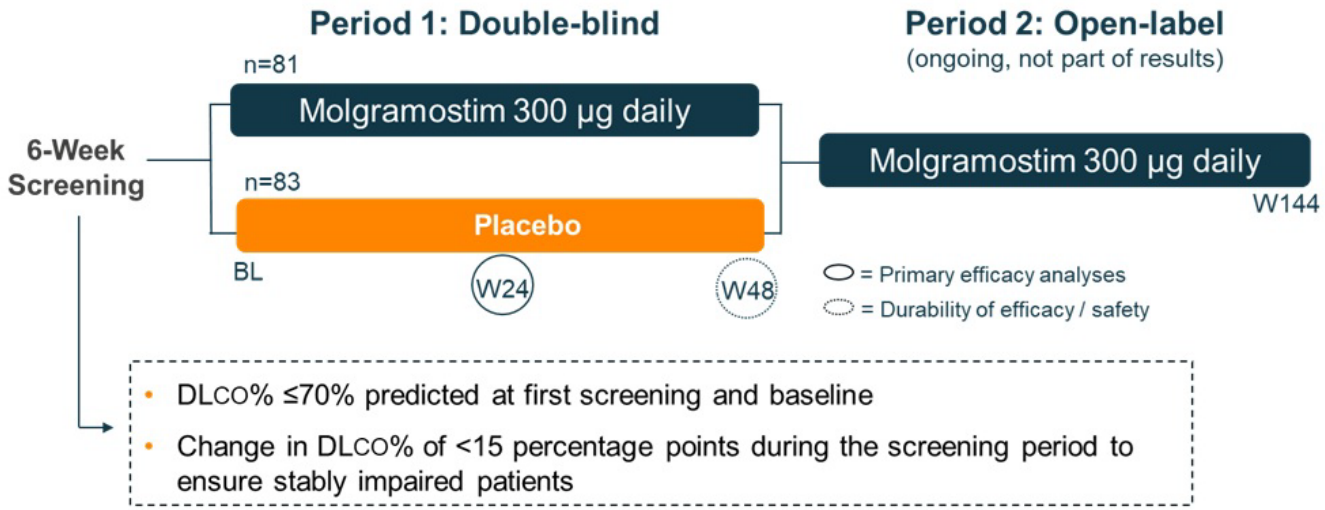
- Randomized, double-blind, placebo-controlled Phase 3 clinical trial being conducted at 43 clinical sites across 16 countries
- 48-week double-blind intervention period followed by a 96-week open-label treatment period (ongoing)

Endpoints

- Primary: Change from baseline in DLCO% at week 24
- Secondary: Change from baseline in:
  - DLCO% at week 48
  - 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

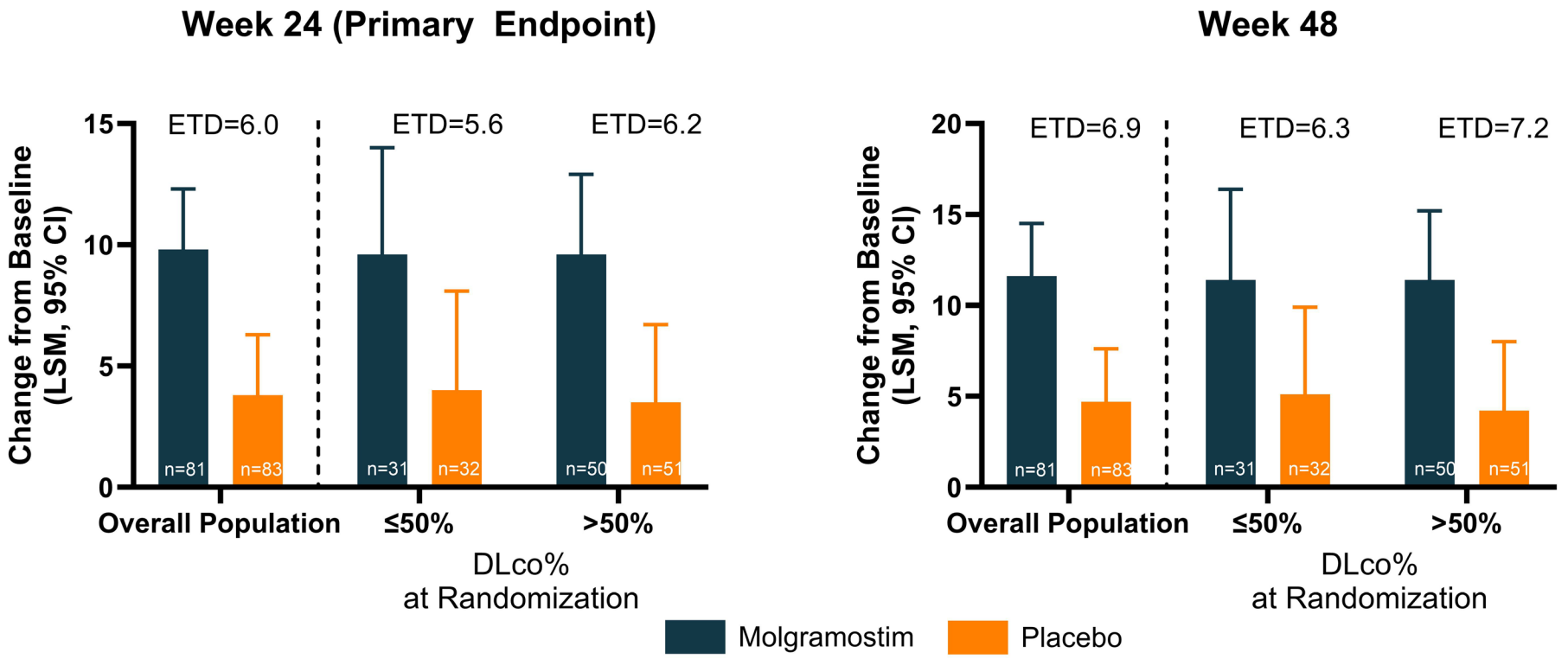
- Efficacy of molgramostim on primary and secondary endpoints were conducted in subgroups of patients with DLCO% ≤50% or >50% at randomization (prespecified)



BL, baseline; DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; SGRQ, St. George's Respiratory Questionnaire; W24, week 24; W48, week 48; W144, week 144.

Molgramostim Improved Pulmonary Gas Transfer Overall and in Both DLCO% Subgroups: DLCO%

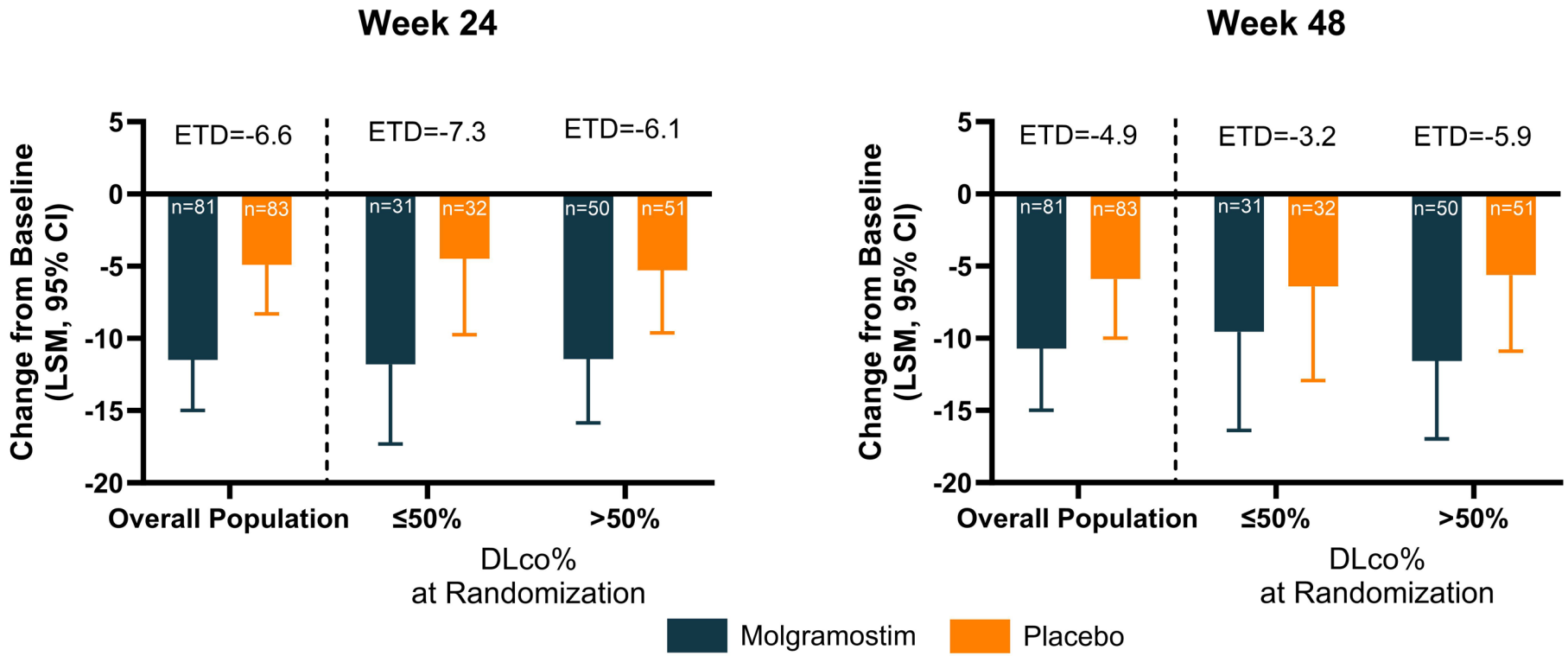
- Similar treatment effects on the primary endpoint were observed in subgroups of patients with a DLCO% of ≤50% and those with a DLCO% of >50% at randomization
- The beneficial effect of molgramostim on DLCO% was maintained at week 48 in the overall population and both subgroups



DLCO%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; ETD, estimated treatment difference.

Molgramostim Improved Respiratory Health-Related Quality of Life Overall and in Both DLCO% Subgroups: SGRQ Total Score*

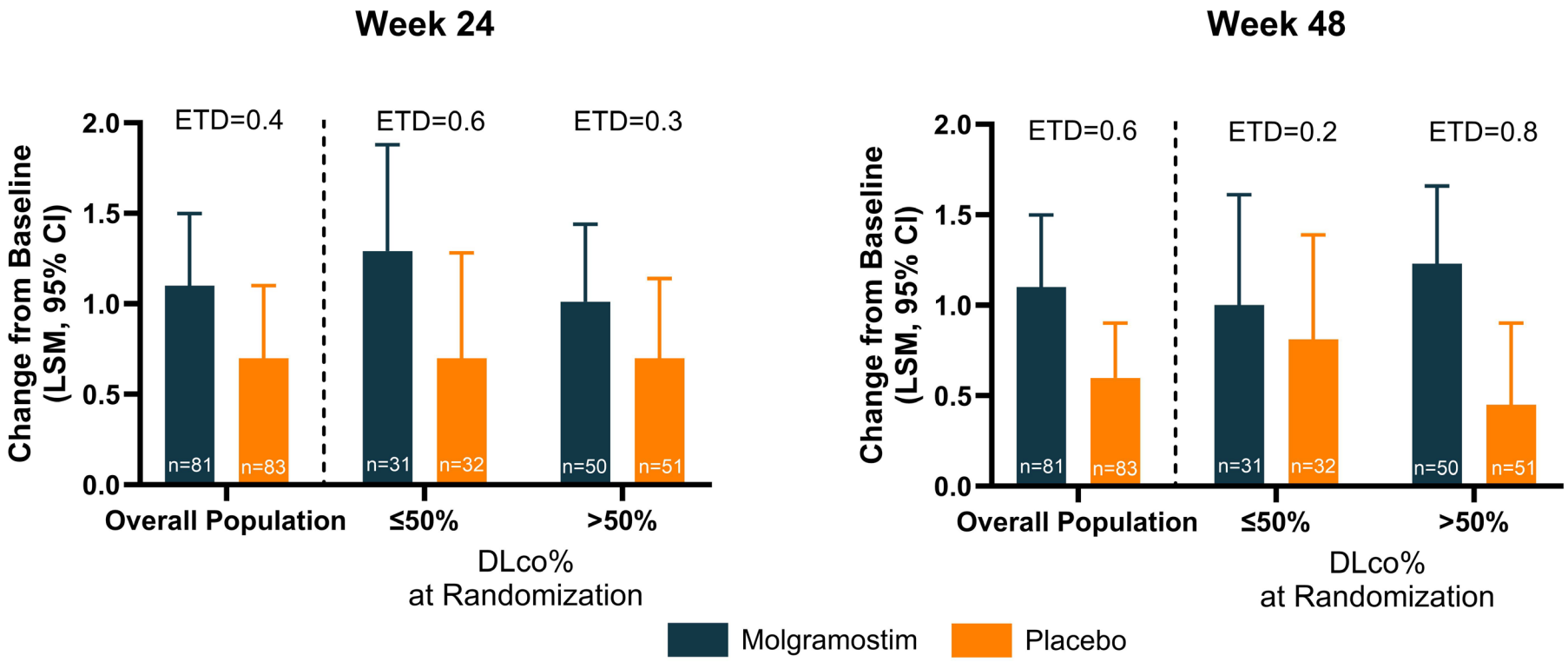
- Similar treatment effects were observed at 24 weeks in subgroups of patients with a DLCO% of ≤50% and those with a DLCO% of >50% at randomization
- At 48 weeks, the effect of molgramostim on SGRQ Total score was slightly lower in patients with a DLCO% of ≤50% and slightly higher in patients with a DLCO% of >50% than that of the overall population



*Similar results were observed for the SGRQ Activity score.
ETD, estimated treatment difference; SGRQ, St. George's Respiratory Questionnaire.

Molgramostim Improved Patient Functionality Overall and in Both DLCO% Subgroups: Exercise Capacity (Peak METs)

- 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 greater in the ≤50% subgroup at 24 weeks and was smaller in the ≤50% subgroup at 48 weeks



ETD, estimated treatment difference; METs, metabolic equivalents.

Conclusions

- Molgramostim improved measures of pulmonary gas transfer, respiratory health-related quality of life, and patient functionality compared with placebo in both subgroups of patients with DLCO% values of ≤50% or >50% at randomization
  - For DLCO%, the magnitude of the treatment effect was similar across DLco% subgroups at 24 and 48 weeks
  - For SGRQ Total score, similar treatment effects were observed at 24 weeks in subgroups of patients with a DLco% of ≤50% and those with a DLco% of >50% at randomization; at 48 weeks, the effect of molgramostim 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. Similar results were observed for SGRQ Activity score
  - For exercise capacity, 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 greater in the ≤50% subgroup at 24 weeks and was smaller in the ≤50% subgroup at 48 weeks
- Molgramostim was effective in patients with autoimmune PAP regardless of disease severity defined by DLCO%