Molgramostim Improves Exercise Distance and Duration in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP): Results From the IMPALA-2 Phase 3 Clinical Trial

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- The IMPALA-2 clinical trial is sponsored by Savara Inc.

Background and Objective

- Autoimmune PAP (aPAP) 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 aPAP 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] and improved exercise capacity (a secondary endpoint), expressed as peak metabolic equivalents, at Week 48

Objective: To report the effects of molgramostim on exploratory exercise capacity-related endpoints – distance walked and duration of exercise – from the IMPALA-2 clinical trial

[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.
DL_{CO}%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide

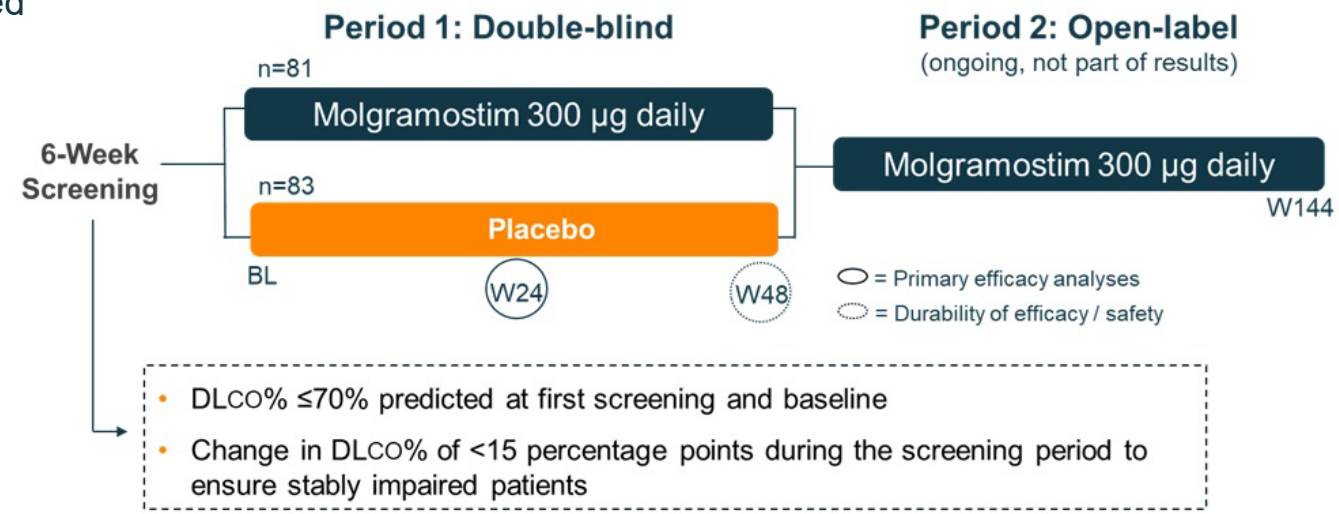
Study Design

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 (completed) 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
- Exploratory: Multiple, including:
  - Change from baseline in distance walked (meters) at Weeks 24 and 48
  - Change from baseline in duration of exercise (minutes) at Weeks 24 and 48

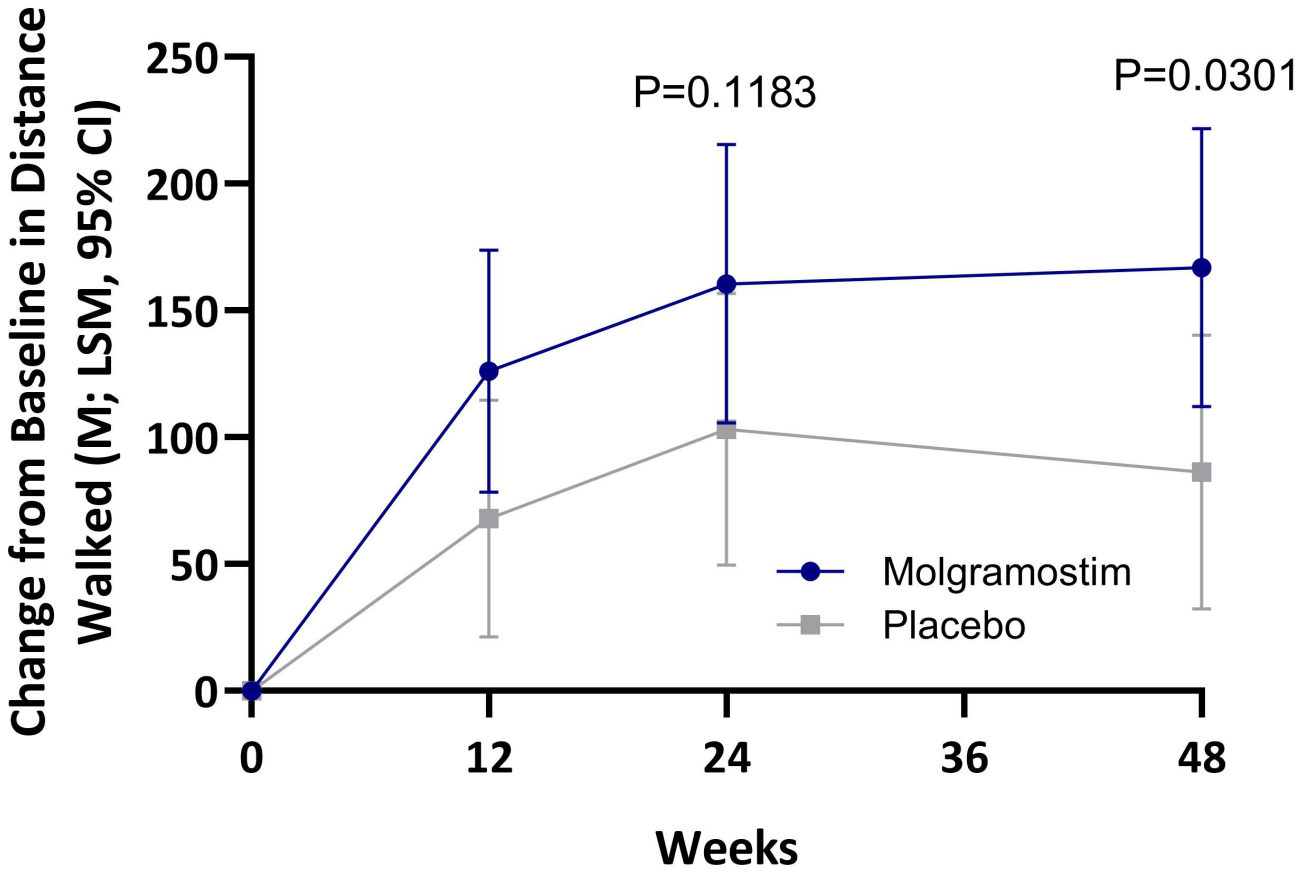


IMPALA-2 used a standardized exercise treadmill test to assess exercise capacity during the double-blind period at Baseline, Week 12, Week 24, and Week 48

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 Distance Walked (Meters)

Greater mean improvement in distance walked was observed in molgramostim-treated patients compared with placebo at Week 48



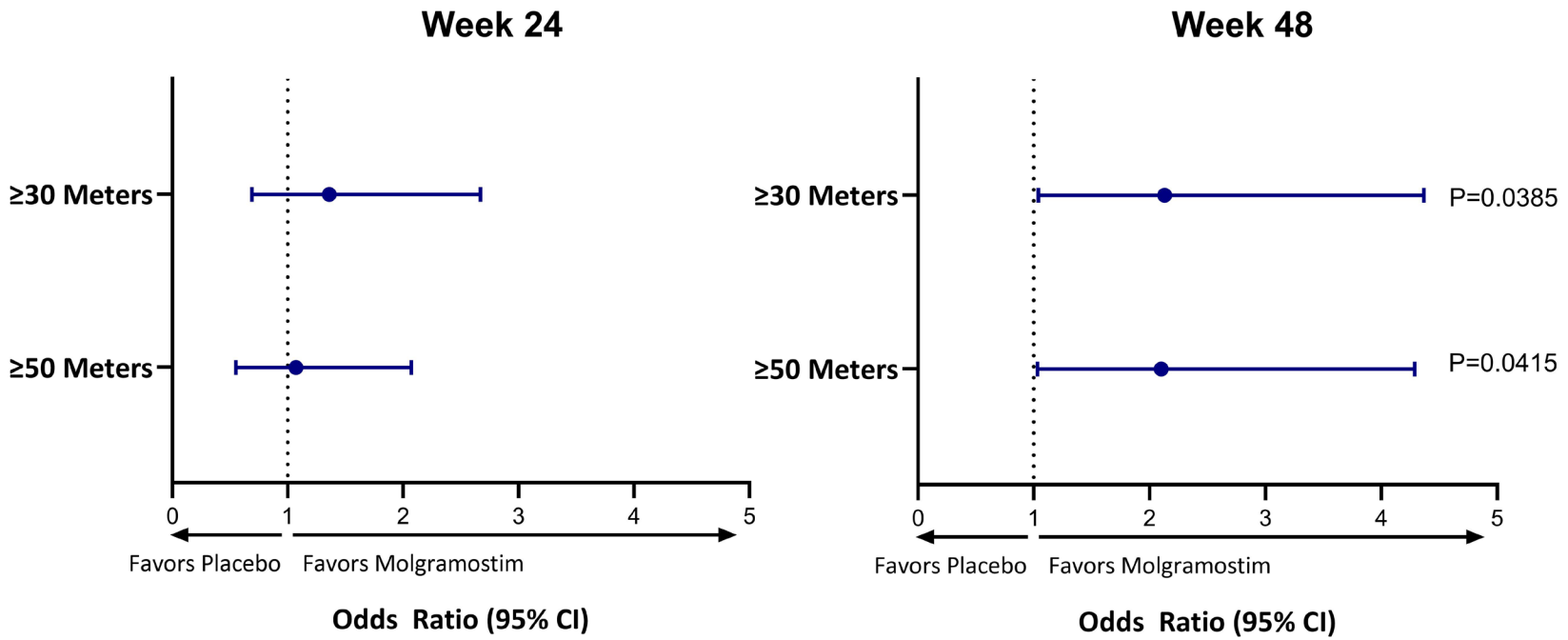
	LSM Change from Baseline	ETD	P-Value
Week 48	MOL: 167.0 PBO: 86.4	80.6	0.0301

CI, confidence interval; ETD, estimated treatment difference; LSM, least-squares mean; M, meters; MOL, molgramostim; PBO, placebo.

Molgramostim Improved Distance Walked (Meters)

Responder Analysis*

Responder Defined as Having an Increase from Baseline of ≥30 Meters[1] or ≥50 Meters[2]

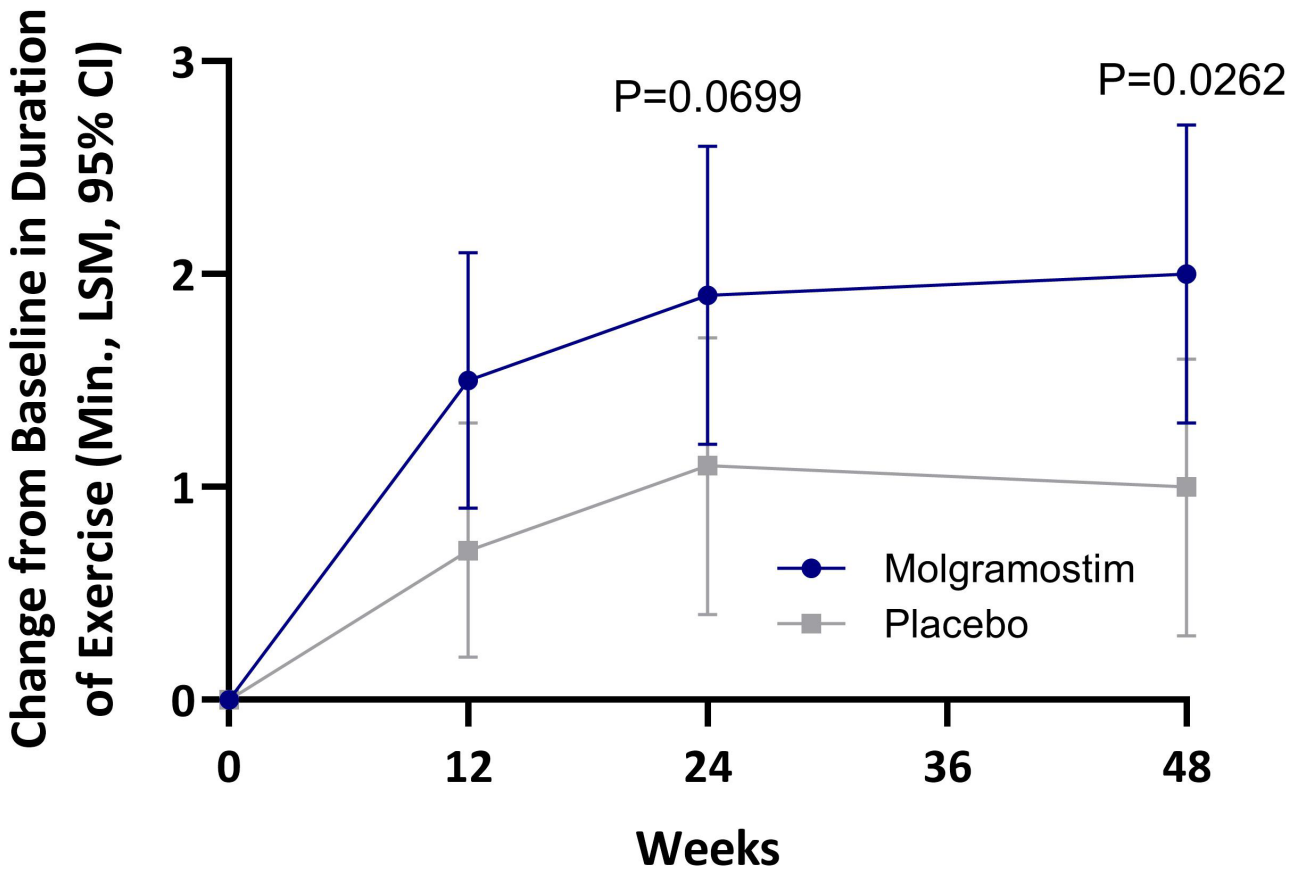


*Logistic regression model was used and adjusted for baseline distance walked as a continuous covariate, and treatment, region, and percent predicted DLCO% severity stratification as recorded at randomization as factors. A responder is defined as a patient with a change from baseline to Week 24 or Week 48 in distance walked of ≥ 30 or ≥ 50 meters. Patients with missing distance walked data at Week 24 or Week 48 are considered non-responders. An odds ratio > 1 favored molgramostim. CI, confidence interval.

[1]Bohannon RW, Crouch R. *J Eval Clin Pract.* 2017;23:377-381; [2]Scrutinio D, et al. *Int J Cardiol.* 2022;352:92-97.

Molgramostim Improved Duration of Exercise (Minutes)

Molgramostim patients were able to exercise for longer periods of time compared with patients who received placebo



	LSM Change from Baseline	ETD	P-Value
Week 48	MOL: 2.0 PBO: 1.0	1.0	0.0262

CI, confidence interval; ETD, estimated treatment difference; LSM, least-squares mean; Min., minutes; MOL, molgramostim; PBO, placebo.

Conclusions

- IMPALA-2 is the first aPAP trial to assess exercise capacity using a standardized exercise treadmill test
- Consistent with improvement in peak metabolic equivalents, molgramostim improved distance walked and duration of exercise at Week 48 compared with placebo, supporting the potential clinical benefit of molgramostim treatment in patients with aPAP
- Further, there was a higher likelihood of achieving both distance walked responder thresholds (≥ 30 m or ≥ 50 m) at Week 48 in the molgramostim group compared with placebo
- The exercise treadmill test may represent a valuable test for measuring physical functioning in aPAP clinical trials

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Thank you!

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