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

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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

CONCLUSION

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

DISCLOSURES
- IMPALA-2 is sponsored by Savara Inc.
- YI has received financial compensation from Savara Inc. for consultant services.

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Background

- Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease caused by autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF)[1]
- aPAP 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) is an investigational recombinant human GM-CSF that was studied for the treatment of patients with aPAP in a randomized, double-blind Phase 3 clinical trial (IMPALA-2)[4]
- IMPALA-2 achieved statistical significance on its primary endpoint and multiple secondary endpoints, and molgramostim was generally well tolerated[4]
- Molgramostim also improved exercise capacity expressed as peak metabolic equivalents at Week 48[4]

Methods

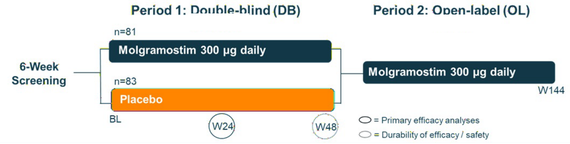
Patients

- Patients were required to:
  - Have a positive (abnormal) anti-GM-CSF autoantibody test result
  - Have a DLCO% ≤70% at the first screening and baseline visits
  - Have a change in DLCO% of <15 percentage points during the screening period to ensure stability of impaired patients
  - Be willing and able to come off supplemental oxygen use prior to and during the treadmill exercise test, the DLCO% assessment, and the arterial blood gas sampling
- Patients with a physical disability or other condition that precludes safe and adequate exercise testing were excluded from participation in the clinical trial

Study Design

- IMPALA-2 was a randomized, double-blind, placebo-controlled Phase 3 clinical trial conducted at 43 clinical sites across 16 countries
- The trial consisted of a 48-week double-blind period followed by a 96-week open-label period (**Figure 1**)

Figure 1. Study Design



BL, baseline; W, week.

Exercise Treadmill Test (ETT) and Exercise Capacity

- Distance walked and duration of exercise were assessed using a standardized ETT at screening/baseline and at 12, 24, and 48 weeks. An established, conservative, ramp-up treadmill protocol was used[5]
- Supplemental oxygen was not allowed during ETTs. ETTs were not initiated in patients with peripheral oxygen saturation (SpO_2) ≤85% at rest or after supplemental oxygen discontinuation
- Changes from baseline in distance walked and duration of exercise were modelled using a general linear mixed model for repeated measures adjusted for baseline value as a continuous covariate, and region, DLCO% severity at randomization, treatment, visit, and treatment-visit interaction as factors. An unstructured covariance matrix was used. There was no imputation of missing data.
- For responder analyses, a responder was defined as having an increase from baseline in walking distance of ≥30 m (*post hoc*) or ≥50 m (prespecified)
  - As the ETT has not been used extensively in respiratory clinical trials, the response thresholds for distance walked were selected based on the more commonly used six-minute walk test (6MWT)[6-10]

Results

Patients

- A total of 164 patients with aPAP underwent randomization; 81 patients were assigned to receive molgramostim and 83 to receive placebo
- At baseline, distance walked and duration of exercise were similar between treatment groups (**Table 1**)

Table 1. Baseline distance walked and duration of exercise

	Molgramostim (n=81)	Placebo (n=83)
Baseline distance walked, m*		
n†	78	82
Mean (SD)	660.1 (322.2)	675.5 (319.2)
Baseline duration of exercise, min*		
n†	78	82
Mean (SD)	10.8 (4.0)	11.0 (3.9)

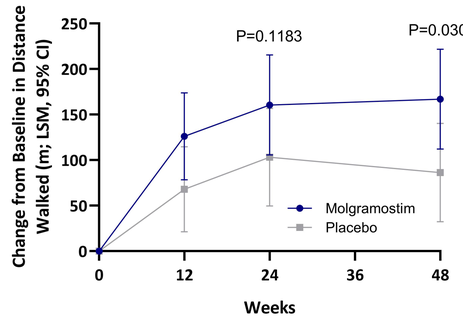
*Baseline values were defined as the last non-missing value prior to the first dose of treatment at Visit 3. No imputation of missing data was performed for the descriptive baseline data. †Baseline data were not available for 3 patients in the molgramostim group and 1 patient in the placebo group. m, meters; min, minutes; SD, standard deviation.

Distance Walked

Least-squares Mean (LSM) Change From Baseline Over Time

- At Week 24, LSM change from baseline in distance walked was 160.6 m (95% confidence interval [CI], 105.8–215.5) for molgramostim (n=72) and 103.2 m (95% CI, 49.6–156.8) for placebo (n=73). The estimated between-group treatment difference based on LSM changes (ETD) was 57.4 m (95% CI, –14.8–129.7; P=0.1183) (**Figure 2**)
- At Week 48, LSM change from baseline in distance walked was greater for molgramostim (167.0 m [95% CI, 112.1–221.8]; n=71) versus placebo (86.4 m [95% CI, 32.4–140.4]; *n*=73). The ETD was 80.6 m (95% CI, 7.9–153.2; P=0.0301) (**Figure 2**)

Figure 2. LSM Change From Baseline in Distance Walked Over Time



CI, confidence interval; LSM, least-squares mean; m, meters.

Responder Analysis

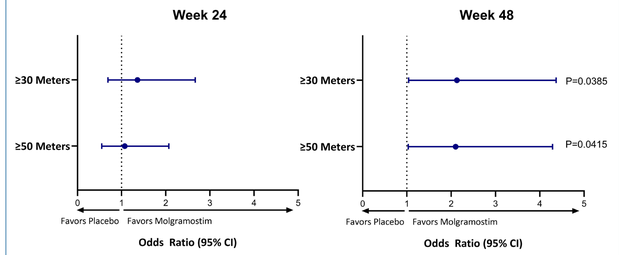
- At Week 24, the proportions of patients who met the ≥30 m and ≥50 m thresholds were 53% (41/78) and 46% (36/78) for molgramostim, and 45% (37/82) and 44% (36/82) for placebo, respectively; the estimated odds ratios versus placebo were 1.4 (≥30 m; 95% CI, 0.7–2.7) and 1.1 (≥50 m; 95% CI, 0.6–2.1) (P>0.05) (**Figure 3**)

Results

Responder Analysis (cont'd)

- At Week 48, significantly higher proportions of patients treated with molgramostim met the ≥30 m and ≥50 m thresholds versus placebo; 55% (43/78) and 53% (41/78) for molgramostim, respectively, and 39% (32/82) and 37% (30/82) for placebo, respectively
- Estimated odds ratios versus placebo were 2.1 (≥30 m; 95% CI, 1.0–4.4; P=0.0385) and 2.1 (≥50 m; 95% CI, 1.0–4.3; P=0.0415) (**Figure 3**)

Figure 3. Improvement from Baseline in Distance Walked, Responder Analysis

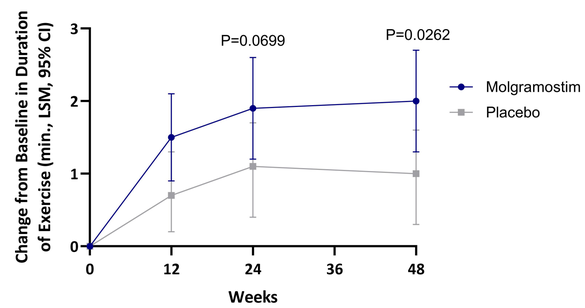


A logistic regression model was used and adjusted for baseline distance walked as a continuous covariate, and treatment, region, and DLCO% severity at randomization as factors. CI, confidence interval.

Duration of Exercise

- At Week 24, the LSM change from baseline in duration of exercise was 1.9 min (95% CI, 1.2–2.6) for molgramostim (*n*=72) and 1.1 min (95% CI, 0.4–1.7) for placebo (n=73). The ETD was 0.8 min (95% CI, –0.1–1.7; P=0.0699) (**Figure 4**)
- At Week 48, the LSM change from baseline in duration of exercise was greater for molgramostim (2.0 min [95% CI, 1.3–2.7]; n=71) compared with placebo (1.0 min [95% CI, 0.3–1.6]; n=73). The ETD was 1.0 min (95% CI, 0.1–1.9; P=0.0262) (**Figure 4**)

Figure 4. LSM Change From Baseline in Duration of Exercise



CI, confidence interval; LSM, least-squares mean; min, minutes.