

Molgramostim Treatment Effects in Autoimmune Pulmonary Alveolar Proteinosis Patients with a Baseline DLco% >70%

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OBJECTIVE

To evaluate the effects of molgramostim in autoimmune pulmonary alveolar proteinosis (aPAP) patients with mildly decreased or normal DLco%, defined as baseline DLco% >70%

CONCLUSIONS

In patients with mildly decreased or normal DLco% (baseline DLco% >70%), daily molgramostim was associated with improvements in pulmonary gas transfer as measured by A–aDO₂, quality of life, and radiologic evidence of excessive surfactant accumulation

These findings suggest molgramostim may provide additional clinical benefit in aPAP patients with normal diffusion or mild diffusion impairment

DISCLOSURES

- IMPALA was sponsored by Savara Inc.
- BCT has received financial compensation from Savara Inc. for consultant services.

REFERENCES

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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 a recombinant human GM-CSF in development as a targeted therapy for aPAP
- The randomized, double-blind, placebo-controlled IMPALA and IMPALA-2 clinical trials demonstrated that daily molgramostim had a favorable benefit/risk profile in aPAP patients with predominantly moderate-to-severe diffusion impairment^{4,5}
- However, treatment effects in patients with milder diffusion impairment remain incompletely characterized
- This post hoc analysis of the IMPALA dataset evaluated the effects of molgramostim in aPAP patients with mildly decreased or normal percent predicted hemoglobin-adjusted diffusing capacity of the lungs for carbon monoxide (DLco%), defined as a DLco% >70%

Methods

Patients

- Patients enrolled in IMPALA were required to have:
 - A diagnosis of aPAP based on chest CT, either lung biopsy or cytologic analysis of bronchoalveolar lavage fluid, and a positive serum test for GM-CSF autoantibodies
 - An alveolar–arterial oxygen gradient (A–aDO₂) of ≥25 mm Hg, a partial pressure of arterial oxygen (PaO₂) of <75 mm Hg at rest while breathing ambient air, or a decrease in oxygen saturation of >4 percentage points during the 6-minute walk test
 - Stable or progressive aPAP as indicated by improvement in vital capacity of <5% or improvement in DLco of <10% within 2 months before enrollment

Study Design

- IMPALA was a randomized, double-blind, placebo-controlled Phase 2/3 trial conducted at 34 clinical sites across 18 countries⁴
- Patients were randomized 1:1:1 to inhaled molgramostim 300 µg once daily (continuous), molgramostim 300 µg once daily for 7 days every other week (intermittent), or matching placebo during a 24-week double-blind intervention period, followed by an open-label extension of up to 48 weeks
- This post hoc analysis included IMPALA patients with a baseline hemoglobin-adjusted DLco% >70%. Analyses were restricted to the continuous once-daily molgramostim 300 µg and placebo arms; the intermittent dosing arm (7 days every other week) was excluded since only the continuous once-daily regimen was carried forward into IMPALA-2

Study Endpoints

- Changes from baseline to Week 24 were assessed for:
 - A–aDO₂ (mm Hg), a measure of pulmonary gas transfer
 - St. George’s Respiratory Questionnaire (SGRQ) Total and Activity scores (range 0–100), measures of respiratory health-related quality of life (HRQoL); higher scores indicate worse HRQoL
 - Ground-glass opacity (GGO) score on chest CT (range 0–15), a marker of pulmonary surfactant burden; higher scores indicate greater burden
 - DLco%

Statistical Analysis

- Baseline and Week 24 values are summarized descriptively as mean (SD) or mean (range)
- Given the small number of patients meeting the DLco% >70% criterion, all findings are considered exploratory and hypothesis-generating
- All comparisons are descriptive; no formal hypothesis testing was performed and no adjustment for multiplicity was applied

Results

Patients

- Of 138 patients randomized in IMPALA, 13 (9%) had a baseline DLco% >70%; this analysis includes the 8 randomized to molgramostim once daily and the 3 randomized to placebo (N=11)
- The 8 molgramostim once-daily patients represented 17% of the 46 patients randomized to once-daily treatment; 7 had complete Week 24 data and are included in the figures below
- Among these 7 patients, mean (range) baseline DLco% was 81.9% (72.1–97.5%) and mean (range) age was 63.1 (50–75) years
- Despite relatively preserved diffusing capacity, patients had elevated A–aDO₂, impaired respiratory HRQoL, and a high surfactant burden at baseline (**Table 1**)

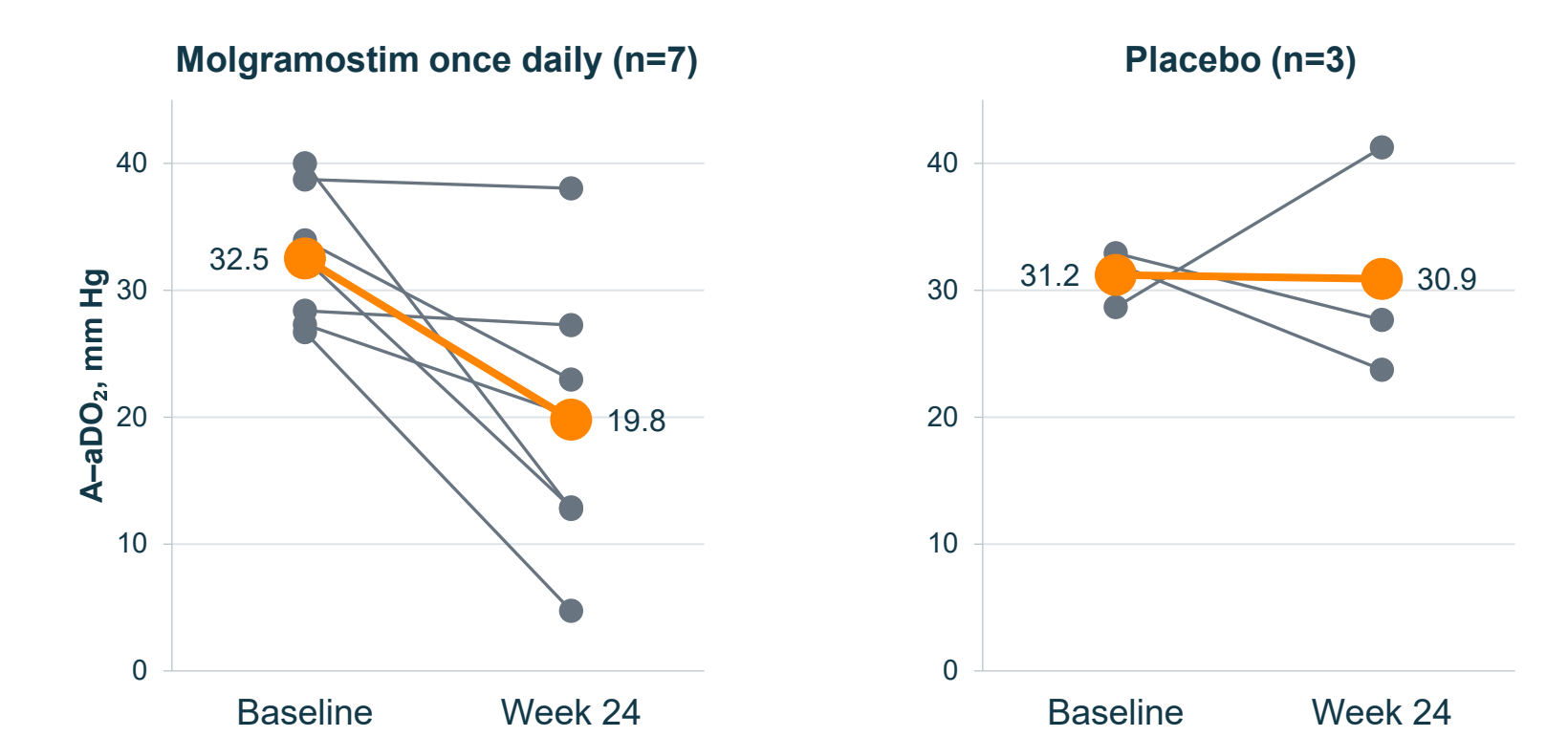
Table 1. Baseline demographic and clinical characteristics of IMPALA patients with baseline DLco% >70% randomized to once-daily molgramostim or placebo

Characteristic	Molgramostim once daily (n=8)	Placebo (n=3)
Age, years, mean (SD)	61.3 (10.7)	43.0 (17.6)
Male, n (%)	7 (87.5)	2 (66.7)
Region, Europe / Japan / other, n	2 / 5 / 1	2 / 1 / 0
DLco%, mean (SD) min, max	81.4 (10.2) 72.1, 97.5	76.9 (1.6) 75.2, 78.3
A–aDO ₂ , mm Hg, mean (SD)	31.9 (5.3)	31.2 (2.3)
SGRQ Total score, mean (SD)	29.6 (13.9)	40.5 (27.3)
SGRQ Activity score, mean (SD)	45.5 (22.6)	48.6 (19.4)
GGO score, mean (SD)	8.8 (2.6)	7.0 (2.6)
Previous WLL, n (%)	3 (37.5)	2 (66.7)

Table 1 includes the 8 patients randomized to molgramostim once daily and the 3 randomized to placebo; the 2 patients randomized to intermittent molgramostim are not shown.
A–aDO₂, alveolar–arterial oxygen gradient; DLco%, percent predicted diffusing capacity of the lungs for carbon monoxide adjusted for hemoglobin; GGO, ground-glass opacity; SGRQ, St. George’s Respiratory Questionnaire; SD, standard deviation; WLL, whole-lung lavage.

Efficacy

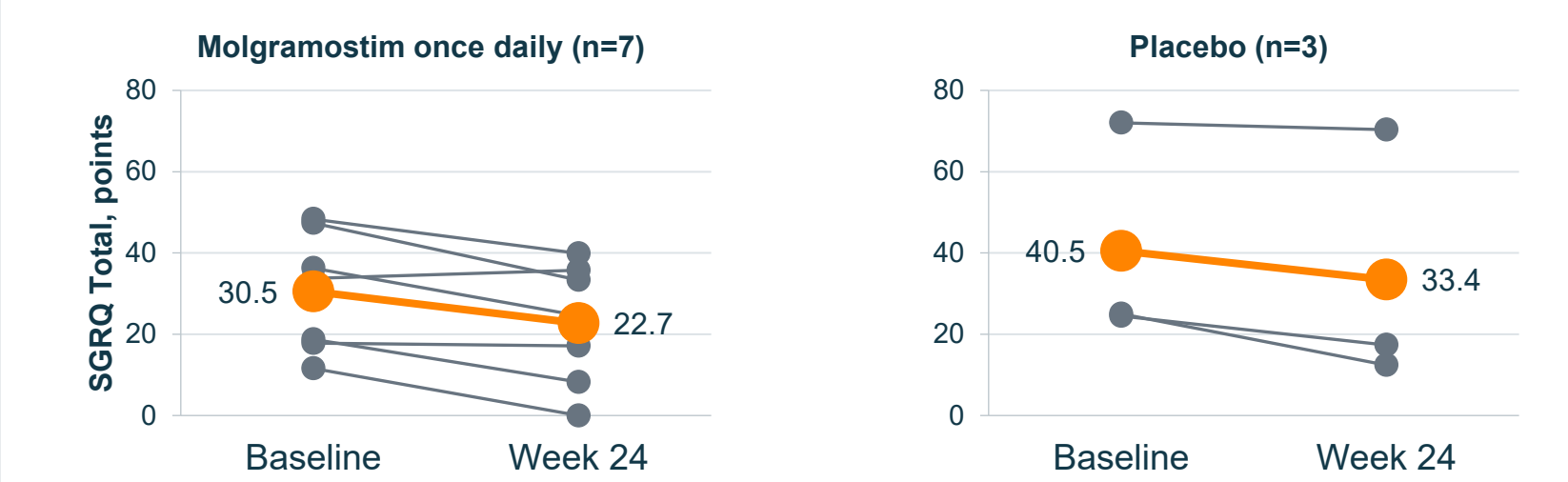
Figure 1. A–aDO₂ improved with daily molgramostim in patients with mild diffusion impairment at baseline



Each gray line is one patient; the thick orange line is the group mean. Lower A–aDO₂ indicates better gas transfer. Once-daily molgramostim 300 µg vs placebo; intermittent-dosing arm not included. A–aDO₂, alveolar–arterial oxygen gradient.

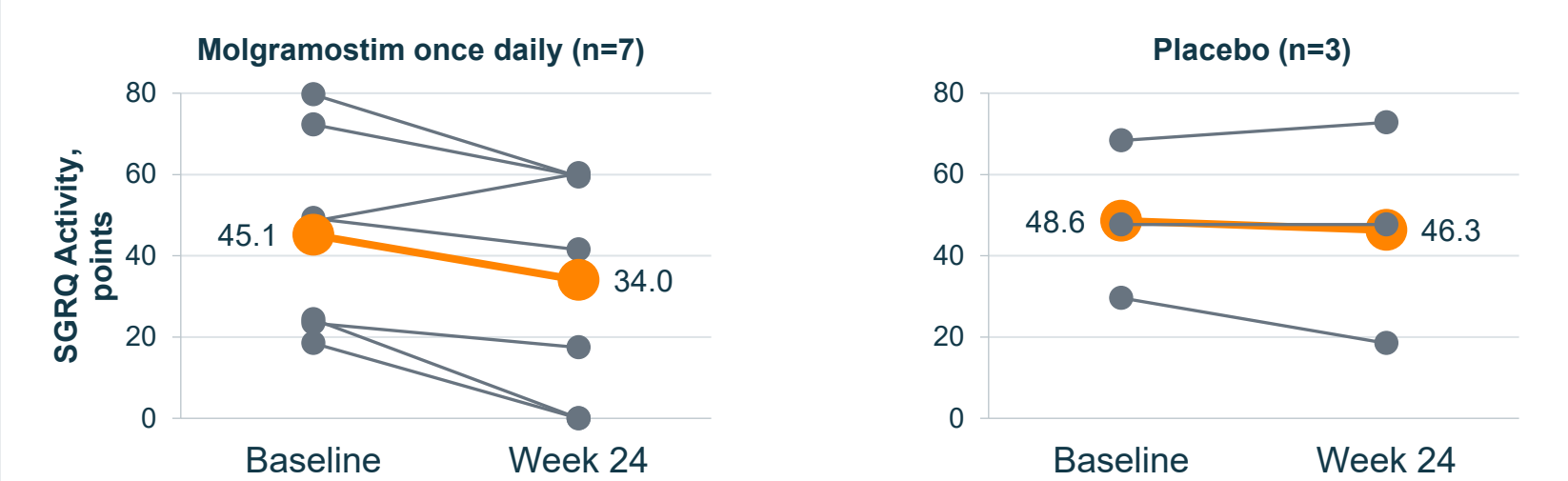
Results

Figure 2. SGRQ Total score at baseline and Week 24 in patients with mild diffusion impairment



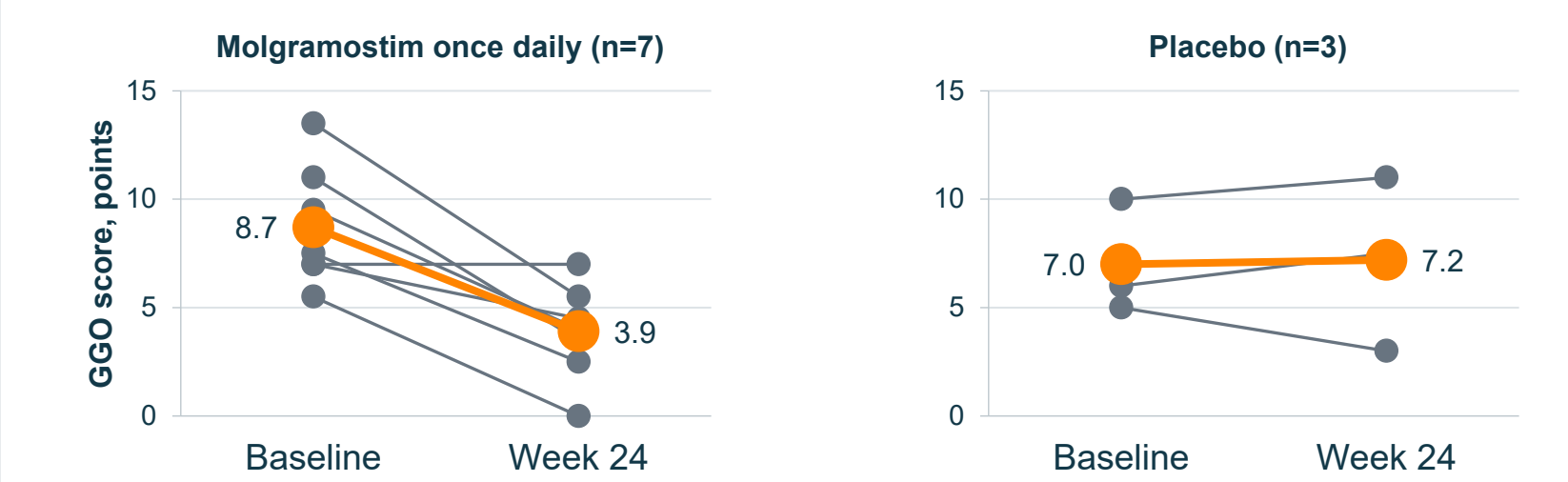
Each gray line is one patient; the thick orange line is the group mean. SGRQ scores range from 0 to 100; lower scores indicate better respiratory health-related quality of life. SGRQ, St. George’s Respiratory Questionnaire.

Figure 3. SGRQ Activity score improved with daily molgramostim in patients with mild diffusion impairment at baseline



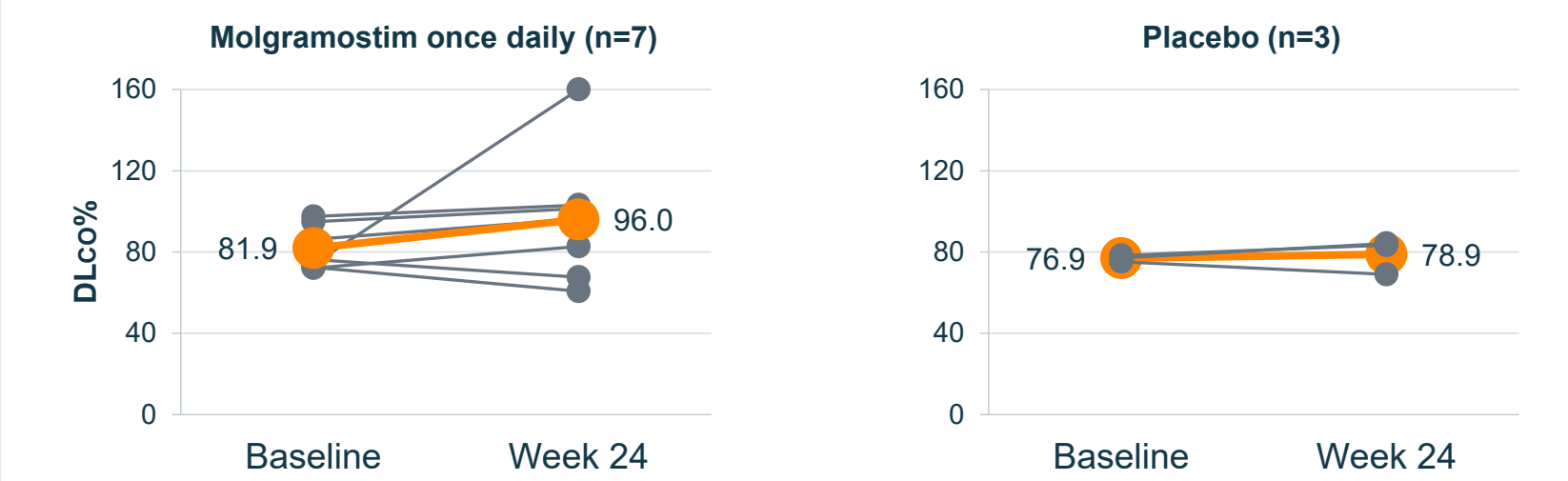
Each gray line is one patient; the thick orange line is the group mean. SGRQ scores range from 0 to 100; lower scores indicate better respiratory health-related quality of life. SGRQ, St. George’s Respiratory Questionnaire.

Figure 4. GGO score improved with daily molgramostim in patients with mild diffusion impairment at baseline



Each gray line is one patient; the thick orange line is the group mean. GGO scores range from 0 to 15; lower scores indicate lower alveolar surfactant burden. GGO, ground-glass opacity.

Figure 5. DLco% was maintained with daily molgramostim in patients with near-normal diffusing capacity at baseline



Each gray line is one patient; the thick orange line is the group mean. DLco% is the percent predicted diffusing capacity of the lungs for carbon monoxide (hemoglobin-adjusted); higher values indicate better gas transfer. The Week 24 group mean is influenced by one patient whose DLco% increased from 74% to 160%; excluding this patient, mean DLco% was 83.3% at baseline and 85.3% at Week 24. DLco%, percent predicted diffusing capacity of the lungs for carbon monoxide adjusted for hemoglobin.