Biomarker Levels in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP): Results From the IMPALA-2 Phase 3 Clinical Trial

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OBJECTIVE

To report serum biomarker levels in patients with aPAP from the IMPALA-2 Phase 3 clinical trial

CONCLUSIONS

Levels of biomarkers associated with aPAP disease severity decreased more in patients treated with molgramostim compared with placebo

Decreased levels of most biomarkers were strongly associated with improvements in pulmonary gas transfer

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]
- Biomarkers for the assessment of aPAP disease severity and therapeutic response are well-reported, and include serum cytokeratin 19 fragments (CYFRA21-1), carcinoembryonic antigen (CEA), Krebs von den Lungen-6 (KL-6), and lactate dehydrogenase (LDH)[4-10]
- Molgramostim inhalation solution (molgramostim), an investigational recombinant human GM-CSF, was evaluated for the treatment of aPAP in a Phase 3 clinical trial (IMPALA-2)
- IMPALA-2 achieved statistical significance on its primary endpoint, change from baseline in hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide (DLco%) at Week 24, and multiple secondary endpoints. In addition, molgramostim was generally well tolerated[11]
- Here we report biomarker results from the IMPALA-2 clinical trial double-blind period

Methods

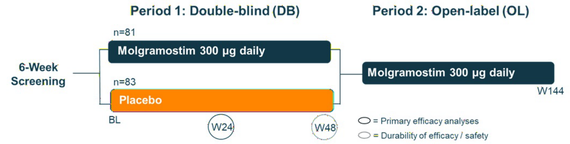
Patients

- Patients were required to have:
  - A positive (abnormal) anti-GM-CSF autoantibody test result
  - DLco% ≤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 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 (DB) period followed by a 96-week open-label (OL) period (**Figure 1**)

Figure 1. Study Design



BL, baseline; W, week.

Measurement of Serum Biomarkers

- Blood samples for assessment of the following aPAP-related biomarkers were taken at baseline and Weeks 4, 12, 24, and 48: KL-6, CYFRA21-1, CEA, LDH, hemoglobin (Hb), and hematocrit (Hct)
- Analysis of KL-6, CYFRA21-1, and CEA was performed by a central laboratory using validated methods
- LDH was analyzed from the standard biochemistry safety laboratory sample, and Hb and Hct from the standard hematology safety laboratory sample

Post-Hoc Statistical Analyses

- Changes from baseline in biomarker levels over the double-blind period were analyzed using a general linear mixed model for repeated measures adjusted for baseline biomarker as a continuous covariate and region, DLco% severity at randomization (≤50%, >50%), treatment, visit, and treatment by visit interaction as factors. There was no imputation for missing data
- Spearman's Rank correlation coefficients (r) were calculated to determine the relationship between change from baseline in DLco% and each biomarker

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, biomarker levels were similar between treatment groups (**Table 1**)

Table 1. Baseline biomarker levels

Biomarker	Molgramostim n=81	Placebo n=83	Total N=164
LDH (U/L)			
n	81	83	164
Mean (SD)	281.9 (79.7)	289.4 (103.0)	285.7 (92.0)
Median (min, max)	270.0 (137, 646)	267.0 (167, 893)	267.5 (137, 893)
CYFRA21-1 (ng/mL)			
n	79	76	155
Mean (SD)	10.2 (6.8)	9.5 (7.3)	9.8 (7.0)
Median (min, max)	8.7 (2.1, 36.2)	8.0 (0.8, 47.7)	8.5 (0.8, 47.7)
KL-6 (U/mL)			
n	79	80	159
Mean (SD)	4946.5 (3105.4)	5129.3 (2859.9)	5038.5 (2976.4)
Median (min, max)	4334.0 (143, 10,000)	5270.5 (575, 10,000)	4569.0 (143, 10,000)
CEA (ng/mL)			
n	78	79	157
Mean (SD)	7.6 (5.6)	8.8 (7.1)	8.2 (6.4)
Median (min, max)	6.3 (1.8, 28.3)	7.1 (1.8, 37.2)	6.4 (1.8, 37.2)
Hb (g/L)			
n	81	83	164
Mean (SD)	148.2 (21.9)	152.5 (20.7)	150.4 (21.4)
Median (min, max)	149.0 (88, 197)	155.0 (83, 207)	152.5 (83, 207)
Hct (%)			
n	81	83	164
Mean (SD)	46.6 (5.7)	47.5 (5.4)	47.0 (5.6)
Median (min, max)	46.0 (31, 59)	47.0 (33, 60)	47.0 (31, 60)

CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; Hb, hemoglobin; Hct, hematocrit; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; max, maximum; min, minimum; n, number of patients; SD, standard deviation.

Serum Biomarker Levels During the Double-Blind Treatment Period

- Least-squares mean (LSM) changes from baseline in levels of CYFRA21-1, KL-6, CEA, and LDH in the molgramostim and the placebo groups over the 48-week DB treatment period are shown in **Figure 2**
- LSM decreases in CYFRA21-1, KL-6, and LDH levels were significantly more in the molgramostim group than in the placebo group at Weeks 24 and 48; there were no significant differences between treatment groups in LSM changes in CEA (**Figure 2**)
- LSM changes from baseline in Hb and Hct were similar between the treatment groups (data not shown)

Relationship Between Serum Biomarkers and Pulmonary Gas Transfer

- **Figure 3** shows the relationship between change from baseline in DLco% and changes from baseline in CYFRA21-1, KL-6, CEA, and LDH biomarker levels at Week 24 and at Week 48; correlation coefficients are for all patients (pooled data from molgramostim and placebo groups)
  - Interpretation of strength of correlations: <|0.3| is weak, |0.3-0.5| is moderate, and ≥|0.5| is strong[12]
- Strong negative correlations (increase in DLco% was associated with decreases in biomarker levels) were observed between DLco% and KL-6, DLco% and CYFRA21-1, DLco% and CEA, and DLco% and LDH (**Figure 3**)
- Moderate negative correlations were observed between DLco% and Hct (**Table 2**)
- Weak negative correlations were observed between DLco% and Hb (**Table 2**)

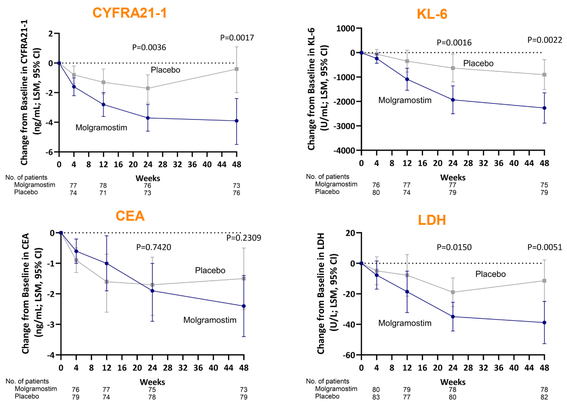
Table 2. Correlations* between change in DLco% and Hct and Hb

Time point	Hct r (P-value) n	Hb r (P-value) n
Week 24	-0.32 (P<0.0001); 152	-0.27 (P=0.0009); 153
Week 48	-0.32 (P<0.0001); 148	-0.25 (P=0.0019); 150

*Correlation coefficients are for all patients (pooled data from molgramostim and placebo groups)
Hct, hematocrit; Hb, hemoglobin; n, number of patients; r, Spearman's Rank correlation coefficient.

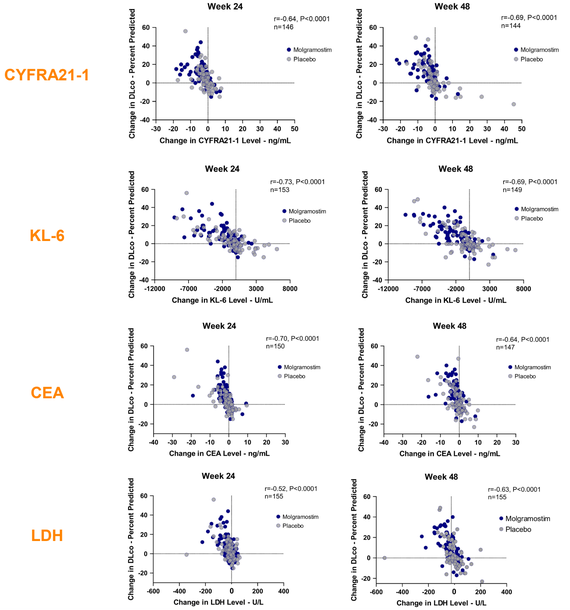
Results

Figure 2. LSM Change From Baseline in Biomarker Levels Over Time



CEA, carcinoembryonic antigen; CI, confidence interval; CYFRA21-1, cytokeratin 19 fragments; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LSM, least-squares mean; No., number.

Figure 3. Correlations Between Change from Baseline in DLco% and Biomarker Levels



CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragments; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; r, Spearman's Rank correlation coefficient.