

# Relationship Between Pulmonary Gas Transfer, Respiratory Health-related Quality of Life (HRQoL), Exercise Capacity, and Surfactant Burden in Autoimmune Pulmonary Alveolar Proteinosis (PAP)

Francesco Bonella,<sup>1</sup> Cormac McCarthy,<sup>2</sup> Yoshikazu Inoue,<sup>3,4</sup> Bruce C. Trapnell,<sup>5</sup> Brian Robinson,<sup>6</sup> Rosanna Fleming,<sup>6</sup> Yasmine Wasfi,<sup>6</sup> Raymond Pratt<sup>6</sup>

1. Center for Interstitial and Rare Lung Diseases, Pneumology Department, Ruhlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany; 2. School of Medicine, University College Dublin, St. Vincent's University Hospital, Elm Park, Dublin, Ireland; 3. Clinical Research Center, NHO Kinki Chuo Chest Medical Center, Osaka, Japan; 4. Internal Medicine, Osaka Anti-tuberculosis Association Osaka Fukujiji Hospital, Osaka, Japan; 5. Translational Pulmonary Science Center, Cincinnati Children's Hospital, Cincinnati, OH USA  
6. Savara Inc., Langhorne, PA USA

## OBJECTIVE

To evaluate the relationship between hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide (DLco%) and selected secondary/exploratory endpoints in IMPALA-2

## CONCLUSIONS

Changes in DLco% were significantly correlated with changes in measures of respiratory HRQoL (St. George's Respiratory Questionnaire [SGRQ]), patient functionality (exercise capacity), and surfactant burden (ground-glass opacity score)

Results indicate that changes in DLco% are associated with clinical outcomes and the extent of pulmonary pathology in patients with autoimmune PAP

### ACKNOWLEDGEMENTS

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- Disclosure: FB is an advisory board member and consultant to Savara Inc.

### REFERENCES

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## 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<sup>1-3</sup>
- Autoimmune PAP is caused by autoantibodies that block granulocyte-macrophage colony stimulating factor (GM-CSF) signaling, resulting in impaired surfactant clearance<sup>3</sup>
- 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 DLco% from baseline to week 24
- DLco% was chosen as the primary endpoint because it is a standardized measure of pulmonary gas transfer widely used in clinical practice.<sup>4</sup> In addition, changes in DLco% correlate with changes in autoimmune PAP disease severity (i.e., surfactant accumulation/burden)<sup>4-8</sup> and predict the need for whole-lung lavage<sup>9,10</sup>
- Post-hoc* correlation analyses of the IMPALA-2 data were conducted to evaluate the relationship between DLco% (a measure of pulmonary gas transfer) and measures of HRQoL, patient functionality, and surfactant burden in patients with autoimmune PAP

## Methods

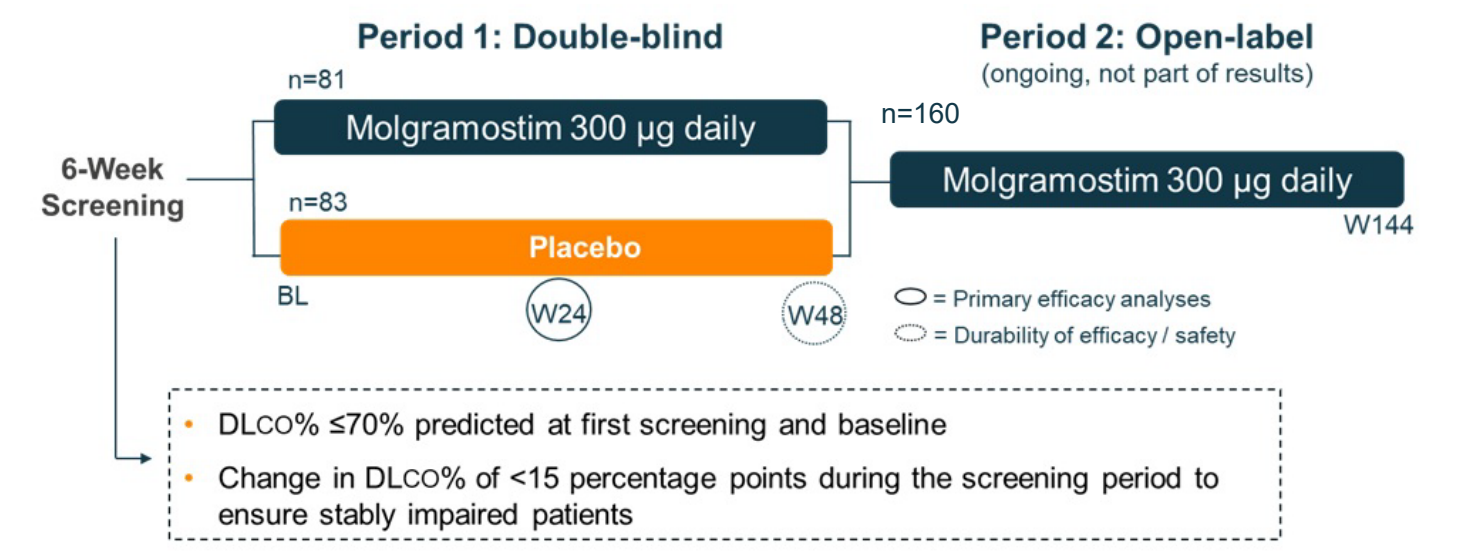
### Patients

- Adult patients with autoimmune PAP were required to have:
  - A positive 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 is a randomized, double-blind, placebo-controlled Phase 3 clinical trial being conducted at 43 clinical sites across 16 countries
- The trial consists of a 48-week double-blind intervention period followed by a 96-week open-label treatment period, which is currently ongoing (**Figure 1**)
- For the double-blind period, patients were randomly assigned, in a 1:1 ratio, to self-administer inhaled molgramostim 300 µg or matching placebo once daily using a proprietary nebulizer (eFlow® Nebulizer System, PARI)

**Figure 1. Study Design**



BL, Baseline; DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; W24, week 24; W48, week 48; W144, week 144.

### Endpoints

- Primary endpoint:
  - Change from baseline in DLco% at week 24
- Secondary endpoints:
  - 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

## Methods (cont.)

### Post-hoc Analyses

- Spearman's rank correlation coefficients were calculated for all patients between change from baseline in DLco% at 24 and 48 weeks and each of the following endpoints:
  - Change from baseline in SGRQ Total score
  - Change from baseline in SGRQ Activity score
  - Change from baseline in exercise capacity (peak METs)
  - Change from baseline in ground-glass opacity (GGO) score at 24 weeks only, which was an exploratory endpoint in the study

## Results

### Patients

- A total of 164 patients with autoimmune PAP underwent randomization; 81 were assigned to receive molgramostim and 83 to receive placebo
- Baseline demographic and clinical characteristics were similar between treatment groups (**Table 1**)

**Table 1. Baseline Demographic and Clinical Characteristics**

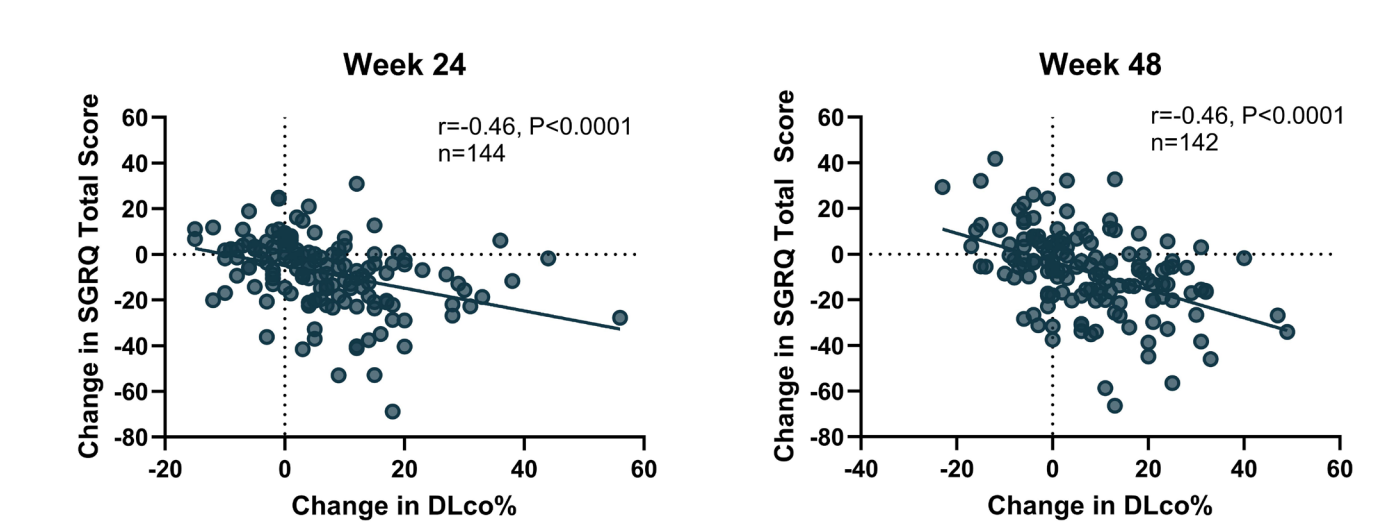
		Molgramostim n=81	Placebo n=83	Total N=164
Age years	Mean (SD)	50.8 (13.0)	48.4 (12.7)	49.6 (12.9)
	Range	20-80	21-79	20-80
Sex n (%)	Male	44 (54.3)	54 (65.1)	98 (59.8)
	Female	37 (45.7)	29 (34.9)	66 (40.2)
Race n (%)	White	38 (46.9)	40 (48.2)	78 (47.6)
	Asian	36 (44.4)	37 (44.6)	73 (44.5)
	Black or African American	3 (3.7)	2 (2.4)	5 (3.0)
	Other	4 (4.9)	4 (4.8)	8 (4.9)
DLco%	Mean (SD)	52.6 (11.7)	52.6 (10.4)	52.6 (11.0)
	Median	54	55	55
	Range	25-72	28-71	25-72

DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; n, number; SD, standard deviation.

### DLco% is Correlated with Respiratory HRQoL

- Respiratory HRQoL was measured using the SGRQ
- SGRQ scores range from 0 to 100, with higher scores indicating poorer HRQoL and reductions in SGRQ score indicating improvement in HRQoL
- Significant negative correlations were observed between change from baseline in DLco% and change from baseline in SGRQ Total score at week 24 ( $r=-0.46$ ,  $P<0.0001$ ;  $n=144$ ) and at week 48 ( $r=-0.46$ ,  $P<0.0001$ ;  $n=142$ ) (**Figure 2**)
- Similarly, significant negative correlations were observed between changes from baseline in DLco% and SGRQ Activity score at week 24 ( $r=-0.46$ ,  $P<0.0001$ ;  $n=144$ ) and at week 48 ( $r=-0.48$ ,  $P<0.0001$ ;  $n=142$ ) (**Figure 3**)

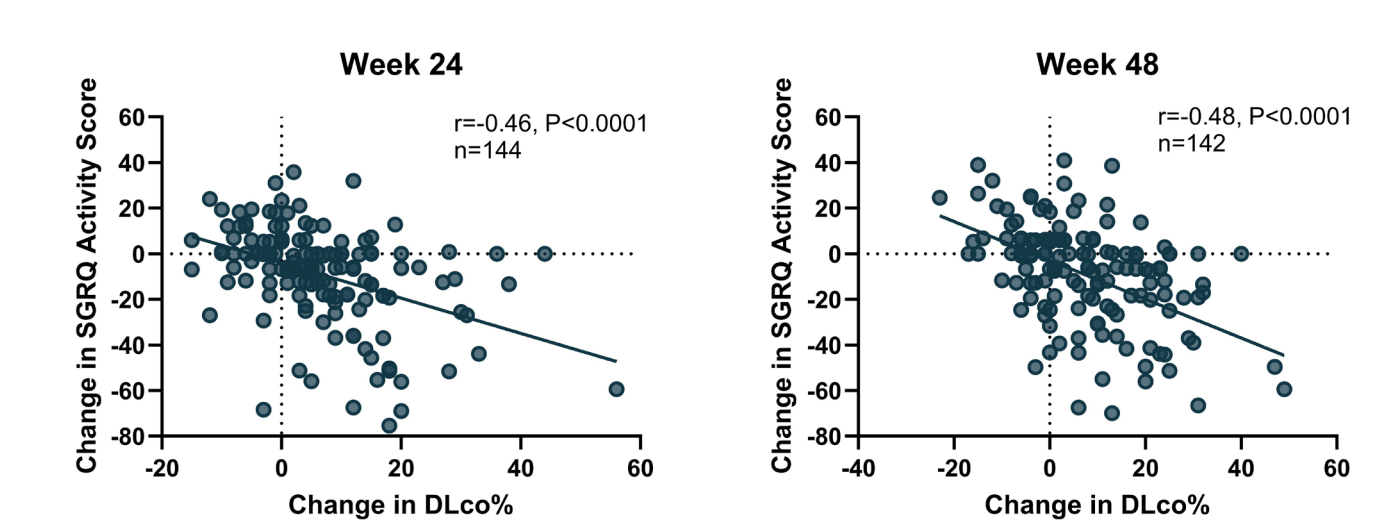
**Figure 2. SGRQ Total Score**  
Changes from Baseline in DLco% and SGRQ Total Score



DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; n, number; r, Spearman's rank correlation coefficient; SGRQ, St. George's Respiratory Questionnaire.

## Results (cont.)

**Figure 3. SGRQ Activity Score**  
Changes from Baseline in DLco% and SGRQ Activity Score

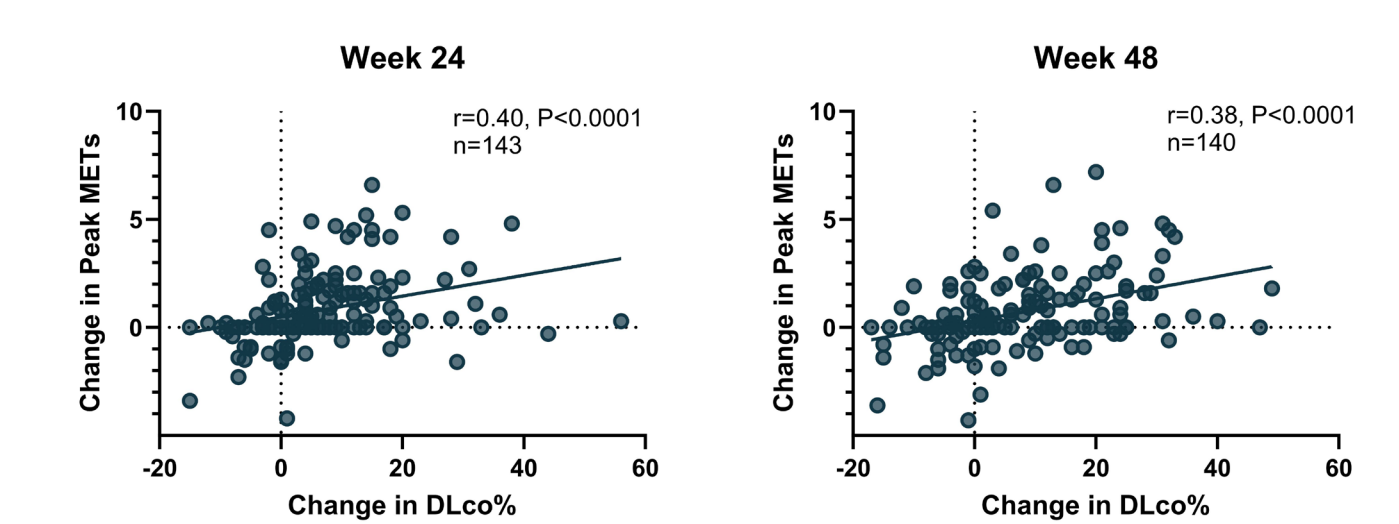


DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; n, number; r, Spearman's rank correlation coefficient; SGRQ, St. George's Respiratory Questionnaire.

### DLco% is Correlated with Patient Functionality

- Exercise capacity was measured using a treadmill test and reported as peak METs reflecting changes in oxygen consumption; higher peak MET values indicate greater patient functionality
- Significant positive correlations were observed between change from baseline in DLco% and change from baseline in peak METs at week 24 ( $r=0.40$ ,  $P<0.0001$ ;  $n=143$ ) and at week 48 ( $r=0.38$ ,  $P<0.0001$ ;  $n=140$ ) (**Figure 4**)

**Figure 4. Exercise Capacity**  
Changes from Baseline in DLco% and Peak METs

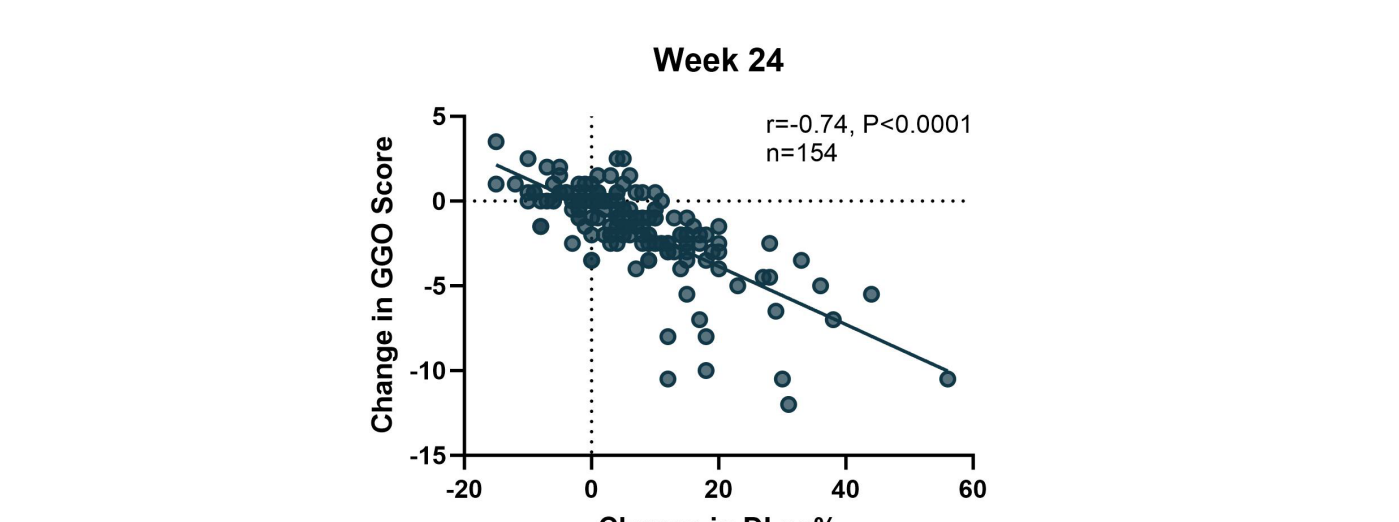


DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; METs, metabolic equivalents; n, number; r, Spearman's rank correlation coefficient.

### DLco% is Correlated with Surfactant Burden

- GGO score, a measure of surfactant accumulation/burden, was determined from a chest CT scan by two radiologists blinded to treatment
- GGO scores range from 0 to 15, with higher scores indicating greater surfactant burden
- A significant negative correlation was observed between change from baseline in DLco% and change from baseline in GGO score at week 24 ( $r=-0.74$ ,  $P<0.0001$ ;  $n=154$ ) (**Figure 5**)

**Figure 5. GGO Score**  
Changes from Baseline in DLco% and GGO Score



DLco% hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; GGO, ground-glass opacity; n, number; r, Spearman's rank correlation coefficient.