

# Inhaled Molgramostim Improves Pulmonary Gas Exchange and Respiratory Health-Related Quality of Life in Patients with Autoimmune Pulmonary Alveolar Proteinosis: Results from IMPALA-2

Cormac McCarthy, MD, PhD, FRCPI

UCD School of Medicine

St Vincent's University Hospital, Dublin 4, Ireland

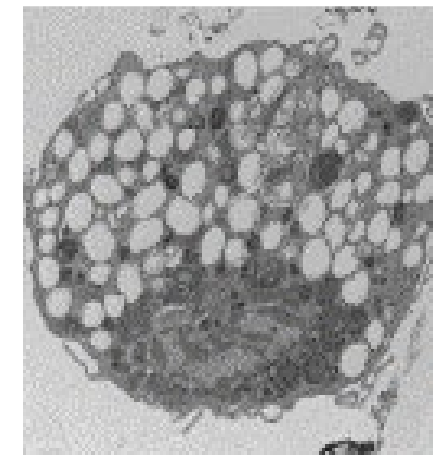
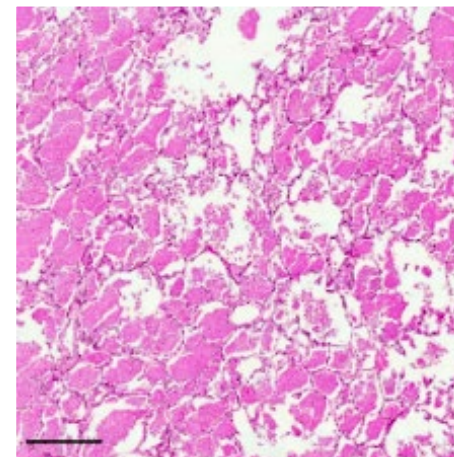
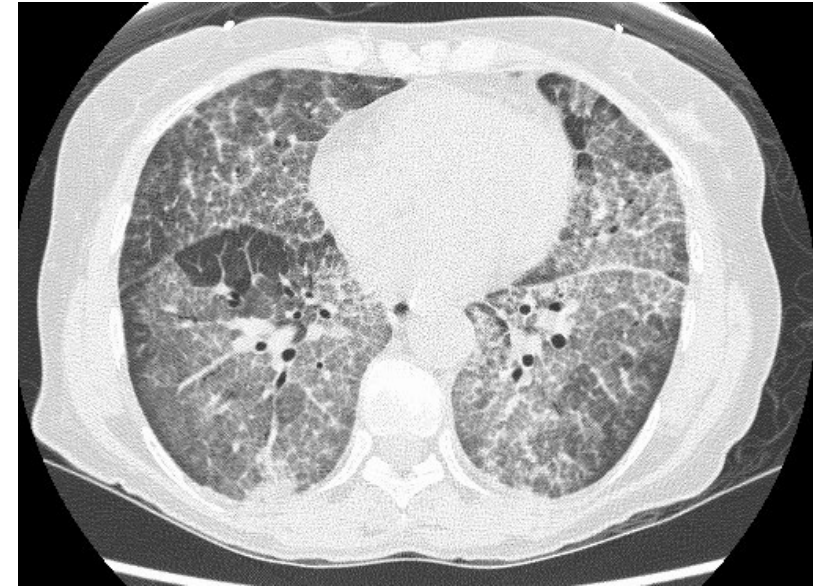
# Disclosures

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- Savara Inc., Scientific Advisory Board and Consultancy
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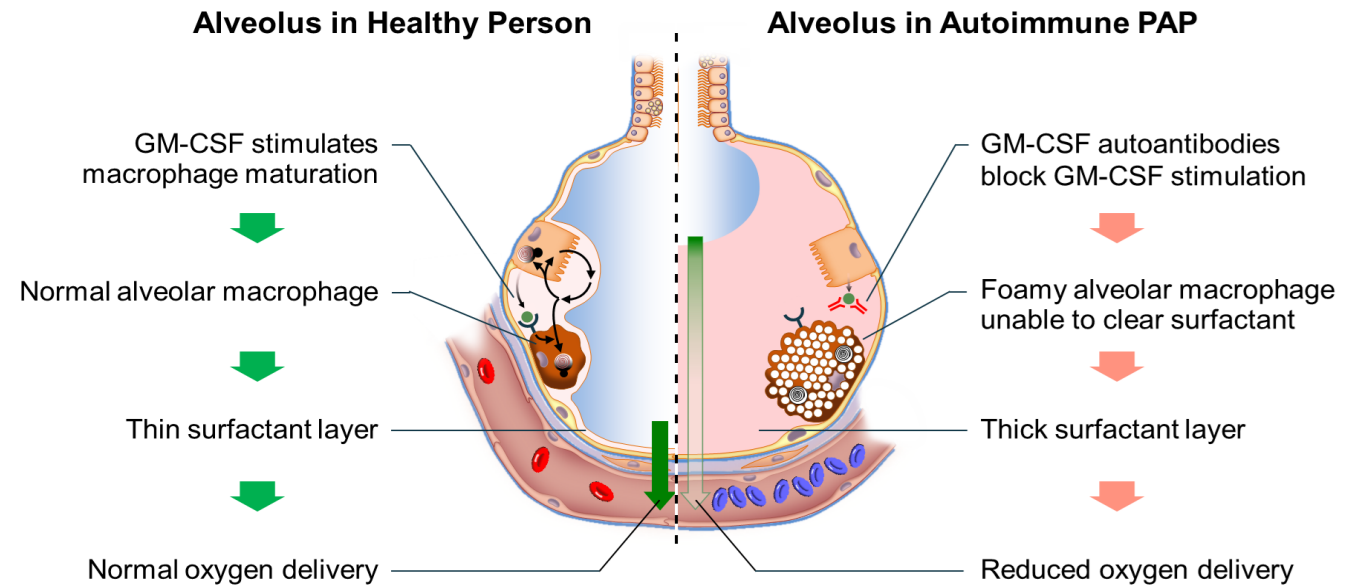
# Pulmonary Alveolar Proteinosis (PAP)

- Rare syndrome, not a specific disease
- Characterised by progressive accumulation of alveolar surfactant
- Foamy lipid-laden alveolar macrophages
- Restrictive lung impairment, hypoxic respiratory insufficiency, and, in severe cases, respiratory failure and death



# Autoimmune PAP (aPAP)

- aPAP is caused by autoantibodies to GM-CSF<sup>1,2</sup>
- The prevalence of aPAP is 6 to 27 per 1 million in the general population<sup>3-5</sup>
- Accounts for 90% of all PAP cases<sup>3</sup>
- Molgramostim inhalation solution is a form of recombinant GM-CSF
  - Administered using a proprietary investigational eFlow® Nebulizer System (PARI)
- Molgramostim is being evaluated for the treatment of aPAP in the IMPALA-2 Phase 3 clinical trial



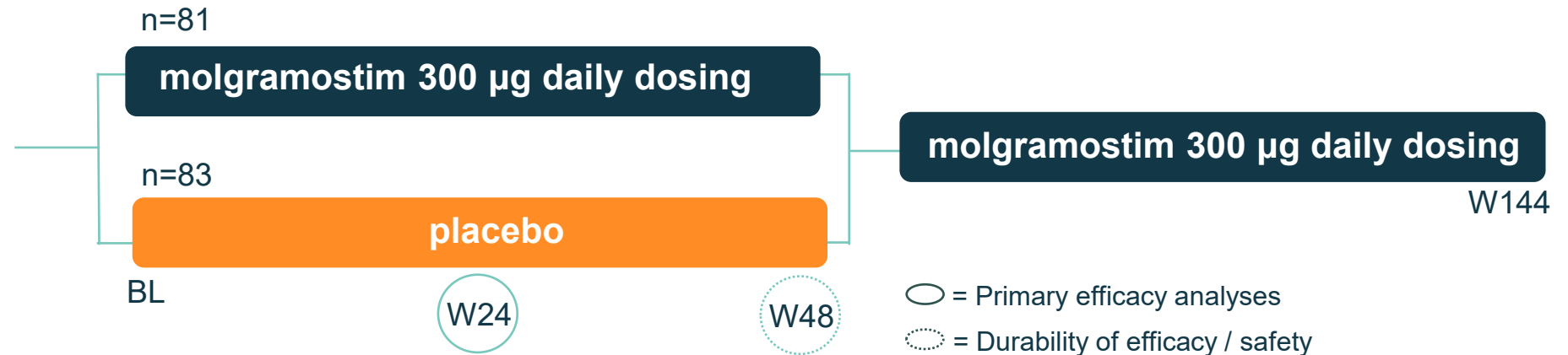
# Phase 3 IMPALA-2 Trial Design

## Period 1: Double-blind

## Period 2: Open-label (ongoing, not part of results)

### 6-Week Screening

- DLco%  $\leq 70\%$  predicted at first screening and baseline
- Change in % predicted DLco%  $< 15\%$  points to ensure stably impaired patients



### PRIMARY ENDPOINT

- Change from baseline in DLco% at W24

### SECONDARY ENDPOINTS

Change from baseline in:

- DLco% at W48
- SGRQ Total Score at W24 and W48
- SGRQ Activity Score at W24 and W48
- Exercise Capacity at W24 and W48

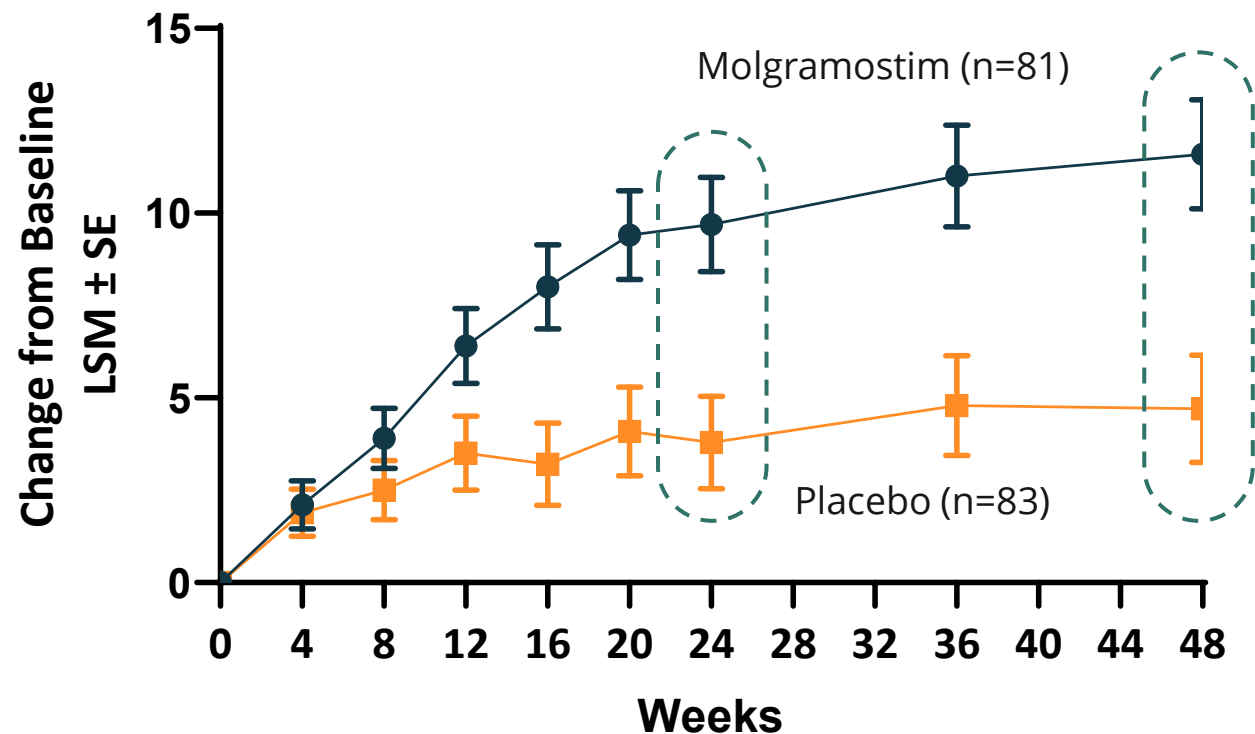
# IMPALA-2: Baseline Clinical Characteristics

		Molgramostim N=81	Placebo N=83
<b>DLco%</b>	Mean (SD)	52.6 (11.7)	52.6 (10.4)
	Median	54	55
	Range	25-72	28-71
<b>SGRQ Total Score*</b>	Mean (SD)	39.5 (19.2)	41.2 (18.1)
	Median	42.2	44.0
	Range	0-87	2-84
<b>Exercise Capacity Peak METs<sup>†</sup></b>	Mean (SD)	7.1 (2.2)	7.2 (2.1)
	Median	7.3	7.6
	Range	2.6-9.8	2.5-9.8
<b>Disease Severity Score (DSS), n (%)</b>	DSS 1 (Mild)	12 (15.6)	16 (19.5)
	DSS 2	30 (39.0)	35 (42.7)
	DSS 3	25 (32.5)	19 (23.2)
	DSS 4	9 (11.7)	9 (11.0)
	DSS 5 (Severe)	1 (1.3)	3 (3.7)
	Total	77 (100)	74 (100)

\*n=74, molgramostim; n=78, placebo. <sup>†</sup>n=78, molgramostim; n=82, placebo. DLco%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; METs, metabolic equivalents; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

# IMPALA-2 Results: Molgramostim Improves Pulmonary Gas Transfer

## DLco%



	LSM Change from Baseline	Between-group LSM difference*	P-value
Week 24	Mol: 9.8 Pbo: 3.8	6.00	0.0007
Week 48	Mol: 11.6 Pbo: 4.7	6.90	0.0008

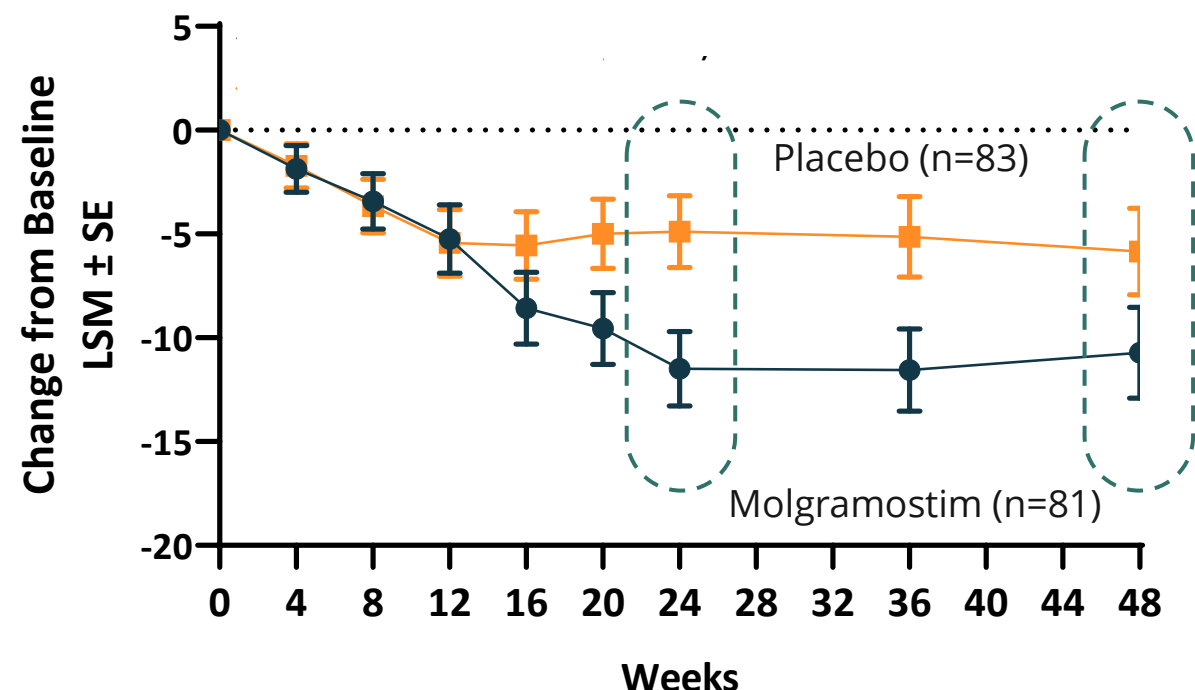
**Absolute mean DLco% increased from 52.6 at Baseline to 64.8 at 48 weeks in the molgramostim group and from 52.6 to 56.5 in the placebo group**

\*Mean change from baseline compared with placebo. P-values are for difference in LSM compared with placebo and met the threshold required in the pre-specified hierarchical testing procedure to control the overall Type 1 error rate at 0.05.

DLco%, hemoglobin-adjusted percent predicted diffusing capacity of the lungs for carbon monoxide; LSM, least squares mean; Mol, molgramostim; Pbo, placebo; SE, standard error.

# IMPALA-2 Results: Molgramostim Improves Respiratory Health-Related Quality of Life

## SGRQ Total Score



	LSM Change from Baseline	Between-group LSM difference*	P-value
Week 24	Mol: -11.5 Pbo: -4.9	-6.59	0.0072 <sup>†</sup>
Week 48	Mol: -10.7 Pbo: -5.9	-4.87	0.1046

**Absolute mean SGRQ Total Score decreased from 39.5 at Baseline to 29.4 at 48 weeks in the molgramostim group and from 41.2 to 35.9 in the placebo group**

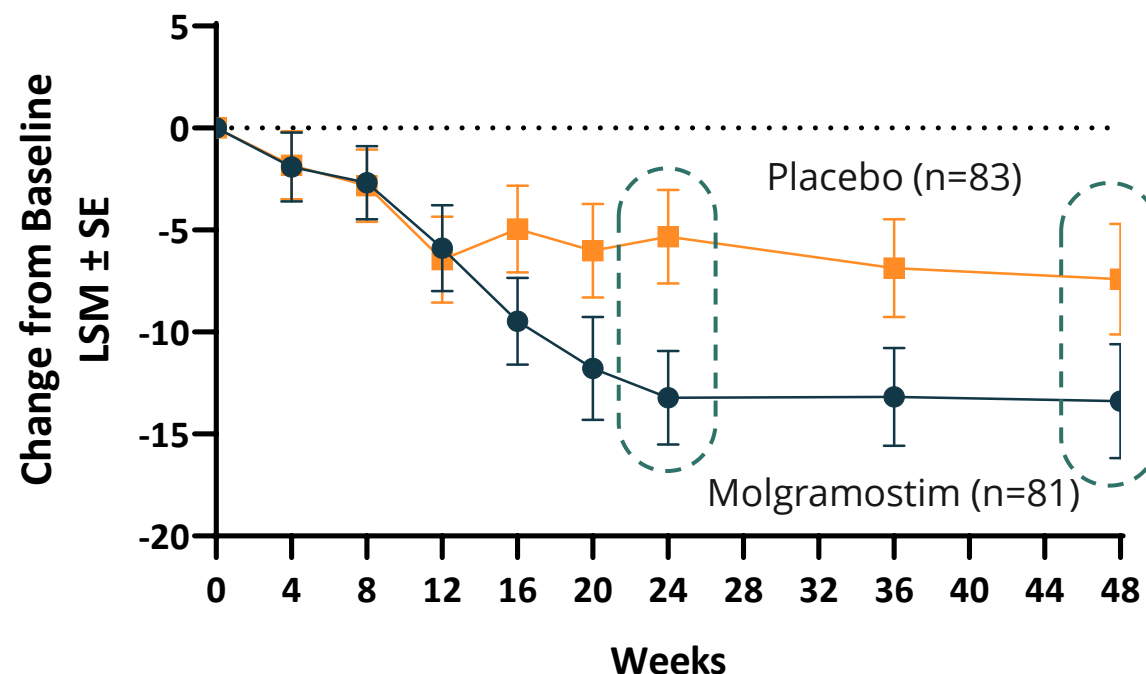
\*Mean change from baseline compared with placebo. P-values are for difference in LSM compared with placebo. <sup>†</sup>Statistically significant: met the threshold required in the pre-specified hierarchical testing procedure to control the overall Type 1 error rate at 0.05.

HRQoL, health-related quality of life; LSM, least squares mean; Mol, molgramostim; Pbo, placebo; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.



# IMPALA-2 Results: Molgramostim Improves Respiratory Health-Related Quality of Life

## SGRQ Activity Score



	LSM Change from Baseline	Between-group LSM difference*	P-value
Week 24	Mol: -13.0 Pbo: -5.2	-7.81	0.0149 <sup>†</sup>
Week 48	Mol: -13.4 Pbo: -7.4	-5.99	0.1216

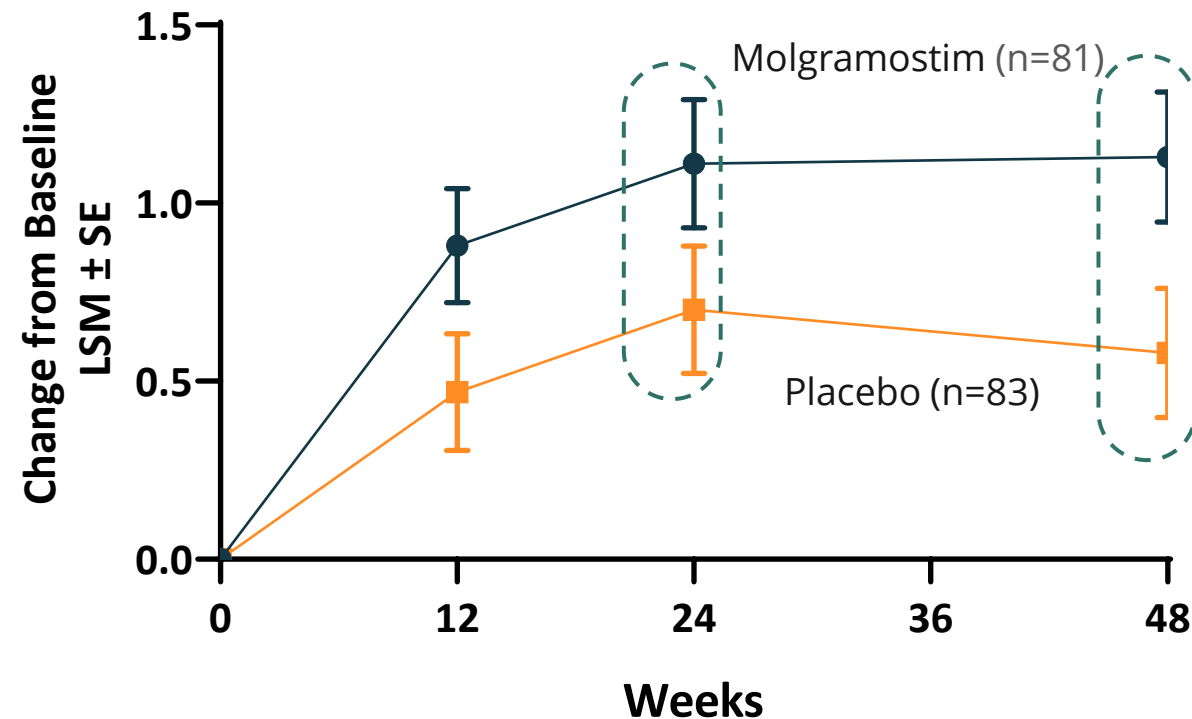
**Absolute mean SGRQ Activity Score decreased from 54.6 at Baseline to 41.9 at 48 weeks in the molgramostim group and from 57.8 to 51.0 in the placebo group**

\*Mean change from baseline compared with placebo. P-values are for difference in LSM compared with placebo. <sup>†</sup>P-value nominally significant: P-value ≤0.05 but did not meet the p-value threshold required in the pre-specified hierarchical testing procedure.

HRQoL, health-related quality of life; LSM, least squares mean; Mol, molgramostim; Pbo, placebo; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

# IMPALA-2 Results: Molgramostim Improves Patient Function

## Peak Exercise Capacity (METs)



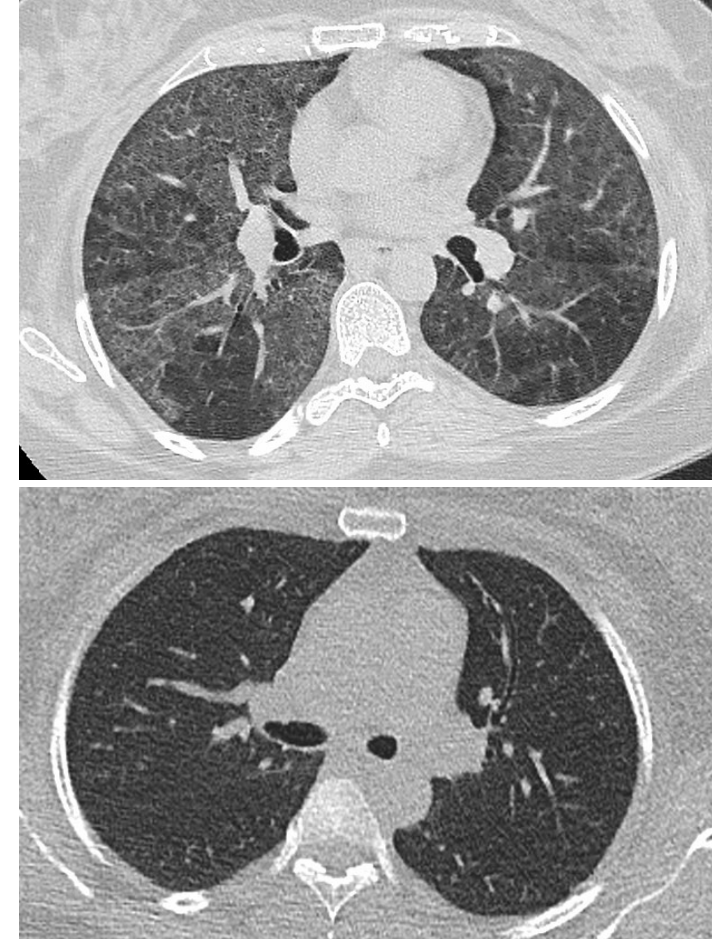
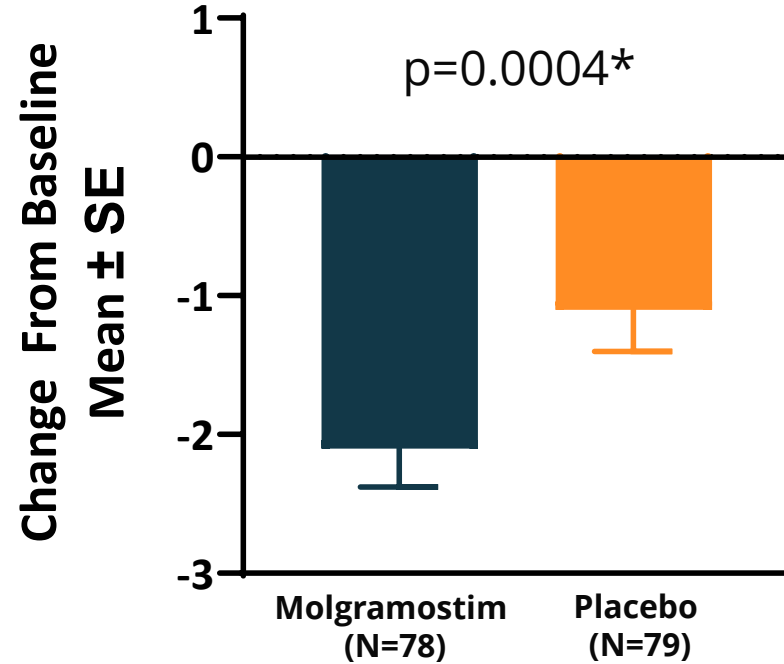
	LSM Change from Baseline	Between-group LSM difference*	P-value
Week 24	Mol: 1.11 Pbo: 0.70	0.41	0.0845
Week 48	Mol: 1.13 Pbo: 0.58	0.55	0.0234†

**Absolute mean METs increased from 7.1 at Baseline to 8.2 at 48 weeks in the molgramostim group and from 7.2 to 7.7 in the placebo group**

\*Mean change from baseline compared with placebo. P-values are for difference in LSM compared with placebo. †P-value nominally significant: P-value  $\leq 0.05$  but did not meet the p-value threshold required in the pre-specified hierarchical testing procedure. LSM, least squares mean; MET, metabolic equivalent; Mol, molgramostim; Pbo, placebo; SE, standard error.

# IMPALA-2 Results: Molgramostim Reduces Pulmonary Surfactant Burden

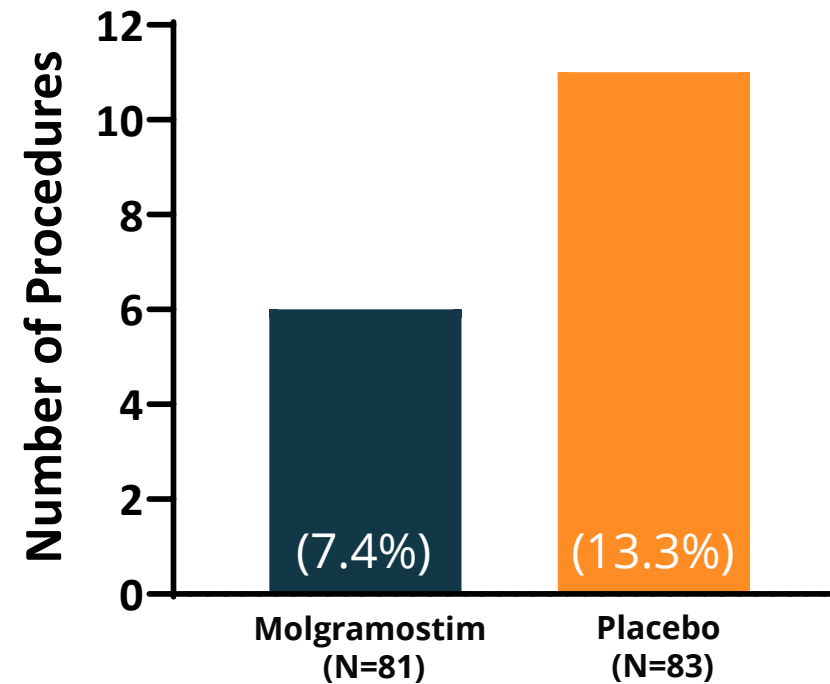
## Ground Glass Opacity Score (Week 24)



\*P-value based on post-hoc analysis. GGO, ground glass opacity.

# IMPALA-2 Results: Molgramostim Reduces Pulmonary Surfactant Burden

## Rescue WLL Use (entire 48-week period)



# IMPALA-2 Results: Molgramostim Is Well Tolerated

## Adverse events (AEs)

### AEs during the double-blind treatment period

Treatment-Emergent Adverse Event	Molgramostim N=81 n (%)	Placebo N=83 n (%)
Any adverse event	69 (85)	71 (86)
Severe adverse events	13 (16)	16 (19)
Treatment related	20 (25)	16 (19)
Serious adverse events	14 (17)	20 (24)
Not treatment related	13 (16)	20 (24)
Treatment related*	1 (1)	0
Leading to death	0	0
Leading to drug discontinuation	2 (2)	1 (1)
Special interest	9 (11)	6 (7)
Serious special interest	0	1 (1)

### AEs in >10% of patients in any treatment arm during the double-blind treatment period

Treatment-Emergent Adverse Event	Molgramostim N=81 n (%)	Placebo N=83 n (%)
Most common		
COVID-19	18 (22)	8 (10)
Cough	17 (21)	18 (22)
Pyrexia	11 (14)	9 (11)
Nasopharyngitis	11 (14)	7 (8)
Arthralgia	9 (11)	7 (8)
Headache	9 (11)	7 (8)
Diarrhea	9 (11)	2 (2)
Alveolar proteinosis	4 (5)	12 (14)

**97% of Patients Completed the Double-Blind Treatment Period**

\*Serious adverse event of delusions resulting in psychiatric hospitalization in patient with a past medical history of seizure disorder treated with levetiracetam, which is labeled for psychiatric side effects, including delusions; the event was assessed as possibly related to study drug by the investigator.

# IMPALA-2: Conclusions

- Largest and longest controlled trial of inhaled GM-CSF therapy for aPAP ever conducted
- Improvement in DLCO% demonstrated
- Achieved improvement in multiple secondary and exploratory endpoints
  - Pulmonary surfactant burden
  - Pulmonary gas exchange
  - Quality of life
  - Exercise capacity
- Molgramostim was well-tolerated with a favorable risk-benefit profile
  - 97% of patients completed the entire blinded treatment period

# Questions