

# Developing New Therapies for Rare Respiratory Diseases

July 2024



#### Safe Harbor Statement

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Please note that molgramostim is an investigational product that has not been approved for sale or determined to be safe or effective by the U.S. Food & Drug Administration or any regulatory authority.

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### **Executive Leadership Team**

Matthew Pauls, J.D., M.B.A.

**Chair & Chief Executive Officer** 

Anne Erickson
Chief Business Officer

Dave Lowrance
Chief Financial & Administrative Officer

Rob Lutz, M.B.A.

Chief Operating Officer

Ray Pratt, M.D. FACP Chief Medical Officer

Scott Wilhoit EVP, Global Commercial

Yasmine Wasfi, M.D., Ph.D. SVP, Head of Clinical Development

Sid Advant, Ph.D. *EVP, Global Technical Operations* 



#### **Investment Thesis**



#### **Successful Pivotal Phase 3 Program in aPAP**

- Molgramostim achieved statistical significance on primary endpoint and multiple secondary endpoints in IMPALA-2 trial
- Favorable safety profile observed from the first and second IMPALA trials
- BLA submission expected to be complete 1H 2025



#### Strong global commercial opportunity

- Significant unmet need
- Claims dataset estimate indicates ~5,000 U.S. patients
- Chronic dosing expected
- Assumed pricing power consistent with orphan drug analogs (i.e., in U.S. ~\$300-\$500K p/patient, p/year)



#### As a novel inhaled biologic, molgramostim has:

- 12-year biologic exclusivity in U.S. upon approval
- Potential for a long-term, durable revenue stream with biosimilar competition unlikely



# aPAP and Molgramostim

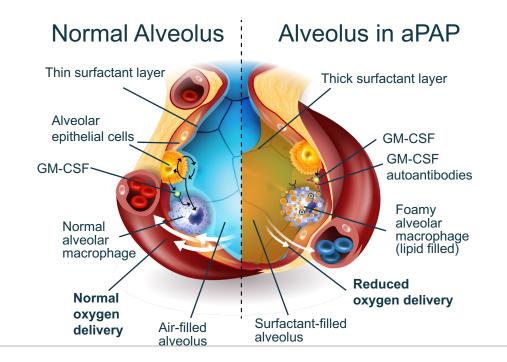


## aPAP: An Autoimmune Disease of Alveolar Macrophage Dysfunction

#### NORMAL LUNG FUNCTION

Alveoli need surfactant to keep from collapsing

**GM-CSF** is critical for alveolar macrophage function and allows for alveolar surfactant homeostasis, structure, function, and host defense

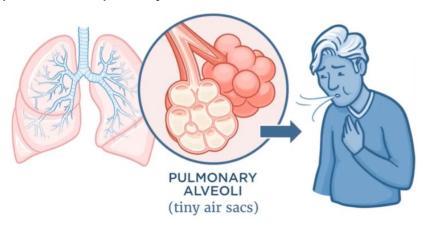




Rare lung disease caused by GM-CSF autoantibodies which block GM-CSF signaling and reduce surfactant clearance. This results in:

Surfactant accumulation that blocks movement of oxygen from the alveoli into the blood

Reduced blood oxygenation results in difficulty breathing and, ultimately, hypoxemic respiratory failure





## aPAP is a Rare, Long-Term, Chronic Disease

# **Progressive Shortness of Breath**

- Gas exchange in the lungs is impaired and patients may experience shortness of breath
- At first it occurs upon exertion, but as disease progresses, it can occur even when a person is at rest

# Cough and Episodes of Fever

 Cough, sputum production, and episodes of fever, especially if secondary lung infection develops

# Fatigue, Decreased Exercise Tolerance

 Fatigue and significantly reduced exercise capacity can dramatically impact the simplest of daily activities, e.g., getting winded walking up a flight of stairs

# Fibrosis and Lung Transplant

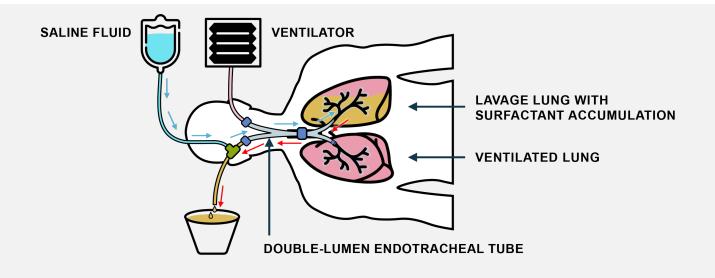
 In the long-term, the disease can lead to serious complications, including fibrosis, and may lead to the need for lung transplantation



There are no approved drugs for the treatment of aPAP. Only option is a lung lavage, an invasive procedure.



- A lung lavage physically removes excess surfactant from the lungs and requires hospitalization
- Performed under general anesthesia
- Unavailable at many medical institutions



A Lung Lavage is an Invasive Procedure Performed in a Tertiary Center and is Not Standardized



Requires insertion of doublelumen endobronchial tube for lung separation Treated lung is repeatedly filled with up to 15-50L of saline and then drained by gravity

Patient is percussed to emulsify the surfactant sediment

Saline is drained by gravity and continued until lavage fluid becomes clear

Sources: 1: Campo, Assessment and Management of PAP in a Reference Center, Orphanet Jour. of Rare Dis., 2013; 2: Campo, Nat. History of PAP Data from Italian Nat. Reference Center, ERJ, 2019.; Seymour, J. J. Pulmonary alveolar proteinosis: Progress in the First 44 Years, Am. J. Respir Crit. Care Med, 2002. 3: Udwadia, Jain. NEJM (2007) 357:19, 4 McCarthy, Autoimmune Pulmonary Alveolar Proteinosis, Amer. Journal of Respiratory and Critical Care Med., 2022.



# Unmet Need: aPAP Patients Have Significantly Higher Rates of Healthcare Utilization and Comorbidities<sup>1</sup>



Charlson
Comorbidity Index
(CCI)\*

3.5x Vs. matched controls

**PAP:** 1.84 ± 2.48

Age and Gender Matched Controls:  $0.55 \pm 1.44$ 

**P value: <0.0001** 

\*Developed to classify comorbid conditions which may influence mortality risk. Most widely used comorbidity index used to determine survival rates in patients with multiple comorbidities.



Outpatient visits

(~17 per year)



**PAP:** 17.30 ± 13.77

Age and Gender Matched Controls: 10.40 ± 11.38

**P value: <0.01** 



#### **Emergency Room Visits**

(~1.5 per year)

+38%
Vs.
matched
controls

**PAP:** 1.49 ± 1.17

Age and Gender Matched Controls:  $1.08 \pm 0.27$ 

P value: 0.014



Longer hospital stays

(~16 days per year)



**PAP:** 15.96 ± 20.71

Age and Gender Matched Controls:  $5.40 \pm 5.07$ 

P value: 0.027



# Savara Investigational Drug-Device Treatment for aPAP

- Once daily 300 μg inhaled molgramostim
- Proprietary eFlow<sup>®</sup> Nebulizer System (PARI)
  - Optimized for molgramostim administration
  - Well-established manufacturer of devices used for inhalation therapy
  - 5 FDA approved nebulizers based on eFlow<sup>®</sup> Technology





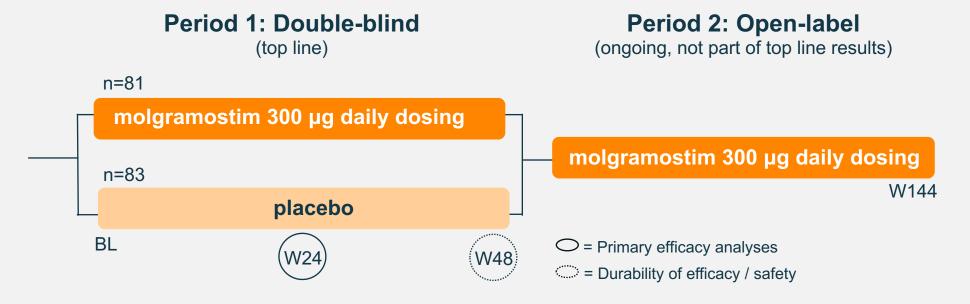
# **IMPALA-2 Top Line Results**



## Phase 3 IMPALA-2 Trial Design

#### 6-Week Screening

- DLCO ≤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

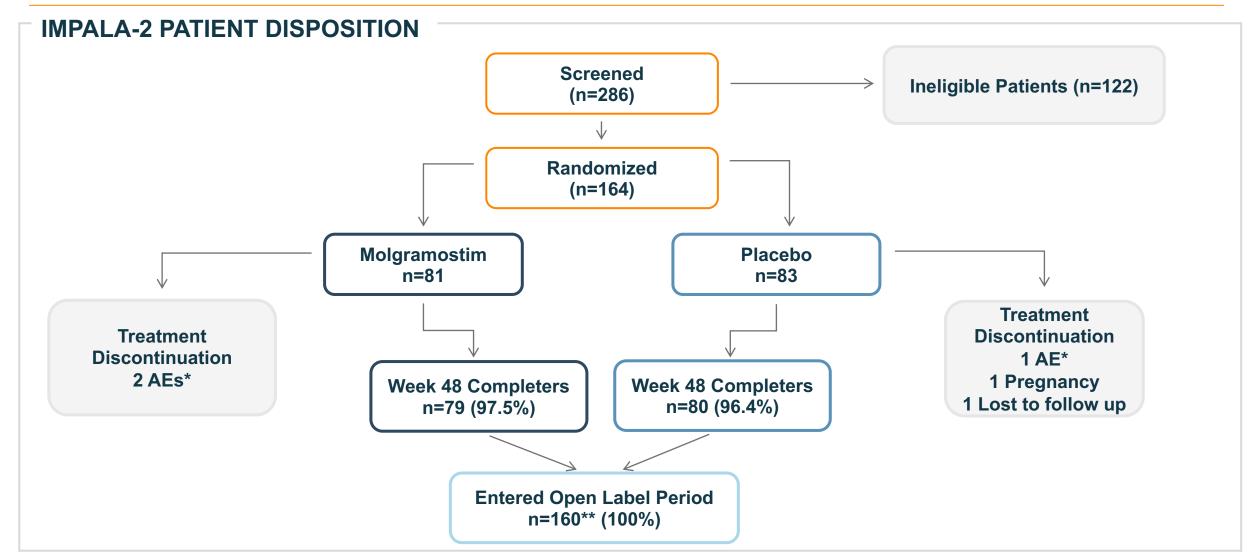
#### **SECONDARY ENDPOINTS**

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 48



# Discontinuations in Double-Blind Period Were Low: 3% Participation in Open Label Period Was High: 100% of Double-Blind Period Completers



<sup>\*</sup>Not considered trial drug related



<sup>\*\*</sup>One placebo patient stopped blinded trial drug but continued trial participation through Week 48 and entered the open label period

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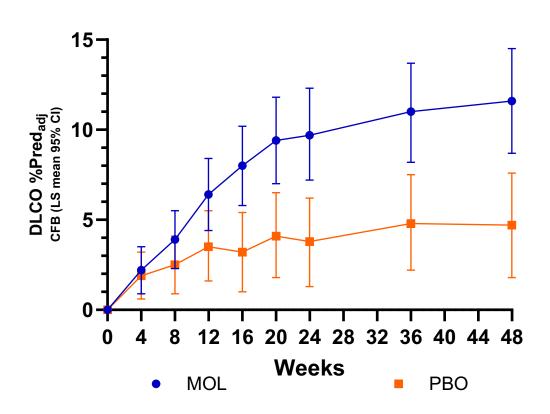
## **Demographics Were Well-Balanced Across Treatment Groups**

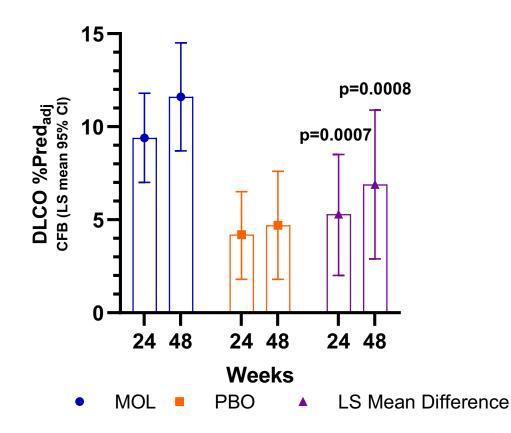
		Molgramostim N=81	Placebo N=83
Age years	Mean (SD)	50.8 (13.03)	48.4 (12.69)
Sex n (%)	Male Female	44 (54.3) 37 (45.7)	54 (65.1) 29 (34.9)
Race n (%)	White Asian Black or African American Other	38 (46.9) 36 (44.4) 3 (3.7) 4 (4.9)	40 (48.2) 37 (44.6) 2 (2.4) 4 (4.8)
DLCO at baseline	Mean (SD)	52.6 (11.71)	52.6 (10.39)
DLCO stratification group	≤ 50% > 50%	31 (38.3) 50 (61.7)	32 (38.6) 51 (61.4)



## **Primary Endpoint Met**

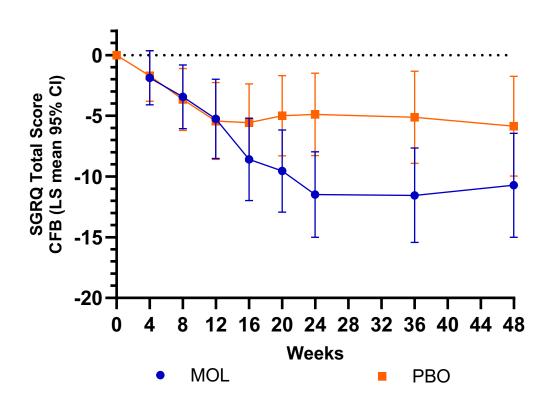
Molgramostim Superior to Placebo on Change From Baseline in DLCO at W24 (Primary Endpoint) and W48 (Secondary Endpoint)

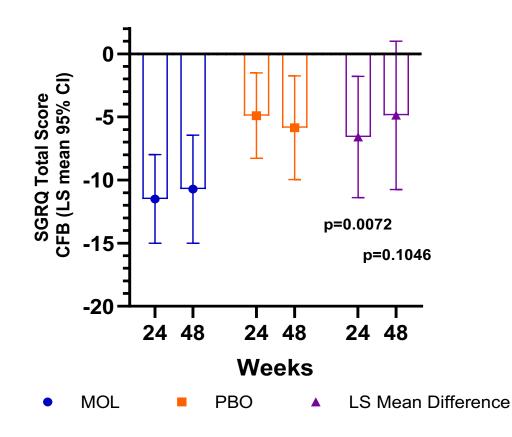






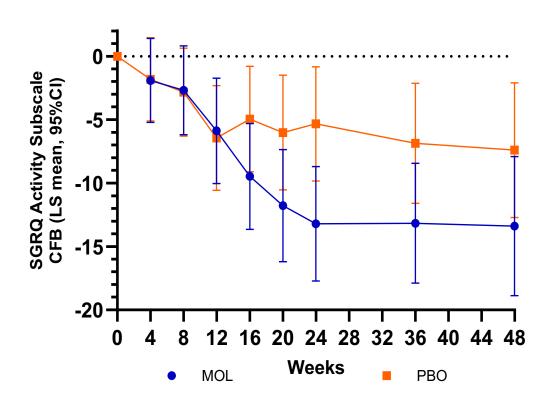
# Molgramostim Superior to Placebo on Change From Baseline in SGRQ Total Score at W24, Favorability Continues Through W48

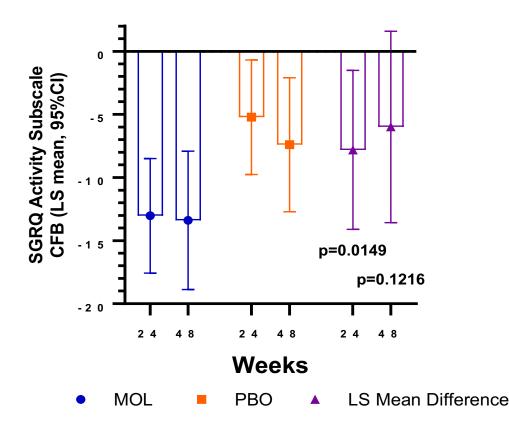






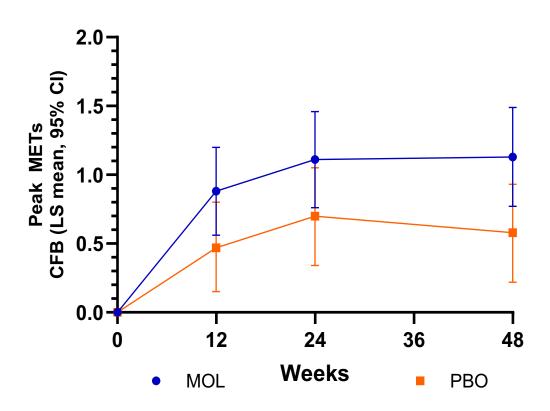
# Molgramostim Nominally Significant on Change From Baseline in SGRQ Activity Score at W24, Favorability Continues Through W48

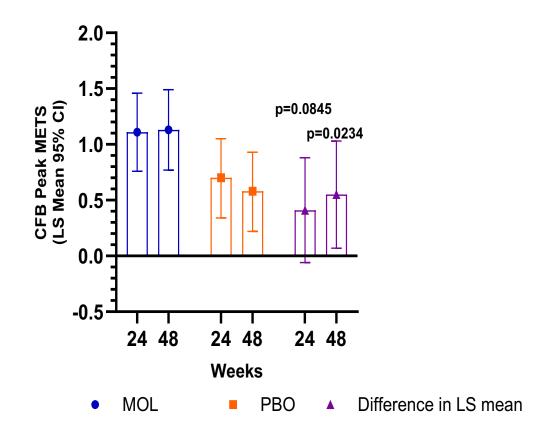






# Molgramostim Nominally Significant on Change From Baseline in Exercise Capacity (Peak METs) at W48







## Lung Lavage Was Permitted as a Rescue Therapy During the Trial

#### **During 48-week double-blind period**

- 17 (~10%) patients underwent at least one lung lavage
  - Molgramostim: n=6 (7.4%)
  - Placebo: n=11 (13.3%)



## IMPALA-2 Safety Summary: Molgramostim Was Well-Tolerated

Treatment Emergent Adverse Events	Molgramostim N=81 n (%)	Placebo N=83 n (%)
Any	69 (85)	71 (86)
Severe	13 (16)	16 (19)
Treatment related	20 (25)	16 (19)
Serious	14 (17)	20 (24)
Not treatment related	13 (16)	20 (24)
Treatment related <sup>1</sup>	1 (1)	0
Leading to death	0	0
Leading to trial drug discontinuation	2 (2)	1 (1)
Special interest (chest pain, hypersensitivity)	9 (11)	6 (7)
Serious and of special interest	0	1 (1)

<sup>&</sup>lt;sup>1</sup>SAE 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 Safety Summary: Most Common Adverse Events**

# ADVERSE EVENTS IN >10% OF PATIENTS IN ANY TREATMENT ARM DURING DOUBLE-BLIND TREATMENT PERIOD

Treatment Emergent Adverse Events	Molgramostim (N=81) n (%)	Placebo (N=83) n (%)
Any	69 (85)	71 (86)
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)
Treatment related	20 (25)	16 (19)



# Regulatory and Intellectual Property



# 1H 2025: BLA Submission Expected to be Complete

#### MOLGRAMOSTIM IN aPAP REGULATORY DESIGNATIONS

- Orphan Drug Designation, Europe (eligible for 10 years exclusivity)
- Orphan Drug Designation, U.S. (eligible for 7 years exclusivity)
- Fast Track Designation, U.S.
- Breakthrough Therapy Designation, U.S.
- Innovation Passport Designation, U.K.
- Promising Innovative Medicine Designation, U.K.

#### **IMPALA-2**

 Trial design endorsed by regulatory authorities in the U.S., Canada, Japan, South Korea, Australia, U.K., and countries in Europe where the trial is being conducted

#### **BIOLOGIC EXCLUSIVITY**

 Upon Biologics License Application (BLA) approval FDA would grant 12 years marketing exclusivity

#### INTELLECTUAL PROPERTY

- Pending patent applications for molgramostim drug formulation and methods of use including treating aPAP with molgramostim
- Worldwide exclusive license to proprietary eFlow<sup>®</sup> Nebulizer System (PARI) for molgramostim in aPAP and pending joint patent application with PARI for the drug/device combination
- Proprietary cell bank for molgramostim



# **Commercial Outlook**



## aPAP Diagnosed Prevalence Before and After Broad Availability of **GM-CSF Autoantibody Testing**

Current **Diagnosed Prevalence GM-CSF** 

**Before Broad Autoantibody Testing** 

**Diagnosed Prevalence After Broad GM-CSF Autoantibody Testing** 

Published aPAP Epidemiology Studies				
REFERENCE	METHODOLOGY	INCIDENCE PER MILLION	DIAGNOSED PREVALENCE PER MILLION	
DIAGNOSED PREVALENCE				
Inoue 2008	Registry based in Niigata, Japan	<b>0.48</b> (0.23-1.00)	<b>6.2</b> (3.8-10.3)	
McCarthy 2018	US insurance claims data, 2008-2012	Not reported	<b>6.3</b> (5.2-7.6)	
REFERENCE	METHODOLOGY	INCIDENCE PER MILLION	DIAGNOSED PREVALENCE PER MILLION	
DIAGNOSED PREVALENCE				
Kitamura 2019	Update of Niigata registry	<b>1.66</b> (1.2-2.2)	<b>26.6</b> (9.0-73.0)	
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IMPLIED US PATIENTS	IMPLIED EU PATIENTS	IMPLIED JAPAN PATIENTS	TOTAL IMPLIED PATIENTS
~2,058	~2,325	~775	~5,158
~2,092	~2,363	~788	~5,243

IMPLIED US PATIENTS	IMPLIED EU PATIENTS	IMPLIED JAPAN PATIENTS	TOTAL IMPLIED PATIENTS
~8,831	~9,975	~3,325	~22,131



# Re-analysis of Claims Dataset Estimates There Are ~5,000 aPAP Patients in the U.S.

## ANALYSIS OF COMPREHENSIVE CLAIMS DATASET

#### **Real-World Claims Dataset:**

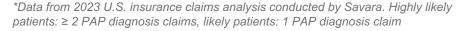
- 300M+ unique, active patients
- 89-99% providers/sites of care
- Counted PAP ICD9/10 diagnosis claims

## APPLIED MACHINE LEARNING (ML) MODEL TO SAME CLAIMS DATASET

ML model identified patients who have high likelihood of PAP, but are not yet diagnosed (patients were required to have either a bronchoscopy, BAL, or lung lavage in their claims history)



~5,000 estimated aPAP patients in the U.S., based on identified PAP claims history and machine learning assessment

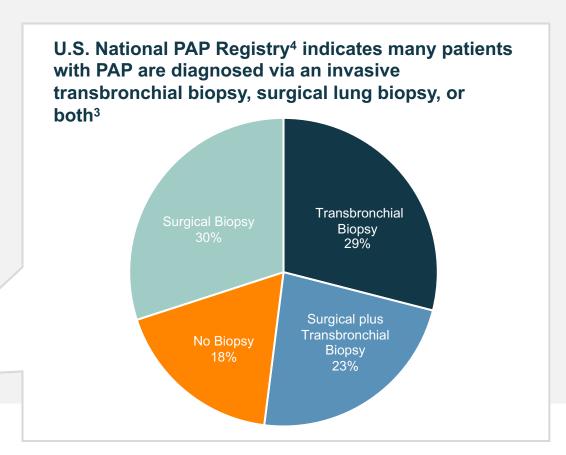






# Historically, Without a Broadly Available Diagnostic for aPAP, the Journey to Diagnosis Can Be Long and Misdiagnosis Common

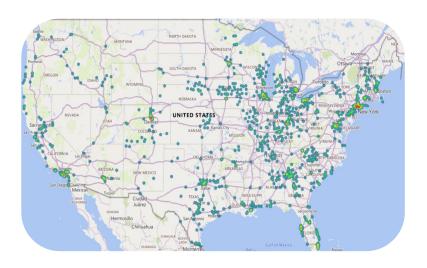
- 3-36 months<sup>1</sup>: Range for aPAP time-todiagnosis
- 18 months<sup>2</sup>: Average delay caused by misdiagnosis (e.g., pneumonia or asthma)
- Diagnostic workup frequently involves multiple tests and invasive procedures, including
  - Pulmonary function tests
  - Arterial blood gas analysis
  - Chest radiographs
  - CT scans
  - Bronchoalveolar lavage (BAL) cytology and/or lung histopathology<sup>3</sup>
  - Transbronchial biopsy, surgical lung biopsy, or both





# Launched HCP Disease Awareness Campaign and No-Cost GM-CSF Autoantibody Testing in U.S.

#### 1,111 affiliated accounts\* with ≥2 aPAP diagnosis claims



~15K

Pulmonologists in the US

~5K

HCPs with diagnosed or machinelearning suspected PAP patients

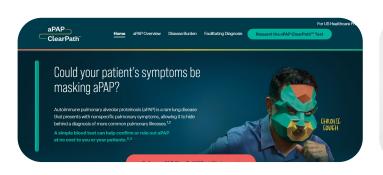
~120

Pulmonology centers

~10

PAP clinical centers

#### www.apapclearpath.com





#### U.S. HCP Website

- Increase HCP awareness of aPAP, including hallmark symptoms of the disease
- Educate HCPs on need for routine GM-CSF autoantibody testing
- REQUEST THE TEST: Order a simple, non-invasive, no-cost GM-CSF autoantibody blood test

# Patient Advocacy Group Partnerships/Memberships







American Lung Association.

- \*Any hospital and health system the diagnosing HCP is affiliated with (within the U.S. claims database).
- Data on file.



## Molgramostim: Global Commercial Opportunity

#### **Significant Unmet Need**

- High disease burden
- Strong market expansion potential via disease awareness campaign, broad access to GM-CSF autoantibody testing

#### Rare Disease Infrastructure

- Orphan disease-like infrastructure in U.S. - field-based team of ~15-30
- OUS commercial strategy **optionality** – go-it-alone, regional partnerships, etc.



#### Molgramostim

- WLL (standard of care) is invasive and not standardized
- Dosing expected to be chronic, providing long-term revenue stream
- Assumed pricing power consistent with recently approved orphan drug analogs (i.e., in U.S. ~\$300-\$500K p/patient, p/year)

#### **Long Term Exclusivity**

12-year biologic exclusivity in the U.S. and biosimilar competition unlikely



# **Financials**



- Cash runway through 2026
  - ~\$237M in cash\*
- Strong investor support with coverage from 7 equity research analysts

#### **ANALYST COVERAGE**

Jefferies	Andrew Tsai
Piper Sandler	Yasmeen Rahimi, PhD
Guggenheim Securities	Vamil Divan, MD, MBA
Oppenheimer	Francois Brisebois
JMP	Jonathan Wolleben
H.C. Wainwright	Andrew Fein
Evercore ISI	Liisa Bayko, MSC, MBA

#### \*Pro forma for cash, cash equivalents, and short-term investments as of 03/31/24, including July 2024 equity offering of \$94M (net).

# Financial Highlights



#### **Investment Thesis**



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# Thank You

