A randomised, double-blind, placebo-controlled, international trial of inhaled rhGM-CSF (molgramostim) in patients with autoimmune pulmonary alveolar proteinosis

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Disclosures

Relationships that could be relevant for this meeting	**Company names**
Speakers and advisor honoraria	InterMune, Boehringer Ingelheim, Gilead, Serendex, Roche Pharma
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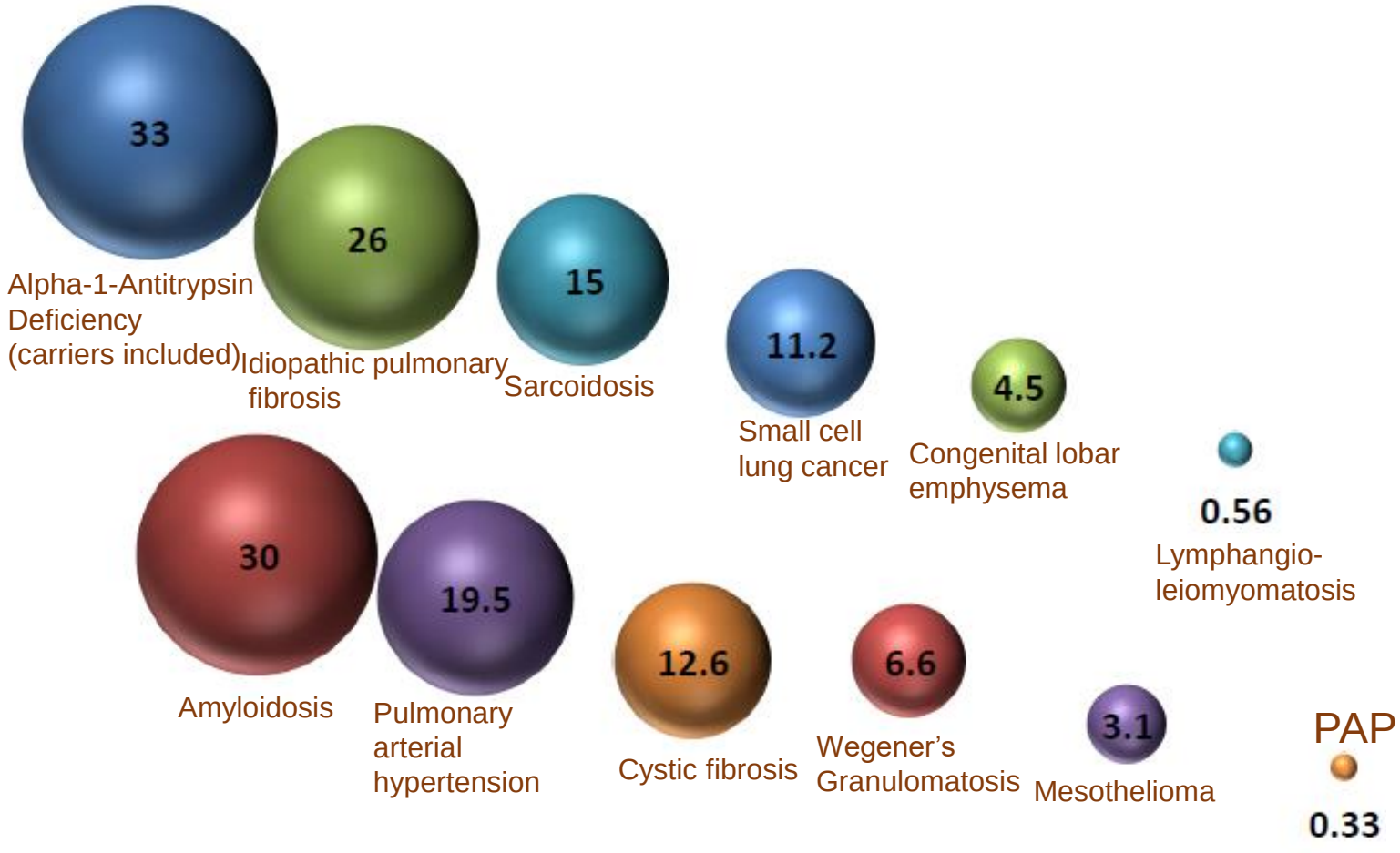
Pulmonary Alveolar Proteinosis (PAP)

- The term pulmonary alveolar proteinosis (PAP) comprises a heterogeneous group of rare disorders characterized by abundant deposition of surfactant and lipoproteins in the alveoli, leading to respiratory insufficiency.
- The autoimmune form accounts for 90 % of cases and is characterized by the presence of GM-CSF autoantibodies.



Bonellla F & Campo I, Pneumologia 2014

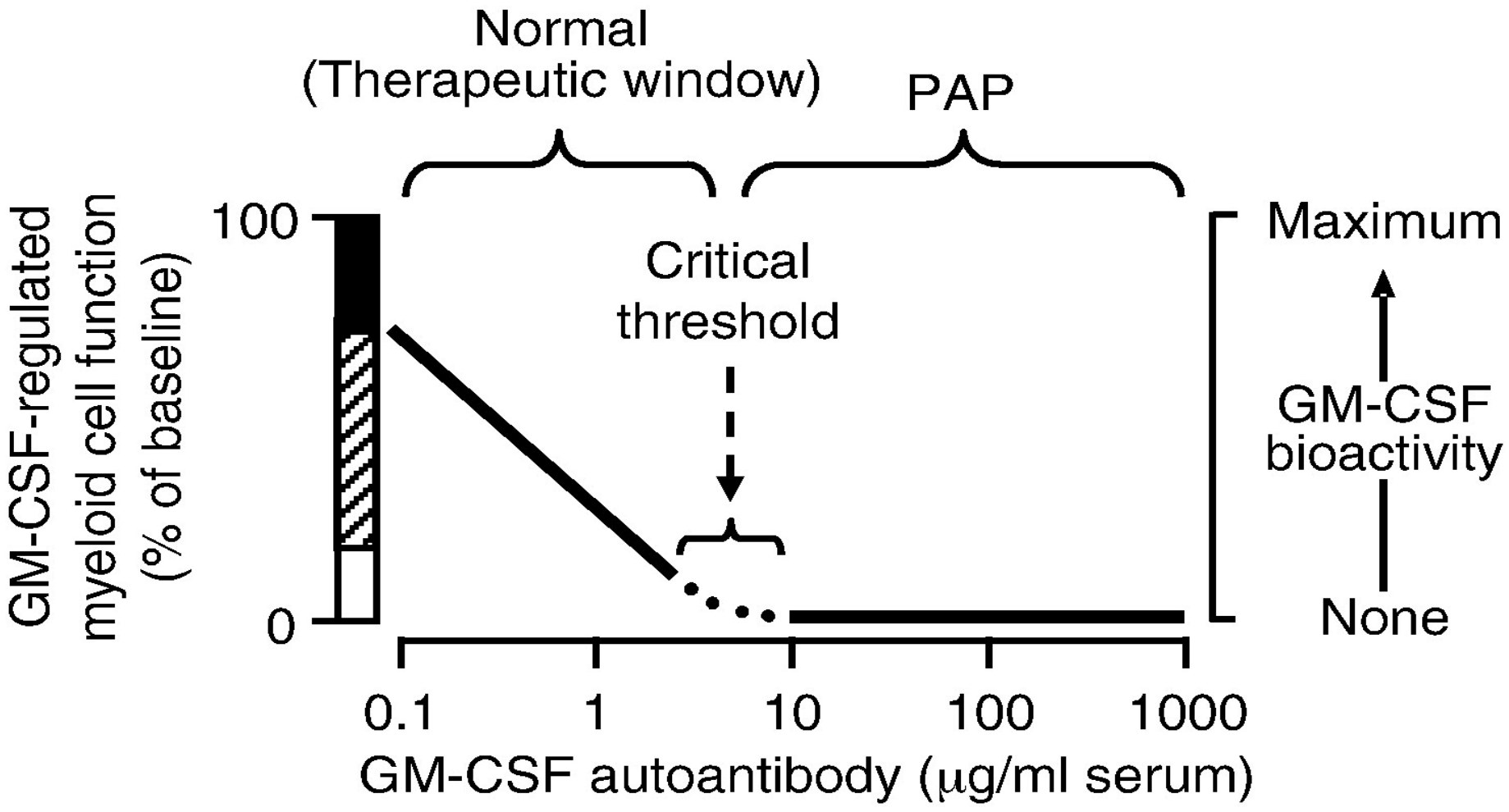
Orphanet Report Series-Prevalence of rare diseases: Bibliographic data-May 2012:www.orpha.net

PAP classification

Primary PAP	**Impaired GM-CSF signalling**
	- autoimmune: GM-CSF autoantibodies
	- hereditary: GM-CSF receptor mutations
Secondary PAP	**Reduction in number and function of AM**
	- infections
	- haematological disorders
	- immunodeficiency
	- inhalation (silica, various metal dusts and chemicals)
PAP-like diseases	**Impaired surfactant production or homeostasis**
	- SP-B and SP-C mutations
	- ABCA3 mutations
	- NKX2-1 mutations

Bonellla F & Campo I, Pneumologia 2014

GM-CSF autoantibody level and development of PAP



Carey B, Trapnell BC, Clin Immunol 2010

Treatment of PAP

- Whole lung lavage (WLL), first applied in the late 1960s by Ramirez, is still the gold standard of therapy for pulmonary alveolar proteinosis (PAP)

- This technique has been not yet standardized but has been improved over the years, in order to enhance the removal of material from the alveoli

- WLL can improve respiratory insufficiency and induce remission in more than two third of patients but it is expensive and time-consuming

Campo, OJRD 2016

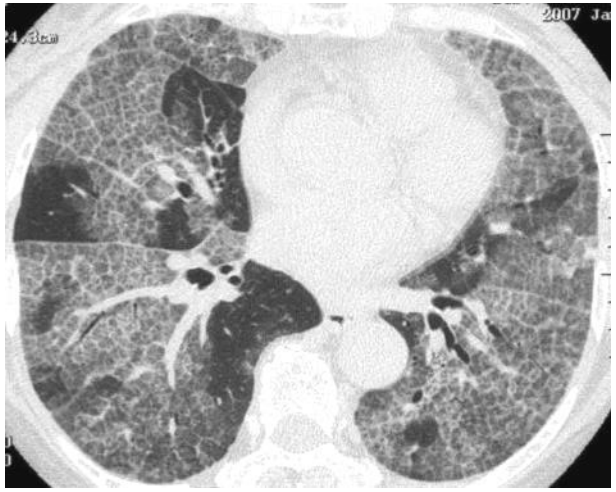
GM-CSF Therapy for aPAP

Trial	Intervention	Doses/repeats	Duration	Effect in % (patients)
Seymour *et al.*[41]	GM-CSF subcutaneously	5 µg/kg/day (7,5–20)†	10–26 weeks	36% (*n* = 14)
Kavuru *et al.*[42]	GM-CSF subcutaneously	250 µg/day; increased to 5–9 µg/kg/day†	12 weeks	75% (*n* = 4)
Bonfield *et al.*[43]	GM-CSF subcutaneously	250 µg/day; increased to 18 µg/kg/day†	12–48 weeks	55% (*n* = 11)
Venkateshiah *et al.*[44]	GM-CSF subcutaneously	250 µg/day increased to 5–18 µg/kg/day†	12–52 weeks	48% (*n* = 21)
Tazawa *et al.*[45]	GM-CSF inhaled	250 µg/day; every second week	24 weeks	100% (*n* = 3)
Tazawa *et al.*[46]	GM-CSF inhaled	250 µg/day; every second week for 12 week tapered to 4 days every second week for 12 weeks	24 weeks	62% (*n* = 39)

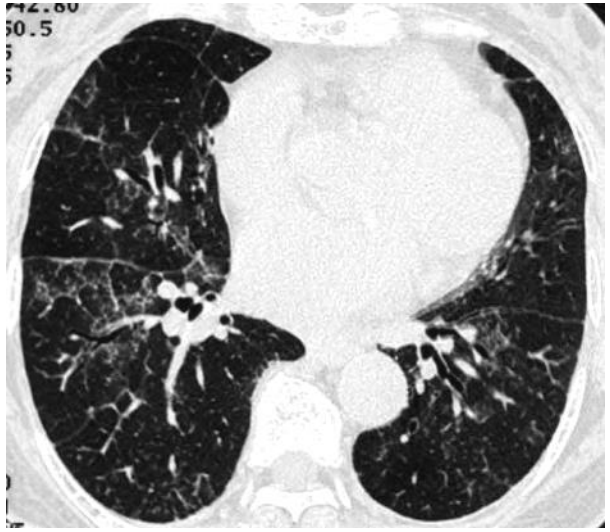
response in > 50% of patients

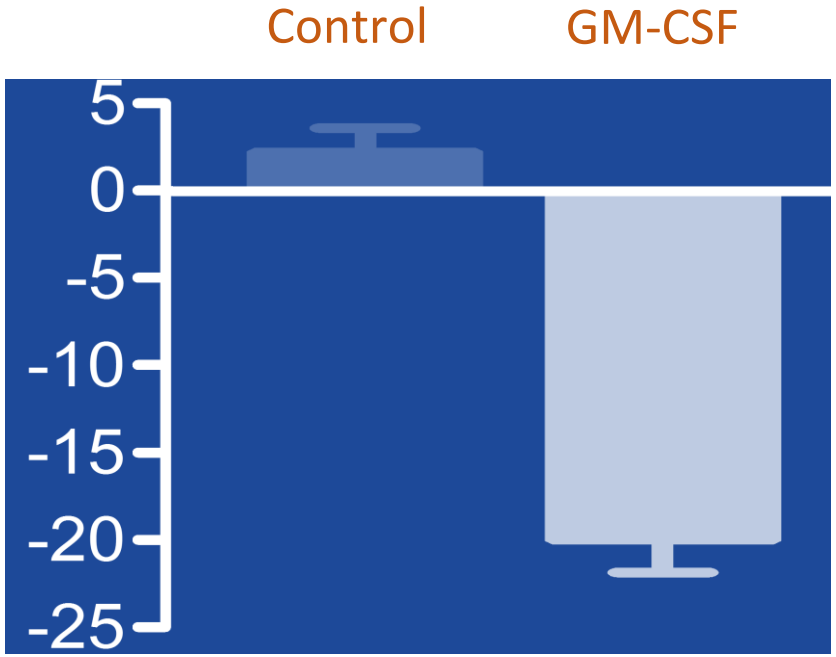
Prior Evidence for Inhaled GM-CSF in aPAP

Before



After





Tazawa et al. *AJRCCM*. 181:1345; 2010.

Improvement in oxygen delivery
(reduction in (A-a)DO_2)

Molgramostim Nebuliser Solution for PAP

(Savara Pharmaceuticals)

Novel Formulation of rhGM-CSF

PARI eFlow® nebulizer

Direct delivery to the lungs to overcome functional deficiency

Promising results in academically sponsored studies*

No approved drug treatments

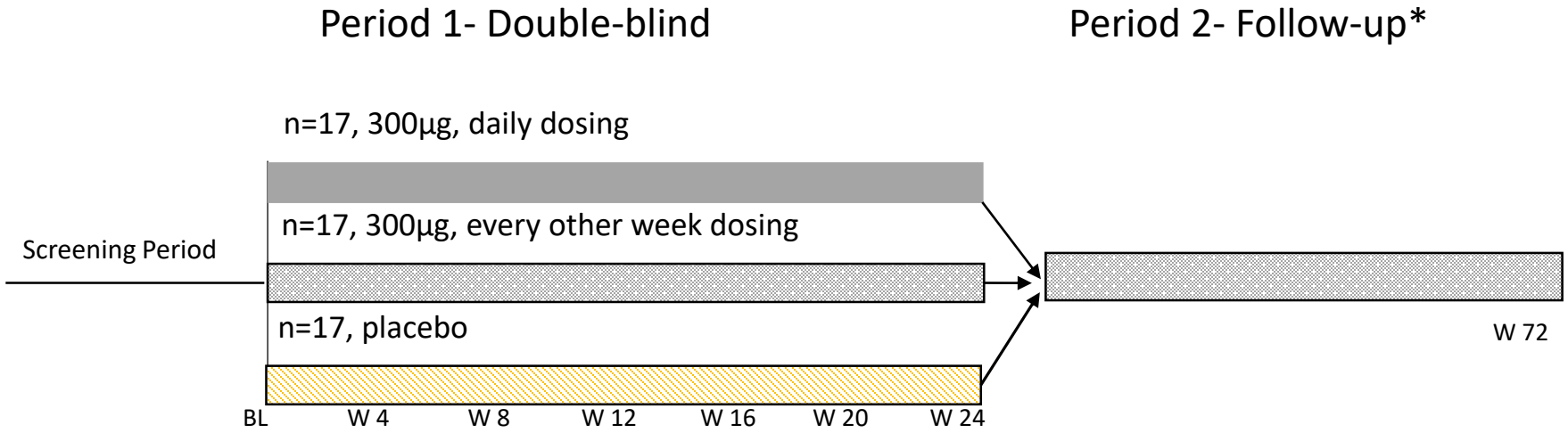
Orphan drug designation

*Tazawa et al. *AJRCCM*. 181:1345; 2010.

The IMPALA trial

A Randomised, Double-Blind, Placebo-Controlled Multicentre Clinical Trial of Inhaled Molgramostim in Autoimmune Pulmonary AlveoLAr Proteinosis Patients

Study design



WLL is applied as rescue treatment

*Open-label treatment with Molgradex intermittent treatment if required during the 48-week follow-up period

Participating sites

Country	City	Institution	PI
Denmark	Århus	University Hospital Århus	Elisabeth Bendstrup
France	Rennes	CHU Rennes	Stephane Jouneau
Germany	Essen	Ruhrlandklinik	Francesco Bonella
Germany	Heidelberg	Thoraxklinik am Universitätsklinikum	Michael Kreuter
Germany	Homburg/Saar	Universitätsklinikum des Saarlandes	Robert Bals
Germany	Gauting	Asklepios-Fachkliniken München	Wolfgang Gesierich
Greece	Athens	Attikon University Hospital	Spyros Papiris
Italy	Pavia	Fondazione IRCCS Policlinico San Matteo	Francesca Mariani
Israel	Beilinson	Rabin Medical Center	Mordechai Kremer
Japan	Osaka	National Hospital Kinki-Chuo Chest Medical Center	Youshikazu Inoue
Japan	Miyagi	Tohoku University Hospital	Makoto Kobayashi
Japan	Niigata	Niigata University	Ryushi Tazawa
Japan	Nagakute	Aichi Medical Center	Etsuro Yamaguchi
Japan	Yokohama	Kanagawa Cardiovascular and Respiratory Center	Tomohisa Baba
Netherlands	Nieuwegein	St. Antonius Hospital	Marcel Veltkamp
Russia	St. Petersburg	City Hospital	Julia Ilkovich
Spain	Barcelona	Hospital de Bellvitge	Maria Molina Molina
Switzerland	Lausanne	Centre Hospitalier Universitaire Vaudois	Romain Lazor
United Kingdom	London	Royal Brompton	Cliff Morgan

Main Inclusion criteria

- aPAP diagnosed by CT, or by biopsy, or by Broncho Alveolar Lavage (BAL), and by increased GM-CSF autoantibodies in serum

- Stable or progressive aPAP (i.e. absolute VC not improved by more than 5% and/or DLCO not improved by more than 10% - assessed from medical records) during a minimum period of two months prior to the Baseline visit

- PaO_2 <75 mmHg/<10 kPa at rest, OR desaturation of >4 percentage points on the 6 Minute Walk Test (6MWT)

- An (A-a)DO_2 at Screening of minimum 25 mmHg/3.33 kPa

- Age ≥18 years

Main Exclusion criteria

- Diagnosis of hereditary or secondary pulmonary alveolar proteinosis (PAP)
- WLL within two months of Baseline
- Treatment with GM-CSF within three months of Baseline
- Treatment with rituximab within six months of Baseline
- Treatment with plasmapheresis within three months of Baseline
- Treatment with any investigational medicinal product within four weeks of Screening
- Concomitant use of sputum modifying drugs such as carbocystein or ambroxol
- Connective tissue disease, inflammatory bowel disease or other autoimmune disorder requiring treatment associated with significant immunosuppression, e.g. more than 10 mg/day systemic prednisolone
- Previous experience of severe and unexplained side-effects during aerosol delivery of any kind of medicinal product
- History of, or present, myeloproliferative disease or leukaemia
- Significant liver impairment (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >4 times the upper normal limit) or renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m^2) at Screening
- Known active infection (viral, bacterial, fungal or mycobacterial)
- Apparent pre-existing concurrent pulmonary fibrosis

Outcome measures

Primary Endpoint:

- Absolute change from baseline to 24 weeks of Alveolar - arterial oxygen concentration (A-a(DO2))

Key Secondary Endpoints:

- Number of subjects in need of Whole Lung Lavage (WLL)
- Time to WLL
- Absolute change from baseline to 24 weeks in Vital Capacity (% predicted)

Outcome measures

Other Outcome Measures:

- Pulmonary function tests and blood gases
- Exercise tolerance (6MWT)
- Symptom scores (dyspnoea, cough)
- High Resolution Computed Tomography (HRCT)
- Quality of Life
- Treatment-emergent adverse events (AEs), serious AEs, Adverse Drug Reactions and Severe AEs

Conclusion

- Autoimmune PAP is a medical condition with a high unmet medical need.
- Inhaled GM-CSF is a promising medical therapy for aPAP, but it is currently not licensed.
- This is the first global initiative and placebo-controlled randomized trial, with the overall aim of getting an inhaled medical therapy licensed for treatment of aPAP.

Thank you for your attention

Fondazione IRCCS
Policlinico San Matteo

RUHRLAND
KLINIK
Westdeutsches
Lungenzentrum

EuPAPNet
European Pulmonary Alveolar Proteinosis Network