rhGM-CSF (molgramostim) is being developed for the treatment of ARDS and Pulmonary Alveolar Proteinosis - This is Phase I SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF INHALED MOLGRAMOSTIM, A RECOMBINANT HUMAN GRANULOCYTE MACROPHAGE-COLONY STIMULATING FACTOR (RHGM-CSF), IN AN ASCENDING SINGLE AND MULTIPLE-DOSE TRIAL IN HEALTHY SUBJECTS

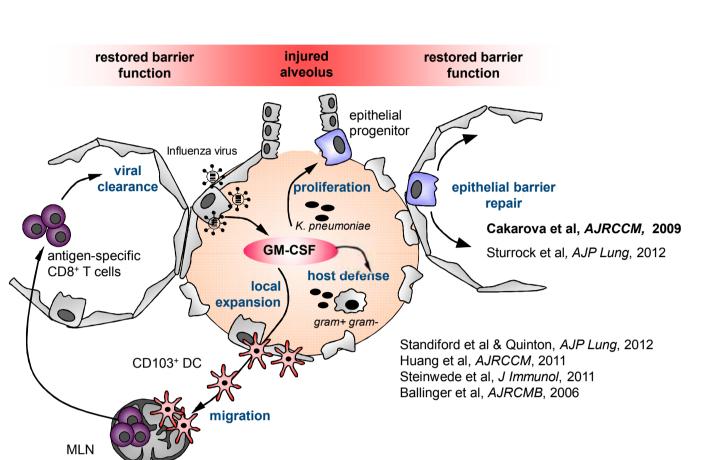
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INTRODUCTION

GM-CSF is a cytokine and a hematopoietic growth factor produced by a variety of cells. In the lungs GM-CSF regulates surfactant homeostasis and lung host defense through innate immune functions. Alveolar macrophages from GM-CSF-/- mice have reduced capacity for surfactant catabolism, cell adhesion, phagocytosis and bacterial killing. Disruption of surfactant homeostasis by autoantibodies to GM-CSF cause autoimmune pulmonary alveolar proteinosis, an ultra-rare disease in which clinical effect of exogenous rhGM-CSF has been documented in several case reports and uncontrolled clinical trials. GM-CSF is highly protective in non-clinical models of pneumonia-associated lung injury, where GM-CSF protects the host in both early phase of acute lung infection and during regeneration phase.

Molgramostim is an un-glycosylated rhGM-CSF produced in a strain of Escherichia coli bearing a genetically engineered plasmid which contains a human GM-CSF gene. A nebuliser solution containing molgramostim has been formulated and developed specifically for inhalation treatment of respiratory conditions



Unkel et al, *J Clin Invest*, 2012

Picture courtesy of Professor S. Herold, University of Giessen-Marburg Lung Center, Germany

FORMULATION AND DELIVERY TO THE LUNGS

Molgramostim nebuliser solution is a liquid formulation containing molgramostim 250 µg/mL and is delivered using eFlow® nebuliser system (PARI Pharma GmbH, Germany)

The eFlow® handset is a single patient use, reusable nebuliser, which has been optimised for nebulisation of molgramostim nebuliser solution:

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ticle size distribution	Mass Median Diameter: 3.5 μm (SD 0.37) Geometric Standard Deviation: 1.6 (SD 0.1) Respirable fraction < 5 μm: 76.9% (SD 8.03)

Delivered dose

Results from breath simulation experiments

Delivered dose	60.4
Respirable dose < 5 µm	46.3

METHODS

The trial adhered to the principles of the Declaration of Helsinki and Good Clinical Practice. The trial was approved by The Medicines and Healthcare Products Regulatory Agency (UK) and Office for Research Ethics Committees, Northern Ireland, UK, and conducted at a specialized Phase I clinic in Belfast, UK (Celerion Inc.)

Study design

- Randomised, double-blind, placebo-controlled, single and multiple-dose trial
- Single ascending dose part (SAD) 150 μg, 300 μg og 600 μg molgramostim (n=4 per dose level) or placebo (n=6) daily
- Multiple ascending dose part (MAD) 300 μg og 600 μg molgramostim (n=9 per dose level) or placebo (n=6) daily for 6 days
 Follow-up visits 8 and 15 days after last dose
- Dose escalation only after review of safety and tolerability findings of preceding dose
- All dose levels in the SAD part included a sentinel group of 2 subjects
- Dose selection based on previous clinical experience with inhaled rhGM-CSF

Subjects

- All provided written informed consent
- 2 females and 40 males aged 18 53 years, Body mass index (BMI) ≥ 20.5 and ≤ 31.7 kg/m² at screening
- Life-long non-smoker, not using nicotine-containing products
- Healthy assessed by medical history, physical examination, spirometry, ECG, vital signs, and clinical laboratory test

OBJECTIVES

Primary objective:

To assess the safety and tolerability of single and multiple ascending inhaled doses of molgramostim when administered to healthy adult subjects

new treatment for respiratory conditions with a high unmet medical need

Clinical trials of inhaled molgramostim have been initiated in 2016

Israel, Russia and Japan (NCT02702180)

Trapnell and Whitsett. Annu Rev Physiol 2002. 64: 775-802, Trapnell et al. Curr Opin Immunol 2009. 21: 514-521,

Unkel et al. J Clin Invest 2012. 122: 3652-3664, Cakarova et al. Am J Respir Crit Care Med 2009. 180: 521-532

CONCLUSIONS

FUTURE WORK

REFERENCES

Herold et al. Am J Respir Crit Care Med 2014. 189: 609-611

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Inhaled molgramostim is well-tolerated in healthy subjects, is absorbed systemically at picogram levels, and shows a clear ef-

fect on White Blood Cell (WBC) differentials mostly within normal reference ranges. Inhaled molgramostim may be a promising

Autoimmune pulmonary alveolar proteinosis (Phase II/III pivotal trial) to be conducted at 16 centres in Europe,

(Phase II) to be conducted at two centers in Germany (NCT02595060)

Secondary and exploratory objectives:

To assess the pharmacokinetics (PK) of inhaled

molgramostim when administered to healthy adult subjects

To assess the effect on white blood cell (WBC) differentials

RESULTS - SAFETY

No treatment-related effects on

- Vital signs including pulse oximetrySpirometry
- ECG (including Holter monitoring)
- Serum chemistry, and coagulation

No development of anti-molgramostim antibodies

Adverse event (AE) rates similar across groups, although higher number of events in 600 µg dose group in MAD part

Overview of reported Adverse Events (AEs) by treatment, only AEs reported in 2 or more subjects or AEs rated as related to treatment by the Principal Investigator (PI) are listed here

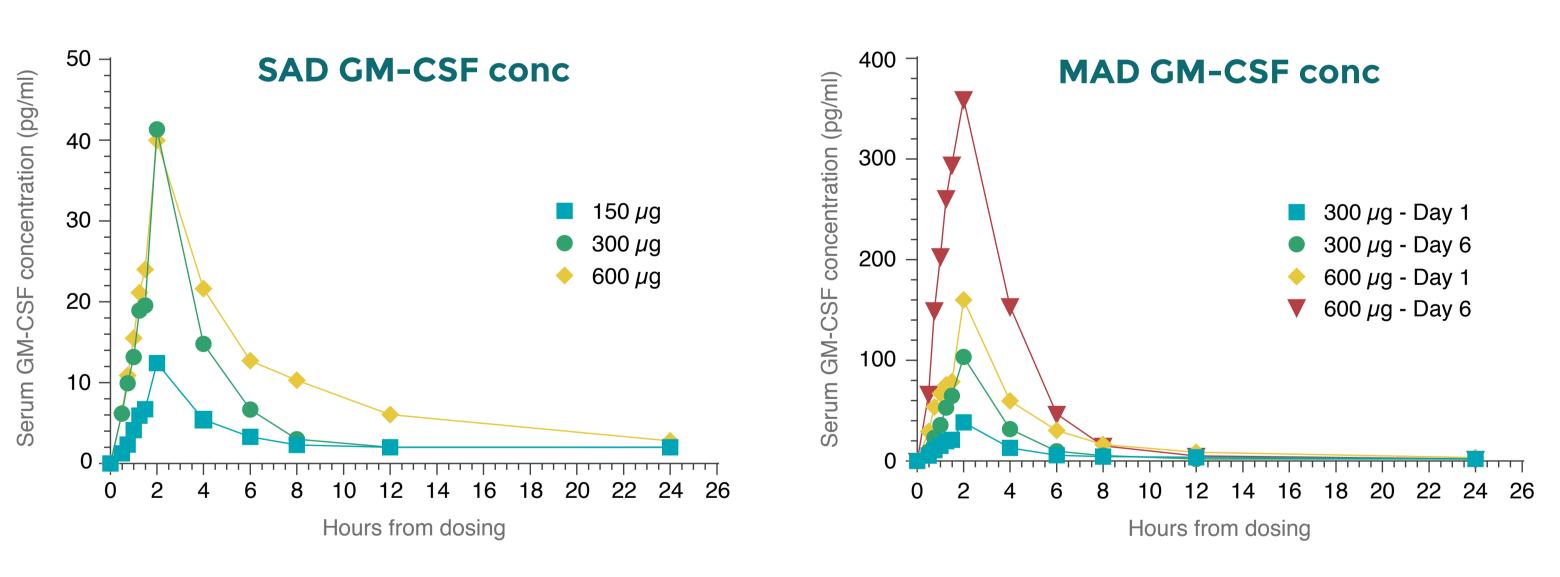
Treatment Number of subjects	Part 1 (SAD)				Part 2 (MAD)		
	150 μg N=4	300 <i>µ</i> g N=4	600 μg N=4	Placebo N=6	300 µg N=9	600 <i>µ</i> g N=9	Placebo N=6
No. (%) of Subjects Reporting AEs No. of AE Episodes	2 (50%) 4	4 (100%) 13	1 (25%) 3	4 (67%) 7	7 (78%) 64	8 (89%) 103	6 (100%) 59
AE	Number of	f subjects rep	porting AE				
Cough*	1	4	1	2	7	8	6
Productive cough*	0	0	0	1	1	2	2
Throat irritation*	0	0	0	0	0	0	2
Dizziness*	0	0	0	0	2	2	2
Headache*	0	0	0	0	5	2	1
Eosinophilia*	0	0	0	0	0	1	0
Mild WBC increase*	0	0	0	0	0	1	0
Diarrhoea*	1	0	0	1	0	0	0
Tachycardia*	0	0	0	0	0	1	0

Assessed as possibly, probably or likely related to blinded treatment by PI

Assessed as possibly related in one subject treated with 600 µg molgramostim, the AEs in the remaining 3 subjects were unrelated

RESULTS - PK

Molgramostim was absorbed from the lungs into the circulation resulting in serum GM-CSF concentration at picogram levels. GM-CSF in serum measured by electrochemiluminescence GLP-validated assay (Mesoscale), optimized to detect molgramostim in human serum



	Part 1 (SAD)			Part 2 (MAD)				
Parameter	150 µg	300 μg	600 μg	300 μg Day 1	600 <i>μ</i> g Day 1	300 <i>µ</i> g Day 6	600 μg Day 6	
C _{max} (pg/mL)ª	9.07 (116)	40.7 (57.4)	34.1 (73.6)	32.1 (73.4)	90.1 (63.4)	96.4 (139)	251 (109)	
T _{max} (hr) ^b	2.01	2.00	2.00	2.00	2.01	2.00	2.02	
	(2.00, 2.01)	(1.25, 2.00)	(2.00, 2.00)	(2.00, 2.01)	(2.00, 2.04)	(2.00, 2.02)	(1.96, 2.10)	
AUC _{0-last}								
(pg*hr/mL) ^a	12.5 (662)	85.9 (100)	138 (122)	97.1 (72.5)	248 (53.5)	350 (125)	802 (119)	
T _{1/2} (hr) ^c	1.82	1.73 ± 0.0398	5.91 ± 0.854	3.95 ± 1.97	_	3.68 ± 0.784	-	

a: Geometric mean (CV%)b: Median (min, max)c: Arithmetic mean ± SDev

RESULTS - WBC

Inhaled molgramostim resulted in dose-dependent, temporary increases from baseline in WBC, neutrophils, monocytes, and eosinophils

