



Clinical trial results:

An open-label, non-controlled, multicentre clinical trial of inhaled molgramostim in autoimmune pulmonary proteinosis patients

Summary

EudraCT number	2017-004078-32
Trial protocol	DK NL DE FR GB GR IT
Global end of trial date	14 January 2021

Results information

Result version number	v2 (current)
This version publication date	29 December 2022
First version publication date	28 January 2022
Version creation reason	• Correction of full data set - Change of Sponsor contact person

Trial information

Trial identification

Sponsor protocol code	SAV006-03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03482752
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Savara Pharmaceuticals
Sponsor organisation address	6836 Bee Cave Road, Building 3, Suite 201, Austin, United States, TX 78746
Public contact	Chief Medical Officer, Savara Inc, +1 5127848757, ray.pratt@savarapharma.com
Scientific contact	Chief Medical Officer, Savara Inc, +1 5127848757, ray.pratt@savarapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2021
Global end of trial reached?	Yes
Global end of trial date	14 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate safety of long-term use of inhaled molgramostim nebulizer solution.

Protection of trial subjects:

Subjects were free to discontinue their participation in the trial at any time with no prejudice or effect on the subject's further care or treatment.

Subjects could be discontinued from treatment and assessments at any time, if deemed necessary by the investigator.

Pulmonary function and respiratory symptoms were monitored during the trial and treatment were to be discontinued if significant worsening occurred.

Pregnancy testing was performed in women of childbearing potential at each trial visit where molgramostim was dispensed and at home at monthly intervals during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 9
Worldwide total number of subjects	60
EEA total number of subjects	38

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

SAV006-03 was an open-label extension trial for subjects who had completed MOL-PAP-002. Among the 30 sites enrolling subjects in MOL-PAP-002, 13 sites participated in SAV006-03.

Pre-assignment

Screening details:

SAV006-03 enrolled subjects who had completed MOL-PAP-002. A total of 62 subjects were screened and 60 were enrolled. The same dose regimen was used in SAV006-03 as was used in the follow-up period of MOL-PAP-002 (molgramostim nebulizer solution 300 µg intermittently, repetitive cycles of 7 days of treatment - 7 days off-treatment).

Period 1

Period 1 title	Open-label treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Molgramostim nebulizer solution (300 µg)
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Arm description:

Open-label treatment with molgramostim nebulizer solution (300 µg) administered intermittently (repetitive cycles of 7 days of treatment followed by 7 days off-treatment).

Arm type	Experimental
Investigational medicinal product name	Molgramostim nebulizer solution (300 µg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution and dispersion for nebuliser dispersion
Routes of administration	Inhalation use

Dosage and administration details:

Molgramostim nebulizer solution (300 µg) was administered intermittently (repetitive cycles of 7 days of treatment followed by 7 days off-treatment).

It was administered using an investigational version of the PARI nebulizer system (eFlow), adapted specifically for the delivery of molgramostim nebulizer solution by PARI Pharma GmbH, Germany.

Subjects were to administer the first dose at the baseline visit under the supervision of trial personnel, unless they had already dosed within the MOL-PAP-002 trial on the same day, and were retrained in administration and medical device maintenance procedure, if required.

The molgramostim nebulizer solution was administered once daily with no defined timing in relation to time of day or meals.

Number of subjects in period 1	Molgramostim nebulizer solution (300 µg)
Started	60
Completed	0
Not completed	60
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Early termination of trial	56

Lost to follow-up	1
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Baseline characteristics

Reporting groups

Reporting group title	Molgramostim nebulizer solution (300 µg)
Reporting group description: Open-label treatment with molgramostim nebulizer solution (300 µg) administered intermittently (repetitive cycles of 7 days of treatment followed by 7 days off-treatment).	

Reporting group values	Molgramostim nebulizer solution (300 µg)	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Adults (18-64 years)	55	55	
From 65-84 years	5	5	
Gender categorical Units: Subjects			
Female	24	24	
Male	36	36	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set included all subjects enrolled into the trial.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set included all enrolled subjects who were exposed to molgramostim nebulizer solution in SAV006-03.	

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	60	59	
Age categorical Units: Subjects			
Adults (18-64 years)	55	54	
From 65-84 years	5	5	
Gender categorical Units: Subjects			
Female	24	24	
Male	36	35	

End points

End points reporting groups

Reporting group title	Molgramostim nebulizer solution (300 µg)
Reporting group description: Open-label treatment with molgramostim nebulizer solution (300 µg) administered intermittently (repetitive cycles of 7 days of treatment followed by 7 days off-treatment).	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set included all subjects enrolled into the trial.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set included all enrolled subjects who were exposed to molgramostim nebulizer solution in SAV006-03.	

Primary: Number of adverse events (AEs)

End point title	Number of adverse events (AEs) ^[1]
End point description: The primary objective of this trial was safety assessed by AE reporting. Definitions and reporting procedures for AEs were done according to current regulatory standards. AEs were collected by the investigator by a non-leading question and by reporting events directly observed or spontaneously volunteered by subjects. Subjects were also encouraged to contact the clinic in between visits if they experienced AEs or had any concerns.	
End point type	Primary
End point timeframe: AEs were collected from the baseline visit up to a follow-up telephone call, which occurred 2 weeks after trial completion (i.e. Week 158).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: According to the protocol, no hypothesis/statistical testing was planned for any of the endpoints of this long-term safety extension study but only descriptive statistics were to be used.

End point values	Molgramostim nebulizer solution (300 µg)	Safety analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	59		
Units: event	165	165		

Statistical analyses

No statistical analyses for this end point

Primary: Number of serious adverse events (SAEs)

End point title	Number of serious adverse events (SAEs) ^[2]
End point description:	

End point type	Primary
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End point timeframe:

SAEs were collected from the baseline visit up to a follow-up telephone call, which occurred 2 weeks after trial completion (i.e. Week 158).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: According to the protocol, no hypothesis/statistical testing was planned for any of the endpoints of this long-term safety extension study but only descriptive statistics were to be used.

End point values	Molgramostim nebulizer solution (300 µg)	Safety analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	59		
Units: events	8	8		

Statistical analyses

No statistical analyses for this end point

Primary: Number of adverse drug reactions (ADRs)

End point title	Number of adverse drug reactions (ADRs) ^[3]
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End point description:

All AEs were assessed by the investigator for causality (unlikely, possible, probable, not applicable) according to current regulatory standards. AEs which had a 'possible' or 'probable' causality were classified as ADRs.

End point type	Primary
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End point timeframe:

AEs were collected from the baseline visit up to a follow-up telephone call, which occurred 2 weeks after trial completion (i.e. Week 158).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: According to the protocol, no hypothesis/statistical testing was planned for any of the endpoints of this long-term safety extension study but only descriptive statistics were to be used.

End point values	Molgramostim nebulizer solution (300 µg)	Safety analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	59		
Units: events	3	3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of adverse events leading to treatment discontinuation

End point title	Number of adverse events leading to treatment
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End point description:

End point type	Primary
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End point timeframe:

AEs were collected from the baseline visit up to a follow-up telephone call, which occurred 2 weeks after trial completion (i.e. Week 158).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: According to the protocol, no hypothesis/statistical testing was planned for any of the endpoints of this long-term safety extension study but only descriptive statistics were to be used.

End point values	Molgramostim nebulizer solution (300 µg)	Safety analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	59		
Units: events	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the baseline visit up to a follow-up telephone call, which occurred 2 weeks after trial completion (i.e. Week 158).

Adverse event reporting additional description:

AEs were collected by the investigator by a non-leading question and by reporting events directly observed or spontaneously volunteered by subjects. Subjects were also encouraged to contact the clinic in between visits if they experienced adverse events or had any concerns.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Safety analysis set
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Reporting group description: -

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 59 (13.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Alveolar proteinosis			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

HIV infection CDC Group IV subgroup A			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 59 (64.41%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	7		
Alveolar proteinosis			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 6		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 7		
Respiratory tract infection subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 7		
COVID-19 subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Bronchitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 6		
Pneumonia subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2018	Changes implemented in 2 local amendments were made global in substantial global amendment 3.0. In addition: - Revision of note to inclusion criterion 2. - Exploratory endpoint added for GM-CSF levels before and 2 hours after dosing. - Clarification that spirometry and DLCO should be performed in accordance with ERS/ATS guidance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 January 2021	SAV006-03 was initiated before the evaluation and advice on the MOL-PAP-002 results which investigated an intermittent dosing regimen as well as continuous (daily) dosing regimen. The continuous daily dosing regimen did demonstrate clinical improvements in patients with aPAP and will continue to be investigated in a phase 3 confirmatory study. Considering the MOL-PAP-002 results and the authority advice, there would not be adequate efficacy and safety data on the intermittent dosing regimen to support a marketing authorization application for this regimen. Consequently, the sponsor decided to discontinue SAV006-03. At the point of termination, 60 subjects were enrolled in the trial. As expected, due to the early termination, the number of subjects decreased during the trial. However, 44 subjects (74.6%) reached ≥ 12 months of exposure and 15 subjects (25.4%) reached ≥ 24 months of exposure.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Efficacy endpoints were secondary and no hypothesis testing was carried out. Due to early termination, limited efficacy data were available for evaluation and in general, firm conclusion based on efficacy data are not applicable.

Notes: