



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 | <ul style="list-style-type: none">• Correction of full data setChange of Sponsor contact person |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | SAV006-03 |
|-----------------------|-----------|

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) |
|-----------|--|

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 |
|-------------------|---|

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 |
|----------------|---------|

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] |
|-----------------|--|

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 |
|----------------|---------|

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 |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| 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:

[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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Safety analysis set |
|-----------------------|---------------------|

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: <ul style="list-style-type: none">- 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: