



Clinical trial results:

A Phase 1/2A, Dose Escalation, Randomized, Placebo Controlled Study of the Safety, Feasibility, and Efficacy of Subcutaneous Plasminogen (Human) 10 for the Treatment of Chronic Tympanic Membrane Perforation

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-002927-68 |
| Trial protocol | SE |
| Global end of trial date | 04 February 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 May 2021 |
| First version publication date | 28 May 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 2002C015G |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Prometic Biotherapeutics Ltd |
| Sponsor organisation address | 1330 Piccard Dr # 201, Rockville, United States, |
| Public contact | Medical Officer, Joseph Parker, MD , clinical@prometic.com |
| Scientific contact | Medical Officer, Joseph Parker, MD , clinical@prometic.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 | 04 February 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 February 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 February 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 5 mg and 10 mg Plasminogen (Human) 10 injected subcutaneously (SC) near the tympanic membrane in adult subjects with chronic tympanic membrane perforation (TMP).

Protection of trial subjects:

The protocol and the amendments were submitted to a properly constituted IEC and the concerned CA, in accordance with the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines, the applicable European Directives, and local legal requirements, for approval of the study. Approvals had been obtained in writing before the first subject was recruited. The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP), and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association. All subjects received written and verbal information regarding the study at a prior interview. The given information emphasized that participation in the study was voluntary and that the subject could withdraw from the study at any time and for any reason. All subjects were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study. Before any study-related procedures, the ICF was signed and personally dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the person who conducted the informed consent discussion.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 16 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 | Sweden: 9 |
| Worldwide total number of subjects | 9 |
| EEA total number of subjects | 9 |

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) | 8 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment was stopped after 9 subjects had been included and completed the study.

Pre-assignment

Screening details:

Consenting subjects were screened for eligibility per the defined inclusion/exclusion criteria during the 2 weeks preceding the first injection at the baseline visit.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|--|---|
| Are arms mutually exclusive? | Yes |
| Arm title | 0.5 mL IMP - 5 mg SC Plasminogen (human) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | SC Plasminogen (human) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

During each low dose injection session, 0.5 mL IMP - 5 mg SC Plasminogen (human), divided into 4 (approximately 125 µL aliquots), were injected.

| | |
|--|------------------------|
| Arm title | 0.5 mL placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | 0.9% [w/v] NaCl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

During each low dose injection session, 0.5 mL of placebo divided into 4 (approximately 125 µL aliquots) were injected.

| Number of subjects in period 1 | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo |
|--------------------------------|--|----------------|
| | | |
| Started | 7 | 2 |
| Completed | 7 | 2 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--|
| Reporting group title | 0.5 mL IMP - 5 mg SC Plasminogen (human) |
| Reporting group description: - | |
| Reporting group title | 0.5 mL placebo |
| Reporting group description: - | |

| Reporting group values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | Total |
|---------------------------------------|--|----------------|-------|
| Number of subjects | 7 | 2 | 9 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 6 | 2 | 8 |
| From 65-84 years | 1 | 0 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 35 | 62.5 | |
| full range (min-max) | 19 to 67 | 62 to 63 | - |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 1 | 5 |
| Male | 3 | 1 | 4 |
| Weight Units: kilogram(s) | | | |
| arithmetic mean | 75.7 | 63.8 | |
| full range (min-max) | 51.5 to 108.0 | 58.8 to 68.8 | - |

End points

End points reporting groups

| | |
|--------------------------------|--|
| Reporting group title | 0.5 mL IMP - 5 mg SC Plasminogen (human) |
| Reporting group description: - | |
| Reporting group title | 0.5 mL placebo |
| Reporting group description: - | |

Primary: Number, type, severity, and causality of TEAEs by treatment

| | |
|------------------------|--|
| End point title | Number, type, severity, and causality of TEAEs by treatment ^[1] |
| End point description: | |

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

AEs were recorded during the study period from administration of first dose of study drug (Visit 2) to the completion of the End-of-study visit (Visit 6).

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: The statistical analysis methods described in the protocol for primary and secondary endpoints were planned according to the intended number of subjects to be included. With only 9 subjects included in the study, it was not considered meaningful to do the safety and efficacy analyses as planned and was thus not conducted.

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: adverse event | | | | |
| Severity - MILD | 20 | 2 | | |
| Severity - MODERATE | 1 | 0 | | |
| Severity - SEVERE | 0 | 0 | | |
| Causality - not related | 7 | 0 | | |
| Causality - possible | 6 | 0 | | |
| Causality - probable | 2 | 1 | | |
| Causality - definite | 6 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of injections that are technically feasible by treatment, defined as the ability to insert needle SC in the ear canal less or equal to 5 mm from the tympanic annulus and deliver entire volume of IMP or placebo SC without spillage.

| | |
|-----------------|--|
| End point title | Proportion of injections that are technically feasible by treatment, defined as the ability to insert needle SC in the ear |
|-----------------|--|

canal less or equal to 5 mm from the tympanic annulus and deliver entire volume of IMP or placebo SC without spillage.

End point description:

End point type Secondary

End point timeframe:

Recorded during the study period from administration of first dose of study drug (Visit 2) to the completion of the End-of-study visit (Visit 6).

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| visit 2 - less than 20% not injected | 5 | 1 | | |
| visit 2 - no spillage reported | 2 | 1 | | |
| visit 3 - less than 20% not injected | 4 | 1 | | |
| visit 3 - no spillage reported | 2 | 1 | | |
| visit 4 - less than 20% not injected | 2 | 1 | | |
| visit 4 - no spillage reported | 4 | 1 | | |
| visit 3 - 20-50% not injected | 1 | 0 | | |
| visit 4 - 20-50% not injected | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with more than 50% reduction in the percentage of TMSA occupied by the TMP at 1 month compared with baseline by treatment.

End point title Proportion of subjects with more than 50% reduction in the percentage of TMSA occupied by the TMP at 1 month compared with baseline by treatment.

End point description:

End point type Secondary

End point timeframe:

assessed at 1 month

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|----------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| equal or more than 50% reduction | 1 | 0 | | |
| less than 50% reduction | 6 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with TMP closure at 1 month compared with baseline by treatment, defined as the absence of visible perforation by otomicroscopy AND the presence of tympanic membrane movement with pneumatic pressure change in the ear canal.

| | |
|-----------------|--|
| End point title | Proportion of subjects with TMP closure at 1 month compared with baseline by treatment, defined as the absence of visible perforation by otomicroscopy AND the presence of tympanic membrane movement with pneumatic pressure change in the ear canal. |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
assessed at 1 month

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| TMP closure at 1 month | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with more than 50% reduction in the percentage of TMSA occupied by the TMP at 3 months compared with baseline by treatment.

| | |
|-----------------|--|
| End point title | Proportion of subjects with more than 50% reduction in the percentage of TMSA occupied by the TMP at 3 months compared with baseline by treatment. |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

assessed at 3 months

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|----------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| equal or more than 50% reduction | 1 | 0 | | |
| less than 50% reduction | 6 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with TMP closure at 3 months compared with baseline by treatment, defined as the absence of visible perforation by otomicroscopy AND the presence of tympanic membrane movement with pneumatic pressure change in the ear canal.

| | |
|-----------------|---|
| End point title | Proportion of subjects with TMP closure at 3 months compared with baseline by treatment, defined as the absence of visible perforation by otomicroscopy AND the presence of tympanic membrane movement with pneumatic pressure change in the ear canal. |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

assessed at 3 months

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| TMP closure at 3 months | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in visual analogue scale (VAS) score for ear discomfort (pain or other unpleasant sensation) at 1 month compared with baseline by treatment.

| | |
|-----------------|---|
| End point title | Change in visual analogue scale (VAS) score for ear discomfort (pain or other unpleasant sensation) at 1 month compared with baseline by treatment. |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
assessed at 1 month

| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 1 | | |
| Units: number | | | | |
| improved ear discomfort | 2 | 1 | | |
| similar ear discomfort | 2 | 0 | | |
| worsened ear discomfort | 3 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VAS score for ear discomfort at 3 months compared with baseline by treatment.

| | |
|-----------------|---|
| End point title | Change in VAS score for ear discomfort at 3 months compared with baseline by treatment. |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
assessed at 3 months

| | | | | |
|-----------------------------|---|-----------------|--|--|
| End point values | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 2 | | |
| Units: number | | | | |
| improved ear discomfort | 2 | 1 | | |
| similar ear discomfort | 2 | 0 | | |
| worsened ear discomfort | 3 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded during the study period from the administration of the first dose of the study drug (Visit 2) to the completion of the End-of-study visit (Visit 6).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | 0.5 mL IMP - 5 mg SC Plasminogen (human) |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|----------------|
| Reporting group title | 0.5 mL Placebo |
|-----------------------|----------------|

Reporting group description: -

| Serious adverse events | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL Placebo | |
|---|--|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 2 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | 0.5 mL IMP - 5 mg SC Plasminogen (human) | 0.5 mL Placebo | |
|---|--|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 7 (85.71%) | 2 / 2 (100.00%) | |
| Nervous system disorders | | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |

| | | | |
|--|----------------|-----------------|--|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 2 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Ear pain | | | |
| subjects affected / exposed | 5 / 7 (71.43%) | 2 / 2 (100.00%) | |
| occurrences (all) | 5 | 2 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin reaction | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |

| | | | |
|---|----------------|---------------|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 12 February 2018 | Update of: inclusion/exclusion criteria, identified risks, and minimization actions, urinalysis, time windows for follow-up and end-of-study visit, study the administrative structure of the study, and contact prior safety reporting. Other implemented changes: revision of needle and syringe specifications, modification of screening number format, and clarification of safety procedure– unblinding. |
| 24 September 2018 | Some changes were implemented on the protocol in relation to the addition of an interim analysis after the last subject in cohort 1 completed a 1-month follow-up, and clarification of the study stopping rules for dose escalation and dose-limiting toxicities and added unblinding of subjects with SNHL assessed to be at least possibly related to study drug administration; update of language about masking of the non-test ear during PTA and removed the 0.25 kHz frequency for bone conduction, local anesthetic dosage, and chemistry tests; revision of timing of TMP size measurement, estimated last subject last visit date, and section to reflect under what circumstances unblinding would occur. At last, it was also clarified the injection performance language, the specific serum virology tests performed by the site's laboratory, and added asymptomatic abnormal physical examination finding to AE criteria. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 04 February 2019 | The study was prematurely terminated after 9 subjects were included. Study termination was due to slow enrollment and Prometic's development of a new formulation, and not based on any safety concerns. | - |

Notes:

Limitations and caveats

None reported