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