

**Clinical trial results:****A Phase 2/3, Open-Label, Repeat-Dose Study of the Pharmacokinetics, Efficacy, and Safety of ProMetic Plasminogen Intravenous Infusion in Subjects with Hypoplasminogenemia****Summary**

EudraCT number	2015-005490-20
Trial protocol	NO
Global end of trial date	08 October 2018

Results information

Result version number	v1 (current)
This version publication date	29 May 2021
First version publication date	29 May 2021

Trial information**Trial identification**

Sponsor protocol code	2002C011G
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02690714
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Prometic Biotherapeutics Inc.
Sponsor organisation address	1330 Piccard Drive, Suite 201, Rockville, United States, MD 20850
Public contact	Medical Officer, Prometic Biotherapeutics Inc., 301 549-9761, clinical@prometic.com
Scientific contact	Medical Officer, Prometic Biotherapeutics Inc., 301 549-9761, 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	23 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2018
Global end of trial reached?	Yes
Global end of trial date	08 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To achieve an increase of individual trough plasminogen activity by at least an absolute 10% (i.e., 10 U/dL) from baseline during the 12 weeks of plasminogen replacement therapy in Segment 2; and to evaluate the efficacy of plasminogen replacement therapy on clinically evident or visible symptoms of hypoplasminogenia during the 48 weeks of dosing in Segments 2 and 3.

Protection of trial subjects:

A Safety Monitoring Committee (SMC) composed of the sponsor's Medical Monitor and an independent Medical Monitor reviewed study safety data biweekly during Segments 1 and 2, and periodically during Segment 3.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	15
EEA total number of subjects	3

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)	4
Adolescents (12-17 years)	2
Adults (18-64 years)	9
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

This study was conducted at 2 sites, 1 in the United States (US) and 1 in Norway. The first participant was screened in May 2016 and the last participant visit was in October 2018.

Pre-assignment

Screening details:

Subjects were screened for study eligibility within a period of no more than 21 days before the start of dosing.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Plasminogen (Human) Intravenous
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Arm description:

6.6 mg/kg Plasminogen (Human) Intravenous given every 2 to 4 days by a 10- to 30- minute intravenous infusion

Arm type	Experimental
Investigational medicinal product name	Ryplazim
Investigational medicinal product code	
Other name	Plasminogen (Human)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

6.6 mg/kg given as a single dose in segment 1, and repeat doses in Segments 2 and 3

Number of subjects in period 1	Plasminogen (Human) Intravenous
Started	15
Segment 1	9 ^[1]
Segment 2	15
Segment 3	15
Segment 3 (Wk 48 - Completed)	15
Post Week-48	12
Completed	10
Not completed	5
Consent withdrawn by subject	1
Physician decision	1
Norway participants did not continue on post Wk48	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Six participants skipped Segment 1 as they had PK data from Phase 1 study 2002C005G (allowed per protocol).

Baseline characteristics

Reporting groups

Reporting group title	Plasminogen (Human) Intravenous
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Reporting group description:

6.6 mg/kg Plasminogen (Human) Intravenous given every 2 to 4 days by a 10- to 30- minute intravenous infusion

Reporting group values	Plasminogen (Human) Intravenous	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	4	4	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	9	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	23.0		
standard deviation	± 13.05	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	4	4	
Race (NIH/OMB)			
Units: Subjects			
White	15	15	
Race/Ethnicity, Customised			
Units: Subjects			
Hispanic/Latino	1	1	
Non-Hispanic/Latino	14	14	
Region of Enrollment			
Units: Subjects			
United States	12	12	
Norway	3	3	
Visible and Non-Visible Lesions by Participant			
Units: Subjects			
None	4	4	
> = 1 Visible or non-visible lesion	11	11	
Plasminogen Activity			
Units: Subjects			

Plasminogen activity <5-10%	3	3	
Plasminogen activity 11-20%	4	4	
Plasminogen activity 21-30%	6	6	
Plasminogen activity 31-40%	1	1	
Plasminogen activity 41-45%	1	1	
Plasminogen activity >45%	0	0	
Plasminogen antigen Units: Subjects			
Plasminogen antigen <0.5-3.0 mg/dL	4	4	
Plasminogen antigen 3.1-6.0 mg/dL	10	10	
Plasminogen antigen 6.1-2.0 mg/dL	1	1	
Plasminogen antigen >20.0 mg/dL	0	0	
Quality of Life Assessment			
For the Quality of Life (QOL) assessment, participants were asked to rate their overall QOL using an 11-point scale (0 = Non functioning, 10 = normal);the QOL scale was adapted from a scale developed by the American Chronic Pain Association			
Units: Subjects			
QOL score = 0	0	0	
QOL score = 1	0	0	
QOL score = 2	0	0	
QOL score = 3	0	0	
QOL score = 4	0	0	
QOL score = 5	0	0	
QOL score = 6	1	1	
QOL score = 7	3	3	
QOL score = 8	1	1	
QOL score = 9	1	1	
QOL score = 10	9	9	
Weight Units: kilogram(s)			
arithmetic mean	60.37		
standard deviation	± 26.803	-	
Plasminogen Activity			
Plasminogen % activity is a measurement of functional plasminogen levels.			
Units: percent			
arithmetic mean	21.1		
standard deviation	± 10.83	-	
Plasminogen antigen Units: mg/dL			
arithmetic mean	4.7		
standard deviation	± 3.7	-	

End points

End points reporting groups

Reporting group title	Plasminogen (Human) Intravenous
Reporting group description:	
6.6 mg/kg Plasminogen (Human) Intravenous given every 2 to 4 days by a 10- to 30- minute intravenous infusion	

Primary: Overall Clinical Success in Number and Size of Lesions as Measured by Photographic or Other Imaging Modality Depending on the Organ System Affected or Change in Affected Organ Functionality at 48 Weeks

End point title	Overall Clinical Success in Number and Size of Lesions as Measured by Photographic or Other Imaging Modality Depending on the Organ System Affected or Change in Affected Organ Functionality at 48 Weeks ^[1]
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End point description:

Overall clinical success was defined as 50% of participants with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Visible lesions were defined as dimensions could have been assessed by medical imaging studies (eg, computed tomography, magnetic resonance imaging, ultrasound, etc) or functional assessments (eg, spirometry, audiogram, oximetry, etc.). Visible lesions that had both a length and width as measured by the 1mm scale, were referred to as "measurable lesions", and visible lesions that were too small to measure by the 1mm scale (length and/or width could not have been measured) were referred to as "non-measurable lesions".

End point type	Primary
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End point timeframe:

48 Weeks

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: Given the ultra-rarity of the disease and study design, all data were presented descriptively.

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[2]			
Units: Lesions				
Number of lesions analysed at baseline	47			
Visible lesions at baseline	32			
Non-Visible lesions at baseline	15			
Total Visible/Non-Visible lesions resolved Wk 48	34			
Total Visible/Non-Visible lesions improved Wk 48	10			
Not applicable (not assessed) Wk 48	3			

Notes:

[2] - All 15 participants were assessed, but only 11 had visible and/or non-visible lesions at baseline.

Statistical analyses

No statistical analyses for this end point

Primary: Number and Percentage of Participants Who Achieved the Target Plasminogen Activity Trough Levels for at Least 3 Measurements in 12 weeks During Segment 2

End point title	Number and Percentage of Participants Who Achieved the Target Plasminogen Activity Trough Levels for at Least 3 Measurements in 12 weeks During Segment 2 ^[3]
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End point description:

Plasminogen activity is a measurement of functional plasminogen levels and is therefore the most accurate and specific method to quantify active Plasminogen (Human) Intravenous concentration in participant's plasma. Primary endpoint success was defined as at least 80% of evaluable participants (ie, 8 or more) achieving the target trough levels for at least 3 measurements in 12 weeks. The target trough level was defined as an increase in plasminogen activity level of at least an absolute 10% (10 U/dL) from the participants individual baseline level.

End point type	Primary
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End point timeframe:

12 Weeks

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: Given the ultra-rarity of the disease and study design, all data were presented descriptively.

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants				
Number of participants	15			
Percentage of participants	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Clinical Success in Number and Size of Lesions as Measured by Photographic or Other Imaging Modality Depending on the Organ System Affected of Change in Affected Organ Functionality at 12 Weeks

End point title	Overall Clinical Success in Number and Size of Lesions as Measured by Photographic or Other Imaging Modality Depending on the Organ System Affected of Change in Affected Organ Functionality at 12 Weeks
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End point description:

Overall clinical success was defined as 50% of participants with visible of other measurable lesions achieving at least a 50% improvement in lesion number/size of functionality impact from baseline. Visible lesions were defined as lesions that could be imaged and analysed with digital photography. Non-visible lesions were defined as lesions whose dimensions could have been assessed by medical imaging studies (eg, computed tomography, magnetic resonance imaging, ultrasound, etc) or functional assessments (eg, spirometry, audiogram, oximetry, etc). Visible lesions that were too small to measure by the 1mm scale (length and/or width could not have been measured) were referred to as "non-measurable lesions".

End point type	Secondary
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End point timeframe:

12 Weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15 ^[4]			
Units: Number of Lesions				
Number of lesions analysed at baseline	47			
Visible lesions at baseline	32			
Non-visible lesions at baseline	15			
Total Visible/Non-Visible lesions resolved Wk 12	26			
Total Visible/Non-Visible lesions improved Wk 12	14			
Total Visible/Non-Visible lesions unchanged Wk 12	2			
Not applicable/Not assessed Wk 12	5			

Notes:

[4] - All 15 participants were assessed, but only 11 had visible and/or non-visible lesions at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression -Global Improvement (CGI-I) Scores at Week 12

End point title	Clinical Global Impression -Global Improvement (CGI-I) Scores at Week 12
End point description:	
CGI-I scores are measured at 12 and 48 weeks after study drug treatment. The CGI-I scale is a single, clinician completed scale designed to capture the clinician's impression of the participant's disease improvement over time.	
For this scale, clinicians were asked to consider their experience in this population and rate the change relative to the participant's state at Baseline using a 7-point scale (1 = very much improved, 7 = very much worse).	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants				
CGI score 0 = Not assessed : Week 12	0			
CGI score 1 = Very much improved : Week 12	11			
CGI score 2 = Much improved : Week 12	4			

CGI score 3 = Minimally improved : Week 12	0			
CGI score 4 = No change : Week 12	0			
CGI score 5 = Minimally worse : Week 12	0			
CGI score 6 = Much worse : Week 12	0			
CGI score 7 = Very much worse : Week 12	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression -Global Improvement (CGI-I) Scores at Week 48

End point title	Clinical Global Impression -Global Improvement (CGI-I) Scores at Week 48
End point description:	
CGI-I scores are measured at 12 and 48 weeks after study drug treatment. The CGI-I scale is a single, clinician completed scale designed to capture the clinician's impression of the participant's disease improvement over time. For this scale, clinicians were asked to consider their experience in this population and rate the change relative to the participant's state at Baseline using a 7-point scale (1 = very much improved, 7 = very much worse).	
End point type	Secondary
End point timeframe:	
48 weeks	

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants				
CGI score 0 = Not assessed : Week 48	0			
CGI score 1 = Very much improved : Week 48	13			
CGI score 2 = Much improved : Week 48	2			
CGI score 3 = Minimally improved : Week 48	0			
CGI score 4 = No change : Week 48	0			
CGI score 5 = Minimally worse : Week 48	0			
CGI score 6 = Much worse : Week 48	0			
CGI score 7 = Very much worse : Week 48	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Improved Quality of Life (QOL) Score After 12 Weeks of Study Treatment

End point title	Number of Participants With Improved Quality of Life (QOL) Score After 12 Weeks of Study Treatment
End point description: Quality of life score (QOL) was measured at baseline and at 12 and 48 weeks after study drug treatment. For the QOL assessment, participants were asked to rate their overall QOL using an 11-point scale (0 = non-functioning, 10 = normal). The QOL scale was adapted from a scale developed by the American Chronic Pain Association.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants				
QOL score = 0 : Week 12	0			
QOL score = 1 : Week 12	0			
QOL score = 2 : Week 12	0			
QOL score = 3 : Week 12	0			
QOL score = 4 : Week 12	0			
QOL score = 5 : Week 12	1			
QOL score = 6 : Week 12	0			
QOL score = 7 : Week 12	0			
QOL score = 8 : Week 12	0			
QOL score = 9 : Week 12	1			
QOL score = 10 : Week 12	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Improved Quality of Life (QOL) Score After 48 Weeks of Study Treatment

End point title	Number of Participants With Improved Quality of Life (QOL) Score After 48 Weeks of Study Treatment
End point description: Quality of life score (QOL) was measured at baseline and at 12 and 48 weeks after study drug treatment. For the QOL assessment, participants were asked to rate their overall QOL using an 11-point scale (0 = non-functioning, 10 = normal). The QOL scale was adapted from a scale developed by the American Chronic Pain Association.	
End point type	Secondary

End point timeframe:

48 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants				
QOL score = 0 : Week 48	0			
QOL score = 1 : Week 48	0			
QOL score = 2 : Week 48	0			
QOL score = 3 : Week 48	0			
QOL score = 4 : Week 48	0			
QOL score = 5 : Week 48	1			
QOL score = 6 : Week 48	0			
QOL score = 7 : Week 48	0			
QOL score = 8 : Week 48	0			
QOL score = 9 : Week 48	1			
QOL score = 10 : Week 48	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasminogen Activity Trough Levels between Week 2 and Week 120

End point title	Plasminogen Activity Trough Levels between Week 2 and Week 120
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End point description:

Plasminogen activity trough levels were measured at Weeks 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120.

End point type	Secondary
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End point timeframe:

Week 2 to Week 120

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Percentage of Activity				
arithmetic mean (standard deviation)				
Week 2 (n=14)	45.1 (± 15.05)			
Week 4 (n=15)	48.9 (± 14.56)			
Week 6 (n=15)	52.4 (± 11.45)			

Week 8 (n=15)	48.3 (± 17.43)			
Week 10 (n=15)	50.2 (± 12.39)			
Week 12 (n=15)	51.0 (± 12.01)			
Week 24 (n=15)	45.0 (± 12.88)			
Week 36 (n=15)	45.5 (± 13.18)			
Week 48 (n=15)	41.7 (± 16.99)			
Week 60 (n=13)	49.0 (± 8.88)			
Week 72 (n=12)	46.7 (± 10.97)			
Week 84 (n=12)	51.7 (± 20.76)			
Week 96 (n=9)	50.1 (± 20.08)			
Week 108 (n=7)	45.0 (± 25.19)			
Week 120 (n=2)	36.5 (± 12.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasminogen Antigen Trough Levels between Week 2 and Week 120

End point title	Plasminogen Antigen Trough Levels between Week 2 and Week 120
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End point description:

Plasminogen antigen trough levels were measured at weeks 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120.

End point type	Secondary
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End point timeframe:

Week 2 to Week 120

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 2 (n=14)	6.550 (± 3.0457)			
Week 4 (n=15)	7.800 (± 3.8813)			
Week 6 (n=15)	7.268 (± 3.3155)			
Week 8 (n=15)	6.607 (± 3.0046)			
Week 10 (n=15)	9.460 (± 7.1543)			
Week 12 (n=15)	7.340 (± 2.9342)			
Week 24 (n=15)	5.913 (± 2.2181)			
Week 36 (n=15)	6.667 (± 2.7336)			

Week 48 (n=15)	6.973 (± 3.1299)			
Week 60 (n=13)	6.415 (± 1.7578)			
Week 72 (n=12)	6.083 (± 2.2851)			
Week 84 (n=12)	7.183 (± 3.8129)			
Week 96 (n=9)	7.656 (± 4.2030)			
Week 108 (n=7)	6.529 (± 4.0852)			
Week 120 (n=2)	6.550 (± 6.2933)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) of Plasminogen Activity After First Dose and at Week 12

End point title	Half-life (t1/2) of Plasminogen Activity After First Dose and at Week 12
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End point description:

t1/2 is time required for the plasma concentration of Plasminogen to decrease 50% in the final stages of its elimination

End point type	Secondary
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End point timeframe:

First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Hours				
arithmetic mean (standard deviation)				
Mean (SD) t1/2 of plasminogen after the first dose	34 (± 11.73)			
Mean (SD) t1/2 of plasminogen at week 12	39.2 (± 6.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of Plasminogen Activity After the First Dose and at Week 12

End point title	AUClast of Plasminogen Activity After the First Dose and at Week 12
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End point description:

AUCLast is the area under the plasma concentration-curve of Plasminogen from time 0 to the last measured concentration

End point type	Secondary
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End point timeframe:

First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hr*%				
arithmetic mean (standard deviation)				
Mean (SD) AUCLast after first dose of plasminogen	3063.6 ($\pm$ 778.67)			
Mean (SD) AUCLast at Week 12	4656.0 ($\pm$ 1012.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Plasminogen Activity After First Dose and at Week 12

End point title	Cmax of Plasminogen Activity After First Dose and at Week 12
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End point description:

Cmax is the maximum plasma concentration of Plasminogen

End point type	Secondary
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End point timeframe:

First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: % of plasminogen activity				
arithmetic mean (standard deviation)				
Mean (SD) Cmax of plasminogen after first dose	95 ($\pm$ 23.5)			
Mean (SD) Cmax of plasminogen at Week 12	125 ($\pm$ 23.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: CI of Plasminogen Activity After First Dose and at Week 12

End point title	CI of Plasminogen Activity After First Dose and at Week 12
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End point description:

CI is the volume of plasma cleared of Plasminogen per unit time

End point type	Secondary
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End point timeframe:

First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mL/hr/kg				
arithmetic mean (standard deviation)				
Mean (SD) CI of plasminogen after first dose	1.44 (± 0.460)			
Mean (SD) CI of plasminogen at Week 12	0.92 (± 0.257)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCInf of Plasminogen Activity After First Dose and at Week 12

End point title	AUCInf of Plasminogen Activity After First Dose and at Week 12
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End point description:

AUCInf is the area under the plasma concentration-curve of Plasminogen from time 0 extrapolated to infinity

End point type	Secondary
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End point timeframe:

First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hr*%				
arithmetic mean (standard deviation)				

Mean (SD) AUCinf of plasminogen after first dose	3605.8 ($\pm$ 1023.88)			
Mean (SD) AUCinf of plasminogen at Week 12	5731.8 ($\pm$ 1431.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: MRTlast for Plasminogen Activity After First Dose and at Week 12

End point title	MRTlast for Plasminogen Activity After First Dose and at Week 12
End point description:	MRTlast is the mean residence time of Plasminogen from time 0 to the last measured concentration
End point type	Secondary
End point timeframe:	First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
arithmetic mean (standard deviation)				
Mean (SD) MRTlast of plasminogen after first dose	30.6 ($\pm$ 3.22)			
Mean (SD) MRTlast of plasminogen at Week 12	33.5 ($\pm$ 1.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vss for Plasminogen Activity After First Dose and at Week 12

End point title	Vss for Plasminogen Activity After First Dose and at Week 12
End point description:	Vss is the apparent volume of distribution at steady state of Plasminogen
End point type	Secondary
End point timeframe:	First dose and 12 weeks

End point values	Plasminogen (Human) Intravenous			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mL/kg				
arithmetic mean (standard deviation)				
Mean (SD) Vss of plasminogen after first dose	63.3 (± 11.44)			
Mean (SD) Vss of plasminogen at Week 12	49.3 (± 10.36)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety was assessed during the treatment period (up to 124 weeks) and a 30-day post-treatment period

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study drug treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Plasminogen (Human) Intravenous
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Reporting group description:

6.6 mg/kg Plasminogen (Human) Intravenous given every 2 to 4 days by a 10- to 30- minute intravenous infusion

Serious adverse events	Plasminogen (Human) Intravenous		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Surgical and medical procedures			
Ear operation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ossiculoplasty			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Plasminogen (Human) Intravenous		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	6		
Surgical and medical procedures			
Artificial crown procedure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Venipuncture			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Central venous catheter removal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth repair			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wisdom teeth removal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Feeling abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Infusion site erythema			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Infusion site discomfort			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site bruising			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Infusion site extravasation			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	11		
Infusion site swelling			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	11		
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	13		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Ovulation pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Uterine pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Vulvovaginal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	7		
Diaphragmatic disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Nasal oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasal discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasal congestion			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Haemoptysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Oropharyngeal discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	9		
Paranasal sinus discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	7		
Sinus congestion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sputum increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	6		

Mood altered subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3		
Panic attack subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Restlessness subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood iron decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood pressure systolic increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Progesterone decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Arthropod sting subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Contusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Joint injury			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chest injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Procedural vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Road traffic accident			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Scratch			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Tongue injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Procedural nausea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Ehlers-Danlos syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			

Cardiac flutter subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders			
Burning sensation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Dizziness subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 4		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Headache subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 37		
Migraine subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 4		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Post-traumatic headache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood and lymphatic system disorders			
Lymph node pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Ear and labyrinth disorders			

Deafness unilateral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Excessive cerumen production			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Motion sickness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tympanic membrane perforation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			
Conjunctival deposit			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye discharge			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eye inflammation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Eye irritation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	7		
Eye swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Abdominal pain lower			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	13		
Abdominal pain upper			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	14		
Aphthous ulcer			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Colitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Crohn's disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Dental caries			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	9		
Dry mouth			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Gastric dilatation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	6		
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Gingival bleeding			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	12		
Mouth ulceration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Hypoaesthesia oral subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Paraesthesia oral subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Proctalgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Tooth development disorder subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vomiting subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 7		
Skin and subcutaneous tissue disorders			
Petechiae subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Erythema subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rash erythematous subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rash subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 6		
Pruritus			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Swelling face			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin exfoliation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tumour pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Urinary tract pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Back pain			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Flank pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	7		
Fungal infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastroenteritis norovirus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Influenza			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Hordeolum			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
H1N1 influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences (all)	17		
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	9		
Tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2016	- Change to PK sampling time at 96 hours post-dose for PK profile - Option of every fourth day dosing interval, according to the PK profile - Peak expiratory flow (PEF) added as an indicator of lung functionality tests - A definition of primary endpoint success added - Description of CGI scale updated - Description of the quality-of-life scale updated Additional administrative corrections and clarifications.
13 June 2016	- Added 1 primary and 1 secondary objective - Modified the secondary endpoint to reflect 48 weeks of duration - Added 3 subjects to the total number of subjects in order to increase the number of subjects with potentially measurable or visible lesions - Added a specified duration of treatment for Segment 3 in Norway and clarified that only subjects in the US will receive at home administration of IMP - Added a maximum dose adjustment algorithm in the event that a subject does not have a complete clinical response - Change made to allow for flexibility in the selection of the clinical specialty laboratory and added retention samples for plasminogen activity and antigen levels to allow for repeat testing if requested - Added retention samples for plasminogen antibodies to allow for repeat testing if requested - Added graded evaluation of clinical responses to provide additional details to the efficacy analysis Additional administrative clarifications and corrections.
03 November 2016	- Remove US specific wording to allow subjects in Norway to receive at home administration of IMP during Segment 3 - The duration window of the Plasminogen IV infusion was expanded to 10 to 30 minutes based on the actual experience of the subjects - The results of the Phase 1 study were updated to reflect the current findings from the study - Visit windows extended for Segment 3 visits and added for Safety Follow-up, 30 days post final dose, to allow flexibility in scheduling visits - The requirement for chest X-ray at Week 12 was revised to "at the investigator's discretion" as this test was only relevant for subjects who had lesions with respiratory involvement Additional administrative clarifications and corrections.
19 December 2016	- The requirement for chest X-ray at baseline was revised to "at the investigator's discretion" as this test was only relevant for subjects who had lesions with respiratory involvement - Added that Clinical Global Impression and Quality of life assessment will be performed at the Week 48 Visit only in Segment 3 Additional administrative clarifications and corrections.

08 August 2018	- IMP vial concentration has been revised from 5.0 mg/mL to 5.5 mg/mL to reflect the true concentration and dosing - Subject dosing was revised from 6.0 mg/kg to 6.6 mg/kg of plasminogen to reflect the true concentration and dosing - Due to delay in market approval, subjects at the United States site will be given the option to enroll in Treatment Protocol 2002C018G without interrupting treatment - Clinical experience with Plasminogen has been revised to include most recent data - Revision was implemented to add an End of Study visit for Subjects at the US Site Only who decide to enter Treatment Protocol 2002C018G and related assessments -Subjects' infusions window for both Segment 2 and Segment 3 has been specified as +/- 1 day per Addendum dated 28Apr2017 - No backup sample for Plasminogen activity and antigen/antibody testing is needed at the End of Study visit for subjects who decide to enter the treatment protocol - Text updated to indicate that subjects will return the diary at the End of Study visit or Safety Follow-Up visit - Plasminogen administration procedures were updated per Addendum dated 24May2017. In June 2017, Prometic Biotherapeutics started using the 5 µM B.Braun disk filters instead of the MINSART 1.2 µM Syringe Filters Additional administrative clarifications and corrections.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported