Clinical trial results:
A Historically-Controlled Phase II/III study to Evaluate Efficacy and Safety of Kedrion Human Plasminogen Eye Drop Preparation in Patients Diagnosed with Ligneous Conjunctivitis

Summary

EudraCT number	2012-001340-21
Trial protocol	IT
Global end of trial date	04 December 2020

Results information

Result version number	v1 (current)
This version publication date	26 December 2021
First version publication date	26 December 2021

Trial information

Trial identification

Sponsor protocol code	KB046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01554956
WHO universal trial number (UTN)	-
Other trial identifiers	14953: IND Number

Notes:

Sponsors

Sponsor organisation name	Kedrion SpA
Sponsor organisation address	Loc. Ai Conti , Castelvecchio Pascoli Barga (Lucca), Italy, 55051
Public contact	Clinical Operations, Kedrion SpA, +39 05831969231, a.lotti@kedrion.com
Scientific contact	Clinical Operations, Kedrion SpA, +39 05831969231, a.lotti@kedrion.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	20 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2014
Global end of trial reached?	Yes
Global end of trial date	04 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.Evaluation of the efficacy of the IMP, Kedrion Human Plasminogen eye drop preparation, for the treatment of Ligneous Conjunctivitis associated with Type I plasminogen deficiency in symptomatic subjects, measured by relapse of pseudomembranes after complete regression due to surgery or treatment with the IMP .
2.Evaluation of the safety of the IMP in symptomatic subjects and asymptomatic subjects with a history of ocular pseudomembranes.

Protection of trial subjects:

This study was conducted in compliance with the United States (US) Food and Drug Administration (FDA) regulations and guidelines, International Conference on harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1 and R2), 2002, European Medicinal Agency (EMA) regulations, Italian applicable regulations, and guidelines and principles of the Declaration of Helsinki.
Informed consent or assent for patients deemed legally incompetent (such as a minor child) was obtained in compliance with GCP, the recommendations of the Declaration of Helsinki before entering into the study or commencement of study procedure/investigations. An additional Consent Form for Genetic Test optional was collected. There also was a separate ICF and/or assent for additional subjects entering only into the Part 2 of the study (Continuation Segment).

Background therapy:

Kedrion Human Plasminogen is a sterile human plasma derived plasminogen preparation in the pharmaceutical form of an eye drop solution for topical ocular use. The final plasminogen eluate was formulated in saline, concentrated to a protein concentration of 1 g/L, nanofiltered, and dispensed. The IMP was a frozen solution, supplied in a vial of neutral clear glass containing 1ml of a 1 mg/ml sterile solution of protein of which at least 93% is plasminogen.

Evidence for comparator: -

Actual start date of recruitment	22 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	77 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	12
EEA total number of subjects	4

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)	3
Children (2-11 years)	7
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 13 subjects were screened (11 in Part 1 and 2 in Part 2) of which 12 subjects (24 eyes) were enrolled in the study (11 in Part 1 and 1 in Part 2) and 1 subject who failed screeening in Part 2. All subjects enrolled in Part 1 of the study were symptomatic at screening, so all were included in Group 1. No subjects were included in Group 2.

Pre-assignment

Screening details:

The study was divided in Part 1 (Segment 1 and Segment 2) and Part 2 (Continuation Segment). The screening procedures were performed within a 30-day window prior to receiving the first study IMP administration. A second screening for additional two subjects was performed before entering in the Part 2 of the study.

Period 1

Period 1 title	Treatment (part 1 + part 2) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Group 1 (1A)

Arm description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing complete pseudomembranes regression (defined as >90%). They have continued to received IMP at a reduced dose for an additional 8 weeks (Segment 2).

Arm type	Experimental
Investigational medicinal product name	Kedrion Plasminogen (Human) eye drop preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

The study product was administered at a dose of 2 drops/eye, 8 times/day for 4 weeks (Segment 1). Then the IMP was administered at a reduced dose of 2 drops/eye 6 times/day for an additional 8 weeks (Segment 2). Subjects self-applied IMP by dropping solution into the open eye, directly from a syringe barrel. Subjects were given strict instructions about the storage and use of the IMP during their home treatment regimen. Study participants collected data on IMP administrations occurring at home in a Sponsor-issued Subject Diary.

Arm title	Group 1 (1B)

Arm description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing partial (defined as between 20% and 90%) or no pseudomembranes regression (defined as <20%). They were to undergo surgery, within 2 weeks from the end of Segment 1, to remove the pseudomembranes. After surgery, subjects were to continue receiving IMP for an additional 8 weeks, at the decreasing frequency.

Arm type	Experimental
Investigational medicinal product name	Kedrion Plasminogen (Human) eye drop preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

The study product was administreted at a dose of 2 drops/eye, 8 times/ for 4 weeks. After surgery, the IMP was administered 2 drops per eye at a descending dose for an additional 8 weeks: 12 times/day for 1 week, then 8 times/day for 3 weeks, and lastly, 6 times/day for the remaining 4 weeks. Subjects awaiting surgery (within 2 weeks from the end of Segment 1) were to receive up to 2-week continued IMP treatment at the Segment 1 dose. In case of relapse occurring more than 2 weeks after surgery, the subject was given the option to repeat the IMP treatment according to the above described descending dose frequency. Subjects self-applied IMP by dropping solution into the open eye, directly from a syringe barrel. Subjects were given strict instructions about the storage and use of the IMP during their home treatment regimen. Study participants collected data on IMP administrations occurring at home in a Sponsor-issued Subject Diary

Arm title	Continuation Segment (Part 2)

Arm description:

Subjects demonstrating complete treatment success (defined as regression of pseudomembranes in Segment 1 and no relapse of pseudomembranes through Segment 2) at the end of the Segment 2 were entered the Continuation Segment and one additional patient, who entered directly in the Part 2, without previously completing the first part of the study.

Arm type	Experimental
Investigational medicinal product name	Kedrion Plasminogen (Human) eye drop preparation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

The study product was administreted at a dosage regimen of 2 drops/eye 4 to 6 times/day at Investigator’s discretion. Subjects self-applied IMP by dropping solution into the open eye, directly from a syringe barrel. Subjects were given strict instructions about the storage and use of the IMP during their home treatment regimen. Study participants collected data on IMP administrations occurring at home in a Sponsor-issued Subject Diary.

Number of subjects in period 1	Group 1 (1A)	Group 1 (1B)	Continuation Segment (Part 2)
Started	4	7	10
Completed	4	6	11
Not completed	0	1	0
Consent withdrawn by subject	-	1	-
Joined	0	0	1
Late recruitment	-	-	1
Late recruitment reason			due to amendment

Baseline characteristics

Reporting groups[1]	
Reporting group title	Group 1 (1A)

Reporting group description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing complete pseudomembranes regression (defined as >90%). They have continued to received IMP at a reduced dose for an additional 8 weeks (Segment 2).

Reporting group title	Group 1 (1B)

Reporting group description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing partial (defined as between 20% and 90%) or no pseudomembranes regression (defined as <20%). They were to undergo surgery, within 2 weeks from the end of Segment 1, to remove the pseudomembranes. After surgery, subjects were to continue receiving IMP for an additional 8 weeks, at the decreasing frequency.

Reporting group title	Continuation Segment (Part 2)

Reporting group description:

Subjects demonstrating complete treatment success (defined as regression of pseudomembranes in Segment 1 and no relapse of pseudomembranes through Segment 2) at the end of the Segment 2 were entered the Continuation Segment and one additional patient, who entered directly in the Part 2, without previously completing the first part of the study.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of subjects enrolled in the trial was 12. According to study design 11 subjects were enrolled in the first part of the study and an additional subject was enrollled directly in the second part of the study.

Reporting group values	Group 1 (1A)	Group 1 (1B)	Continuation Segment (Part 2)
Number of subjects	4	7	11
Age categorical			
The Demographics and baseline characteristics were tabulated only for the reporting groups.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	2	1	3
Children (2-11 years)	1	5	7
Adults (18-64 years)	1	1	1
Age continuous			
Units: years			
arithmetic mean	12.0	8.4	7.7
standard deviation	± 21.34	± 10.66	± 12.41
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	1	3	4
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
White	4	7	11
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
other	0	0	0

Reporting group values	Total		
Number of subjects	12		
Age categorical			
The Demographics and baseline characteristics were tabulated only for the reporting groups.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	3		
Children (2-11 years)	7		
Adults (18-64 years)	2		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	7		
Male	5		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
White	12		
Black or African American	0		
Native Hawaiian or other Pacific Islander	0		
other	0		

End points

End points reporting groups

Reporting group title	Group 1 (1A)

Reporting group description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing complete pseudomembranes regression (defined as >90%). They have continued to received IMP at a reduced dose for an additional 8 weeks (Segment 2).

Reporting group title	Group 1 (1B)

Reporting group description:

Symptomatic subjects with ocular pseudomembranes in one or both eyes at screening who received the IMP for 4 weeks (Segment 1) and with eyes showing partial (defined as between 20% and 90%) or no pseudomembranes regression (defined as <20%). They were to undergo surgery, within 2 weeks from the end of Segment 1, to remove the pseudomembranes. After surgery, subjects were to continue receiving IMP for an additional 8 weeks, at the decreasing frequency.

Reporting group title	Continuation Segment (Part 2)

Reporting group description:

Subjects demonstrating complete treatment success (defined as regression of pseudomembranes in Segment 1 and no relapse of pseudomembranes through Segment 2) at the end of the Segment 2 were entered the Continuation Segment and one additional patient, who entered directly in the Part 2, without previously completing the first part of the study.

Subject analysis set title	Group 1A_mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified ITT (mITT) population consists of all eyes of subjects assigned to Groups 1A at the start of Study Segment 2, who received at least one dose of the study treatment, and underwent at least one efficacy assessment in Segment 2

Subject analysis set title	Group 1B _mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified ITT (mITT) population consists of all eyes of subjects assigned to Group 1B at the start of Study Segment 2, who received at least one dose of the study treatment, and underwent at least one efficacy assessment in Segment 2

Subject analysis set title	Group 1_ mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population consists of all eyes assigned to Groups 1A and 1B at the start of study segment 2, who received at least one dose of the study treatment, and had at least one efficacy assessment in Segment 2.

Subject analysis set title	Group 1A_PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol population consists of all eyes of Group 1A subjects included in the mITT population, who have completed both Segment 1 and Segment 2 of the study and received at least 80% of the protocol-required doses of the study treatment without any major protocol violations or exceptions that could impact the integrity of study data.

Subject analysis set title	Group 1B_PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol population consists all eyes of Gruop 1B subjects included in the mITT population, who have completed both Segment 1 and Segment 2 of the study and received at least 80% of the protocol-required doses of the study treatment without any major protocol violations or exceptions that could impact the integrity of study data.

Subject analysis set title	Group 1_PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol population includes all eyes of patients included in the mITT population, who have

completed both Segment 1 and Segment 2 of the study and received at least 80% of the protocol-required doses of the study treatment without any major protocol violations or exceptions that could impact the integrity of study data.

Subject analysis set title	Group 1A_Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population consists of all Group 1A enrolled subjects who received at least one dose of the study treatment

Subject analysis set title	Group 1B_Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population consists of all Group 1B enrolled subjects who received at least one dose of the study treatment

Subject analysis set title	Continuation Segment_Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population includes all subjects who received at least one dose of the study drug in the continuation segment period.

Primary: Proportion of Success to Prevent Pseudomembranes Relapse

End point title	Proportion of Success to Prevent Pseudomembranes Relapse[1]

End point description:

The primary endpoint (prevention of pseudomembrane relapse) was presented descriptively based on the predefined success levels: complete success (defined as no relapse by the end of Segment 2), partial success(defined as relapse appearing 2 weeks or longer after the start of Segment 2, or if following the 3 rd cycle of Segment 2 for Group 1A no relapse occurred while maintaining the higher dose) or failure (defined as relapse within 2 weeks of the start of Segment 2 or if at repeat cycles of Segment 1 for Group 1A, the pseudomembranes did not regress after Segment 1).
Ninety-five percent confidence intervals for the relapse rate (complete success, and complete plus partial success) were calculated on the assumption of a binomial distribution. The responses were tabulated for the mITT and Per Protocol populations.

End point type	Primary

End point timeframe:

The prevention of pseudomembrane relapse was calculated in the Segment 2 after initial total regression at the end of Segment 1 or after surgical excision in cases where there was no regression of pseudomembranes or partial regression.

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: Descriptive statistics was applied to describe the study observations.

End point values	Group 1A_mITT	Group 1B _mITT	Group 1A_PP	Group 1B_PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[2]	7[3]	3[4]	6[5]
Units: percentage of eyes				
number (confidence interval 95%)				
success	75 (19.4 to 99.4)	81.8 (48.2 to 97.7)	100 (29.2 to 100)	100 (66.4 to 100)
partial success	0 (0 to 60.2)	18.2 (2.3 to 51.8)	0 (0 to 70.8)	0 (0 to 33.6)
failure	25 (0.6 to 80.6)	0 (0 to 28.5)	0 (0 to 70.8)	0 (0 to 33.6)

Notes:

[2] - number of eyes evaluable = 4

[3] - number of eyes evaluable = 11

[4] - number of eyes evaluable = 3

[5] - number of eyes evaluable = 9

Statistical analyses

No statistical analyses for this end point

Secondary: Regression in Surface Area of Existing Ligneous Pseudomembranes

End point title	Regression in Surface Area of Existing Ligneous Pseudomembranes

End point description:

The secondary endpoint was presented descriptively based on the predefined success levels: complete success (defined as regression of PSAs >90%), partial success (defined as regression of PSAs between 20% and 90%) or failure (defined as regression of PSAs <20%). The responses were tabulated for the mITT and the Per Protocol populations.

End point type	Secondary

End point timeframe:

The regression of pseudomembrane surface area (PSA) of Existing Ligneous Pseudomembranes was calculated from baseline to the end of Segment 1.

End point values	Group 1_ mITT	Group 1_PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[6]	9[7]		
Units: percentage of eyes				
number (confidence interval 95%)				
complete success	20 (4.3 to 48.1)	25 (5.5 to 57.2)		
partial success	46.7 (21.3 to 73.4)	58.3 (27.7 to 84.8)		
failure	33.3 (11.8 to 61.6)	16.7 (2.1 to 48.4)		

Notes:

[6] - number of eyes evaluable = 15

[7] - number of eyes evaluable = 12

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Antibody Development against aprotinin

End point title	Antibody Development against aprotinin

End point description:

The safety parameters were presented descriptively and tabulated for the Gruop 1A, Group 1B and Continuation Segment safety population.

End point type	Other pre-specified

End point timeframe:

The antibody development was detected during Part 1 and Part 2 of the study.

End point values	Group 1A_Safety population	Group 1B_Safety population	Continuation Segment_Safety population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	7	11	
Units: number of subjects				
New antibody development	0	3	3	
Antibodies Increasing	0	1	0	
Antibody Decreasing	0	1	0	
Antibody no changes	0	1	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Antibody Development against human plasminogen

End point title	Antibody Development against human plasminogen

End point description:

The safety parameters were presented descriptively and tabulated for the Gruop 1A, Group 1B and Continuation Segment safety population.

End point type	Other pre-specified

End point timeframe:

The antibody development was detected during the Part 1 and Part 2 of the study.

End point values	Group 1A_Safety population	Group 1B_Safety population	Continuation Segment_Safety population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	7	11	
Units: number of subjects				
New Antibodies Development	0	1	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the screening visit and throughout the study.

Adverse event reporting additional description:

AEs were collected by spontaneous reporting by the patient, by review of the Subject Diaries, and, during the visits at site, by asking the patient non-leading questions about how they felt since their last study visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Group 1 (1A)

Reporting group description:

Patients with eyes showing complete pseudomembranes regression (defined as >90%) who have received IMP at a dose of 2 drops/eye 6 times/day for 8 weeks.

Reporting group title	Group 1 (1B)

Reporting group description:

Patients with eyes showing partial (defined as between 20% and 90%) or no pseudomembranes regression (defined as <20%) were to undergo surgery, within 2 weeks from the end of Segment 1, to remove the pseudomembranes. After surgery, patients were to continue receiving IMP (2 drops/eye) for an additional 8 weeks, at the decreasing frequency.

Reporting group title	Continuation Segment

Reporting group description:

Subjects demonstrating complete treatment success (defined as regression of pseudomembranes in Segment 1 and no relapse of pseudomembranes through Segment 2) at the end of part 1 and one additional patient, who entered directly, without previously completing the first part of the study were to receive IMP at a dosage regimen of 2 drops/eye 4 to 6 times/day at Investigator's discretion.

Serious adverse events	Group 1 (1A)	Group 1 (1B)	Continuation Segment
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	3 / 7 (42.86%)	3 / 11 (27.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug specific antibody present	Additional description: Anti-plasminogen antibody		

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Varicella			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group 1 (1A)	Group 1 (1B)	Continuation Segment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	7 / 7 (100.00%)	10 / 11 (90.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 7 (42.86%)	7 / 11 (63.64%)
occurrences (all)	3	3	7
Axillary pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Immune system disorders			
Multiple allergies			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Cervix disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Genital labial adhesions			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 4 (75.00%)	2 / 7 (28.57%)	6 / 11 (54.55%)
occurrences (all)	3	2	6
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	3 / 4 (75.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	3	0	2
Rhinorrhoea			
subjects affected / exposed	2 / 4 (50.00%)	1 / 7 (14.29%)	3 / 11 (27.27%)
occurrences (all)	2	1	3
Sneezing			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	4 / 11 (36.36%)
occurrences (all)	0	0	4
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pharyngeal erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Wheezing			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Investigations			
Liver palpable subcostal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Antibody test positive	Additional description: Antibody anti-aprotinin		
subjects affected / exposed	0 / 4 (0.00%)	4 / 7 (57.14%)	4 / 11 (36.36%)
occurrences (all)	0	4	4
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Heart rate irregular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Procedural pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	2 / 11 (18.18%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Middle ear effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tympanic membrane perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Conjunctivitis bacterial			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	2
Ectropion			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Eyelid margin crusting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	3 / 11 (27.27%)
occurrences (all)	0	1	3
Ocular hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Blepharitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Conjunctival disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Conjunctival oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	4 / 11 (36.36%)
occurrences (all)	0	0	4
Eye discharge			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Eye swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Pinguecula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	2	0	2
Hypoaesthesia oral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dental caries			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Gingival disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Gingival oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Rectal prolapse			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Teething			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tooth loss			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Rash papular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Subcutaneous haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Osteoarthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Synovial cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Infections and infestations			
Candida nappy rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	5 / 11 (45.45%)
occurrences (all)	1	0	5
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	5 / 11 (45.45%)
occurrences (all)	0	1	5
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vulvovaginitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Acute tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gingivitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Herpangina			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Molluscum contagiosum			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	4 / 11 (36.36%)
occurrences (all)	0	0	4
Skin papilloma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2013	Protocol Amendment 1 - The main revisions were: Revision of the Inclusion and Exclusion Criteria for further clarity. Addition in the primary and secondary efficacy endpoints of the definitions: of "no-", "partial-", and "complete pseudomembranes regression". Clarification of the requirements for the Follow-up and Continuation Periods. Clarification of the procedures to be followed in each Study Segment. Revision of the Duration of Treatment section for each Segment to better explain the options of Group Assignment depending on the presence, absence, relapse, or regression of the pseudomembranes.
19 June 2014	Protocol Amendment 2 - The main revisions were: Provisions for the enrolment of up to two additional asymptomatic patients directly into the Continuation Segment (i.e., without completing Segments 1 and 2), after Groups 1 and 2 are fully enrolled. The dosing regimen and assessment schedule for these patients were also clarified. Clarification that enrolment in Group 2 is not mandatory, but should not exceed 5 patients. Clarification of the requirements for taking photographs as part of the ophthalmology examinations. Addition of a mandatory visit (Visit 5) 6 months after the start of the Continuation Segment. Clarification regarding the viral screening tests. The schedule of immunogenicity assessments have been corrected. The maximum study duration was clarified.
08 June 2015	Protocol Amendment 3 - The main revisions were: Extension of the Continuation Segment, with follow-up visits completed every 6 months, to collect safety information. Clarification that any additional (unscheduled) visits and assessments (apart from the 6-month visits) during the Continuation Segment will occur at the investigator's discretion. The ranges for plasminogen antigen and activity for the diagnosis of Type 1 Plasminogen deficiency, were defined. Inclusion of rules for reporting of AEs related to development/increase in the titre of antibodies against plasminogen and aprotinin. End of study was defined as the last safety follow-up visit scheduled after product licensure.
01 September 2016	Protocol Amendment 4 - The main revisions were: The frequency of immunogenicity evaluations during the Continuation Segment was revised from every 6 months to every 2 months. Clarification of assay methods for immunogenicity testing (Enzyme-Linked Immunosorbent Assay [ELISA]), plasminogen antigen (nephelometric immunoassay), and plasminogen activity (chromogenic assay).
04 January 2017	Protocol Amendment 5 - The main revisions were: Provisions for (optional) utilization of a Home Health Agency to collect samples every 2 months outside of the investigational site during the Continuation Segment. These provisions applied to the immunogenicity samples collected every 2 months (apart from the 6-month visits collected at the site), and required patient consent prior to implementation. Requirement to report all events of anti-human plasminogen antibody positivity to Kedrion no later than 48 hours after learning about the event.
10 January 2019	Protocol Amendment 6 - The main revisions were: In order to better monitor the effect of possible development of anti-plasminogen antibodies, specific safety questions were included in the monthly phone calls. Clarification that any event of anti-plasminogen antibody positivity was to be treated as expedited even if this finding was not indicative of the presence of neutralizing antibodies based on clinical evidence. Clarification that patients withdrawn from the study would not be replaced. Removal of the requirement to report AEs occurring during or within 24 hours following treatment with IMP as treatment-related (due to the IMP administration schedule, this requirement was not applicable to the current study). Change in the efficacy analysis population, from ITT to the mITT and Per Protocol populations. Clarification that for each patient, each eye was to be analyzed independently of the other eye.

13 January 2020	Protocol Amendment 7 - The main revisions were: Removal of the plasminogen antigen and activity evaluation at the Termination 2 Visit, considering that 1) the level of serum plasminogen and its activity are not expected to be affected by the treatment; 2) The large majority of the study population are children and it is therefore appropriate to avoid unnecessary blood draws.
15 September 2020	Protocol Amendment 8 - The main revisions were: In order to allow continued product availability and treatment to patients before commercialization, a Sponsor-Initiated EAP was developed in the US. As of 2 April 2020, no patient was treated under the KB046 protocol in Italy. Accordingly, treatment and follow-up in the Continuation Segment was to continue until the Sponsor-Initiated EAP was initiated (instead of until commercialization). End of study was redefined as the last safety follow-up information (immunogenicity results) received by investigators.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported