Clinical trial results:
Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa

Summary

EudraCT number	2016-002066-32
Trial protocol	GB IE AT DE ES GR HU CZ BE DK IT HR FR RO
Global end of trial date	27 May 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	BEB-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03068780
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amryt Research Limited
Sponsor organisation address	45 Mespil Road, Dublin, Ireland, Dublin 4
Public contact	Janet Boylan, Amryt Research Limited, 00353 15180200, janet.boylan@amrytpharma.com
Scientific contact	Janet Boylan, Amryt Research Limited, 00353 15180200, janet.boylan@amrytpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001299-PIP03-17
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	01 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2022
Global end of trial reached?	Yes
Global end of trial date	27 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the double-blind phase was to compare the efficacy of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B) in the promotion of healing of EB partial thickness wounds. This was assessed as evidenced by the incidence of the first complete closure of the EB target wound (defined as EB partial thickness wound of 10 cm2 to 50 cm2 in size aged >=21 days and <9 months in subjects with inherited EB (subtypes DEB, JEB, or Kindler EB) within 45+-7 days of treatment.

Protection of trial subjects:

Adverse events (AEs) were continuously monitored throughout the study from signing of informed consent until the last follow up assessment. Each AE reported was assessed by a trained Research Physician who ensured that the event was dealt with as appropriate based on clinical need, study protocol and the clinical pharmacology unit (CPU) standard operating procedures (SOPs).
The study was conducted by experienced Investigators and well trained medical, nursing and technical staff with ample experience in the conduct of phase 3 clinical trials.
The study was designed to closely monitor, treat and communicate potential expected adverse reactions (based on the known mode of action of the IMP and the previous studies with similar compounds) as well as potential unexpected adverse events.
Subjects and/or his/her legal representatives had the right to withdraw from the study at any time for any reason without prejudice to their future medical care.
Medical information about individual subjects obtained in the course of this study was confidential and could not be disclosed to third parties, except authorized monitors, auditors, or inspectors. In terms of protection of personal data and Ethical considerations, the study protocol complies with the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2017
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	Brazil: 14
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Georgia: 4
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Serbia: 19

Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Argentina: 39
Country: Number of subjects enrolled	Israel: 13
Worldwide total number of subjects	223
EEA total number of subjects	76

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)	8
Children (2-11 years)	94
Adolescents (12-17 years)	54
Adults (18-64 years)	64
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

252 subjects were screened of whom 223 were randomized (109 Oleogel-S10; 114 control gel). 199 completed the Double Blind Phase (DBP) (100 Oleogel-S10; 99 control gel). 6 (all control gel) entered the Open Label Phase (OLP) prematurely. Of the 205 subjects that entered the OLP (100 Oleogel-S10; 105 control gel), 141 completed.

Pre-assignment

Screening details:

Screening details:
All subjects satisfied the inclusion / exclusion criteria based on investigator assessment prior to entry into the study. 29 out of a total of 252 screened patients were reported as screen failures.

Period 1

Period 1 title	Double Blind Phase (DBP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

An independent unblinded biostatistics team maintained the randomization scheme key in a separate location and was only to distribute this to approved personnel. All randomization materials, including the key, were placed in an unblinded folder with restricted access, which remained restricted until after DBP completion and subsequent locking of the study database for DBP. Subjects or investigators were not unblinded except in an emergency when it was necessary to know the treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oleogel-S10

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Oleogel-S10
Investigational medicinal product code	
Other name	Filsuvez
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The gel was to be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel was in direct contact with the wound. The gel was to be reapplied at each wound dressing change, at least every 4 days.

Arm title	Control Gel

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Control Gel
Investigational medicinal product code	
Other name	Vehicle Gel
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The gel was to be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel was in direct contact with the wound. The gel was to be reapplied at each wound dressing change, at least every 4 days.

Number of subjects in period 1	Oleogel-S10	Control Gel
Started	109	114
Completed	100	99
Not completed	9	15
Consent withdrawn by subject	2	4
Adverse event, non-fatal	3	2
Other	4	9

Period 2	
Period 2 title	Open Label Phase (OLP)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Former Oleogel-S10

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Oleogel-S10
Investigational medicinal product code	
Other name	Filsuvez
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The gel was to be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel was in direct contact with the wound. The gel was to be reapplied at each wound dressing change, at least every 4 days.

Arm title	Former Control Gel

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Oleogel-S10
Investigational medicinal product code	
Other name	Filsuvez
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The gel was to be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel was in direct contact with the wound. The gel was to be reapplied at each wound dressing change, at least every 4 days.

Number of subjects in period 2	Former Oleogel-S10	Former Control Gel
Started	100	99
Completed	66	75
Not completed	34	30
Adverse event, serious fatal	7	2
Consent withdrawn by subject	18	15
Adverse event, non-fatal	2	5
Other	7	8
Joined	0	6
Discontinued DBP prematurely and entered OLP	-	6

Baseline characteristics

Reporting groups	
Reporting group title	Oleogel-S10
Reporting group description: -	
Reporting group title	Control Gel
Reporting group description: -	

Reporting group values	Oleogel-S10	Control Gel	Total
Number of subjects	109	114	223
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	5	8
Children (2-11 years)	46	48	94
Adolescents (12-17 years)	25	29	54
Adults (18-64 years)	33	31	64
From 65-84 years	2	1	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	41	48	89
Male	68	66	134
Epidermolysis Bullosa Subtype Units: Subjects			
RDEB (recessive dystrophic epidermolysis bullosa)	91	84	175
DDEB (dominant dystrophic epidermolysis bullosa)	6	14	20
JEB (junctional epidermolysis bullosa)	11	15	26
EBS (epidermolysis bullosa simplex)	1	1	2
Kindler EB	0	0	0

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all randomized subjects treated at least once with study medication. Subjects were analyzed according to the randomized treatment regimen (if different from the received treatment). The FAS was used as the primary analysis set for all efficacy analyses.

Subject analysis set title	SAS
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set included all subjects treated at least once with study medication. Subjects were analyzed according to the treatment regimen received (if different from the randomized treatment). The Safety Analysis Set was used for all analyses of safety endpoints and the presentation of the study population summaries and subject-level data listings.

Reporting group values	FAS	SAS	
Number of subjects	223	223	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	8	22	
Children (2-11 years)	94	80	
Adolescents (12-17 years)	54	54	
Adults (18-64 years)	64	64	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	89	89	
Male	134	134	
Epidermolysis Bullosa Subtype Units: Subjects			
RDEB (recessive dystrophic epidermolysis bullosa)	175	175	
DDEB (dominant dystrophic epidermolysis bullosa)	20	20	
JEB (junctional epidermolysis bullosa)	26	26	
EBS (epidermolysis bullosa simplex)	2	2	
Kindler EB	0	0	

End points

End points reporting groups

Reporting group title	Oleogel-S10
Reporting group description: -	
Reporting group title	Control Gel
Reporting group description: -	
Reporting group title	Former Oleogel-S10
Reporting group description: -	
Reporting group title	Former Control Gel
Reporting group description: -	
Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all randomized subjects treated at least once with study medication. Subjects were analyzed according to the randomized treatment regimen (if different from the received treatment). The FAS was used as the primary analysis set for all efficacy analyses.

Subject analysis set title	SAS
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set included all subjects treated at least once with study medication. Subjects were analyzed according to the treatment regimen received (if different from the randomized treatment). The Safety Analysis Set was used for all analyses of safety endpoints and the presentation of the study population summaries and subject-level data listings.

Primary: Proportion of Patients With First Complete Closure of the EB Target Wound Within 45 Days of Treatment

End point title	Proportion of Patients With First Complete Closure of the EB Target Wound Within 45 Days of Treatment

End point description:

End point type	Primary

End point timeframe:

Wound closure within 45 days during the Double Blind Phase

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Study subjects	45	33		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis

Statistical analysis description:

The primary efficacy endpoint was met as the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment was higher in the Oleogel-S10 group (41.3%) compared to the control gel group (28.9%).

Comparison groups	Oleogel-S10 v Control Gel
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Cui, Hung, Wang (CHW) approach

Notes:

[1] - P-value was adjusted with the CHW method using CMH test statistics. The CMH test statistics based on a test stratified by EB subtype and target wound size class, were estimated separately for subjects assessed before (Stage 1) and after (Stage 2) the interim analysis for sample size re-estimation. Stagewise normal z-statistics were approximated using the square root of the chi-squared CMH statistics with 1 degree of freedom and pooled to derive the CHW statistic for adjusted p-value calculation.

[2] - This finding was statistically significant in favor of Oleogel-S10 based on the CHW method using the CMH test statistics (p=0.013).

Secondary: Time to First Complete Closure of the EB Target Wound as Evidenced by Clinical Assessment Until EDBP (D90±7)

End point title	Time to First Complete Closure of the EB Target Wound as Evidenced by Clinical Assessment Until EDBP (D90±7)

End point description:

The first key secondary endpoint was time to first complete closure of the EB target wound as evidenced by clinical assessment within 90 days using a nonstratified log-rank test.
If the primary analysis of the primary efficacy endpoint showed superiority at the 5% significance level, hierarchical confirmatory testing of the 6 key secondary endpoints was to be performed.
Because the results for the first key secondary endpoint were not statistically significant, the results for all key secondary endpoints are supportive, rather than confirmatory, thus p-values are not reported.

End point type	Secondary

End point timeframe:

90±7 days

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[3]	114[4]		
Units: Days				
Median	92	94		

Notes:

[3] - 95% CI: 50.0, not estimable.
Difference between the 2 groups not statistically significant, p=0.302

[4] - 95% CI: 89.0, not estimable.
Difference between the 2 groups not statistically significant, p=0.302

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With First Complete Closure of the EB Target Wound at D90±7 Based on Clinical Assessment by the Investigator Until Day 90±7.

End point title	Proportion of Patients With First Complete Closure of the EB Target Wound at D90±7 Based on Clinical Assessment by the Investigator Until Day 90±7.

End point description:

The second key secondary endpoint was the proportion of subjects with first complete closure of the EB target wound within 90 days of treatment based on clinical assessment by the investigator.

End point type	Secondary

End point timeframe:

90±7 days

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Percentage of subjects				
number (not applicable)				
Patients With First Complete Target Wound Closure	50.5	43.9		

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Target Wound Infection Between Baseline (DBP D0) and D90±7 as Evidenced by AEs and/or Use of Topical and/or Systemic Antibiotics (Related to Wound Infection)

End point title	The Incidence of Target Wound Infection Between Baseline (DBP D0) and D90±7 as Evidenced by AEs and/or Use of Topical and/or Systemic Antibiotics (Related to Wound Infection)

End point description:

The maximum severity of target wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection) was assessed.

End point type	Secondary

End point timeframe:

90±7 days

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Patients				
Wound Infection incidence	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: The Maximum Severity of Target Wound Infection Between Baseline (DBP D0) and D90±7 as Evidenced by AEs and/or Use of Topical and/or Systemic Antibiotics (Related to Wound Infection)

End point title	The Maximum Severity of Target Wound Infection Between

	Baseline (DBP D0) and D90±7 as Evidenced by AEs and/or Use of Topical and/or Systemic Antibiotics (Related to Wound Infection)

End point description:

Target wound infections between baseline (DBP D0) and D90±7 were assessed for maximum severity.

End point type	Secondary

End point timeframe:

90±7 days

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[5]	114[6]		
Units: Patients with Infected Wounds				
Maximum severity of wound infection: Mild	1	0		
Maximum severity of wound infection: Moderate	0	3		
Maximum severity of wound infection: Severe	0	1		
No wound infection	108	110		

Notes:

[5] - Maximum severity was evaluated if a subject had a wound infection event evidenced by adverse events.

[6] - Maximum severity was evaluated if a subject had a wound infection event evidenced by adverse events.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (DBP D0) in Total Body Wound Burden (TBWB) as Evidenced by Clinical Assessment Using Section I (Assessment of the Skin Except for the Anogenital Region) of the 'EB Disease Activity and Scarring Index' (EBDASI) at D90±7

End point title	Change From Baseline (DBP D0) in Total Body Wound Burden (TBWB) as Evidenced by Clinical Assessment Using Section I (Assessment of the Skin Except for the Anogenital Region) of the 'EB Disease Activity and Scarring Index' (EBDASI) at D90±7

End point description:

The evaluation of total body wound burden (TBWB) was based on clinical assessment using Section I of the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI).

End point type	Secondary

End point timeframe:

90±7 days

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	85		
Units: EBDASI skin activity score				
least squares mean (standard error)				
TBWB based on EBDASI score	-0.44 (± 0.90)	-0.56 (± 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (DBP D0) in Itching Using the 'Itch Man Scale' in Patients ≥ 4 Years and up to 13 Years of Age Before Wound Dressing Changes at D90±7

End point title	Change From Baseline (DBP D0) in Itching Using the 'Itch Man Scale' in Patients ≥ 4 Years and up to 13 Years of Age Before Wound Dressing Changes at D90±7

End point description:

Change from Baseline at Day 90 on Itch Man Scale (patients 4-13 years of age).

End point type	Secondary

End point timeframe:

D90±7

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	43		
Units: Itch Man Scale				
arithmetic mean (standard deviation)	-0.44 (± 1.31)	-1.00 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (DBP D0) in Itching Using the 'Leuven Itch Scale' in Patients ≥ 14 Years of Age Before Wound Dressing Changes at D90±7

End point title	Change From Baseline (DBP D0) in Itching Using the 'Leuven Itch Scale' in Patients ≥ 14 Years of Age Before Wound Dressing Changes at D90±7

End point description:

Change from Baseline at Day 90 on Leuven Itch Scale (patients ≥ 14 years of age).

End point type	Secondary

End point timeframe:

D90±7

End point values	Oleogel-S10	Control Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[7]	37[8]		
Units: Leuven Itch Scale				
arithmetic mean (standard deviation)				
Frequency subscore	-8.13 (± 26.18)	-10.14 (± 27.3)		
Duration subscore	-0.93 (± 35.174)	0.98 (± 39.768)		
Severity subscore	-4.95 (± 19.33)	-10.76 (± 32.68)		
Consequences subscore	-4.39 (± 14.073)	-3.54 (± 19.402)		
Distress subscore	-0.44 (± 22.87)	-0.26 (± 34.87)		
Surface area subscore	-1.54 (± 12.347)	0.68 (± 17.082)		

Notes:

[7] - No. subjects reported for Frequency.
Duration, Severity, Consequences=36
Distress, Surface Area=35
[8] - No. subjects reported for Frequency.
Duration, Severity, Consequences, Distress, Surface Area=34

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Double Blind Phase (DBP) and Open Label Phase (OLP)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Oleogel-S10 (DBP)
Reporting group description: Oleogel-S10 Double Blind Phase (DBP)	
Reporting group title	Control Gel (DBP)
Reporting group description: Control Gel Double Blind Phase (DBP)	
Reporting group title	Former Oleogel-S10 (OLP)
Reporting group description: Patients who were in the experimental Oleogel-S10 arm in the DBP before entering the OLP	
Reporting group title	Former Control Gel (OLP)
Reporting group description: Patients who were in the Placebo Control Gel arm before entering the OLP	

Serious adverse events	Oleogel-S10 (DBP)	Control Gel (DBP)	Former Oleogel-S10 (OLP)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 109 (6.42%)	6 / 114 (5.26%)	26 / 100 (26.00%)
number of deaths (all causes)	0	0	7
number of deaths resulting from adverse events	0	0	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Klebsiella infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic congestion			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Eschar			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	0 / 100 (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
Gastrostomy tube site complication			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal injury			

subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Near drowning			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unintentional medical device removal			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Syndactyly			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Talipes			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 109 (2.75%)	0 / 114 (0.00%)	4 / 100 (4.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal stenosis			

subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oesophageal mucosal blister			

subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	4 / 100 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	0 / 100 (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
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Haematuria			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	0 / 100 (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
Nephropathy			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pseudosyndactyly			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blister infected			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related bacteraemia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis staphylococcal			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	0 / 100 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pseudomonas infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 109 (0.92%)	2 / 114 (1.75%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin bacterial infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection bacterial			
subjects affected / exposed	1 / 109 (0.92%)	1 / 114 (0.88%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	0 / 100 (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
Skin infection			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight gain poor			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Former Control Gel		

	(OLP)		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 105 (22.86%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Klebsiella infection			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic congestion			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications			
Eschar			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrostomy tube site complication			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal injury			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Near drowning			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Unintentional medical device removal			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound complication			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic			

disorders			
Syndactyly			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Talipes			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	6 / 105 (5.71%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Blood loss anaemia				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Anal fissure				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal stenosis				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				

subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal mucosal blister				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	6 / 105 (5.71%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic function abnormal				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Pruritus			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephropathy			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pseudosyndactyly			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blister infected			

subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related bacteraemia				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis staphylococcal				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Medical device site infection				

subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis externa				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pseudomonas infection				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Skin bacterial infection				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal infection				
subjects affected / exposed	1 / 105 (0.95%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	2 / 105 (1.90%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Wound infection bacterial				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 105 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 105 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Weight gain poor			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Oleogel-S10 (DBP)	Control Gel (DBP)	Former Oleogel-S10 (OLP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 109 (81.65%)	92 / 114 (80.70%)	77 / 100 (77.00%)
Injury, poisoning and procedural complications			
Wound complication	Additional description: Wound complications include increase in wound size vs. baseline or previous visit, wound reopening, wound injury, increase in wound burden, worsening of EB wound pain, wound odor, and wound worsening vs baseline.		
subjects affected / exposed	67 / 109 (61.47%)	61 / 114 (53.51%)	38 / 100 (38.00%)
occurrences (all)	100	88	43
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 109 (7.34%)	4 / 114 (3.51%)	16 / 100 (16.00%)
occurrences (all)	10	4	24
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 109 (8.26%)	15 / 114 (13.16%)	10 / 100 (10.00%)
occurrences (all)	11	18	13

Gastrointestinal disorders			
Oesophageal stenosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	8 / 100 (8.00%)
occurrences (all)	0	1	16
Dysphagia			
subjects affected / exposed	2 / 109 (1.83%)	1 / 114 (0.88%)	6 / 100 (6.00%)
occurrences (all)	2	1	8
Diarrhoea			
subjects affected / exposed	2 / 109 (1.83%)	2 / 114 (1.75%)	3 / 100 (3.00%)
occurrences (all)	2	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 109 (2.75%)	8 / 114 (7.02%)	2 / 100 (2.00%)
occurrences (all)	3	9	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 109 (7.34%)	6 / 114 (5.26%)	5 / 100 (5.00%)
occurrences (all)	8	7	5
Infections and infestations			
Wound infection			
subjects affected / exposed	8 / 109 (7.34%)	10 / 114 (8.77%)	6 / 100 (6.00%)
occurrences (all)	9	12	12
Wound infection staphylococcal			
subjects affected / exposed	4 / 109 (3.67%)	3 / 114 (2.63%)	9 / 100 (9.00%)
occurrences (all)	4	3	14
Wound infection bacterial			
subjects affected / exposed	3 / 109 (2.75%)	5 / 114 (4.39%)	7 / 100 (7.00%)
occurrences (all)	4	6	10
Nasopharyngitis			
subjects affected / exposed	3 / 109 (2.75%)	7 / 114 (6.14%)	3 / 100 (3.00%)
occurrences (all)	3	7	3
Influenza			
subjects affected / exposed	2 / 109 (1.83%)	6 / 114 (5.26%)	1 / 100 (1.00%)
occurrences (all)	2	6	4
Metabolism and nutrition disorders			

Hypoalbuminaemia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 114 (1.75%)	5 / 100 (5.00%)
occurrences (all)	0	2	8
Vitamin D deficiency			
subjects affected / exposed	0 / 109 (0.00%)	0 / 114 (0.00%)	4 / 100 (4.00%)
occurrences (all)	0	0	4

Non-serious adverse events	Former Control Gel (OLP)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 105 (77.14%)		
Injury, poisoning and procedural complications			
Wound complication	Additional description: Wound complications include increase in wound size vs. baseline or previous visit, wound reopening, wound injury, increase in wound burden, worsening of EB wound pain, wound odor, and wound worsening vs baseline.		
subjects affected / exposed	46 / 105 (43.81%)		
occurrences (all)	64		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 105 (20.00%)		
occurrences (all)	30		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 105 (9.52%)		
occurrences (all)	15		
Gastrointestinal disorders			
Oesophageal stenosis			
subjects affected / exposed	11 / 105 (10.48%)		
occurrences (all)	14		
Dysphagia			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 9 / 105 (8.57%) 13		
Infections and infestations Wound infection subjects affected / exposed occurrences (all) Wound infection staphylococcal subjects affected / exposed occurrences (all) Wound infection bacterial subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 15 / 105 (14.29%) 26 12 / 105 (11.43%) 15 9 / 105 (8.57%) 14 1 / 105 (0.95%) 2 4 / 105 (3.81%) 4		
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all)	 5 / 105 (4.76%) 5 6 / 105 (5.71%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2018	Protocol version 4.0 •A new exclusion criterion was added to exclude subjects with EBS; stratification of randomization was also updated to remove EBS groups. • The definition of an EB target wound was updated to include a maximum wound age of <9 months •The sample size was re-estimated to 192 subjects. • Update to specify children ≥21 days old and <4 years could be included only after confirmation by the IDMC upon review of the safety and bioanalytical data at the interim safety review stage • Update to allow investigator to implement a dose interruption if considered medically necessary for optimal management of the subject • Electrocardiogram assessments were added • Update to allow safety venous blood samples collected at baseline and Day 90 to be used for determination of betulin levels
01 October 2018	Protocol Version 5.0 • Clarification of the primary endpoint such that the confirmation of closure was no longer included (including statistical analysis). However, the primary endpoint requiring confirmed closure was included as a sensitivity analysis. • Addition of study responsibilities that could be performed by the subject's parent/legal guardian.
18 April 2019	Protocol version 6.0 • Based on the results of a planned sample size re-estimation, the IDMC recommended that the sample size be increased by 48 subjects (24 per arm) for a total of 230 evaluable subjects • Certain efficacy endpoints were elevated to the level of "key secondary endpoints" • Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) added to the efficacy assessments • EuroQol 5 dimensions (EQ-5D) instrument added to the efficacy assessments • Addition of safety laboratory tests at Month 12 • Target wound selection criteria updated to clarify the exclusion of target wounds in the anogenital region

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported