Clinical trial results:
Open, Prospective, Controlled Case Series Documentation to Compare Intra-individually the Efficacy and Tolerance of Sericare versus Non-adhesive Wound Dressing alone in Accelerating the Epithelialisation of Skin Lesions of Patients with Epidermolysis bullosa hereditaria

Summary

EudraCT number	2010-019945-24
Trial protocol	DE
Global end of trial date	14 June 2011

Results information

Result version number	v1 (current)
This version publication date	27 October 2016
First version publication date	27 October 2016

Trial information

Trial identification

Sponsor protocol code	BEB-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01294241
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Birken AG
Sponsor organisation address	Streiflingsweg 11, Niefern-Oeschelbronn, Germany, 75223
Public contact	Clinical Development, Birken AG, +49 723397490, info@birken.eu
Scientific contact	Clinical Development, Birken AG, +49 723397490, info@birken.eu

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 October 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2011
Global end of trial reached?	Yes
Global end of trial date	14 June 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare intra-individually the reepithelialisation of skin lesion(s) in inherited Epidermolysis bullosa (either 1 wound ≥10 cm2 and ≤200 cm2 in size divided in 2 equal halves or 2 comparable wounds of ≥5 cm2 each) treated with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing only.

Protection of trial subjects:

The study was conducted in compliance with the study protocol, ethical principles originating in or derived from the Declaration of Helsinki, ethics committee informed consent regulations, and International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. In addition, all national and local regulatory requirements were followed. Insurance coverage for all participating subjects was guaranteed according to applicable legal requirements. Before undergoing any study-specific procedures, subjects were informed about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy:

Non-adhesive wound dressing

Evidence for comparator:

Non-adhesive wound dressing is standard of care in patients with inherited Epidermolysis bullosa.

Actual start date of recruitment	03 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	3
Adolescents (12-17 years)	2
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 03 Nov 2010 to 14 Jun 2011 at 1 centre (University Medical Centre Freiburg) in 1 country (Germany).

Pre-assignment

Screening details:

The investigator obtained written informed consent, checked eligibility, recorded demographic data, medical history/current medical conditions and EB subtype, performed a urine pregnancy test, did a physical examination, and identified 1 EB wound ≥10 cm2 and ≤200 cm2 in size or selected 2 comparable wounds of ≥5 cm2 each.

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

This was an open-label study. The investigator, the subject and the sponsor knew the identity of the treatment. Two independent experts were blind to treatment and assessed efficacy based on chronological series of cropped and coded photographs by wound (half) that were taken before start of treatment, during wound dressing changes and at the end of treatment on Day 14/Day 28.

Arms

Are arms mutually exclusive?	No
Arm title	Oleogel-S10 and non-adhesive wound dressing

Arm description:

One half of an EB wound ≥10 cm2 and ≤200 cm2 in size or 1 EB wound ≥5 cm2 in size was treated with Oleogel-S10 and non-adhesive wound dressing.

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

Dosage and administration details:

The eligible wound (half) was topically treated with 1 cm or 125 µL or 115 mg Oleogel-S10 per cm2 wound area (corresponds to thickness of approximately 1 mm or 0.04 inches) and covered with a non-adhesive wound dressing (Mepilex®) on Day 0. Oleogel-S10 was administered at wound dressing changes about every 24 to 48 hours until discharge from hospital or until the end of treatment at Day 14 in ‘recent wounds’ or Day 28 in ‘chronic wounds’.

Arm title	Non-adhesive wound dressing only

Arm description:

Standard of care

Arm type	Non-active comparator

Investigational medicinal product name	Non-adhesive wound dressing
Investigational medicinal product code	
Other name	Mepilex® soft silicone faced polyurethane foam dressing
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical use

Dosage and administration details:

The eligible wound (half) was covered with a non-adhesive wound dressing only (Mepilex®) as control. Wound dressings were changed about every 24 to 48 hours until discharge from hospital or until the end of treatment at Day 14 in 'recent wounds' or Day 28 in 'chronic wounds'.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Treatment was open to study subjects and investigators, but independent assessors were blind to treatment and evaluated efficacy based on chronological series of cropped and coded photographs by wound (half).

Number of subjects in period 1	Oleogel-S10 and non-adhesive wound dressing	Non-adhesive wound dressing only
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups	
Reporting group title	Oleogel-S10 and non-adhesive wound dressing
Reporting group description:	
One half of an EB wound ≥10 cm2 and ≤200 cm2 in size or 1 EB wound ≥5 cm2 in size was treated with Oleogel-S10 and non-adhesive wound dressing.	
Reporting group title	Non-adhesive wound dressing only
Reporting group description:	
Standard of care	

Reporting group values	Oleogel-S10 and non-adhesive wound dressing	Non-adhesive wound dressing only	Total
Number of subjects	10	10	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	3	3	3
Adolescents (12-17 years)	2	2	2
Adults (18-64 years)	5	5	5
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	20	20	
full range (min-max)	6 to 48	6 to 48	-
Gender categorical Units: Subjects			
Female	3	3	3
Male	7	7	7

End points

End points reporting groups

Reporting group title	Oleogel-S10 and non-adhesive wound dressing

Reporting group description:

One half of an EB wound ≥10 cm2 and ≤200 cm2 in size or 1 EB wound ≥5 cm2 in size was treated with Oleogel-S10 and non-adhesive wound dressing.

Reporting group title	Non-adhesive wound dressing only

Reporting group description:

Standard of care

Primary: Difference (intra-individual) in reepithelialisation of wound (halves) at Day 14 in 'recent wounds' or Day 28 in 'chronic wounds'

End point title	Difference (intra-individual) in reepithelialisation of wound (halves) at Day 14 in 'recent wounds' or Day 28 in 'chronic wounds'

End point description:

The primary end point was the progress of reepithelialisation from baseline to either Day 14 ('recent wounds') or Day 28 ('chronic wounds') of the EB wound (half) treated with Oleogel-S10 and non-adhesive wound dressing (Mepilex®) compared to the other wound (half) covered with non-adhesive wound dressing only (intra-individual comparison). Two independent experts were blind to treatment and assessed efficacy based on chronological series of cropped and coded photographs by wound (half) that were taken before start of treatment, during wound dressing changes and at the end of treatment on Day 14/Day 28. They evaluated each series and decided whether 1 wound (half) reepithelialised faster than the other ('winner'), or whether there was no difference in reepithelialisation.

End point type	Primary

End point timeframe:

Within 14 days in 'recent wounds', within 28 days in 'chronic wounds'; photographs were taken at wound dressing changes about every 24 to 48 hours until the end of treatment at Day 14 in 'recent wounds' or Day 28 in 'chronic wounds'.

End point values	Oleogel-S10 and non-adhesive wound dressing	Non-adhesive wound dressing only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[1]	10[2]		
Units: Faster reepithelialisation				
Number of wounds analysed	12	12		
Decided cases	8	8		
Faster reepithelialisation	8	0		

Notes:

[1] - As 2 subjects received 2 cycles of treatment each, 12 wounds were treated with study medication.

[2] - As 2 subjects received 2 cycles of treatment each, 12 wounds were treated with study medication.

Statistical analyses

Statistical analysis title	Analysis for primary endpoint

Statistical analysis description:

The intra-individual difference in reepithelialisation of wound (halves) was tested using a two-sided exact binomial test. The test was performed at a significance level of 5% for the null-hypothesis of no

difference δ = 0 against the hypotheses δ ≠ 0: H0: δ = 0 H1: δ ≠ 0

Comparison groups	Oleogel-S10 and non-adhesive wound dressing v Non-adhesive wound dressing only
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.008 [4]
Method	Two-sided exact binomial test

Notes:

[3] - 12 wounds in 10 subjects (intra-individual comparison; 2 cycles of treatment in 2 subjects) were evaluated by assessors that were blind to treatment. Wounds that were either evaluated controversially (n=2) or as being equal (n=2) were excluded from the analysis of the primary efficacy variable.
[4] - Oleogel-S10 + non-adhesive wound dressing (Mepilex®) accelerated the reepithelialisation significantly (8 of 8 decided cases; p=0.008, binomial test) compared to non-adhesive wound dressing only (0 of 8 decided cases).

Secondary: Difference (intra-individual) in median percentage of wound epithelialisation

End point title	Difference (intra-individual) in median percentage of wound epithelialisation

End point description:

The secondary endpoint was the intra-individual difference in median percentage of wound epithelialisation at Day 7±1 and at Day 14±1. Sizes of wound areas were measured using a digital wound evaluation program from the EB Centre at the Department of Dermatology, University Medical Centre Freiburg.

End point type	Secondary

End point timeframe:

Day 7±1, Day 14±1

End point values	Oleogel-S10 and non-adhesive wound dressing	Non-adhesive wound dressing only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[5]	10[6]		
Units: Percentage of reepithelialisation				
median (full range (min-max))				
Median wound epithelialisation (Day 7±1, min, max)	69.7 (17.3 to 90.4)	57.4 (10 to 81.3)		
Median wound epithelialisation (Day 14±1, min, max	87.7 (2.7 to 100)	79.2 (0 to 98.3)		

Notes:

[5] - As 2 subjects received 2 cycles of treatment each, 12 wounds were treated with study medication.

[6] - As 2 subjects received 2 cycles of treatment each, 12 wounds were treated with study medication.

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

The intra-individual difference in median percentage of wound epithelialisation was tested using a two-sided Wilcoxon test.

Comparison groups	Oleogel-S10 and non-adhesive wound dressing v Non-adhesive wound dressing only

Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority[7]
P-value	= 0.21 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - On Day 7±1 the median wound epithelialisation was 69.7% (min. 17.3%; max. 90.4%) in areas treated with Oleogel-S10 + non-adhesive wound dressing compared to 57.4% (min. 10.0%; max. 81.3%) in areas treated with non-adhesive wound dressing only (p=0.21, Wilcoxon-test).
[8] - Day 7±1

Statistical analysis title	Secondary analysis

Statistical analysis description:

The intra-individual difference in median percentage of wound epithelialisation was tested using a two-sided Wilcoxon test.

Comparison groups	Oleogel-S10 and non-adhesive wound dressing v Non-adhesive wound dressing only
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority[9]
P-value	= 0.33 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - On Day 14±1 the median wound epithelialisation was 87.7% (min. 2.7%; max. 100.0%) in areas treated with Oleogel-S10 + non-adhesive wound dressing compared to 79.2% (min. 0.0%; max. 98.3%) in areas treated with non-adhesive wound dressing only (p=0.33, Wilcoxon-test).
[10] - Day 14±1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from start of study treatment to completion of study treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Safety population
Reporting group description:	
All subjects who received at least 1 dose of Oleogel-S10 were included in the safety population.	

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)		
Skin and subcutaneous tissue disorders			
Wound area increased due to trauma/dressing change			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	9		
Wound infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Flu-like syndrome			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2011	Implementation of an undecided efficacy assessment (no difference in epithelialisation) and more precise definition of statistical evaluation in case of controversial assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small sample size, subjects with dystrophic Epidermolysis bullosa only, difficult wound size analysis at fixed study days due to several episodes of re-trauma in both intervention and control wounds

Notes: