Clinical trial results:
Open, Blindly Evaluated, Prospective, Controlled, Randomized, Multicenter Phase III Clinical Trial to Compare Intra-individually the Efficacy and Tolerance of Oleogel-S10 versus Standard of Care in Accelerating the Wound Healing of Split-Thickness Skin Graft Donor Sites

Summary

EudraCT number	2012-000777-23
Trial protocol	DE CZ FI AT BG PL
Global end of trial date	23 August 2013

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	BSH-12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01657305
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Birken AG
Sponsor organisation address	Streiflingsweg 11, Niefern-Oeschelbronn, Germany, 75223
Public contact	Pharmaceutical Development, Birken AG, +49 723397490, info@birken.eu
Scientific contact	Pharmaceutical 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	10 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2013
Global end of trial reached?	Yes
Global end of trial date	23 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare intra-individually the efficacy and tolerance of Oleogel-S10 versus non-adhesive wound dressing alone in
accelerating the wound healing of Split-Thickness Skin Graft Donor Sites (STSG).

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 represents a standard of care for patients with STSG donor sites.

Actual start date of recruitment	03 August 2012
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	Poland: 2
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	111
EEA total number of subjects	111

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	69
From 65 to 84 years	39
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled from 03-Aug-2012 to 25-Jul-2013 at 18 clinical centres in 6 countries: Germany (8 centres), Czech Republic (2 centres), Poland (1 centre), Finland (1 centre), Austria (2 centres), Bulgaria (4 centres).

Pre-assignment

Screening details:

During screening the following was performed: informed consent, demographics, medical history, prior medication, and prenancy test. On day of surgery the inclusion/exclusion criteria were checked. 111 subjects were screened and enrolled, but only 107 subjects were treated as indicated below.

Pre-assignment period milestones

Number of subjects started	111
Number of subjects completed	107

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Not randomised by mistake: 1
Reason: Number of subjects	Violation of inclusion criterion no. 2: 1
Reason: Number of subjects	STSG surgery was cancelled: 1

Period 1

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

Blinding implementation details:

Treatments were intra-individually compared. The STSG donor site was divided into two areas of equal size. Since the distance of the wounds from the centre of the body might influence the wound healing process, the wound halves were randomly assigned to treatment by a temper-proof method. Treatment was open to study subjects and investigators, but assessment of efficacy was primarily based on blinded photo evaluation. Special care was taken to ensure blinding, i.e. all markings were removed.

Arms

Are arms mutually exclusive?	No
Arm title	Oleogel-S10

Arm description:

One half of the study wound was treated with Oleogel-S10 plus non-adhesive dressing.

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

Dosage and administration details:

About 1 cm Oleogel-S10 ointment (approximately 100 mg) per cm^2 (i.e. approximately 1 mm thick) was applied at every wound dressing change (every 3 to 4 days) to one half of the STSG donor site by applying it onto the wound-facing side of the wound dressing.

Arm title	Standard of care

Arm description:

One half of the study wound was treated according to standard of care by applying a non-adhesive dressing.

Arm type	Non-active comparator
Investigational medicinal product name	Non-adhesive dressing
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical use

Dosage and administration details:

The dressing was changed every 3 to 4 days.

Notes:

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

Justification: Treatment was open to study subjects and investigators, but assessment of efficacy was performed by assessors based on blinded photo evaluation.

Number of subjects in period 1	Oleogel-S10	Standard of care
Started	107	107
Completed	82	82
Not completed	25	25
Consent withdrawn by subject	4	4
No full wound closure achieved at Day 28	15	15
Adverse event, non-fatal	1	1
Not adhering to study rules and procedures	4	4
Lost to follow-up	1	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Treatment period
Reporting group description: -	

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: 107 patients were randomised to the study and received at least one dose of treatment.

Reporting group values	Treatment period	Total	
Number of subjects	107	107	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	67	67	
From 65-84 years	38	38	
85 years and over	2	2	
Age continuous Units: years			
median	56		
full range (min-max)	18 to 86	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	68	68	

End points

End points reporting groups

Reporting group title	Oleogel-S10
Reporting group description:	
One half of the study wound was treated with Oleogel-S10 plus non-adhesive dressing.	
Reporting group title	Standard of care
Reporting group description:	
One half of the study wound was treated according to standard of care by applying a non-adhesive dressing.	

Primary: Intra-individual difference in time to wound closure

End point title	Intra-individual difference in time to wound closure
End point description:	
The primary endpoint of this study was the intra-individual difference in time to wound closure (defined as at least 95% epithelialization) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, based on blinded photo evaluation by three independent, blinded experts.	
End point type	Primary
End point timeframe:	
Within 28 days after start of treatment (Day 0 - Day 28). Photos were aquired at every wound dressing change every 3 to 4 days.	

End point values	Oleogel-S10	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Day				
arithmetic mean (confidence interval 95%)	-1.4 (-1.8 to -0.9)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
The difference in time to wound closure was tested using a two-sided paired t-test. The test was performed at a significance level of 5% for the null-hypothesis of no difference $\delta = 0$ against the hypotheses $\delta \neq 0$: H0: $\delta = 0$ H1: $\delta \neq 0$	
Comparison groups	Oleogel-S10 v Standard of care

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	Two-sided paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.9
Variability estimate	Standard deviation
Dispersion value	2.3

Notes:

[1] - Difference in time to wound closure was calculated by comparing wound closure times of corresponding wound halves per patient followed by calculation of the mean of the expert-specific differences for each patient. The primary endpoint was then derived from the mean values for all subjects. If wound closure was not observed in a wound half (2 subjects), specific assumption were made to calculate the difference e.g. wound closure later than the last photo or, intra-individual difference is 0.

[2] - The p-value indicated above is valid for the intra-individual comparison of time to wound healing between the 2 wounds halves for the Intention-To-Treat analysis set (107 subjects).

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	16.0

Reporting groups

Reporting group title	Safety analysis set

Reporting group description:

The safety analysis set (SAF) included all patients who received treatment at least once, i.e. who received any dose of Oleogel S10 or non-adhesive wound dressing. If the application of any treatment was uncertain, the patient was included in the SAF.

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 107 (1.87%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 107 (16.82%)		
Investigations			

Oxygen saturation increased subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Metastatic malignant melanoma subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Injury, poisoning and procedural complications Procedural complication subjects affected / exposed occurrences (all) Wound haemorrhage subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1 1 / 107 (0.93%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
General disorders and administration site conditions Impaired healing subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2		
Skin and subcutaneous tissue disorders Pain of skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2 1 / 107 (0.93%) 1		
Infections and infestations Gastrointestinal infection			

subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences (all)	4		
Urethritis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Wound infection staphylococcal			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2012	• Inclusion criterion 5 (women of childbearing potential were to apply effective method of birth control) was added; • Exclusion criterion 6 (pregnant and breast fe4eding women were excluded) was added; • Pregnancy test was added as a task to be performed at Screening.
29 January 2013	• Frequency of dress changes was reduced from every two to three days to every three to four days • Planned patient number was reduced from 130 to 105 patients • Inclusion criterion 2 was changed to reduce the size of the wound area from 20 cm^2 to 15 cm^2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported