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	2012-003390-26
Trial protocol	LV GR ES
Global end of trial date	25 September 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	BSG-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	15 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2013
Global end of trial reached?	Yes
Global end of trial date	25 September 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 tolerability 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	04 April 2013
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	Spain: 57
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Latvia: 31
Worldwide total number of subjects	113
EEA total number of subjects	113

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)	90
From 65 to 84 years	17
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled from 04-Apr-2013 to 26-Aug-2013 at 14 clinical centres in 4 countries: Spain (6 centres), Greece (3 centres), Latvia (2 centres), France (3 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. 113 subjects were screened and enrolled, but only 112 subjects were treated since the STSG sugery was cancelled for one subject.

Pre-assignment period milestones

Number of subjects started	113
Number of subjects completed	112

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No treatment: 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 cm² (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	In-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	112	112
Completed	92	92
Not completed	20	20
Adverse events or other safety reasons	5	5
Other	2	2
No full wound closing achieved at Day 28	13	13

Baseline characteristics

Reporting groups[1]	
Reporting group title	Treatment period
Reporting group description:	
112 subjects treated had 224 wound halves that were compared.	

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: 112 patients were randomised and received study treatment.

Reporting group values	Treatment period	Total	
Number of subjects	112	112	
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)	89	89	
From 65-84 years	17	17	
85 years and over	6	6	
Age continuous Units: years			
median	49		
full range (min-max)	19 to 90	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	73	73	

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	110	110		
Units: day				
arithmetic mean (confidence interval 95%)	-0.8 (-1.5 to -0.1)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
The test was performed as a two-sided paired t-test 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	220
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0232 [2]
Method	Two-sided paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	3.6

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 assumptions 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 closure between the 2 wound halves for the Intention-To-Treat analysis set (110 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) includes all patients who have been treated at least once, i.e. who received any dose of Oleogel-S10 or non-adhesive wound dressing. If the application of any treatment is not certain, the patient was included in the SAF. Within the SAF, the wound halves were analyzed ´as treated´.

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 112 (4.46%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Postoperative wound complication			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mania			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 112 (0.89%)		
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	60 / 112 (53.57%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences (all)	4		
Hypotension			

subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Lymphoedema			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Thrombophlebitis superficial			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Surgical and medical procedures			
Removal of internal fixation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	3		
Feeling of body temperature change			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences (all)	5		
Injection site reaction			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Mucosal induration			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
Pyrexia			

subjects affected / exposed occurrences (all)	12 / 112 (10.71%) 13		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 112 (0.89%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	 1 / 112 (0.89%) 1 1 / 112 (0.89%) 1 1 / 112 (0.89%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Tobacco withdrawal symptoms subjects affected / exposed occurrences (all)	 2 / 112 (1.79%) 2 1 / 112 (0.89%) 1 1 / 112 (0.89%) 1		
Investigations Haematocrit decreased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all)	 1 / 112 (0.89%) 1 2 / 112 (1.79%) 2		
Injury, poisoning and procedural complications Infusion related reaction			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Medication error			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Post procedural complication			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
Post procedural haematoma			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Wound complication			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Wound dehiscence			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Wound haematoma			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Wound haemorrhage			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Wound secretion			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Myoclonus			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		

Somnolence			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
Leukocytosis			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	8		
Diarrhoea			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Excessive granulation tissue			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Pain of skin			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	10		
Pruritus			
subjects affected / exposed	9 / 112 (8.04%)		
occurrences (all)	9		
Skin burning sensation			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences (all)	1		
Renal and urinary disorders			
Bladder dilatation			

subjects affected / exposed occurrences (all) Cystitis noninfective subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1 1 / 112 (0.89%) 1 1 / 112 (0.89%) 1 1 / 112 (0.89%) 1		
Infections and infestations Skin infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Wound infection subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 9 2 / 112 (1.79%) 2 3 / 112 (2.68%) 3		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2 1 / 112 (0.89%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2013	Main changes were: - In the secondary endpoint 'Percentage of wound epithelialisation at different time points as assessed by....', 'the investigator' was changed to 'study team member during wound dressing change'. - 'Second or third' day was changed to 'third or fourth' day for the interval of dressing change. - The number of sites was increased from 13 to 15. - In the inclusion criterion no. 2 the size of the wound area was reduced from 20 cm^2 to 15 cm^2. - In inclusion criterion no. 5, the phrase 'who are in the period between menarche and menopause' was added to women of childbearing potential. - 'Sexually active, non-vasectomized men must use a barrier method (condoms) during the treatment phase of this clinical trial' was added to inclusion criterion no. 5.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported