



## 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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

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**Subjects enrolled per age group**

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|          |   |
|----------|---|
| 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 pregnancy 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 <sup>[1]</sup>           |

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<sup>2</sup> (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.

|   |                       |
|---|-----------------------|
| <b>Arm title</b>  | Standard of care      |
| Arm description:<br>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:<br>The dressing was changed every 3 to 4 days.   |                       |
| Notes:<br>[1] - The roles blinded appear inconsistent with a simple blinded trial.<br>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<sup>[1]</sup>

|                       |                  |
|-----------------------|------------------|
| 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:<br>One half of the study wound was treated with Oleogel-S10 plus non-adhesive dressing.                       |                  |
| Reporting group title  | Standard of care |
| Reporting group description:<br>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:<br>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:<br>Within 28 days after start of treatment (Day 0 - Day 28). Photos were acquired 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:<br>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 $\delta \neq 0$ :<br>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 <sup>[1]</sup>           |
| P-value                                 | < 0.0001 <sup>[2]</sup>        |
| 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.

| <b>Serious adverse events</b>                     | 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 %

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

|  |  |  |  |
|--|--|--|--|
| Oxygen saturation increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 107 (0.93%)<br>1                             |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Metastatic malignant melanoma<br>subjects affected / exposed<br>occurrences (all)   | 1 / 107 (0.93%)<br>1                             |  |  |
| Injury, poisoning and procedural complications<br>Procedural complication<br>subjects affected / exposed<br>occurrences (all)<br><br>Wound haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 107 (0.93%)<br>1<br><br>1 / 107 (0.93%)<br>1 |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 107 (0.93%)<br>1                             |  |  |
| General disorders and administration site conditions<br>Impaired healing<br>subjects affected / exposed<br>occurrences (all)   | 1 / 107 (0.93%)<br>1                             |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 107 (1.87%)<br>2                             |  |  |
| Skin and subcutaneous tissue disorders<br>Pain of skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 107 (1.87%)<br>2<br><br>1 / 107 (0.93%)<br>1 |  |  |
| Infections and infestations<br>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     | <ul style="list-style-type: none"><li>• Inclusion criterion 5 (women of childbearing potential were to apply effective method of birth control) was added;</li><li>• Exclusion criterion 6 (pregnant and breast feeding women were excluded) was added;</li><li>• Pregnancy test was added as a task to be performed at Screening.</li></ul>         |
| 29 January 2013 | <ul style="list-style-type: none"><li>• Frequency of dress changes was reduced from every two to three days to every three to four days</li><li>• Planned patient number was reduced from 130 to 105 patients</li><li>• Inclusion criterion 2 was changed to reduce the size of the wound area from 20 cm<sup>2</sup> to 15 cm<sup>2</sup></li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported