



## Clinical trial results:

### **Efficacy and Safety of oral Alitretinoin (Toctino®) in the Treatment of Patients with Cutaneous Lupus Erythematosus: A Multicentre, Open-Label, Prospective Pilot Study**

#### **Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-024131-16 |
| Trial protocol           | DE             |
| Global end of trial date | 30 April 2014  |

#### **Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 11 January 2022 |
| First version publication date | 11 January 2022 |

#### **Trial information**

##### **Trial identification**

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | UKM10_0019 |
|-----------------------|------------|

##### **Additional study identifiers**

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

Notes:

##### **Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Universitätsklinikum Münster  |
| Sponsor organisation address | Albert-Schweitzer-Campus 1, Münster, Germany, 48149                               |
| Public contact               | Prof. Dr. Annegret Kuhn, Universitätsklinikum Münster ,<br>kuhnan@uni-muenster.de |
| Scientific contact           | Prof. Dr. Annegret Kuhn, Universitätsklinikum Münster ,<br>kuhnan@uni-muenster.de |

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                       | 14 May 2013   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 14 May 2013   |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 2014 |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the therapeutic effect of alitretinoin (Tocino®) in the treatment of Cutaneous Lupus Erythematosus (CLE) with respect to proportion of responders based on the Revised Cutaneous Lupus Disease Area and Severity Index (RCLASI) activity score for skin lesions at baseline and after 24 weeks of treatment or at the latest assessment for patients who withdrew prematurely (Last Observation Carried Forward, LOCF).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

Throughout the trial, daily use of sunscreen (sun protection factor, SPF $\geq$ 50) was recommended to all patients. The management of CLE could involve the use of topical medications, such as topical steroids, or systemic rescue medications, such as antimalarials.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 08 December 2011 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 1 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Germany: 7 |
| Worldwide total number of subjects   | 7          |
| EEA total number of subjects         | 7          |

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)                     | 6 |
| From 65 to 84 years                      | 1 |
| 85 years and over                        | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from 2 dermatology clinics in Germany. The recruitment period was from December 2011 to April 2013.

### Pre-assignment

Screening details:

7 patients with a clinically and histologically confirmed diagnosis of CLE refractory to topical corticosteroids were included in the study.

### Pre-assignment period milestones

|                              |   |
|------------------------------|---|
| Number of subjects started   | 7 |
| Number of subjects completed | 5 |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Consent withdrawn by subject: 1                |
| Reason: Number of subjects | Patient did not meet the inclusion criteria: 1 |

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment period (overall period) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Not applicable                    |
| Blinding used                | Not blinded                       |

### Arms

|           |              |
|-----------|--------------|
| Arm title | Alitretinoin |
|-----------|--------------|

Arm description:

Patients who received study treatment with alitretinoin (Toctino®).

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Toctino®      |
| Investigational medicinal product code |               |
| Other name                             | Alitretinoin  |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

Patients were treated for 24 weeks with alitretinoin (Toctino®). Study treatment started with 30 mg alitretinoin per day. The daily dose was reduced to 10 mg alitretinoin if adverse reactions such as hyperlipidemia or severe headaches occurred.

| Number of subjects in period 1 <sup>[1]</sup> | Alitretinoin |
|---|--------------|
| Started                                       | 5            |
| Completed                                     | 2            |
| Not completed                                 | 3            |
| Non-Compliance                                | 1            |
| Adverse event, non-fatal                      | 1            |

|                  |   |
|------------------|---|
| Lack of efficacy | 1 |
|------------------|---|

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 7 patients were enrolled in the study and assessed for eligibility. Because one patient did not meet the inclusion criteria and one patient withdrew consent before start of treatment, only 5 patients entered the baseline period.

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values                                | Treatment period | Total |  |
|---|------------------|-------|--|
| Number of subjects                                    | 5                | 5     |  |
| Age categorical                                       |                  |       |  |
| Units: Subjects                                       |                  |       |  |
| In utero  | 0                | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                | 0     |  |
| Newborns (0-27 days)                                  | 0                | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0                | 0     |  |
| Children (2-11 years)                                 | 0                | 0     |  |
| Adolescents (12-17 years)                             | 0                | 0     |  |
| Adults (18-64 years)                                  | 4                | 4     |  |
| From 65-84 years                                      | 1                | 1     |  |
| 85 years and over                                     | 0                | 0     |  |
| Gender categorical                                    |                  |       |  |
| Units: Subjects                                       |                  |       |  |
| Female  | 4                | 4     |  |
| Male  | 1                | 1     |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Alitretinoin       |
| Reporting group description:<br>Patients who received study treatment with alitretinoin (Toctino®). |                    |
| Subject analysis set title  | Visit (Baseline)   |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Examination visit before starting alitretinoin treatment.      |                    |
| Subject analysis set title  | Visit (last)       |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Last examination visit of patients treated with alitretinoin.  |                    |

### Primary: RCLASI activity score for skin lesions

|  |   |
|--|---|
| End point title  | RCLASI activity score for skin lesions <sup>[1]</sup> |
| End point description:<br>Efficacy of alitretinoin on disease severity as evaluated by RCLASI activity score for skin lesions. |   |
| End point type   | Primary   |
| End point timeframe:<br>Week 0, 2, 4, 8, 12, 16, 20, 24 and 28   |   |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The study was terminated prematurely. Since not enough patients were included, no statistical analysis of the results was performed.

| End point values                     | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 5                    | 4                    |  |  |
| Units: Activity score                |                      |                      |  |  |
| arithmetic mean (standard deviation) | 12.8 (± 4.1)         | 10.3 (± 4.3)         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: RCLASI activity score total

|   |                             |
|---|-----------------------------|
| End point title   | RCLASI activity score total |
| End point description:<br>Efficacy of alitretinoin on disease severity as evaluated by total RCLASI activity score. |                             |
| End point type  | Secondary                   |
| End point timeframe:<br>Week 0, 2, 4, 8, 12, 16, 20, 24 and 28  |                             |

| End point values                     | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 5                    | 4                    |  |  |
| Units: Activity score                |                      |                      |  |  |
| arithmetic mean (standard deviation) | 12.8 (± 4.1)         | 11.3 (± 4.1)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: RCLASI damage score total

|                        |   |
|------------------------|---|
| End point title        | RCLASI damage score total   |
| End point description: | Efficacy of alitretinoin on disease severity as evaluated by total RCLASI damage score. |
| End point type         | Secondary   |
| End point timeframe:   | Week 0, 2, 4, 8, 12, 16, 20, 24 and 28  |

| End point values                     | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 5                    | 4                    |  |  |
| Units: Activity score                |                      |                      |  |  |
| arithmetic mean (standard deviation) | 2.0 (± 2.0)          | 2.3 (± 1.7)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: VAS score for itch

|                        |   |
|------------------------|---|
| End point title        | VAS score for itch  |
| End point description: | Efficacy of alitretinoin on disease severity as evaluated by patient assessment score VAS (Visual Analogue Scale) for itch. |
| End point type         | Secondary   |
| End point timeframe:   | Week 0, 2, 4, 8, 12, 16, 20, 24 and 28  |

| End point values                     | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 5                    | 3                    |  |  |
| Units: VAS score                     |                      |                      |  |  |
| arithmetic mean (standard deviation) | 3.5 ( $\pm$ 2.2)     | 2.2 ( $\pm$ 3.8)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: VAS score for pain

|   |                    |
|---|--------------------|
| End point title   | VAS score for pain |
| End point description:<br>Efficacy of alitretinoin on disease severity as evaluated by patient assessment score VAS for pain. |                    |
| End point type  | Secondary          |
| End point timeframe:<br>Week 0, 2, 4, 8, 12, 16, 20, 24 and 28  |                    |

| End point values                     | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 5                    | 3                    |  |  |
| Units: VAS score                     |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0 ( $\pm$ 0)         | 1.8 ( $\pm$ 3.2)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: PAGI Score

|  |            |
|--|------------|
| End point title  | PAGI Score |
| End point description:<br>Efficacy of alitretinoin on disease severity as evaluated by patient assessment score PAGI (Patient Assessment of Global Improvement). |            |
| End point type   | Secondary  |
| End point timeframe:<br>Week 0, 2, 4, 8, 12, 16, 20, 24 and 28   |            |

| <b>End point values</b>              | Visit (Baseline)     | Visit (last)         |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 4                    | 3                    |  |  |
| Units: PAGI score                    |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0 ( $\pm$ 0.8)       | 0 ( $\pm$ 1.0)       |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of informed consent until the final study visit.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Safety group |
|-----------------------|--------------|

Reporting group description:

Patients who received at least one dose of alitretinoin (Toctino®).

| Serious adverse events                            | Safety group   |  |  |
|---|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Nervous system disorders                          |                |  |  |
| Headache  |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Gastrointestinal disorders                        |                |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| occurrences causally related to treatment / all   | 1 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Psychiatric disorders                             |                |  |  |
| Psychotic disorder                                |                |  |  |
| subjects affected / exposed                       | 1 / 5 (20.00%) |  |  |
| occurrences causally related to treatment / all   | 1 / 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 group                                   |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 3 / 5 (60.00%)                                 |  |  |
| Vascular disorders<br>Flushing<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1                            |  |  |
| Nervous system disorders<br>Head discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1 |  |  |
| Blood and lymphatic system disorders<br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1                            |  |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1                            |  |  |
| Gastrointestinal disorders<br>Diarrhoea haemorrhagic<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1                            |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1                            |  |  |
| Infections and infestations<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1                            |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment  |
|-------------|--|
| 13 May 2013 | <ul style="list-style-type: none"><li>- Exclusion criteria were amended. Patients with hereditary myopathy in patient and family history as well as patients with known rhabdomyolysis in patient history (e.g. muscular-toxic complications in association with statin and fibrate therapy) should not participate in the study.</li><li>- In patients with clinical suspicion of myalgia and/ or myopathia, creatine kinase should be determined. If the level was significantly increased, the patient should be excluded from the study.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption  | Restart date |
|---------------|---|--------------|
| 11 April 2013 | Only 7 patients could be enrolled in the study within 18 months and it was not expected that more patients or even all 30 patients would be recruited in the near future. Therefore, recruitment of patients was interrupted on April 11, 2013, and on April 30, 2014, the study was officially terminated. | -            |

Notes:

### Limitations and caveats

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

The study was terminated prematurely because only 7 patients could be enrolled in the study (only 5 patients started study treatment).

Notes: