



## Clinical trial results:

### An exploratory Phase II Study to demonstrate the Safety and Efficacy of A4250 in Children with Cholestatic Pruritus

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-001157-32 |
| Trial protocol           | SE DK DE GB    |
| Global end of trial date | 05 April 2017  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 14 October 2017 |
| First version publication date | 14 October 2017 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | A4250-003 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02630875 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Albireo AB   |
| Sponsor organisation address | Arvid Wallgrens Backe 20, Göteborg, Sweden, 413 46   |
| Public contact               | Albireo AB , Albireo AB, 0046 31 741 14 80,<br>info@albireopharma.com                      |
| Scientific contact           | Responsible Medical Officer, Albireo AB, 0046 703747175,<br>mats.ekelund@albireopharma.com |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-002054-PIP01-16 |
| 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                       | 31 May 2017   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 17 March 2017 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 05 April 2017 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

- Assess the safety and tolerability of A4250, orally administered
- Explore changes in serum total bile acids

Protection of trial subjects:

Each patient made 6 visits to the clinic where the patient was observed for safety variables and laboratory measurements. Physical examination and measurement of vital signs were done at each visit. Each patient received a patient diary to record symptoms during the study. Concomitant medication and any adverse events were collected at each visit.

The study was designed to have six dose cohorts but during the Data Safety Monitoring Board (DSMB) meeting after the fifth cohort (0.2 mg/kg/day), based on a mean increase in ALT, the DSMB recommended that dosing at the same level could continue, but further dose escalation should be discontinued. A sixth cohort was enrolled, but these patients were treated at lower doses.

Background therapy:

There were no general background therapy, but the patients were allowed to be on UDCA and rifampicin during the study.

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 25 August 2015 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Sweden: 2   |
| Country: Number of subjects enrolled | Denmark: 1  |
| Country: Number of subjects enrolled | France: 8   |
| Country: Number of subjects enrolled | Germany: 13 |
| Worldwide total number of subjects   | 24          |
| EEA total number of subjects         | 24          |

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) | 3  |
| Children (2-11 years)                    | 17 |
| Adolescents (12-17 years)                | 4  |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was performed in cohorts followed by a DSMB meeting and decision prior to the start of next cohort. 6 sites participated in Sweden, Denmark, France and Germany. The first patient in was 25 Aug 2015, and last patient out was 17 Mar 2017. The 24 total subjects include 4 subjects who reenrolled and participated in two different dose groups.

### Pre-assignment

Screening details:

Main inclusion criteria was children with cholestatic pruritus and elevated serum bile acids. Eligible patients made 6 site visits. Study baseline was defined as the last assessment prior to administration of the single dose at Visit 2. Patients were allowed to be re-enrolled into a second dose group.

### Period 1

|                              |                |
|------------------------------|----------------|
| Period 1 title               | Enrolment      |
| Is this the baseline period? | Yes            |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|                              |                                   |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes                               |
| <b>Arm title</b>             | Baseline Dose Group 1: 0.01 mg/kg |

Arm description: -

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Baseline Dose Group 2: 0.03 mg/kg |
|------------------|-----------------------------------|

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Baseline Dose Group 3: 0.06 mg/kg |
|------------------|-----------------------------------|

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Baseline Dose Group 4: 0.1 mg/kg |
|------------------|----------------------------------|

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Baseline Dose group 5: 0.2 mg/kg |
|------------------|----------------------------------|

Arm description: -

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b> | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg |
|---------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Started                               | 4                                 | 6                                 | 4                                 |
| Completed                             | 4                                 | 6                                 | 4                                 |

| <b>Number of subjects in period 1</b> | Baseline Dose Group 4: 0.1 mg/kg | Baseline Dose group 5: 0.2 mg/kg |
|---------------------------------------|----------------------------------|----------------------------------|
| Started                               | 6                                | 4                                |
| Completed                             | 6                                | 4                                |

## Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Treatment      |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

## Arms

|                              |                                    |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | Yes                                |
| <b>Arm title</b>             | Treatment Dose Group 1: 0.01 mg/kg |

Arm description: -

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Treatment Dose Group 2: 0.03 mg/kg |
|------------------|------------------------------------|

Arm description: -

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Treatment Dose Group 3: 0.06 mg/kg |
|------------------|------------------------------------|

Arm description: -

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |               |
|--|---------------|
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

**Dosage and administration details:**

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Treatment Dose Group 4: 0.1 mg/kg |
|------------------|-----------------------------------|

**Arm description: -**

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

**Dosage and administration details:**

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Treatment Dose Group 5: 0.2 mg/kg |
|------------------|-----------------------------------|

**Arm description: -**

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | A4250         |
| Investigational medicinal product code | A4250         |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

**Dosage and administration details:**

One single oral dose was given at Visit 2, followed by at least 14 days wash-out. Eligible patients then received daily oral dosing for 4 weeks, starting at Visit 4.

| <b>Number of subjects in period 2</b> | Treatment Dose Group 1: 0.01 mg/kg | Treatment Dose Group 2: 0.03 mg/kg | Treatment Dose Group 3: 0.06 mg/kg |
|---------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Started                               | 4                                  | 6                                  | 4                                  |
| Completed                             | 4                                  | 6                                  | 4                                  |

| <b>Number of subjects in period 2</b> | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |
|---------------------------------------|-----------------------------------|-----------------------------------|
| Started                               | 6                                 | 4                                 |
| Completed                             | 6                                 | 4                                 |

## Baseline characteristics

### Reporting groups

|                                |                                   |
|--------------------------------|-----------------------------------|
| Reporting group title          | Baseline Dose Group 1: 0.01 mg/kg |
| Reporting group description: - |                                   |
| Reporting group title          | Baseline Dose Group 2: 0.03 mg/kg |
| Reporting group description: - |                                   |
| Reporting group title          | Baseline Dose Group 3: 0.06 mg/kg |
| Reporting group description: - |                                   |
| Reporting group title          | Baseline Dose Group 4: 0.1 mg/kg  |
| Reporting group description: - |                                   |
| Reporting group title          | Baseline Dose group 5: 0.2 mg/kg  |
| Reporting group description: - |                                   |

| Reporting group values                             | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg |
|--|-----------------------------------|-----------------------------------|-----------------------------------|
| Number of subjects                                 | 4                                 | 6                                 | 4                                 |
| Age categorical<br>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                                 | 1                                 |
| Children (2-11 years)                              | 3                                 | 5                                 | 2                                 |
| Adolescents (12-17 years)                          | 1                                 | 1                                 | 1                                 |
| Adults (18-64 years)                               | 0                                 | 0                                 | 0                                 |
| From 65-84 years                                   | 0                                 | 0                                 | 0                                 |
| 85 years and over                                  | 0                                 | 0                                 | 0                                 |
| Gender categorical<br>Units: Subjects              |                                   |                                   |                                   |
| Female   | 1                                 | 5                                 | 1                                 |
| Male   | 3                                 | 1                                 | 3                                 |
| Diagnosis<br>Units: Subjects                       |                                   |                                   |                                   |
| PFIC-1   | 0                                 | 0                                 | 1                                 |
| PFIC-2   | 0                                 | 2                                 | 2                                 |
| PFIC-3   | 0                                 | 1                                 | 0                                 |
| Alagille-syndrome                                  | 3                                 | 0                                 | 1                                 |
| Biliary atresia                                    | 0                                 | 3                                 | 0                                 |
| Intrahepatic cholestasis microvillous atrophy      | 1                                 | 0                                 | 0                                 |

| Reporting group values             | Baseline Dose Group 4: 0.1 mg/kg | Baseline Dose group 5: 0.2 mg/kg | Total |
|------------------------------------|----------------------------------|----------------------------------|-------|
| Number of subjects                 | 6                                | 4                                | 24    |
| Age categorical<br>Units: Subjects |                                  |                                  |       |
| In utero                           | 0                                | 0                                | 0     |

|   |   |   |    |
|---|---|---|----|
| Preterm newborn infants<br>(gestational age < 37 wks) | 0 | 0 | 0  |
| Newborns (0-27 days)                                  | 0 | 0 | 0  |
| Infants and toddlers (28 days-23<br>months)           | 0 | 2 | 3  |
| Children (2-11 years)                                 | 6 | 1 | 17 |
| Adolescents (12-17 years)                             | 0 | 1 | 4  |
| Adults (18-64 years)                                  | 0 | 0 | 0  |
| From 65-84 years                                      | 0 | 0 | 0  |
| 85 years and over                                     | 0 | 0 | 0  |
| Gender categorical<br>Units: Subjects                 |   |   |    |
| Female  | 2 | 0 | 9  |
| Male  | 4 | 4 | 15 |
| Diagnosis<br>Units: Subjects                          |   |   |    |
| PFIC-1  | 1 | 0 | 2  |
| PFIC-2  | 3 | 2 | 9  |
| PFIC-3  | 1 | 0 | 2  |
| Alagille-syndrome                                     | 0 | 2 | 6  |
| Biliary atresia                                       | 0 | 0 | 3  |
| Intrahepatic cholestasis microvillous<br>atrophy      | 1 | 0 | 2  |



## End points

### End points reporting groups

|                                |                                    |
|--------------------------------|------------------------------------|
| Reporting group title          | Baseline Dose Group 1: 0.01 mg/kg  |
| Reporting group description: - |                                    |
| Reporting group title          | Baseline Dose Group 2: 0.03 mg/kg  |
| Reporting group description: - |                                    |
| Reporting group title          | Baseline Dose Group 3: 0.06 mg/kg  |
| Reporting group description: - |                                    |
| Reporting group title          | Baseline Dose Group 4: 0.1 mg/kg   |
| Reporting group description: - |                                    |
| Reporting group title          | Baseline Dose group 5: 0.2 mg/kg   |
| Reporting group description: - |                                    |
| Reporting group title          | Treatment Dose Group 1: 0.01 mg/kg |
| Reporting group description: - |                                    |
| Reporting group title          | Treatment Dose Group 2: 0.03 mg/kg |
| Reporting group description: - |                                    |
| Reporting group title          | Treatment Dose Group 3: 0.06 mg/kg |
| Reporting group description: - |                                    |
| Reporting group title          | Treatment Dose Group 4: 0.1 mg/kg  |
| Reporting group description: - |                                    |
| Reporting group title          | Treatment Dose Group 5: 0.2 mg/kg  |
| Reporting group description: - |                                    |

### Primary: Summary of liver biochemistry: Total bile acids (umol/L)

|                        |   |
|------------------------|---|
| End point title        | Summary of liver biochemistry: Total bile acids (umol/L) <sup>[1]</sup> |
| End point description: |   |

|   |         |
|---|---------|
| End point type  | Primary |
| End point timeframe:  |         |
| Change from Study Baseline (Visit 1) to End of 4-week Treatment (Visit 5) |         |

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: All statistics in the study were descriptive.

| End point values                     | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg | Baseline Dose Group 4: 0.1 mg/kg |
|--------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Subject group type                   | Reporting group                   | Reporting group                   | Reporting group                   | Reporting group                  |
| Number of subjects analysed          | 4                                 | 6                                 | 4                                 | 6                                |
| Units: micromole(s)/litre            |                                   |                                   |                                   |                                  |
| arithmetic mean (standard deviation) | 217.8 (± 100.67)                  | 216 (± 177.29)                    | 220.5 (± 159.99)                  | 288.5 (± 126.83)                 |

| End point values | Baseline Dose group 5: 0.2 | Treatment Dose Group 1: | Treatment Dose Group 2: | Treatment Dose Group 3: |
|------------------|----------------------------|-------------------------|-------------------------|-------------------------|
|------------------|----------------------------|-------------------------|-------------------------|-------------------------|

|                                      | mg/kg            | 0.01 mg/kg       | 0.03 mg/kg      | 0.06 mg/kg      |
|--------------------------------------|------------------|------------------|-----------------|-----------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group | Reporting group |
| Number of subjects analysed          | 4                | 4                | 6               | 4               |
| Units: micromole(s)/litre            |                  |                  |                 |                 |
| arithmetic mean (standard deviation) | 213.2 (± 236.61) | 151.4 (± 146.26) | 69.4 (± 42.11)  | 61.9 (± 64.22)  |

| <b>End point values</b>              | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |  |  |
|--------------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                   | Reporting group                   |  |  |
| Number of subjects analysed          | 6                                 | 4                                 |  |  |
| Units: micromole(s)/litre            |                                   |                                   |  |  |
| arithmetic mean (standard deviation) | 163.6 (± 165.81)                  | 107 (± 150.01)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of Daily Questionnaire: VAS Itching

|                        |   |
|------------------------|---|
| End point title        | Summary of Daily Questionnaire: VAS Itching   |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   | Change from Study Baseline (7 days prior to Visit 2) to End of 4-week Treatment (7 days before end of treatment including Visit 5). |

| <b>End point values</b>     | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg | Baseline Dose Group 4: 0.1 mg/kg |
|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Subject group type          | Reporting group                   | Reporting group                   | Reporting group                   | Reporting group                  |
| Number of subjects analysed | 4                                 | 5                                 | 4                                 | 6                                |
| Units: VAS score            |                                   |                                   |                                   |                                  |
| number (not applicable)     | 5.9                               | 6.1                               | 5                                 | 7.5                              |

| <b>End point values</b>     | Baseline Dose group 5: 0.2 mg/kg | Treatment Dose Group 1: 0.01 mg/kg | Treatment Dose Group 2: 0.03 mg/kg | Treatment Dose Group 3: 0.06 mg/kg |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type          | Reporting group                  | Reporting group                    | Reporting group                    | Reporting group                    |
| Number of subjects analysed | 4                                | 4                                  | 6                                  | 4                                  |
| Units: VAS score            |                                  |                                    |                                    |                                    |
| number (not applicable)     | 6.1                              | 4.3                                | 3.6                                | 3.1                                |

| End point values            | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |  |  |
|-----------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                   | Reporting group                   |  |  |
| Number of subjects analysed | 6                                 | 4                                 |  |  |
| Units: VAS score            |                                   |                                   |  |  |
| number (not applicable)     | 4.7                               | 3.9                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Daily Questionnaire: PO-SCORAD Itching

|                 |   |
|-----------------|---|
| End point title | Summary of Daily Questionnaire: PO-SCORAD Itching |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Study Baseline (7 days prior to Visit 2) to End of 4-week Treatment (7 days before end of treatment including Visit 5).

| End point values            | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg | Baseline Dose Group 4: 0.1 mg/kg |
|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Subject group type          | Reporting group                   | Reporting group                   | Reporting group                   | Reporting group                  |
| Number of subjects analysed | 4                                 | 5                                 | 3                                 | 6                                |
| Units: PO-SCORAD score      |                                   |                                   |                                   |                                  |
| number (not applicable)     | 5.1                               | 5.6                               | 5.2                               | 7.3                              |

| End point values            | Baseline Dose group 5: 0.2 mg/kg | Treatment Dose Group 1: 0.01 mg/kg | Treatment Dose Group 2: 0.03 mg/kg | Treatment Dose Group 3: 0.06 mg/kg |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type          | Reporting group                  | Reporting group                    | Reporting group                    | Reporting group                    |
| Number of subjects analysed | 4                                | 4                                  | 5                                  | 4                                  |
| Units: PO-SCORAD score      |                                  |                                    |                                    |                                    |
| number (not applicable)     | 5.8                              | 4                                  | 3.5                                | 3                                  |

| End point values | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |  |  |
|------------------|-----------------------------------|-----------------------------------|--|--|
|------------------|-----------------------------------|-----------------------------------|--|--|

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 6               | 4               |  |  |
| Units: PO-SCORAD score      |                 |                 |  |  |
| number (not applicable)     | 4.5             | 3.5             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Daily Questionnaire: Whittington Scale

|                 |   |
|-----------------|---|
| End point title | Summary of Daily Questionnaire: Whittington Scale |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Study Baseline (7 days prior to Visit 2) to End of 4-week Treatment (7 days before end of treatment including Visit 5).

| End point values            | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg | Baseline Dose Group 4: 0.1 mg/kg |
|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Subject group type          | Reporting group                   | Reporting group                   | Reporting group                   | Reporting group                  |
| Number of subjects analysed | 4                                 | 5                                 | 4                                 | 6                                |
| Units: Whittington score    |                                   |                                   |                                   |                                  |
| number (not applicable)     | 2.3                               | 2.2                               | 2.9                               | 3.5                              |

| End point values            | Baseline Dose group 5: 0.2 mg/kg | Treatment Dose Group 1: 0.01 mg/kg | Treatment Dose Group 2: 0.03 mg/kg | Treatment Dose Group 3: 0.06 mg/kg |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type          | Reporting group                  | Reporting group                    | Reporting group                    | Reporting group                    |
| Number of subjects analysed | 4                                | 4                                  | 6                                  | 4                                  |
| Units: Whittington score    |                                  |                                    |                                    |                                    |
| number (not applicable)     | 2                                | 2.3                                | 1.5                                | 1.3                                |

| End point values            | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |  |  |
|-----------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                   | Reporting group                   |  |  |
| Number of subjects analysed | 6                                 | 4                                 |  |  |
| Units: Whittington score    |                                   |                                   |  |  |
| number (not applicable)     | 2.1                               | 1.5                               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of Daily Questionnaire: PO-SCORAD Sleep

|                 |   |
|-----------------|---|
| End point title | Summary of Daily Questionnaire: PO-SCORAD Sleep |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Study Baseline (7 days prior to Visit 2) to End of 4-week Treatment (7 days before end of treatment including Visit 5).

| End point values             | Baseline Dose Group 1: 0.01 mg/kg | Baseline Dose Group 2: 0.03 mg/kg | Baseline Dose Group 3: 0.06 mg/kg | Baseline Dose Group 4: 0.1 mg/kg |
|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Subject group type           | Reporting group                   | Reporting group                   | Reporting group                   | Reporting group                  |
| Number of subjects analysed  | 4                                 | 5                                 | 3                                 | 6                                |
| Units: PO-SCORAD Sleep Score |                                   |                                   |                                   |                                  |
| number (not applicable)      | 4                                 | 4.4                               | 4.9                               | 7.3                              |

| End point values             | Baseline Dose group 5: 0.2 mg/kg | Treatment Dose Group 1: 0.01 mg/kg | Treatment Dose Group 2: 0.03 mg/kg | Treatment Dose Group 3: 0.06 mg/kg |
|------------------------------|----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type           | Reporting group                  | Reporting group                    | Reporting group                    | Reporting group                    |
| Number of subjects analysed  | 4                                | 4                                  | 5                                  | 4                                  |
| Units: PO-SCORAD Sleep Score |                                  |                                    |                                    |                                    |
| number (not applicable)      | 5                                | 4                                  | 2.7                                | 2.6                                |

| End point values             | Treatment Dose Group 4: 0.1 mg/kg | Treatment Dose Group 5: 0.2 mg/kg |  |  |
|------------------------------|-----------------------------------|-----------------------------------|--|--|
| Subject group type           | Reporting group                   | Reporting group                   |  |  |
| Number of subjects analysed  | 6                                 | 4                                 |  |  |
| Units: PO-SCORAD Sleep Score |                                   |                                   |  |  |
| number (not applicable)      | 4.3                               | 3                                 |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were to be collected throughout the study beginning at the time the patient had signed the ICF.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.1   |

### Reporting groups

|                                |                          |
|--------------------------------|--------------------------|
| Reporting group title          | Dose group 1: 0.01 mg/kg |
| Reporting group description: - |                          |
| Reporting group title          | Dose group 2: 0.03 mg/kg |
| Reporting group description: - |                          |
| Reporting group title          | Dose group 3: 0.06 mg/kg |
| Reporting group description: - |                          |
| Reporting group title          | Dose group 4: 0.1 mg/kg  |
| Reporting group description: - |                          |
| Reporting group title          | Dose group 5: 0.2 mg/kg  |
| Reporting group description: - |                          |

| Serious adverse events                            | Dose group 1: 0.01 mg/kg | Dose group 2: 0.03 mg/kg | Dose group 3: 0.06 mg/kg |
|---|--------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events |                          |                          |                          |
| subjects affected / exposed                       | 0 / 4 (0.00%)            | 0 / 6 (0.00%)            | 0 / 4 (0.00%)            |
| number of deaths (all causes)                     | 0                        | 0                        | 0                        |
| number of deaths resulting from adverse events    | 0                        | 0                        | 0                        |
| Gastrointestinal disorders                        |                          |                          |                          |
| Gastroenteritis                                   |                          |                          |                          |
| subjects affected / exposed                       | 0 / 4 (0.00%)            | 0 / 6 (0.00%)            | 0 / 4 (0.00%)            |
| occurrences causally related to treatment / all   | 0 / 0                    | 0 / 0                    | 0 / 0                    |
| deaths causally related to treatment / all        | 0 / 0                    | 0 / 0                    | 0 / 0                    |
| Respiratory, thoracic and mediastinal disorders   |                          |                          |                          |
| Influenza   |                          |                          |                          |
| subjects affected / exposed                       | 0 / 4 (0.00%)            | 0 / 6 (0.00%)            | 0 / 4 (0.00%)            |
| occurrences causally related to treatment / all   | 0 / 0                    | 0 / 0                    | 0 / 0                    |
| deaths causally related to treatment / all        | 0 / 0                    | 0 / 0                    | 0 / 0                    |

| Serious adverse events             | Dose group 4: 0.1 mg/kg | Dose group 5: 0.2 mg/kg |  |
|------------------------------------|-------------------------|-------------------------|--|
| Total subjects affected by serious |                         |                         |  |

|   |                |               |  |
|---|----------------|---------------|--|
| adverse events                                  |                |               |  |
| subjects affected / exposed                     | 2 / 6 (33.33%) | 0 / 4 (0.00%) |  |
| number of deaths (all causes)                   | 0              | 0             |  |
| number of deaths resulting from adverse events  | 0              | 0             |  |
| Gastrointestinal disorders                      |                |               |  |
| Gastroenteritis                                 |                |               |  |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 4 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Respiratory, thoracic and mediastinal disorders |                |               |  |
| Influenza                                       |                |               |  |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 4 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Dose group 1: 0.01 mg/kg | Dose group 2: 0.03 mg/kg | Dose group 3: 0.06 mg/kg |
|---|--------------------------|--------------------------|--------------------------|
| Total subjects affected by non-serious adverse events |                          |                          |                          |
| subjects affected / exposed                           | 3 / 4 (75.00%)           | 3 / 6 (50.00%)           | 4 / 4 (100.00%)          |
| Investigations  |                          |                          |                          |
| Liver function test abnormal                          |                          |                          |                          |
| subjects affected / exposed                           | 0 / 4 (0.00%)            | 0 / 6 (0.00%)            | 0 / 4 (0.00%)            |
| occurrences (all)                                     | 0                        | 0                        | 0                        |
| Alanine aminotransferase increased                    |                          |                          |                          |
| subjects affected / exposed                           | 0 / 4 (0.00%)            | 1 / 6 (16.67%)           | 0 / 4 (0.00%)            |
| occurrences (all)                                     | 0                        | 1                        | 0                        |
| Injury, poisoning and procedural complications        |                          |                          |                          |
| Traumatic haematoma                                   |                          |                          |                          |
| subjects affected / exposed                           | 1 / 4 (25.00%)           | 0 / 6 (0.00%)            | 0 / 4 (0.00%)            |
| occurrences (all)                                     | 1                        | 0                        | 0                        |
| Toxicity to various agents                            |                          |                          |                          |
| subjects affected / exposed                           | 0 / 4 (0.00%)            | 0 / 6 (0.00%)            | 1 / 4 (25.00%)           |
| occurrences (all)                                     | 0                        | 0                        | 1                        |
| General disorders and administration site conditions  |                          |                          |                          |



|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 2 / 4 (50.00%)<br>2 |
| Hyperthermia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |
| Blood and lymphatic system disorders<br>Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Ear and labyrinth disorders<br>Ear infection<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 4 (25.00%)<br>1 | 0 / 6 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |
| Gastrointestinal disorders<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 | 0 / 6 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 4 (0.00%)<br>0  |
| Haematochezia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 4 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |
| Glossodynia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 | 0 / 4 (0.00%)<br>0  |
| Aphthous ulcer  |                     |                     |                     |

|  |                    |                    |                     |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |
| Respiratory, thoracic and mediastinal disorders  |                    |                    |                     |
| Rhinitis   |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 2 / 4 (50.00%)      |
| occurrences (all)                                | 0                  | 0                  | 2                   |
| Respiratory moniliasis                           |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 1 / 4 (25.00%)      |
| occurrences (all)                                | 0                  | 0                  | 1                   |
| Nasopharyngitis                                  |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Skin and subcutaneous tissue disorders           |                    |                    |                     |
| Perineal erythema                                |                    |                    |                     |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 1                  | 0                  | 0                   |
| Psychiatric disorders                            |                    |                    |                     |
| Sleep disorder                                   |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Infections and infestations                      |                    |                    |                     |
| Bronchitis bacterial                             |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 1 / 4 (25.00%)      |
| occurrences (all)                                | 0                  | 0                  | 1                   |
| Viral infection                                  |                    |                    |                     |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 1                  | 0                  | 0                   |
| Metabolism and nutrition disorders               |                    |                    |                     |
| Xanthochromia                                    |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Decreased appetite                               |                    |                    |                     |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 6 (0.00%)      | 0 / 4 (0.00%)       |
| occurrences (all)                                | 0                  | 0                  | 0                   |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| <b>Non-serious adverse events</b>      | Dose group 4: 0.1 mg/kg | Dose group 5: 0.2 mg/kg |  |
| Total subjects affected by non-serious |                         |                         |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| adverse events                                       |                |                 |  |
| subjects affected / exposed                          | 2 / 6 (33.33%) | 4 / 4 (100.00%) |  |
| Investigations                                       |                |                 |  |
| Liver function test abnormal                         |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 4 (25.00%)  |  |
| occurrences (all)                                    | 0              | 2               |  |
| Alanine aminotransferase increased                   |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Injury, poisoning and procedural complications       |                |                 |  |
| Traumatic haematoma                                  |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Toxicity to various agents                           |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| General disorders and administration site conditions |                |                 |  |
| Pyrexia  |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 1 / 4 (25.00%)  |  |
| occurrences (all)                                    | 0              | 4               |  |
| Hyperthermia   |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Blood and lymphatic system disorders                 |                |                 |  |
| Iron deficiency anaemia                              |                |                 |  |
| subjects affected / exposed                          | 1 / 6 (16.67%) | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 1              | 0               |  |
| Ear and labyrinth disorders                          |                |                 |  |
| Ear infection  |                |                 |  |
| subjects affected / exposed                          | 1 / 6 (16.67%) | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 1              | 0               |  |
| Ear pain   |                |                 |  |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 4 (0.00%)   |  |
| occurrences (all)                                    | 0              | 0               |  |
| Gastrointestinal disorders                           |                |                 |  |
| Gastroenteritis                                      |                |                 |  |

|   |               |                |  |
|---|---------------|----------------|--|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 4 (25.00%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Diarrhoea                                       |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Constipation                                    |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Haematochezia                                   |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Vomiting  |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 4 (25.00%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Glossodynia                                     |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Aphthous ulcer                                  |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Respiratory, thoracic and mediastinal disorders |               |                |  |
| Rhinitis  |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Respiratory moniliasis                          |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Nasopharyngitis                                 |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 1 / 4 (25.00%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Skin and subcutaneous tissue disorders          |               |                |  |
| Perineal erythema                               |               |                |  |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 4 (0.00%)  |  |
| occurrences (all)                               | 0             | 0              |  |
| Psychiatric disorders                           |               |                |  |

|   |                    |                     |  |
|---|--------------------|---------------------|--|
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 6 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |  |
| Infections and infestations<br>Bronchitis bacterial<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 6 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Metabolism and nutrition disorders<br>Xanthochromia<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 6 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 26 June 2015      | Only applicable for France: <ul style="list-style-type: none"><li>- Administration immediately after mixing A4250 into food</li><li>- Nasogastric tube deleted</li><li>- Washout period (min 95 days) added</li><li>- Filling of capsules clarified</li><li>- Blood sample schedule added</li></ul> |
| 02 March 2016     | <ul style="list-style-type: none"><li>- Mats Ekelund as director of medicine to replace Hans Graffner (deceased)</li><li>- Creatine Kinase (CK) added in Routine clinical chemistry</li><li>- Additional cohorts after dose escalation stop (substantial amendment)</li></ul>                       |
| 01 September 2016 | Only applicable for Sweden: <ul style="list-style-type: none"><li>- Age inclusion criteria changed from 18 to 26 years</li></ul>  |
| 13 October 2016   | Only applicable for the United Kingdom: <ul style="list-style-type: none"><li>- Concurrent medications prohibited during the study</li><li>- Correction of the definition of child bearing potential</li></ul>  |

Notes:

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### 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.

Patients completing Cohort 1 could re-enter the study in one of the Cohorts 4, 5 or 6. Patients completing Cohort 2 could re-enter Cohorts 5 or 6 and patients completing Cohort 3 could re-enter Cohort 6. Re-enrolled required new signature of ICF.

Notes: