



## 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
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##### 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, info@albireopharma.com
Scientific contact	Responsible Medical Officer, Albireo AB, 0046 703747175, 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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

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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)	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
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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
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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
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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
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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
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<b>Arm title</b>	Treatment Dose Group 1: 0.01 mg/kg
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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
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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
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Arm description: -

Arm type	Experimental
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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
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**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
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**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 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 Units: Subjects			
Female	1	5	1
Male	3	1	3
Diagnosis 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 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	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 Units: Subjects			
Female	2	0	9
Male	4	4	15
Diagnosis 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 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:
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	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
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End point description:

End point type	Secondary
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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		
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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### 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 subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	2 / 4 (50.00%) 2
Hyperthermia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1
Ear pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Glossodynia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0
Aphthous ulcer			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 4 (25.00%) 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 subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	
Infections and infestations Bronchitis bacterial subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	
Viral infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	
Metabolism and nutrition disorders Xanthochromia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 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: