Clinical trial results:
A double-blind, randomized, placebo-controlled, study to demonstrate the efficacy and safety of 250 mg or 1 g A3384 administered orally twice daily for two weeks to patients with Bile Acid Malabsorption (BAM)/Bile Acid Diarrhoea (BAD)

Summary

EudraCT number	2013-002924-17
Trial protocol	SE GB
Global end of trial date	18 December 2014

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016
Summary attachment (see zip file)	Study report summary (Summary of report A3384-001.pdf)

Trial information

Trial identification

Sponsor protocol code	A3384-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Albireo AB
Sponsor organisation address	Arvid Wallgrens Backe 20, Gothenburg, Sweden,
Public contact	VP Clinical & Regulatory Affairs, Albireo AB, 0046 31 74 114 81, kristina.torfgard@albireopharma.com
Scientific contact	Responsible Medical Officer, Albireo AB, 0046 31 741 1480,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2014
Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study is to demonstrate the efficacy of twice daily oral doses of 250 mg or 1 g A3384 during a two week treatment period in patients with BAM, as determined by the # of bowel movements (BMs).
The primary safety objective of this study is to assess the safety and tolerability of twice daily oral doses of 250 mg or 1 g A3384 during a two week treatment period in patients with BAM, as determined by the occurrence of treatment-emergent SAEs.

Protection of trial subjects:

Vital signs, physical examinations, patient diary, laboratory test (such as haematology, clinical chemistry and urinalysis), concomitant medication review and adverse event data collection were performed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 11
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	14
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were three sites included in this study. Two sites from Sweden, site 001 in Göteborg and site 002 in Skövde and one site, site 003 in London from UK.

Pre-assignment

Screening details:

Thirty-four patients were screened for participation in the study: 19 patients (8 women and 11 men) entered the study and 15 patients were screening failures. All randomized patients completed the study and were included in both the FAS (mITT population) and the safety population.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	250 mg A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental
Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (1 capsule of 250 mg A3384 + 3 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	1 g A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental
Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Capsule
Routes of administration	Oral use, Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 capsules of 250 mg A3384, i.e. one dosage unit) were taken twice daily orally with

water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	Placebo

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Number of subjects in period 1	250 mg A3384	1 g A3384	Placebo
Started	6	7	6
Completed	6	7	6

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	250 mg A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental

Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (1 capsule of 250 mg A3384 + 3 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	1 g A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental
Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Capsule
Routes of administration	Oral use, Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 capsules of 250 mg A3384, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	Placebo

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Number of subjects in period 2	250 mg A3384	1 g A3384	Placebo
Started	6	7	6
Completed	6	7	6

Period 3

Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	250 mg A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental
Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (1 capsule of 250 mg A3384 + 3 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	1 g A3384

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Experimental
Investigational medicinal product name	A3384
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Capsule
Routes of administration	Oral use, Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 capsules of 250 mg A3384, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm title	Placebo

Arm description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Number of subjects in period 3	250 mg A3384	1 g A3384	Placebo
Started	6	7	6
Completed	6	7	6

Baseline characteristics

Reporting groups	
Reporting group title	250 mg A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	1 g A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	Placebo

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group values	250 mg A3384	1 g A3384	Placebo
Number of subjects	6	7	6
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	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	5	5
From 65-84 years	2	2	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	50	46.4	38.7
standard deviation	± 21.28	± 20.4	± 17.57
Gender categorical Units: Subjects			
Female	2	3	3
Male	4	4	3
Ethnic background Units: Subjects			
Asian	0	2	1
Caucasian	5	5	4
Other	1	0	1

Reporting group values	Total		
Number of subjects	19		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	14		
From 65-84 years	5		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		
Male	11		
Ethnic background Units: Subjects			
Asian	3		
Caucasian	14		
Other	2		

End points

End points reporting groups

Reporting group title	250 mg A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	1 g A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	Placebo

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	250 mg A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	1 g A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	Placebo

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	250 mg A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	1 g A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	Placebo

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Primary: Change from baseline period 2 of bowel movements during second treatment week

End point title	Change from baseline period 2 of bowel movements during second treatment week

End point description:

The primary efficacy endpoint was the change in mean (daily) number of BMs from the baseline period 2 diary recordings to the second treatment week diary recordings.

End point type	Primary

End point timeframe:

From the baseline period 2 to the second treatment week.

End point values	250 mg A3384	1 g A3384	Placebo	250 mg A3384
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	5	6
Units: Number of BM				
arithmetic mean (standard deviation)	5.4 (± 2.8)	4.9 (± 1.5)	4.5 (± 0.9)	3.6 (± 1.6)

End point values	1 g A3384	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5[1]		
Units: Number of BM				
arithmetic mean (standard deviation)	3.7 (± 1.9)	4.1 (± 1.3)		

Notes:

[1] - One patient had too few observations, only two Days of assessments for treatment period 2.

Statistical analyses

Statistical analysis title	Change in mean (daily) number of BMs, 250 mg A3384

Statistical analysis description:

Change from baseline

Comparison groups	250 mg A3384 v Placebo
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.697
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.143
upper limit	1.143

Statistical analysis title	Change in mean (daily) number of BMs, 1g A3384
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3258
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.857

Statistical analysis title	Change in mean (daily) number of BMs, (1g+250mg)
Statistical analysis description: Combined A3384 group (1 g + 250 mg) compared to placebo from baseline period 2 to second treatment week	
Comparison groups	250 mg A3384 v 1 g A3384 v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3985
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.429
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.857

Statistical analysis title	Change in mean (daily) number of BMs, 250 mg A3384
Comparison groups	250 mg A3384 v Placebo

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3299
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.976
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.068
upper limit	1.117

Statistical analysis title	Change in mean (daily) number of BMs, 1g A3384
Comparison groups	1 g A3384 v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4855
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.658
upper limit	1.338

Statistical analysis title	Change in mean (daily) number of BMs, (1g+250mg)
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3383
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	0.939

Secondary: Severity of diarrhoea

End point title	Severity of diarrhoea

End point description:

Change from Baseline in average severity of diarrhoea (daily) during the second treatment week or the last 7 Days of reporting. Patient reporting scale 0-10

End point type	Secondary

End point timeframe:

From baseline to second treatment week.

End point values	250 mg A3384	1 g A3384	Placebo	250 mg A3384
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	6	6
Units: severity of diarrhoea				
arithmetic mean (standard deviation)	6 (± 3)	5.8 (± 1.8)	4.9 (± 2.8)	3.7 (± 2.4)

End point values	1 g A3384	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: severity of diarrhoea				
arithmetic mean (standard deviation)	4.1 (± 2.9)	5.5 (± 2.7)		

Statistical analyses

Statistical analysis title	Change in mean (daily) symptoms diar, 250 mg A3384

Statistical analysis description:

Change from baseline

Comparison groups	250 mg A3384 v Placebo
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0823
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-3.429
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.571
upper limit	1.286

Statistical analysis title	Change in mean (daily) symptoms diar, 1 g A3384

Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0732
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-3.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.286
upper limit	0.429

Statistical analysis title	Change in mean (daily) symptoms diarrh, 1g + 250mg
Statistical analysis description: Change from baseline	
Comparison groups	1 g A3384 v Placebo v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-3.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.554
upper limit	-0.286

Statistical analysis title	Change in mean (daily) symptoms diarrh, 250 mg
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-3.138

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.894
upper limit	-0.381

Statistical analysis title	Change in mean (daily) symptoms diarrh, 1 g
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0476
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-2.685
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.336
upper limit	-0.034

Statistical analysis title	Change in mean (daily) symptoms diarrh, 1g+250mg
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0183
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-2.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.204
upper limit	-0.574

Secondary: Severity of abdominal discomfort	
End point title	Severity of abdominal discomfort
End point description: Change in mean (daily) severity of abdominal discomfort from baseline period 2 (last 7 Days prior to	

Clinical visit number 3) to the second treatment week (last 7 Days of reporting)

End point type	Secondary

End point timeframe:

From baseline to second treatment week.

End point values	250 mg A3384	1 g A3384	Placebo	250 mg A3384
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	6	6
Units: severity of abdominal discomfort				
arithmetic mean (standard deviation)	5 (± 3.5)	5 (± 2.7)	5.8 (± 1.3)	3.2 (± 1.8)

End point values	1 g A3384	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: severity of abdominal discomfort				
arithmetic mean (standard deviation)	3.3 (± 3.4)	4.5 (± 2.4)		

Statistical analyses

Statistical analysis title	Change in mean (daily) symptoms abd discom (250mg)
Statistical analysis description:	
Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7922
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.857
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.143
upper limit	3.238

Statistical analysis title	Change in mean (daily) symptoms abd discomfor (1g)
Statistical analysis description:	
Change from baseline	
Comparison groups	Placebo v 1 g A3384

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6061
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	2.286

Statistical analysis title	Change in mean (daily) symptoms abd dis (1g+250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384 v 1 g A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6162
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	2.238

Statistical analysis title	Change in mean (daily) symptoms abd discom (250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5246
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.931
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.028
upper limit	2.165

Statistical analysis title	Change in mean (daily) symptoms abd discomfor (1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5186
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.909
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.887
upper limit	2.069

Statistical analysis title	Change in mean (daily) symptoms abd dis (1g+250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4545
Method	ANCOVA
Parameter estimate	LSmean estimate
Point estimate	-0.919
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.495
upper limit	1.656

Secondary: Severity of abdominal bloating	
End point title	Severity of abdominal bloating
End point description: Change in mean (daily) severity of abdominal bloating from baseline period 2 (last 7 Days prior to clinicla visit number 3) to the second treatment week (last 7 Days of reporting)	
End point type	Secondary
End point timeframe: From baseline to second treatment week.	

End point values	250 mg A3384	1 g A3384	Placebo	250 mg A3384
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	6	6
Units: severity in abdominal bloating				
arithmetic mean (standard deviation)	4.1 (± 3.9)	4.7 (± 1.8)	6 (± 1.5)	3.2 (± 2.4)

End point values	1 g A3384	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: severity in abdominal bloating				
arithmetic mean (standard deviation)	3.4 (± 2.9)	5.1 (± 2.9)		

Statistical analyses

Statistical analysis title	Change in mean (daily) symptoms abd bloati (250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9307
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.881
upper limit	4.143

Statistical analysis title	Change in mean (daily) symptoms abd bloating (1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.714
upper limit	2.143

Statistical analysis title	Change in mean (daily) symptoms abd blo (250mg+1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9799
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.229
upper limit	2

Statistical analysis title	Change in mean (daily) symptoms abd bloati (250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6572
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.028
upper limit	2.636

Statistical analysis title	Change in mean (daily) symptoms abd bloating (1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.573
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.841
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.004
upper limit	2.322

Statistical analysis title	Change in mean (daily) symptoms abd blo (250mg+1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5522
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.778
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.531
upper limit	1.975

Secondary: Stool consistency	
End point title	Stool consistency
End point description: Change in mean (daily) stool consistency (as determined by the Bristol Stool Form Scale (BSFS)) from baseline period 2 (last 7 Days prior to clinic visit number 3) to the second treatment week (last 7 Days of reporting)	
End point type	Secondary
End point timeframe: From baseline to second treatment week.	

End point values	250 mg A3384	1 g A3384	Placebo	250 mg A3384
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	6	6
Units: daily stool consistency				
arithmetic mean (standard deviation)	5.9 (± 0.7)	6.1 (± 0.6)	5.5 (± 1)	4.9 (± 1.3)

End point values	1 g A3384	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: daily stool consistency				
arithmetic mean (standard deviation)	5.4 (± 1.1)	5.3 (± 1.2)		

Statistical analyses

Statistical analysis title	Change in mean stool consistency (250mg)
Statistical analysis description: Change from baseline	
Comparison groups	250 mg A3384 v Placebo
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0823
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-1.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.065
upper limit	0.327

Statistical analysis title	Change in mean stool consistency (1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.515
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.784
upper limit	0.294

Statistical analysis title	Change in mean stool consistency (250mg+1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0593
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.951
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.784
upper limit	0.044

Statistical analysis title	Change in mean stool consistency (250mg)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0289
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-1.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.242
upper limit	-0.145

Statistical analysis title	Change in mean stool consistency (1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0908
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.927
upper limit	0.163

Statistical analysis title	Change in mean stool consistency (250mg+1g)
Statistical analysis description: Change from baseline	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0298
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-1.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.955
upper limit	-0.118

Secondary: self-reported global symptom relief	
End point title	self-reported global symptom relief
End point description: Difference in patients'self-reported global symptom relief rating 1-7.	
End point type	Secondary
End point timeframe: visit 4	

End point values	250 mg A3384	1 g A3384	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	6	
Units: global symptom				
arithmetic mean (standard deviation)	3.5 (± 1.38)	3.4 (± 1.62)	4 (± 1.9)	

Statistical analyses

Statistical analysis title	Global symptom relief (250mg)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	250 mg A3384 v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6234
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2

Statistical analysis title	Global symptom relief (1g)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	Placebo v 1 g A3384
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6393
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2

Statistical analysis title	Global symptom relief (250mg+1g)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5606
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Statistical analysis title	Global symptom relief (250mg)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	Placebo v 250 mg A3384
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.525
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.748
upper limit	1.697

Statistical analysis title	Global symptom relief (1g)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	Placebo v 1 g A3384

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5689
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.707
upper limit	1.549

Statistical analysis title	Global symptom relief (250mg+1g)
Statistical analysis description: Change from global symptoms patient usually have when taking their regular medicine.	
Comparison groups	Placebo v 1 g A3384 v 250 mg A3384
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5279
Method	ANCOVA
Parameter estimate	LSmeanestimate
Point estimate	-0.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.384
upper limit	1.275

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, whether reported by the patient or observed by the Investigator/Investigative Staff, were recorded throughout the study, starting after the patient had signed the ICF and until the post-treatment follow-up (visit 5) 7 days after the final dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	250 mg A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 1 capsule of 250 mg A3384 + 3 placebo capsules) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	1 g A3384

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (i.e. one dosage unit = 4 capsules of 250 mg A3384) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Reporting group title	Placebo

Reporting group description:

Randomized patients received a treatment pack containing 136 capsules (for treatment of 17 days). Four capsules (4 placebo capsules, i.e. one dosage unit) were taken twice daily orally with water, 30 minutes before breakfast and 30 minutes before supper at approximately 5 to 8 pm.

Serious adverse events	250 mg A3384	1 g A3384	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
skeletal metastases	Additional description: Skeletal metastases in spine, unknown primary tumor. Was judged to be not related to the study drug and was classified as post study event		
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	250 mg A3384	1 g A3384	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	5 / 7 (71.43%)	6 / 6 (100.00%)
Investigations			
Increased value pf P-Calcium			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Heart palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rhizophathia right arm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Stomach pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Sweating			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Shoulder pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Chest infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Common cold			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2014	Amendment No. 2 Sweden Substantial Amendment to the Investigational Medicinal Product Dossier, Change in widen of specification for assay from 90-100% to 80-120% to enable the recently manufactured capsules to be used in the study
15 July 2014	Amendment No. 2 UK Substantial Amendment to the Investigational Medicinal Product Dossier, Change in widen of specification for assay from 90-100% to 80-120% to enable the recently manufactured capsules to be used in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported