



Clinical trial results:

A Phase 3 Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)

Summary

EudraCT number	2020-004011-28
Trial protocol	FR PL NL BE DE IT
Global end of trial date	10 November 2022

Results information

Result version number	v1 (current)
This version publication date	18 June 2023
First version publication date	18 June 2023

Trial information

Trial identification

Sponsor protocol code	A4250-012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04674761
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	Medical Director, Albireo Pharma, Inc., medinfo@albireopharma.com
Scientific contact	Medical Director, Albireo Pharma, Inc., medinfo@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-PIP03-20
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2022
Global end of trial reached?	Yes
Global end of trial date	10 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the efficacy of repeated daily doses of 120 µg/kg/day odevixibat in relieving pruritus in patients with ALGS.

Protection of trial subjects:

Safety was evaluated throughout the study, including monitoring for AEs and concomitant medications, physical examinations, vital signs, laboratory tests (including chemistry, haematology, urinalysis, vitamins A and E, 25-hydroxy vitamin D, and INR), and liver ultrasound/ elastography (where available). A Data and Safety Monitoring Board (DSMB) comprised of independent clinical and statistical experts was established to periodically review accumulating study data, including AEs and laboratory data. Cases of suspected drug-induced liver injury (DILI) or other protocol-defined liver-related AEs underwent blinded review and adjudication of aetiology by an independent Hepatic Safety Adjudication Committee (HSAC) comprised of 3 hepatologists with experience assessing events of potential hepatotoxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	17 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	52
EEA total number of subjects	36

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)	8
Children (2-11 years)	39
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between 16 December 2020 to 28 March 2022. Patients were recruited at hospitals or medical specialty centers. Patients were recruited in all countries except Canada, Israel, and New Zealand.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	52
Intermediate milestone: Number of subjects	Subjects Randomised: 52
Number of subjects completed	52

Period 1

Period 1 title	Overall Trial (overall period)
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	Odevixibat

Arm description:

Odevixibat 120 µg/kg/day

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

Dosage and administration details:

120 µg/kg/day was orally administered once daily in the morning for 24 weeks. For young children or in case of difficulties swallowing the capsules, capsules could be opened and the content sprinkled on soft foods.

Arm title	Placebo
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Arm description:

Placebo

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

Dosage and administration details:

Placebo was orally administered once daily in the morning for 24 weeks. For young children or in case of difficulties swallowing the capsules, capsules could be opened and the content sprinkled on soft foods.

Number of subjects in period 1	Odevixibat	Placebo
Started	35	17
Received Treatment	35	17
Completed	35	17

Baseline characteristics

Reporting groups

Reporting group title	Odevixibat
Reporting group description: Odevixibat 120 µg/kg/day	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Odevixibat	Placebo	Total
Number of subjects	35	17	52
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)	3	5	8
Children (2-11 years)	28	11	39
Adolescents (12-17 years)	4	1	5
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	6.73	5.40	
standard deviation	± 3.780	± 4.411	-
Gender categorical Units: Subjects			
Female	14	11	25
Male	21	6	27
Genetic Mutation Units: Subjects			
JAG1	32	16	48
NOTCH2	3	1	4
Age category 1 Units: Subjects			
< 10 years	29	13	42
> = 10 years and < 18 years	6	4	10

End points

End points reporting groups

Reporting group title	Odevixibat
Reporting group description:	
Odevixibat 120 µg/kg/day	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: Change from baseline in average AM and PM scratching score to month 6 (weeks 21 to 24)

End point title	Change from baseline in average AM and PM scratching score to month 6 (weeks 21 to 24)
End point description:	
The post treatment monthly (28-day) average AM and PM scratching score was calculated by averaging 4 weekly average AM and PM scores within the 4-week interval. Monthly score could be calculated only if at least 3 of 4 weekly scores were available within the 4-week interval. The weekly average AM and PM score was calculated by averaging of the average of AM score and the average of PM in a week only if at least 7 of 14 AM or PM assessments were collected. The baseline average AM and PM score was calculated by averaging the two-baseline weekly average AM and PM scores in the 14 days preceding start of treatment. Baseline values could be calculated only if both weeks could be calculated. Change from baseline was calculated as the monthly score minus the baseline score.	
End point type	Primary
End point timeframe:	
Month 6 (weeks 21 to 24)	

End point values	Odevixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	17		
Units: score				
least squares mean (standard error)	-1.69 (± 0.174)	-0.8 (± 0.233)		

Statistical analyses

Statistical analysis title	Change in AM and PM scratching score
Comparison groups	Odevixibat v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0012
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.33
Variability estimate	Standard error of the mean
Dispersion value	0.277

Notes:

[1] - The analysis is based on a mixed model for repeated measures (MMRM) using a restricted maximum likelihood (REML) with baseline score as a covariate, and baseline age stratification, baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction as fixed effects. One-sided p-value was reported.

Secondary: Key Secondary Endpoint: Change in Serum Bile Acids from Baseline to the Average of Weeks 20 and 24 (µmol/L)

End point title	Key Secondary Endpoint: Change in Serum Bile Acids from Baseline to the Average of Weeks 20 and 24 (µmol/L)
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End point description:

Baseline was calculated as the average of the last 2 values prior to the first dose and the average of week 20 and week 24 was calculated as the average of values at week 20 and week 24. Change from baseline was calculated as serum bile acid value at post baseline minus the baseline value.

End point type	Secondary
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End point timeframe:

Average of Week 20 and Week 24

End point values	Odevixibat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	17		
Units: Result				
least squares mean (standard error)	-90.35 (± 21.336)	22.39 (± 28.463)		

Statistical analyses

Statistical analysis title	Change in serum bile acid level (µmol/L)
Comparison groups	Placebo v Odevixibat
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.0006
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-112.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-178.78
upper limit	-46.69

Variability estimate	Standard error of the mean
Dispersion value	32.864

Notes:

[2] - The analysis is based on a mixed model for repeated measures (MMRM) using a restricted maximum likelihood (REML) with baseline serum bile acid (sBA) concentration data as a covariate, and baseline age stratification, treatment group, visits (Weeks 4, 8, 12, 16, 20, 24), and treatment-by-visit interaction as fixed effects. The comparison of treatment difference in change from baseline to the average of Week 20 and Week 24 is estimated and tested using contrast. One-sided p-value was reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety reporting period for adverse events is from the first dose of study drug through the last planned study visit or 28 calendar days after the last dose of the study drug, whichever occurs later.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Odevixibat
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Reporting group description:

Odevixibat 120 µg/kg/day

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	Odevixibat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 35 (14.29%)	2 / 17 (11.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Otitis media chronic			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (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: 0 %

Non-serious adverse events	Odevixibat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 35 (74.29%)	12 / 17 (70.59%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 35 (8.57%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	8 / 35 (22.86%)	4 / 17 (23.53%)	
occurrences (all)	8	7	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	3 / 35 (8.57%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	1 / 35 (2.86%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Blood pressure diastolic increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1	
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 17 (11.76%) 2	
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Vitamin A decreased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Vitamin E decreased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 17 (0.00%) 0	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Ligament sprain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Vaccination complication subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1	
Nervous system disorders Bell's palsy subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1	
Headache			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Coagulopathy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract cortical			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 35 (11.43%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Abdominal pain upper			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	10 / 35 (28.57%)	1 / 17 (5.88%)	
occurrences (all)	11	1	
Faeces discoloured			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 17 (5.88%) 1	
Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin lesion subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	0 / 17 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	4 / 17 (23.53%) 4	
Conjunctivitis			

subjects affected / exposed	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	3	0
Gastroenteritis		
subjects affected / exposed	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	2	0
Influenza		
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	2 / 35 (5.71%)	1 / 17 (5.88%)
occurrences (all)	4	1
Otitis externa		
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	3 / 35 (8.57%)	1 / 17 (5.88%)
occurrences (all)	3	1
Subcutaneous abscess		
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Tonsillitis		
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	3 / 35 (8.57%)	2 / 17 (11.76%)
occurrences (all)	3	2
Viral infection		
subjects affected / exposed	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	1	1
Viral rash		

subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	1 / 35 (2.86%)	1 / 17 (5.88%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2020	Amendment 1. Global amendment to add EudraCT number, redefine adverse event reporting period, and additional minor clarifications. Original protocol under which patients were first enrolled

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported