Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 1)

Summary

EudraCT number	2017-002338-21
Trial protocol	SE DE FR GB NL ES BE PL IT
Global end of trial date	28 July 2020

Results information

Result version number	v2 (current)
This version publication date	23 October 2025
First version publication date	29 April 2021
Version creation reason	• New data added to full data set Addition of Secondary Outcome Results

Trial information

Trial identification

Sponsor protocol code	A4250-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03566238
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Albireo AB, An Ipsen Company
Sponsor organisation address	Arvid Wallgrens backe 20, Göteborg, Sweden, 413 46
Public contact	Patrick Horn, MD, PhD , Albireo AB, An Ipsen Company, +1 (857) 378-2035, medinfo@albireopharma.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2020
Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of repeated daily doses of 40 microgram per kilogram (mcg/kg) per day and 120 mcg/kg/day odevixibat in children with progressive familial intrahepatic cholestasis Types 1 and 2 (PFIC1 and PFIC2), as determined by the following:
• Proportion of participants experiencing at least a 70% reduction in serum bile acid (s-BA) concentration from baseline to end of treatment or reaching a level <=70 micromoles per liter (mcmol/L).
• Proportion of positive pruritus assessments at the participant level over the 24-week treatment period.

Protection of trial subjects:

Safety was evaluated throughout the study, including monitoring for adverse events (AEs) and concomitant medications, physical examinations, vital signs, laboratory tests (including chemistry, hematology, urinalysis, vitamins A and E, 25-hydroxy vitamin D, and international normalized ratio), and abdominal ultrasound at regularly scheduled and ad-hoc meetings. Hepatic events underwent review and adjudication of etiology by an independent Data Safety Monitoring Board.

Background therapy:

Eligible participants were randomized on Day 0 (Visit 3) in a 1:1:1 fashion to receive 40 mcg/kg/day or 120 mcg/kg/day of odevixibat, or matching placebo. Odevixibat was administered orally, once daily at doses of 40 mcg/kg/day or 120 mcg/kg/day based on randomized treatment.
Odevixibat was supplied in 2 capsule sizes and 4 strengths: capsule size 0 (200 or 600 mcg strength) that could be opened and sprinkled on food and capsule size 3 (400 or 1200 mcg strength) to be swallowed intact but could be opened for participants unable to swallow the capsules whole. Treatment duration was 24 weeks with the possibility to continue treatment with odevixibat 120 mcg/kg/day in the open label extension study.

Evidence for comparator:

Placebo controlled

Actual start date of recruitment	16 May 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	19 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 9

Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Saudi Arabia: 3
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	62
EEA total number of subjects	22

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)	23
Children (2-11 years)	34
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:

This Phase 3, double-blind, placebo-controlled study was conducted in children with PFIC at 33 study centers in 12 countries between 16 May 2018 and 28 July 2020.

Pre-assignment

Screening details:

The study included up to an 8-week screening period, a 24-week treatment period, and a 4-week follow-up period. A total of 62 participants were enrolled in the study.

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	Placebo

Arm description:

Capsules for oral administration (to match active) once daily for 24 weeks.
Placebo: Placebo identical in appearance to active drug (A4250).

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.

Arm title	A4250 Low Dose

Arm description:

Capsules for oral administration (40 mcg/kg) once daily for 24 weeks.
A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of ileal bile acid transporter (IBAT).

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:

40 mcg/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	A4250 High Dose

Arm description:

Capsules for oral administration (120 mcg/kg) once daily for 24 weeks.
A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of IBAT.

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 mcg/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.

Number of subjects in period 1	Placebo	A4250 Low Dose	A4250 High Dose
Started	20	23	19
Received treatment	20	23	19
Completed	15	18	16
Not completed	5	5	3
Adverse event, non-fatal	-	-	1
Unspecified	-	1	-
Lack of efficacy	5	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Capsules for oral administration (to match active) once daily for 24 weeks. Placebo: Placebo identical in appearance to active drug (A4250).	
Reporting group title	A4250 Low Dose
Reporting group description:	
Capsules for oral administration (40 mcg/kg) once daily for 24 weeks. A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of ileal bile acid transporter (IBAT).	
Reporting group title	A4250 High Dose
Reporting group description:	
Capsules for oral administration (120 mcg/kg) once daily for 24 weeks. A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of IBAT.	

Reporting group values	Placebo	A4250 Low Dose	A4250 High Dose
Number of subjects	20	23	19
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)	8	9	6
Children (2-11 years)	11	13	10
Adolescents (12-17 years)	1	1	3
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	3.75	3.86	5.24
standard deviation	± 3.853	± 3.660	± 4.188
Gender categorical Units: Subjects			
Female	8	12	11
Male	12	11	8
Type of PFIC			
PFIC Type 1: Familial intrahepatic cholestasis-1 (FIC1) protein deficiency, PFIC Type 2: Bile salt export pump (BSEP) deficiency.			
Units: Subjects			
Type 1	5	7	5
Type 2	15	16	14
Age Category 1			
Age Category 1			
Units: Subjects			
6 months to 5 years	16	17	14
6 to 12 years	3	5	4

13 to 18 years	1	1	1
Race Units: Subjects			
White	17	18	17
Black or African American	0	2	0
Asian	1	0	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	2	3	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	19	23	19
Region of Enrollment Units: Subjects			
United States	3	2	3
United Kingdom	5	6	2
Saudi Arabia	1	0	2
Canada	1	1	0
Netherlands	1	0	2
Turkey	1	7	3
Poland	2	0	1
Italy	1	1	0
Israel	1	0	1
France	1	3	1
Australia	1	0	0
Germany	2	3	4

Reporting group values	Total		
Number of subjects	62		
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)	23		
Children (2-11 years)	34		
Adolescents (12-17 years)	5		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	31		
Male	31		

Type of PFIC			
PFIC Type 1: Familial intrahepatic cholestasis-1 (FIC1) protein deficiency, PFIC Type 2: Bile salt export pump (BSEP) deficiency.			
Units: Subjects			
Type 1	17		
Type 2	45		
Age Category 1			
Age Category 1			
Units: Subjects			
6 months to 5 years	47		
6 to 12 years	12		
13 to 18 years	3		
Race Units: Subjects			
White	52		
Black or African American	2		
Asian	2		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	6		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	61		
Region of Enrollment Units: Subjects			
United States	8		
United Kingdom	13		
Saudi Arabia	3		
Canada	2		
Netherlands	3		
Turkey	11		
Poland	3		
Italy	2		
Israel	2		
France	5		
Australia	1		
Germany	9		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Capsules for oral administration (to match active) once daily for 24 weeks. Placebo: Placebo identical in appearance to active drug (A4250).	
Reporting group title	A4250 Low Dose
Reporting group description:	
Capsules for oral administration (40 mcg/kg) once daily for 24 weeks. A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of ileal bile acid transporter (IBAT).	
Reporting group title	A4250 High Dose
Reporting group description:	
Capsules for oral administration (120 mcg/kg) once daily for 24 weeks. A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of IBAT.	

Primary: Percentage of Participants With at least a 70% Reduction in Fasting Serum Bile Acid Concentration From Baseline to the End of Treatment or Reaching a Level <=70 mcmol/L After 24 Weeks of Treatment

End point title	Percentage of Participants With at least a 70% Reduction in Fasting Serum Bile Acid Concentration From Baseline to the End of Treatment or Reaching a Level <=70 mcmol/L After 24 Weeks of Treatment
End point description:	
Fasting s-BA baseline was calculated as the average of the last 2 values prior to the first dose. The end value was the average of the values at Weeks 22 and 24 after the start of double-blind treatment. Participants who had at least 70% reduction in Fasting s-BA from baseline to the end of treatment or reached <=70 mcmol/L after 24 weeks of treatment were considered as responder. Participants with missing average at the end of treatment were classified as non-responder. Percentages are rounded to hundredth decimal. The FAS included all randomized participants who received at least 1 dose of study treatment.	
End point type	Primary
End point timeframe:	
From Baseline (Day 1) up to Week 24	

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: percentage of participants				
number (confidence interval 95%)	0 (0.00 to 16.84)	43.5 (23.19 to 65.51)	21.1 (6.05 to 45.57)	

Statistical analyses

Statistical analysis title	Fasting s-BA Concentration

Statistical analysis description:

Analysis was based on the Cochran Mantel Haenszel test adjusting PFIC type. A pooled analysis for the closed testing procedure was applied to control multiplicity. The 1-sided adjusted p-value for an individual dose was calculated as the maximum value of the unadjusted p-value for the pooled analysis and the unadjusted p-value for the individual doses.
1-sided adjusted p-value was reported.

Comparison groups	Placebo v A4250 Low Dose
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	0.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2195
upper limit	0.6551

Statistical analysis title	Fasting s-BA Concentration

Statistical analysis description:

Analysis was based on the Cochran Mantel Haenszel test adjusting PFIC type. A pooled analysis for the closed testing procedure was applied to control multiplicity. The 1-sided adjusted p-value for an individual dose was calculated as the maximum value of the unadjusted p-value for the pooled analysis and the unadjusted p-value for the individual doses.
1-sided adjusted p-value was reported.

Comparison groups	Placebo v A4250 High Dose
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.4557

Primary: Proportion of Positive Pruritus Assessments at the Participant Level Based on the Albireo Observer-Reported Outcome (ObsRO) Instrument Over the 24-Week Treatment Period

End point title	Proportion of Positive Pruritus Assessments at the Participant Level Based on the Albireo Observer-Reported Outcome (ObsRO) Instrument Over the 24-Week Treatment Period

End point description:

A positive pruritus assessment was defined as a scratching score of <=1 or at least 1 point drop from baseline. The proportion of positive pruritus assessment was calculated as the number of positive

pruritus assessments divided by the total number of reported assessments only when more than 50% of planned assessment recorded by each participant. The FAS included all randomized participants who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

From Baseline (Day 1) up to Week 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: proportion of pruritus-participant-level				
arithmetic mean (standard error)	28.74 (± 5.209)	58.31 (± 6.205)	47.69 (± 8.110)	

Statistical analyses

Statistical analysis title	Proportion of Positive Pruritus Assessments

Statistical analysis description:

Analysis of the Proportion of Positive Pruritus Assessments at Participant Level over the 24-Week Treatment Period - Albireo ObsRO Instrument (AM and PM Scores).

Comparison groups	Placebo v A4250 Low Dose
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0019
Method	ANCOVA
Parameter estimate	Least Square (LS) mean difference
Point estimate	28.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.83
upper limit	46.64
Variability estimate	Standard error of the mean
Dispersion value	9.182

Notes:

[1] - Analysis of Covariance (ANCOVA) model including treatment, baseline pruritus score at AM and PM, PFIC type, and age category was used for treatment comparisons. A pooled analysis for the closed testing procedure was applied to control multiplicity. The 1-sided adjusted p-value for an individual dose was calculated as the maximum value of the unadjusted p-value for the pooled analysis and the unadjusted p-value for the individual doses.
1-sided adjusted p-value was reported.

Statistical analysis title	Proportion of Positive Pruritus Assessments

Statistical analysis description:

Analysis of the Proportion of Positive Pruritus Assessments at Participant Level over the 24-Week Treatment Period - Albireo ObsRO Instrument (AM and PM Scores).

Comparison groups	Placebo v A4250 High Dose
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0163
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	21.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	41.54
Variability estimate	Standard error of the mean
Dispersion value	9.892

Notes:

[2] - An ANCOVA model including treatment, baseline pruritus score at AM and PM, PFIC type, and age category was used for treatment comparisons. A pooled analysis for the closed testing procedure was applied to control multiplicity. The 1-sided adjusted p-value for an individual dose was calculated as the maximum value of the unadjusted p-value for the pooled analysis and the unadjusted p-value for the individual doses.
1-sided adjusted p-value was reported.

Secondary: Change From Baseline in Fasting Serum Bile Acid at Weeks 12 and 24

End point title	Change From Baseline in Fasting Serum Bile Acid at Weeks 12 and 24

End point description:

Blood samples for analysis of s-BA were drawn at all visits. Participants were to fast (water intake only was permissible) for at least 4 hours prior to the collection of samples. Exceptions could be made for infants <12 months of age if they were unable to fast for the full 4 hours. Baseline was the average of the last 2 non-missing values of fasting s-BA concentration prior to the first dose of study treatment. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at Baseline and Weeks 12 and 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	16	
Units: mcmol/L				
arithmetic mean (standard error)				
Week 12 (n=17,20,16)	7.44 (± 24.588)	-113.70 (± 38.011)	-106.44 (± 41.201)	
Week 24 (n=11,17,15)	18.64 (± 31.559)	-145.03 (± 41.951)	-72.90 (± 52.617)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Alanine Aminotransferase (ALT) Concentration at Weeks 12 and 24

End point title	Change From Baseline in Serum Alanine Aminotransferase (ALT) Concentration at Weeks 12 and 24

End point description:

Blood samples were collected to determine the ALT concentration. Baseline was the last available assessment before the first dose of study treatment. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at Baseline and Weeks 12 and 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	22	18	
Units: units/L				
arithmetic mean (standard error)				
Week 12 (n=18,22,18)	1.7 (± 10.50)	-25.9 (± 23.36)	-13.8 (± 19.42)	
Week 24 (n=11,17,15)	3.7 (± 4.95)	-27.9 (± 17.97)	-25.3 (± 22.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Parameters at Weeks 12 and 24

End point title	Change From Baseline in Growth Parameters at Weeks 12 and 24

End point description:

The summary was based on linear growth deficit [height (centimeter), weight (kilogram) and body mass index (BMI) (kg/meter square] for age compared to a standard growth curve (Z-score, standard deviation from median or 50th percentile standard growth curve), calculated by using the software or methods from the Centers for Disease Control and Prevention (CDC) website for participants with age >=2 years old and from the World Health Organization website for participants with age <2 years old. Baseline was the last available assessment before the first dose of study treatment. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at Baseline and Weeks 12 and 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	22	16	
Units: z-score				
arithmetic mean (standard error)				
Height deficit: Week 12 (n=18,22,16)	-0.03 (± 0.127)	0.01 (± 0.108)	-0.06 (± 0.100)	
Height deficit: Week 24 (n=12,17,15)	-0.16 (± 0.104)	0.05 (± 0.105)	0.00 (± 0.163)	
Weight deficit: Week 12 (n=18,22,16)	0.13 (± 0.066)	0.20 (± 0.078)	0.00 (± 0.100)	
Weight deficit: Week 24 (n=12,18,15)	0.10 (± 0.102)	0.29 (± 0.106)	0.15 (± 0.124)	
BMI deficit: Week 12 (n=18,22,16)	0.18 (± 0.148)	0.23 (± 0.114)	0.08 (± 0.147)	
BMI deficit: Week 24 (n=12,17,15)	0.26 (± 0.156)	0.36 (± 0.113)	0.20 (± 0.203)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders for Pruritus Assessments Based on Bi-Weekly and Monthly Scores Using the Albireo Observer-Reported Outcome Instrument at Weeks 12 and 24

End point title	Percentage of Responders for Pruritus Assessments Based on Bi-Weekly and Monthly Scores Using the Albireo Observer-Reported Outcome Instrument at Weeks 12 and 24

End point description:

The responder for pruritus scores was defined as a participant who achieved at least a 1-point reduction in the ObsRO pruritus score. Percentages are rounded to hundredth decimal. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at specific timepoints.

End point type	Secondary

End point timeframe:

Weeks 12 and 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[3]	23[4]	19[5]	
Units: percentage of participants				
number (confidence interval 95%)				
AM and PM scores combined:Week 12(Bi-weekly score)	5.0 (0.13 to 24.87)	60.9 (38.54 to 80.29)	42.1 (20.25 to 66.50)	
AM and PM scores combined:Week 12(Monthly score)	10.0 (1.23 to 31.70)	52.2 (30.59 to 73.18)	42.1 (20.25 to 66.50)	
AM and PM scores combined:Week 24(Bi-weekly score)	11.8 (1.46 to 36.44)	43.5 (23.19 to 65.51)	33.3 (13.34 to 59.01)	
AM and PM scores combined:Week 24(Monthly score)	10.5 (1.30 to 33.14)	52.2 (30.59 to 73.18)	31.6 (12.58 to 56.55)	
AM score: Week 12 (Bi-weekly score)	10.0 (1.23 to 31.70)	60.9 (38.54 to 80.29)	42.1 (20.25 to 66.50)	

AM score: Week 12 (Monthly score)	10.0 (1.23 to 31.70)	56.5 (34.49 to 76.81)	42.1 (20.25 to 66.50)	
AM score: Week 24 (Bi-weekly score)	11.8 (1.46 to 36.44)	39.1 (19.71 to 61.46)	33.3 (13.34 to 59.01)	
AM score: Week 24 (Monthly score)	15.8 (3.38 to 39.58)	52.2 (30.59 to 73.18)	42.1 (20.25 to 66.50)	
PM score: Week 12 (Bi-weekly score)	10.0 (1.23 to 31.70)	65.2 (42.73 to 83.62)	36.8 (16.29 to 61.64)	
PM score: Week 12 (Monthly score)	10.0 (1.23 to 31.70)	60.9 (38.54 to 80.29)	36.8 (16.29 to 61.64)	
PM score: Week 24 (Bi-weekly score)	11.8 (1.46 to 36.44)	56.5 (34.49 to 76.81)	33.3 (13.34 to 59.01)	
PM score: Week 24 (Monthly score)	10.5 (1.30 to 33.14)	52.2 (30.59 to 73.18)	31.6 (12.58 to 56.55)	

Notes:

[3] - n=20,20,17,19,20,20,17,19,20,20,17,19.

[4] - n=23,23,23,23,23,23,23,23,23,23,23,23.

[5] - n=19,19,18,19,19,19,18,19,19,19,18,19.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sleep Parameters Based on the Albireo Observer-reported Outcome Instrument Over the 24- Week Treatment Period

End point title	Change From Baseline in Sleep Parameters Based on the Albireo Observer-reported Outcome Instrument Over the 24-Week Treatment Period

End point description:

The sleep disturbance were recorded twice daily via electronic diary (eDiary). Participants and/or caregivers completed eDiary every day in the morning and evening. Morning diary was completed shortly after participant woke up and was used to record nighttime itching and scratching severity, aspects of sleep disturbance, and tiredness upon waking (AM scores). Evening/bedtime diary was completed just before participant went to bed and recorded participant's itching and scratching severity, and tiredness during the day (PM scores). Both morning and bedtime diaries included Albireo ObsRO and PRO items. Baseline was the average of 14-day scores before the first dose of study treatment. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n=number of participants with data collected at specific timepoints. SBS=Seeing blood due to scratching; HFA=Help falling asleep; SwC=Sleeping with the caregiver; TMIS=Taking medications to induce sleep.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 1 to 4, Weeks 5 to 8, Weeks 9 to 12, Weeks 13 to 16, Weeks 17 to 20, and Weeks 21 to 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: percentage of days				
arithmetic mean (standard error)				
SBS: Weeks 1 to 4 (n=20,23,19)	-15.79 (± 4.700)	-14.42 (± 5.854)	-12.97 (± 6.036)	
SBS: Weeks 5 to 8 (n=20,22,19)	-12.10 (± 6.353)	-26.22 (± 7.427)	-13.99 (± 7.770)	
SBS: Weeks 9 to 12 (n=20,23,18)	-13.49 (± 6.320)	-29.22 (± 7.593)	-16.89 (± 9.258)	

SBS: Weeks 13 to 16 (n=17,19,16)	-15.75 (± 6.264)	-33.38 (± 8.219)	-18.16 (± 9.403)	
SBS: Weeks 17 to 20 (n=15,20,16)	-22.02 (± 7.999)	-32.14 (± 8.531)	-18.02 (± 9.967)	
SBS: Weeks 21 to 24 (n=14,19,16)	-23.72 (± 8.563)	-30.82 (± 8.184)	-15.52 (± 10.465)	
HFA: Weeks 1 to 4 (n=20,23,19)	-0.91 (± 1.596)	-14.73 (± 5.683)	-20.37 (± 6.390)	
HFA: Weeks 5 to 8 (n=20,22,19)	-2.35 (± 2.397)	-25.03 (± 7.527)	-31.49 (± 10.209)	
HFA: Weeks 9 to 12 (n=20,23,18)	-0.90 (± 1.152)	-31.03 (± 8.061)	-36.72 (± 11.154)	
HFA: Weeks 13 to 16 (n=17,19,16)	-0.86 (± 1.392)	-46.10 (± 9.677)	-37.76 (± 12.013)	
HFA: Weeks 17 to 20 (n=15,20,16)	-6.27 (± 3.862)	-45.65 (± 9.524)	-40.51 (± 12.566)	
HFA: Weeks 21 to 24 (n=14,19,16)	-3.19 (± 2.890)	-51.75 (± 9.857)	-32.58 (± 14.573)	
Soothing: Weeks 1 to 4 (n=20,23,19)	-1.15 (± 1.338)	-12.92 (± 5.911)	-21.88 (± 6.228)	
Soothing: Weeks 5 to 8 (n=20,22,19)	-3.76 (± 2.773)	-17.89 (± 7.562)	-35.97 (± 9.795)	
Soothing: Weeks 9 to 12 (n=20,23,18)	-5.00 (± 2.819)	-29.79 (± 8.570)	-41.21 (± 10.796)	
Soothing: Weeks 13 to 16 (n=17,19,16)	-2.12 (± 3.006)	-42.79 (± 10.364)	-40.23 (± 11.611)	
Soothing: Weeks 17 to 20 (n=15,20,16)	-4.73 (± 3.742)	-44.96 (± 10.485)	-40.13 (± 12.324)	
Soothing: Weeks 21 to 24 (n=14,19,16)	-7.64 (± 6.182)	-51.48 (± 10.323)	-34.87 (± 13.369)	
SwC: Weeks 1 to 4 (n=20,23,19)	-4.49 (± 1.961)	-15.30 (± 6.396)	-24.57 (± 7.024)	
SwC: Weeks 5 to 8 (n=20,22,19)	-5.93 (± 3.649)	-19.73 (± 7.061)	-35.58 (± 10.053)	
SwC: Weeks 9 to 12 (n=20,23,18)	-5.74 (± 3.585)	-26.12 (± 9.543)	-36.00 (± 10.361)	
SwC: Weeks 13 to 16 (n=17,19,16)	-4.96 (± 3.481)	-40.55 (± 10.501)	-37.52 (± 11.083)	
SwC: Weeks 17 to 20 (n=15,20,16)	-2.59 (± 3.688)	-42.20 (± 10.247)	-35.14 (± 11.563)	
SwC: Weeks 21 to 24 (n=14,19,16)	-5.45 (± 4.844)	-49.35 (± 10.466)	-33.14 (± 11.801)	
TMIS: Weeks 1 to 4 (n=20,23,19)	-1.78 (± 1.921)	-0.61 (± 1.913)	0.98 (± 2.320)	
TMIS: Weeks 5 to 8 (n=20,22,19)	1.44 (± 4.292)	0.18 (± 3.018)	-2.43 (± 3.036)	
TMIS: Weeks 9 to 12 (n=20,23,18)	2.40 (± 4.271)	1.31 (± 3.656)	-5.74 (± 4.967)	
TMIS: Weeks 13 to 16 (n=17,19,16)	0.16 (± 4.647)	-1.61 (± 2.556)	-4.58 (± 4.681)	
TMIS: Weeks 17 to 20 (n=15,20,16)	3.53 (± 5.384)	-1.99 (± 2.141)	-3.26 (± 6.403)	
TMIS: Weeks 21 to 24 (n=14,19,16)	5.50 (± 5.307)	-0.03 (± 2.251)	2.04 (± 8.413)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sleep Parameters Based on the Albireo Patient-Reported Outcome (PRO) Instrument Over the 24-Week Treatment Period

End point title	Change From Baseline in Sleep Parameters Based on the Albireo Patient-Reported Outcome (PRO) Instrument Over the 24-Week Treatment Period

End point description:

The sleep disturbance were recorded twice daily via the electronic diary (eDiary). Participants and/or caregivers completed the eDiary every day in the morning and in the evening. The morning diary was completed shortly after the participant woke up and was used to record nighttime itching and scratching severity, aspects of sleep disturbance, and tiredness upon waking (AM scores). The evening/bedtime diary was completed just before the participant went to bed and recorded participant's itching and scratching severity, and tiredness during the day (PM scores). Both morning and bedtime diaries included Albireo ObsRO and PRO items. Baseline was the average of 14-day scores before the first dose of study treatment. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at specific timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 1 to 4, Weeks 5 to 8, Weeks 9 to 12, Weeks 13 to 16, Weeks 17 to 20, and Weeks 21 to 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	5	
Units: scores on a scale				
arithmetic mean (standard error)				
Difficulty falling asleep: Weeks 1 to 4	-0.46 (± 0.143)	-0.72 (± 0.494)	-0.59 (± 0.394)	
Difficulty falling asleep: Weeks 5 to 8	-0.34 (± 0.018)	-1.40 (± 1.009)	-0.65 (± 0.571)	
Difficulty falling asleep: Weeks 9 to 12	-0.38 (± 0.339)	-2.31 (± 0.499)	-0.95 (± 0.650)	
Difficulty falling asleep: Weeks 13 to 16	-0.16 (± 0.268)	-2.07 (± 0.863)	-1.01 (± 0.665)	
Difficulty falling asleep: Weeks 17 to 20	-0.52 (± 0.228)	-2.12 (± 0.974)	-1.02 (± 0.710)	
Difficulty falling asleep: Weeks 21 to 24	-0.25 (± 0.179)	-2.22 (± 0.823)	-0.82 (± 0.658)	
Difficulty staying asleep: Weeks 1 to 4	-0.13 (± 0.411)	-0.70 (± 0.548)	-0.43 (± 0.440)	
Difficulty staying asleep: Weeks 5 to 8	0.09 (± 0.518)	-1.48 (± 0.932)	-0.50 (± 0.553)	
Difficulty staying asleep: Weeks 9 to 12	0.02 (± 0.661)	-2.51 (± 0.352)	-0.77 (± 0.670)	
Difficulty staying asleep: Weeks 13 to 16	0.13 (± 0.625)	-2.46 (± 0.464)	-0.89 (± 0.626)	
Difficulty staying asleep: Weeks 17 to 20	-0.15 (± 0.147)	-2.36 (± 0.637)	-0.95 (± 0.644)	
Difficulty staying asleep: Weeks 21 to 24	0.25 (± 0.429)	-2.55 (± 0.448)	-0.78 (± 0.633)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo ObsRO Instrument Over the 24-Week Treatment Period

End point title	Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo ObsRO Instrument Over the 24-Week Treatment Period

End point description:

A positive pruritus assessment was defined as a scratching score of <=1 or at least 1 point drop from baseline based on the Albireo ObsRO instrument. The proportion of positive pruritus assessment was calculated as the number of positive pruritus assessments divided by the total number of reported assessments only when more than 50% of planned assessment recorded by each participant. At each assessment, the AM or PM score was compared to the baseline AM
or PM average, respectively. The FAS included all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: proportion of pruritus-participant-level				
arithmetic mean (standard error)				
AM and PM scores combined: Weeks 0 to 4	33.48 (± 5.881)	51.40 (± 5.818)	42.48 (± 7.508)	
AM and PM scores combined: Weeks 0 to 8	32.72 (± 5.871)	54.23 (± 5.887)	48.21 (± 7.479)	
AM and PM scores combined: Weeks 0 to 12	32.35 (± 5.945)	58.85 (± 5.738)	49.15 (± 7.428)	
AM and PM scores combined: Weeks 0 to 16	30.67 (± 5.522)	58.83 (± 5.925)	48.31 (± 7.624)	
AM and PM scores combined: Weeks 0 to 18	29.88 (± 5.462)	58.80 (± 6.004)	48.25 (± 7.809)	
AM and PM scores combined: Weeks 0 to 20	29.45 (± 5.376)	58.68 (± 6.079)	48.10 (± 7.975)	
AM score: Weeks 0 to 4	31.07 (± 5.436)	48.14 (± 6.161)	47.37 (± 8.439)	
AM score: Weeks 0 to 8	31.07 (± 5.213)	51.16 (± 6.129)	51.79 (± 8.001)	
AM score: Weeks 0 to 12	31.07 (± 5.374)	56.06 (± 5.922)	52.26 (± 7.693)	
AM score: Weeks 0 to 16	29.91 (± 5.246)	56.41 (± 6.183)	50.47 (± 7.660)	
AM score: Weeks 0 to 18	28.93 (± 5.224)	56.35 (± 6.249)	49.92 (± 7.800)	
AM score: Weeks 0 to 20	28.50 (± 5.206)	56.27 (± 6.293)	49.74 (± 7.993)	
AM score: Weeks 0 to 24	28.17 (± 5.276)	55.73 (± 6.396)	48.92 (± 8.197)	

PM score: Weeks 0 to 4	35.89 (± 7.055)	54.66 (± 6.594)	37.59 (± 7.629)	
PM score: Weeks 0 to 8	34.38 (± 7.290)	57.30 (± 6.478)	44.64 (± 7.804)	
PM score: Weeks 0 to 12	33.63 (± 7.404)	61.65 (± 6.330)	46.05 (± 7.884)	
PM score: Weeks 0 to 16	31.43 (± 7.006)	61.26 (± 6.205)	46.15 (± 8.178)	
PM score: Weeks 0 to 18	30.83 (± 6.898)	61.25 (± 6.225)	46.57 (± 8.363)	
PM score: Weeks 0 to 20	30.39 (± 6.812)	61.09 (± 6.284)	46.47 (± 8.434)	
PM score: Weeks 0 to 24	29.31 (± 6.592)	60.89 (± 6.385)	46.47 (± 8.456)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo PRO Instrument Over the 24-Week Treatment Period

End point title	Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo PRO Instrument Over the 24-Week Treatment Period

End point description:

A positive pruritus assessment was defined as a scratching score of <=1 or at least 1 point drop from baseline based on the Albireo PRO instrument, only participants >=8 years of age completed the Albireo PRO instrument. The proportion of positive pruritus assessment was calculated as the number of positive pruritus assessments divided by the total number of reported assessments only when more than 50% of planned assessment recorded by each participant. At each assessment, the AM or PM score was compared to the baseline AM or PM average, respectively. The FAS included all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	5	
Units: proportion of pruritus-participant-level				
arithmetic mean (standard error)				
AM and PM scores combined: Weeks 0 to 4	64.29 (± 8.929)	43.75 (± 25.893)	38.93 (± 15.272)	
AM and PM scores combined: Weeks 0 to 8	46.88 (± 12.946)	52.68 (± 25.893)	41.96 (± 16.178)	
AM and PM scores combined: Weeks 0 to 12	41.96 (± 10.417)	63.39 (± 18.155)	45.00 (± 16.939)	
AM and PM scores combined: Weeks 0 to 16	38.62 (± 3.348)	66.74 (± 18.080)	46.96 (± 17.477)	

AM and PM scores combined: Weeks 0 to 18	37.50 (± 0.198)	67.66 (± 18.849)	47.14 (± 17.558)	
AM and PM scores combined: Weeks 0 to 20	34.82 (± 0.179)	67.32 (± 20.179)	48.07 (± 18.010)	
AM and PM scores combined: Weeks 0 to 24	31.70 (± 1.637)	68.88 (± 19.772)	47.65 (± 17.997)	
AM score: Weeks 0 to 4	55.36 (± 8.929)	41.07 (± 23.214)	37.86 (± 16.115)	
AM score: Weeks 0 to 8	39.29 (± 14.286)	50.00 (± 21.429)	38.93 (± 16.243)	
AM score: Weeks 0 to 12	33.93 (± 10.119)	61.31 (± 11.310)	41.43 (± 16.562)	
AM score: Weeks 0 to 16	31.70 (± 1.339)	65.18 (± 12.500)	42.68 (± 16.554)	
AM score: Weeks 0 to 18	31.35 (± 1.190)	66.67 (± 13.492)	42.22 (± 16.343)	
AM score: Weeks 0 to 20	28.93 (± 0.357)	66.07 (± 15.357)	43.71 (± 16.860)	
AM score: Weeks 0 to 24	26.19 (± 1.190)	66.72 (± 16.718)	43.24 (± 16.835)	
PM score: Weeks 0 to 4	73.21 (± 8.929)	46.43 (± 28.571)	40.00 (± 15.042)	
PM score: Weeks 0 to 8	54.46 (± 11.607)	55.36 (± 30.357)	45.00 (± 16.545)	
PM score: Weeks 0 to 12	50.00 (± 10.714)	65.48 (± 25.000)	48.57 (± 17.715)	
PM score: Weeks 0 to 16	45.54 (± 5.357)	68.30 (± 23.661)	51.25 (± 18.751)	
PM score: Weeks 0 to 18	43.65 (± 1.587)	68.65 (± 24.206)	52.06 (± 19.230)	
PM score: Weeks 0 to 20	40.71 (± 0.000)	68.57 (± 25.000)	52.43 (± 19.568)	
PM score: Weeks 0 to 24	37.20 (± 2.083)	71.04 (± 22.825)	52.06 (± 19.595)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo ObsRO Instrument Over the 24-Week Treatment Period

End point title	Proportion of Individual Assessments Meeting the Definition of a Positive Pruritus Assessment at the Participant Level Using the Albireo ObsRO Instrument Over the 24-Week Treatment Period

End point description:

A positive pruritus assessment was defined as a scratching score of <=1 or at least 1 point drop from baseline based on the Albireo ObsRO instrument. The proportion of positive pruritus assessment was calculated as the number of positive pruritus assessments divided by the total number of reported assessments only when more than 50% of planned assessment recorded by each participant. At each assessment, the AM or PM score was compared to the baseline AM or PM average, respectively. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected at specific timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 1 to 4, Weeks 5 to 8, Weeks 9 to 12, Weeks 13 to 16, Weeks 17 to 20, and Weeks 21 to 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: proportion of pruritus-participant level				
arithmetic mean (standard error)				
AM and PM scores combined:Weeks 1 to 4(n=20,23,19)	33.48 (± 5.881)	51.40 (± 5.818)	42.48 (± 7.508)	
AM and PM scores combined:Weeks 5 to 8(n=20,23,19)	31.96 (± 6.515)	57.07 (± 6.714)	53.95 (± 8.423)	
AM and PM scores combined:Weeks 9 to12(n=20,23,18)	31.61 (± 6.794)	68.09 (± 6.357)	53.67 (± 9.404)	
AM and PM scores combined:Weeks 13to16(n=17,20,16)	28.36 (± 7.534)	67.59 (± 7.779)	54.35 (± 9.802)	
AM and PM scores combined:Weeks 17to20(n=15,20,16)	32.62 (± 8.583)	66.79 (± 7.805)	56.14 (± 10.655)	
AM and PM scores combined:Weeks 21to24(n=14,19,16)	35.42 (± 8.783)	68.57 (± 6.926)	55.12 (± 10.047)	
AM score: Weeks 1 to 4 (n=20,23,19)	31.07 (± 5.436)	48.14 (± 6.161)	47.37 (± 8.439)	
AM score: Weeks 5 to 8 (n=20,23,19)	31.07 (± 5.812)	54.19 (± 6.783)	56.20 (± 8.483)	
AM score: Weeks 9 to 12 (n=20,23,18)	31.07 (± 6.747)	65.84 (± 6.854)	55.95 (± 9.383)	
AM score: Weeks 13 to 16 (n=17,20,16)	29.62 (± 8.502)	66.07 (± 8.042)	53.57 (± 9.550)	
AM score: Weeks 17 to 20 (n=15,20,16)	30.24 (± 8.733)	64.11 (± 8.121)	55.58 (± 11.171)	
AM score: Weeks 21 to 24 (n=14,19,16)	37.30 (± 10.909)	64.37 (± 7.324)	54.35 (± 10.801)	
PM score: Weeks 1 to 4 (n=20,23,19)	35.89 (± 7.055)	54.66 (± 6.594)	37.59 (± 7.629)	
PM score: Weeks 5 to 8 (n=20,23,19)	32.86 (± 8.138)	59.94 (± 7.355)	51.69 (± 9.051)	
PM score: Weeks 9 to 12 (n=20,23,18)	32.14 (± 8.078)	70.34 (± 6.816)	51.39 (± 10.015)	
PM score: Weeks 13 to 16 (n=17,20,16)	27.10 (± 8.997)	69.11 (± 7.783)	55.13 (± 10.664)	
PM score: Weeks 17 to 20 (n=15,20,16)	35.00 (± 10.323)	69.46 (± 7.848)	56.70 (± 10.554)	
PM score: Weeks 21 to 24 (n=14,19,16)	33.54 (± 9.699)	72.76 (± 7.185)	55.90 (± 9.976)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Underwent Biliary Diversion Surgery and Liver Transplantation

End point title	Number of Participants Underwent Biliary Diversion Surgery and Liver Transplantation

End point description:

The number of participants underwent biliary diversion surgery and liver transplantation was determined. The FAS included all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: participants				
Biliary diversion surgery	0	0	0	
Liver transplantation	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieved Positive Pruritus Assessment for >50% of the Time Based on the Albireo ObsRO and PRO Instruments Over the 24-Week Treatment Period

End point title	Number of Participants Achieved Positive Pruritus Assessment for >50% of the Time Based on the Albireo ObsRO and PRO Instruments Over the 24-Week Treatment Period

End point description:

A positive pruritus assessment was defined as a scratching score of <=1 or at least 1 point drop from baseline based on the Albireo ObsRO and PRO instruments. The proportion of positive pruritus assessment was calculated as the number of positive pruritus assessments divided by the total number of reported assessments only when more than 50% of planned assessment recorded by each participant. The FAS included all randomized participants who received at least 1 dose of study treatment. Here, n= number of participants with data collected for each specific instrument.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 24

End point values	Placebo	A4250 Low Dose	A4250 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[6]	23[7]	19[8]	
Units: participants				
Albireo ObsRO Instrument:AM and PM scores combined	4	17	9	
Albireo ObsRO Instrument: AM score	3	13	10	
Albireo ObsRO Instrument: PM score	5	16	9	
Albireo PRO Instrument: AM and PM scores combined	0	1	3	

Albireo PRO Instrument: AM score	0	1	3	
Albireo PRO Instrument: PM score	0	1	3	

Notes:

[6] - n=20,20,20,2,2,2.

[7] - n=23,23,23,2,2,2.

[8] - n=19,19,19,5,5,5.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All serious and non-serious AEs were collected once the caregiver/participant had signed the informed consent form (ICF) and until the post-treatment follow-up (Visit 10) or 28 days after the last dose of study treatment, approximately 28 weeks

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) were defined as any AE that occurred after first dose or AE occurred before first dose but worsened in severity on or after first dose. Treatment emergent serious adverse events and treatment emergent non-serious AEs are reported here.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Capsules for oral administration (to match active) once daily for 24 weeks.
Placebo: Placebo identical in appearance to active drug (A4250).

Reporting group title	A4250 Low Dose

Reporting group description:

Capsules for oral administration (40 mcg/kg) once daily for 24 weeks.
A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of IBAT.

Reporting group title	A4250 High Dose

Reporting group description:

Capsules for oral administration (120 mcg/kg) once daily for 24 weeks.
A4250 (odevixibat): A4250 is a small molecule and selective inhibitor of IBAT.

Serious adverse events	Placebo	A4250 Low Dose	A4250 High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	0 / 23 (0.00%)	3 / 19 (15.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Auricular haematoma			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Neurodermatitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight gain poor			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	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	Placebo	A4250 Low Dose	A4250 High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	19 / 23 (82.61%)	16 / 19 (84.21%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Cardiac ablation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injection site swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	5 / 20 (25.00%)	7 / 23 (30.43%)	5 / 19 (26.32%)
occurrences (all)	7	10	13
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 20 (15.00%)	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	3	0	2
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Nasal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	4
Selective eating disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	3 / 23 (13.04%)	3 / 19 (15.79%)
occurrences (all)	1	3	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	2 / 23 (8.70%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
Bilirubin conjugated increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	2 / 19 (10.53%)
occurrences (all)	1	1	3
Blood bilirubin increased			
subjects affected / exposed	2 / 20 (10.00%)	3 / 23 (13.04%)	2 / 19 (10.53%)
occurrences (all)	2	4	3
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Blood creatinine decreased			

subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Liver palpable			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Platelet count increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Product residue present			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vitamin E increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Auricular haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Scar			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Scratch			
subjects affected / exposed	2 / 20 (10.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Skin abrasion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Tibia fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Splenomegaly			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Otorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	4 / 20 (20.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	4	0	0
Dental caries			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)	9 / 23 (39.13%)	4 / 19 (21.05%)
occurrences (all)	1	11	10
Frequent bowel movements			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	4 / 23 (17.39%)	3 / 19 (15.79%)
occurrences (all)	0	5	4
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hepatomegaly			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Jaundice			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nail discolouration			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Neurodermatitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Rash			
subjects affected / exposed	3 / 20 (15.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	4	0	0
Rash vesicular			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cystitis haemorrhagic			

subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Neck mass			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
H1N1 influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hand-foot-and-mouth disease			

subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Klebsiella infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 23 (4.35%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Otitis media			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Parotitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Post procedural infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Sinusitis bacterial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin candida			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			

subjects affected / exposed	2 / 20 (10.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Viral diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 23 (4.35%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	5
Viral rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 23 (8.70%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)	3 / 23 (13.04%)	5 / 19 (26.32%)
occurrences (all)	5	4	7
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vitamin A deficiency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	1 / 20 (5.00%)	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Vitamin E deficiency			
subjects affected / exposed	0 / 20 (0.00%)	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2017	Number of participants: 15. • Original protocol under which participants were first enrolled.
10 May 2018	Number of participants: 16. •Clarified that enrolment of participants with PFIC1 was targeted to 15%. •Exclusion criterion 9 was revised to clarify that participants listed for liver transplant was not excluded if primary reason for listing was symptomatic pruritus and not disease progression. •Guidelines for contraceptive requirements were updated that required participants to use reliable contraceptive methods throughout duration of study and 90 days thereafter. •Additional examples of prohibited medications, including erythromycin and 4-phenylbutyrate were added. •Requirement for genetic testing at screening was removed for participants with prior genotyping results confirming PFIC1 or 2. •Procedure for breaking randomization code was clarified. •Calculation to determine participant eligibility relating to ObsRO data collection was revised. •Primary efficacy endpoint for US (and secondary endpoint for EU and RoW) was revised to include more data collected in analysis. Statistical analyses were modified to align with that change. •All secondary and exploratory endpoints referring to patient-related outcome/ObsRO instrument using a reference time point of Week 24 were revised to include a specified duration over treatment period, for example over first of last 3 or 5 months of treatment period. •Assessment of change in gamma-glutamyl transferase was added to exploratory endpoint. •Clarification was made to include all laboratory tests related to safety including vitamins, and alpha-fetoprotein. •Additional assessments for physical examination, vitamins, urine pregnancy test and blood sampling for Pharmacokinetic analysis were added. •Approach to calculate baseline weekly itching and scratching scores was revised. •Requirement of cholestatic marker elevations without alternative explanation was removed; alkaline phosphatase was removed from list of repeat liver profile assessments; The criterion of international normalized ratio increase was revised.

22 November 2018	Number of participants: 6. • Exclusion criterion 17 was revised to remove barrier protection as an acceptable contraceptive method. • Exclusion criterion 9 was revised to specify that participants will be excluded if their liver transplant is planned within 6 months of randomization. • Statistical methodology to analyze the primary efficacy endpoint for United States (and secondary endpoint of EU and ROW) of change in pruritus between active and placebo arms was revised. • Secondary endpoints of change from baseline to Week 24 in s-BA, alanine transaminase (ALT), and growth were updated to include additional assessments at Week 12. As a result, change from baseline in ALT and s-BA at Week 12 were removed from the list of exploratory endpoints. • The secondary endpoint of percentage of participants achieving meaningful reduction in caregiver-reported observed scratching was revised to include assessment of patient-reported outcomes and to indicate how "meaningful reduction" was defined. An additional assessment timepoint of Week 12 was also added. • The secondary endpoint of change from baseline in sleep parameters was updated so multiple timepoints were evaluated in the study period rather than a single timepoint at end of therapy. • The following additional secondary endpoints were added for all regions: - Proportion of individual assessments and of individual AM and PM assessments meeting the definition of a positive pruritus assessment at the participant level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval. • The exploratory efficacy endpoint of change in patient-reported and observer-reported night-time itching and scratching severity scores was revised so both morning and evening scores were analyzed rather than a single daily score.
01 March 2019	Number of participants: 8. • Exclusion criterion 8 was updated so participants post biliary diversion surgery were eligible for the study. • Clarification was made to the secondary endpoint to assess liver transplantation events. • Revised baseline covariate in the ANCOVA model of US primary efficacy analysis to include both AM baseline and PM baseline pruritus scores, instead of the averaged value.
29 April 2019	Number of participants: 9. • The timing for rescreening was removed; participants could be rescreened at any time after failing eligibility criteria after consultation with the Medical Monitor. • Exclusion criterion 14 was revised to exclude participants with total bilirubin >10×upper limit of normal.
24 June 2019	Number of participants: 8. • The provision to allow participants experiencing intolerable symptoms of underlying disease to roll over to active treatment after completion of 12 weeks of the treatment period was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported