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	v1 (current)
This version publication date	29 April 2021
First version publication date	29 April 2021

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
Sponsor organisation address	Arvid Wallgrens backe 20, Göteborg, Sweden, 413 46
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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 µg/kg/day and 120 µg/kg/day odevixibat in children with progressive familial intrahepatic cholestasis Types 1 and 2 (PFIC1 and PFIC2), as determined by the following:

- Proportion of patients experiencing at least a 70% reduction in serum bile acid concentration from baseline to end of treatment or reaching a level ≤70 µmol/L.
- Proportion of positive pruritus assessments at the patient level over the 24-week treatment period.

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 abdominal ultrasound at regularly scheduled and ad-hoc meetings. Hepatic events underwent review and adjudication of aetiology by an independent Data Safety Monitoring Board (DSMB).

Background therapy:

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

Recruitment took place between 16 May 2018 to 10 February 2020. Patients were recruited at hospitals or medical specialty centers. Patients were recruited in all countries except Spain and Sweden.

Pre-assignment

Screening details:

Patients were screened for eligibility according to the trial inclusion and exclusion criteria. 45 out of 107 patients were screening failures.

Pre-assignment period milestones

Number of subjects started	62
Intermediate milestone: Number of subjects	Subjects Randomised: 62
Number of subjects completed	62

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:

Placebo once daily

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	Odevixibat 40 ug/kg/day

Arm description:

Odevixibat
40 ug/kg once daily

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 ug/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	Odevixibat 120 ug/kg/day

Arm description:

Odevixibat
120 ug/kg once daily

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 ug/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	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day
Started	20	23	19
Received treatment	20	23	19
Completed	15	18	16
Not completed	5	5	3
Adverse event, non-fatal	-	-	1
Other	-	1	-
Lack of efficacy	5	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily	
Reporting group title	Odevixibat 40 ug/kg/day
Reporting group description:	
Odevixibat 40 ug/kg once daily	
Reporting group title	Odevixibat 120 ug/kg/day
Reporting group description:	
Odevixibat 120 ug/kg once daily	

Reporting group values	Placebo	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day
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
PFIC TYPE			
TYPE of PFIC			
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

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		
PFIC TYPE			
TYPE of PFIC			
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		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo once daily	

Reporting group title	Odevixibat 40 ug/kg/day
Reporting group description:	
Odevixibat 40 ug/kg once daily	

Reporting group title	Odevixibat 120 ug/kg/day
Reporting group description:	
Odevixibat 120 ug/kg once daily	

Primary: European Union (EU) and rest of the world (RoW): Proportion of patients experiencing at least a 70% reduction in fasting s-BA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L after 24 weeks of treatment

End point title	European Union (EU) and rest of the world (RoW): Proportion of patients experiencing at least a 70% reduction in fasting s-BA concentration from baseline to the end of treatment or reaching a level ≤70 µmol/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.	
End point type	Primary
End point timeframe:	
After 24 weeks of treatment	

End point values	Placebo	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: subjects				
Number of Responders	0	10	4	

Statistical analyses

Statistical analysis title	Fasting Serum Bile Acid Concentration
Statistical analysis description:	
Analysis of Number (%) of Patients Experiencing at Least a 70% Reduction in Fasting Serum Bile Acid Concentration from Baseline to End of Treatment or Reaching a Level <=70 umol/L after 24 Weeks of Treatment	
Comparison groups	Placebo v Odevixibat 40 ug/kg/day

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0015
Method	Cochran-Mantel-Haenszel
Parameter estimate	proportion difference
Point estimate	0.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2195
upper limit	0.6551

Notes:

[1] - 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 one-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.
One-sided adjusted p-value was reported.

Statistical analysis title	Fasting Serum Bile Acid Concentration
Comparison groups	Placebo v Odevixibat 120 ug/kg/day
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0174
Method	Cochran-Mantel-Haenszel
Parameter estimate	proportion difference
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.4557

Notes:

[2] - 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 one-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.
One-sided adjusted p-value was reported.

Primary: United States (US): Proportion of positive pruritus assessments at the subject level over the 24-week treatment period based on the Albireo ObsRO instrument.

End point title	United States (US): Proportion of positive pruritus assessments at the subject level over the 24-week treatment period based on the Albireo ObsRO instrument.

End point description:

A positive pruritus assessment was defined as a scratching score of ≤1 or at least a one-point drop from baseline on the Albireo ObsRO instrument.

End point type	Primary

End point timeframe:

Over 24 weeks of treatment

End point values	Placebo	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	23	19	
Units: measurable				
least squares mean (standard error)	30.10 (± 9.119)	58.34 (± 8.580)	51.81 (± 9.459)	

Statistical analyses

Statistical analysis title	Proportion of Positive Pruritus Assessments

Statistical analysis description:

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

Comparison groups	Placebo v Odevixibat 40 ug/kg/day
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0019
Method	ANCOVA
Parameter estimate	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:

[3] - 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 one-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.
One-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 Patient Level over the 24-Week Treatment Period - Albireo ObsRO Instrument (AM and PM Scores)

Comparison groups	Placebo v Odevixibat 120 ug/kg/day
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[4]
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:

[4] - 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 one-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.
One-sided adjusted p-value was reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All serious and non-serious AEs were collected once the caregiver/patient had signed the ICF and until the post-treatment follow-up (Visit 10) or 28 days after the last dose of study drug.

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) were defined as any AE that occurred after 1st dose or AE occurred before 1st dose but worsened in severity on or after 1st dose. Treatment emergent SAEs 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:

Placebo once daily

Reporting group title	Odevixibat 40 ug/kg/day

Reporting group description:

Odevixibat
40 ug/kg once daily

Reporting group title	Odevixibat 120 ug/kg/day

Reporting group description:

Odevixibat
120 ug/kg once daily

Serious adverse events	Placebo	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day
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	Odevixibat 40 ug/kg/day	Odevixibat 120 ug/kg/day
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	Amendment 1. No. of patients: 15 • Original protocol under which patients were first enrolled
10 May 2018	Amendment 2. No. of patients: 16. •Clarified that enrolment of patients with PFIC1 will be targeted to 15% Exclusion criterion 9 was revised to clarify that patients listed for liver transplant will not be excluded if primary reason for listing was symptomatic pruritus and not disease progression •Guidelines for contraceptive requirements were updated that required patients 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 patients with prior genotyping results confirming PFIC1 or 2 •Procedure for breaking the randomisation code was clarified •Calculation to determine patient eligibility relating to the ObsRO data collection was revised •Primary efficacy endpoint for US (and secondary endpoint for Europe and RoW) was revised to include more data collected in the analysis. The statistical analyses were modified to align with that change •All secondary and exploratory endpoints referring to PRO/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 PK analysis were added to schedule of assessments •Approach to calculate baseline weekly itching and scratching scores was revised •Following changes were made to liver monitoring criteria: requirement of cholestatic marker elevations without alternative explanation was removed; ALP was removed from list of repeat liver profile assessments; INR criteria increase was revised

22 November 2018	Amendment 3. No. of patients: 6 • Exclusion criterion 17 was revised to remove barrier protection as an acceptable contraceptive method • Exclusion criterion 9 was revised to specify that patients will be excluded if their liver transplant is planned within 6 months of randomisation • Statistical methodology to analyse the primary efficacy endpoint for United States (and secondary endpoint of Europe and rest of world) of change in pruritus between active and placebo arms was revised • Secondary endpoints of change from baseline to Week 24 in serum bile acid, ALT, and growth were updated to include additional assessments at Week 12. As a result, change from baseline in ALT and serum bile acid at Week 12 were removed from the list of exploratory endpoints • The secondary endpoint of proportion of patients 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 patient 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 analysed rather than a single daily score.
01 March 2019	Amendment 4. No. of patients: 8 • Exclusion criterion 8 was updated so patients 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	Amendment 5. No. of patients: 9 • The timing for rescreening was removed; patients could be rescreened at any time after failing eligibility criteria after consultation with the Medical Monitor • Exclusion criterion 14 was revised to exclude patients with total bilirubin >10×ULN
24 June 2019	Amendment 6. No. of patients: 8 • The provision to allow patients 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