Clinical trial results:
A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with primary biliary cholangitis (PBC) and an inadequate response to or intolerance to ursodeoxycholic acid (UDCA).

Summary

EudraCT number	2018-001171-20
Trial protocol	GR HU DE FR AT PL NL ES BE IT RO
Global end of trial date	16 February 2020

Results information

Result version number	v1 (current)
This version publication date	04 April 2021
First version publication date	04 April 2021

Trial information

Trial identification

Sponsor protocol code	CB8025-31735

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03602560
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CymaBay Therapeutics, Inc.
Sponsor organisation address	7575 Gateway Blvd, Suite 110, Newark, United States, 94560
Public contact	Mary Standen, CymaBay Therapeutics, Inc., +1 5102938800, mstanden@cymabay.com
Scientific contact	Elaine Watkins, CymaBay Therapeutics, Inc., +1 5102938800, ewatkins@cymabay.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2020
Global end of trial reached?	Yes
Global end of trial date	16 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and effect on cholestasis of two seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placebo.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its revisions and the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP). The study was also in compliance with the applicable local regulatory requirements and laws of each country in which the study was conducted, as well as with any applicable guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	United States: 108

Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Mexico: 9
Worldwide total number of subjects	265
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	221
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 159 clinical sites in the Asia Pacific, Europe, Latin America, and North America regions between 01 October 2018 and 16 February 2020.

Pre-assignment

Screening details:

A total of 501 subjects were screened, and 265 subjects were randomized into the study. All 265 subjects received at least 1 randomized dose: 87 subjects received placebo, 89 subjects received seladelpar 5 mg, and 89 subjects received seladelpar 10 mg at Day 1.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Seladelpar 5 mg (initial Dose)

Arm description:

Subjects received seladelpar 5 milligram (mg) capsules orally once daily for the study duration

Arm type	Experimental
Investigational medicinal product name	Seladelpar
Investigational medicinal product code	MBX-8025
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received seladelpar 5 milligram (mg) capsules orally once daily for the treatment period

Arm title	Seladelpar 10 mg (initial dose)

Arm description:

Subjects received seladelpar 10 mg capsules orally once daily for the study duration

Arm type	Experimental
Investigational medicinal product name	Seladelpar
Investigational medicinal product code	MBX-8025
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received seladelpar 10 milligram (mg) capsules orally once daily for the treatment period

Arm title	Placebo

Arm description:

Subjects received matched placebo capsules orally once daily for the study duration

Arm type	Placebo

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

Dosage and administration details:

Subjects received matching placebo capsules orally once daily for the study duration

Number of subjects in period 1	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo
Started	89	89	87
Completed	1	1	0
Not completed	88	88	87
Consent withdrawn by subject	2	-	-
Other - early termination by sponsor	84	86	86
Adverse event, non-fatal	-	2	-
Lost to follow-up	1	-	1
Other than listed	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Seladelpar 5 mg (initial Dose)
Reporting group description:	
Subjects received seladelpar 5 milligram (mg) capsules orally once daily for the study duration	
Reporting group title	Seladelpar 10 mg (initial dose)
Reporting group description:	
Subjects received seladelpar 10 mg capsules orally once daily for the study duration	
Reporting group title	Placebo
Reporting group description:	
Subjects received matched placebo capsules orally once daily for the study duration	

Reporting group values	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo
Number of subjects	89	89	87
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	75	73	73
From 65-84 years	14	16	14
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.7	55.6	55.9
standard deviation	± 9.70	± 9.12	± 8.17
Gender categorical Units: Subjects			
Female	82	83	85
Male	7	6	2
Race Units: Subjects			
White	83	77	80
Black or African-American	1	4	2
Asian	4	8	5
American Indian or Alaska Native	1	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0

Reporting group values	Total		
Number of subjects	265		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	221		
From 65-84 years	44		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	250		
Male	15		
Race Units: Subjects			
White	240		
Black or African-American	7		
Asian	17		
American Indian or Alaska Native	1		
Native Hawaiian or other Pacific Islander	0		
Other	0		

End points

End points reporting groups

Reporting group title	Seladelpar 5 mg (initial Dose)
Reporting group description:	
Subjects received seladelpar 5 milligram (mg) capsules orally once daily for the study duration	
Reporting group title	Seladelpar 10 mg (initial dose)
Reporting group description:	
Subjects received seladelpar 10 mg capsules orally once daily for the study duration	
Reporting group title	Placebo
Reporting group description:	
Subjects received matched placebo capsules orally once daily for the study duration	

Primary: Percentage of Subjects with Response to Composite Endpoint of ALP <1.67 × Upper Limit of Normal [ULN], ≥15% reduction in ALP, and total bilirubin ≤ ULN) at Endpoint

End point title	Percentage of Subjects with Response to Composite Endpoint of ALP <1.67 × Upper Limit of Normal [ULN], ≥15% reduction in ALP, and total bilirubin ≤ ULN) at Endpoint

End point description:

Percentage of Subjects with Response to Composite Endpoint of ALP <1.67 × Upper Limit of Normal [ULN], ≥15% reduction in ALP, and total bilirubin ≤ ULN) at Month 3. The mITT analysis set included all randomized subjects who received at least one study drug dose.
n, denotes number of subjects evaluable for the respective timepoints

End point type	Primary
End point timeframe:	
At Month 3 (Endpoint)	

End point values	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	55	56	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Month 3 (n= 56, 55, 56)	57.1 (43.2 to 70.3)	78.2 (65.0 to 88.2)	12.5 (5.2 to 24.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Seladelpar 10 mg vs Placebo	
Comparison groups	Seladelpar 10 mg (initial dose) v Placebo

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Cochran-Mantel-Haenszel (CMH) test adjusted for both randomization stratification variables (ALP level: < 350 U/L and ≥ 350 U/L; pruritus NRS: < 4 and ≥ 4) was used to test the association between treatment groups

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Seladelpar 5 mg vs Placebo

Comparison groups	Seladelpar 5 mg (initial Dose) v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Subjects With Response Defined by Normalized Alkaline Phosphatase Levels at Endpoint

End point title	Percentage of Subjects With Response Defined by Normalized Alkaline Phosphatase Levels at Endpoint

End point description:

The response was defined by normalized ALP levels (ALP ≤1.0 × ULN) at endpoint. The mITT analysis set included all randomized subjects who received at least one study drug dose.

End point type	Secondary

End point timeframe:

At Month 3 (Endpoint)

End point values	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	55	56	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Month 3 (n= 56, 55, 56)	5.4 (1.1 to 14.9)	27.3 (16.1 to 41.0)	0 (0 to 6.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test adjusted for both randomization stratification variables (ALP level: < 350 U/L and ≥ 350 U/L; pruritus NRS: < 4 and ≥ 4) was used to test the association between

treatment groups. Breslow-Day test is used to check the homogeneity of treatment effects across stratum.

Comparison groups	Seladelpar 10 mg (initial dose) v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Cochran-Mantel-Haenszel (CMH) test adjusted for both randomization stratification variables (ALP level: < 350 U/L and ≥ 350 U/L; pruritus NRS: < 4 and ≥ 4) was used to test the association between treatment groups. Breslow-Day test is used to check the homogeneity of treatment effects across stratum.

Comparison groups	Seladelpar 5 mg (initial Dose) v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0839
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline in Pruritus as Assessed by Numerical Rating Scale (NRS) for Subjects with Baseline NRS ≥4

End point title	Change From Baseline in Pruritus as Assessed by Numerical Rating Scale (NRS) for Subjects with Baseline NRS ≥4

End point description:

Pruritus NRS at Month 3 is the key secondary efficacy endpoint. The weekly pruritus score was calculated by recording the daily pruritus score each day for seven days and later taking the mean value of the seven days' daily recorded data. If any data was available for a given week, the available NRS results was used for the calculation of the weekly mean. If no NRS results was available in a given week, the mean of the prior week was used to impute those missing results using the LOCF method. Only assessments before or within 2 days after the last dose was used in determining weekly means. Baseline pruritus NRS is defined as the mean of the all daily recorded scores during run-in. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary

End point timeframe:

Baseline, Month 3 (Endpoint)

End point values	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	18	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 3 (n=17, 18, 18)	-1.95 (± 2.226)	-3.01 (± 1.952)	-1.44 (± 1.831)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Seladelpar 10 mg (initial dose) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0164
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	-0.3

Statistical analysis title	Statistical Analysis 2
Comparison groups	Seladelpar 5 mg (initial Dose) v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4781
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	0.84

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to week 56	
Adverse event reporting additional description:	
Adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Seladelpar 5 mg (initial Dose)
Reporting group description:	
Subjects received seladelpar 5 milligram (mg) capsules orally once daily for the study duration	
Reporting group title	Seladelpar 10 mg (initial dose)
Reporting group description:	
Subjects received seladelpar 10 mg capsules orally once daily for the study duration	
Reporting group title	Placebo
Reporting group description:	
Subjects received matched placebo capsules orally once daily for the study duration	

Serious adverse events	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 89 (3.37%)	1 / 89 (1.12%)	3 / 87 (3.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoid cystic carcinoma			
subjects affected / exposed	1 / 89 (1.12%)	0 / 89 (0.00%)	0 / 87 (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
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 89 (1.12%)	0 / 89 (0.00%)	0 / 87 (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
Partial seizures			

subjects affected / exposed	0 / 89 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 89 (0.00%)	0 / 87 (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
Gastrointestinal disorders			
Rectal polyp			
subjects affected / exposed	0 / 89 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 89 (0.00%)	0 / 89 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Seladelpar 5 mg (initial Dose)	Seladelpar 10 mg (initial dose)	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 89 (61.80%)	58 / 89 (65.17%)	62 / 87 (71.26%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 89 (5.62%)	7 / 89 (7.87%)	1 / 87 (1.15%)
occurrences (all)	5	8	1
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	2 / 89 (2.25%)	4 / 89 (4.49%)	8 / 87 (9.20%)
occurrences (all)	2	4	8
Asthenia			
subjects affected / exposed	0 / 89 (0.00%)	3 / 89 (3.37%)	0 / 87 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 89 (3.37%)	3 / 89 (3.37%)	2 / 87 (2.30%)
occurrences (all)	3	3	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 89 (8.99%)	6 / 89 (6.74%)	3 / 87 (3.45%)
occurrences (all)	9	6	3
Nausea			
subjects affected / exposed	5 / 89 (5.62%)	7 / 89 (7.87%)	4 / 87 (4.60%)
occurrences (all)	6	8	5
Diarrhoea			
subjects affected / exposed	4 / 89 (4.49%)	4 / 89 (4.49%)	4 / 87 (4.60%)
occurrences (all)	4	6	5
Constipation			
subjects affected / exposed	5 / 89 (5.62%)	3 / 89 (3.37%)	2 / 87 (2.30%)
occurrences (all)	5	3	2
Dyspepsia			
subjects affected / exposed	3 / 89 (3.37%)	4 / 89 (4.49%)	3 / 87 (3.45%)
occurrences (all)	3	4	3
Abdominal distension			
subjects affected / exposed	1 / 89 (1.12%)	3 / 89 (3.37%)	3 / 87 (3.45%)
occurrences (all)	1	4	3
Dry mouth			
subjects affected / exposed	5 / 89 (5.62%)	1 / 89 (1.12%)	0 / 87 (0.00%)
occurrences (all)	5	1	0
Vomiting			
subjects affected / exposed	0 / 89 (0.00%)	3 / 89 (3.37%)	3 / 87 (3.45%)
occurrences (all)	0	3	3
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 89 (1.12%)	3 / 89 (3.37%)	0 / 87 (0.00%)
occurrences (all)	1	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 89 (4.49%)	2 / 89 (2.25%)	4 / 87 (4.60%)
occurrences (all)	4	2	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 89 (3.37%)	10 / 89 (11.24%)	11 / 87 (12.64%)
occurrences (all)	4	11	16
Pruritus generalised			
subjects affected / exposed	3 / 89 (3.37%)	3 / 89 (3.37%)	3 / 87 (3.45%)
occurrences (all)	3	3	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 89 (1.12%)	4 / 89 (4.49%)	0 / 87 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 89 (5.62%)	4 / 89 (4.49%)	5 / 87 (5.75%)
occurrences (all)	5	4	5
Back pain			
subjects affected / exposed	2 / 89 (2.25%)	4 / 89 (4.49%)	3 / 87 (3.45%)
occurrences (all)	2	5	3
Muscle spasms			
subjects affected / exposed	1 / 89 (1.12%)	3 / 89 (3.37%)	1 / 87 (1.15%)
occurrences (all)	2	3	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 89 (0.00%)	3 / 89 (3.37%)	0 / 87 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 89 (6.74%)	4 / 89 (4.49%)	2 / 87 (2.30%)
occurrences (all)	7	4	2
Sinusitis			

subjects affected / exposed	2 / 89 (2.25%)	1 / 89 (1.12%)	5 / 87 (5.75%)
occurrences (all)	2	1	5
Nasopharyngitis			
subjects affected / exposed	3 / 89 (3.37%)	2 / 89 (2.25%)	2 / 87 (2.30%)
occurrences (all)	3	2	2
Urinary tract infection			
subjects affected / exposed	2 / 89 (2.25%)	5 / 89 (5.62%)	0 / 87 (0.00%)
occurrences (all)	2	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2018	Protocol amendment (version 1.1) for sites outside of US •Clarified that an abdominal ultrasound was to be performed, and liver elastography was to be performed at selected sites. •Added the requirement that subjects perform a urine pregnancy test monthly (every 30±3 days) through the duration of treatment. •Clarified that platelet counts were to be measured by local laboratories, if deemed necessary by the investigator. •Cystatin C was added as an analyte.
29 November 2018	Protocol amendment (version 1.1ES) for Spain •Clarified that the subject population included only those subjects with an inadequate response to UDCA; subjects with UDCA intolerance were excluded. •Clarified that the assessment of TEAEs was based on CTCAE Version 5.0.
18 January 2019	Protocol amendment (version 1.1RU) for Russia •Changes were made to the protocol to address comments received by the Ministry of Health of the Russian Federation: An update on the CB8025-21629 study was provided, efficacy and safety data were updated with a July 2018 cut-off. •Clarified that Version 5.0 rather than Version 4.0 of the CTCAE was to be used for this study. •Included the window for obtaining the pre-dose liver elastography which could have been performed from the Run-in Visit (Week -2) to study drug dosing at Day 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 November 2019	On 25 November 2019, as a precautionary measure until the NASH study (CB8025-21730) histology findings could be understood, Study CB8025-31735 was put on hold and subjects stopped treatment with study drug. At that time, the study was fully enrolled and subjects had a broad range of study drug treatment durations. Based on the receipt of information requests from the United States Food and Drug Administration (FDA) for the Phase 2 NASH study and the PBC studies, it was concluded that it would not be reasonable to maintain the PBC studies on hold given the time it would take to resolve the FDA requests. On 20 December 2019 the sites were informed of the ENHANCE study termination and requested to perform necessary safety evaluations on all active subjects.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As a result of early termination of study while the study was still blinded the primary endpoint and key secondary endpoints were revised to be assessed at Month 3 instead of Month 12 based on the number of subjects who reached 3 months of treatment.

Notes: