



Clinical trial results:

RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients with Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)

Summary

EudraCT number	2020-004348-27
Trial protocol	DE HU FR PL NL IT AT DK RO
Global end of trial date	11 August 2023

Results information

Result version number	v1
This version publication date	17 July 2024
First version publication date	17 July 2024

Trial information

Trial identification

Sponsor protocol code	CB8025-32048
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04620733
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CymaBay Therapeutics, Inc.
Sponsor organisation address	7601 Dumbarton Circle, Fremont, CA, United States, 94555
Public contact	7601 Dumbarton Circle, Fremont, CA 94555, CymaBay Study Director, +1 510-293-8800, medinfo@cymabay.com
Scientific contact	7601 Dumbarton Circle, Fremont, CA 94555, CymaBay Study Director, +1 510-293-8800, medinfo@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	11 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2023
Global end of trial reached?	Yes
Global end of trial date	11 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purposes of this study are to evaluate the treatment effect of seladelpar on composite biochemical improvement in cholestasis markers based on ALP and total bilirubin and to evaluate the safety of seladelpar over 12 months of treatment compared to placebo.

The study also checked the effect of treatment on the symptoms of PBC, including pruritus.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Participants who were able to tolerate ursodeoxycholic acid (UDCA) continued to take it during the study.

Evidence for comparator: -

Actual start date of recruitment	21 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 29
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 8

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Türkiye: 8
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Russian Federation: 9
Worldwide total number of subjects	193
EEA total number of subjects	43

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)	152
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the Asia Pacific, Europe, Latin America, and North America.

Pre-assignment

Screening details:

360 participants were screened.

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
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Arm title	Placebo
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Arm description:

Participants received placebo to match seladelpar, orally, once daily, for a duration of up to 12 months.

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

Dosage and administration details:

One capsule daily for double-blind period, for a duration of up to 12 months.

Arm title	Seladelpar
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Arm description:

Participants received seladelpar 10 mg, orally, once daily, for a duration of up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Seladelpar 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Seladelpar 10 mg one capsule daily for double-blind period, for a duration of up to 12 months.

Number of subjects in period 1	Placebo	Seladelpar
Started	65	128
Completed	57	117
Not completed	8	11
Protocol Deviation	1	1

Adverse event	4	3
Lost to follow-up	1	1
Reason not Specified	-	1
Withdrawal by subject	2	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match seladelpar, orally, once daily, for a duration of up to 12 months.	
Reporting group title	Seladelpar
Reporting group description:	
Participants received seladelpar 10 mg, orally, once daily, for a duration of up to 12 months.	

Reporting group values	Placebo	Seladelpar	Total
Number of subjects	65	128	193
Age categorical			
Units: Subjects			
Adults (18 – 64 Years)	53	99	152
Geriatrics (65 – 84 Years)	12	29	41
Age continuous			
Units: years			
arithmetic mean	57	57	-
standard deviation	± 9.2	± 10.0	-
Gender categorical			
Units: Subjects			
Female	60	123	183
Male	5	5	10
Race			
Units: Subjects			
American Indian or Alaska Native	3	3	6
Asian	4	7	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	56	114	170
Unknown or Not Reported	0	2	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	27	29	56
Not Hispanic or Latino	38	97	135
Unknown or Not Reported	0	2	2
Alkaline Phosphatase Levels			
Units: U/L			
arithmetic mean	313.8	314.6	-
standard deviation	± 117.68	± 122.96	-
Pruritus NRS for Participants With Baseline Pruritus NRS ≥ 4			
Measure Analysis Population Description: Moderate to Severe Pruritus NRS (MSPN) Analysis Set included participants in the Intent-to-Treat (ITT) Analysis Set who had a baseline NRS value.			
Units: score on a scale			
arithmetic mean	6.6	6.1	-
standard deviation	± 1.44	± 1.42	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match seladelpar, orally, once daily, for a duration of up to 12 months.	
Reporting group title	Seladelpar
Reporting group description:	
Participants received seladelpar 10 mg, orally, once daily, for a duration of up to 12 months.	

Primary: Percentage of Participants With Response Criteria for the Composite Endpoint of ALP <1.67 × Upper Limit of Normal (ULN), ≥15% Reduction in ALP, and Total Bilirubin ≤ 1.0× ULN at Month 12

End point title	Percentage of Participants With Response Criteria for the Composite Endpoint of ALP <1.67 × Upper Limit of Normal (ULN), ≥15% Reduction in ALP, and Total Bilirubin ≤ 1.0× ULN at Month 12
End point description:	
Percentages were rounded-off. The Intend-to-treat Analysis Set was defined as any participant who was randomized into the study and received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Month 12	

End point values	Placebo	Seladelpar		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	128		
Units: percentage of participants				
number (confidence interval 95%)	20.0 (10.3 to 29.7)	61.7 (53.3 to 70.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Composite Endpoint
Comparison groups	Placebo v Seladelpar
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	41.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	27.7
upper limit	53.4

Notes:

[1] - Two-sided p-value for pair-wise comparison was based on the CMH test adjusted for both randomization stratification variables (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline Pruritus NRS: < 4 and ≥ 4).

Primary: Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs ^[2]
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End point description:

Percentages were rounded-off. The Safety Analysis Set was defined as any participant who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

First dose date up to last dose plus 30 days (up to 13.4 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

End point values	Placebo	Seladelpar		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	128		
Units: percentage of participants				
number (not applicable)				
TEAEs	84.6	86.7		
Serious TEAEs	6.2	7.0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Shift of ≥ 2 CTCAE Grades from Baseline in Treatment-emergent Laboratory Abnormalities Related to Hematology and Select Liver Biochemistry

End point title	Percentage of Participants With Shift of ≥ 2 CTCAE Grades from Baseline in Treatment-emergent Laboratory Abnormalities Related to Hematology and Select Liver Biochemistry ^[3]
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End point description:

Treatment-emergent graded laboratory abnormalities were defined as values that increase at least 2 toxicity grade from baseline at any time post baseline. The laboratory abnormalities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, where Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: potentially life-threatening laboratory abnormality.

The data is reported for shift of ≥ 2 grades from baseline in values for hematology and biochemistry. Hematology includes parameters like RBCs (erythrocytes), hemoglobin, hematocrit, platelets, WBCs, WBC differentials (absolute and percentage) including basophils, neutrophils, lymphocytes, eosinophils, and monocytes, etc. Biochemistry included select liver function tests like blood bilirubin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase.

Participants in the Safety Analysis Set were analysed. Percentages were rounded-off.

End point type	Primary
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End point timeframe:

First dose date up to last dose (up to 13.4 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

End point values	Placebo	Seladelpar		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	128		
Units: percentage of participants				
number (not applicable)				
Shift ≥ 2 CTCAE grades in haematology	12.3	14.1		
Shift ≥ 2 CTCAE grades in biochemistry	6.2	7.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ALP $\leq 1.0 \times$ ULN at Month 12

End point title	Percentage of Participants with ALP $\leq 1.0 \times$ ULN at Month 12
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End point description:

Percentages were rounded-off. Participants in Intent-to-treat Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Month 12

End point values	Placebo	Seladelpar		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	128		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 0.0)	25.0 (17.5 to 32.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis for ALP Normalization
Comparison groups	Placebo v Seladelpar

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.3
upper limit	33.2

Notes:

[4] - Two-sided p-value for pair-wise comparison is based on the Cochran Mantel Haenszel test adjusted for both stratification variables (baseline ALP level: < 350 U/L and ≥ 350 U/L; baseline pruritus NRS: < 4 and ≥ 4).

Secondary: Change from Baseline (CFB) in Weekly Averaged Pruritus Numerical Rating Scale (NRS) in Participants with NRS ≥ 4 at Month 6

End point title	Change from Baseline (CFB) in Weekly Averaged Pruritus Numerical Rating Scale (NRS) in Participants with NRS ≥ 4 at Month 6
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End point description:

Pruritus NRS is used to rate the intensity of the itching experienced by the participants in the past 24 hours from no itching to worst possible itching by selecting a number from 0 to 10 on Itch Scale. Zero means no itching and 10 means worst imaginable itching. The Moderate to Severe Pruritus NRS Analysis Set included participants in the Intent-to-treat Analysis Set who had a baseline NRS value ≥ 4. Participants with available data were analysed.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	Placebo	Seladelpar		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	45		
Units: score on scale				
least squares mean (standard error)	-1.7 (± 0.41)	-3.2 (± 0.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis for NRS
Comparison groups	Placebo v Seladelpar
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	MMRM
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to 20.6 months;

Adverse events: Up to last dose plus 30 days (Up to 13.4 months)

Adverse event reporting additional description:

All-cause mortality: All-Randomized Analysis Set was defined all participants randomized in the study.

Adverse events: Safety Analysis Set was defined as any participant who received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Seladelpar 10 mg
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Reporting group description:

Patients who received Seladelpar 10 mg

Reporting group title	Placebo
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Reporting group description:

Patients who received Placebo

Serious adverse events	Seladelpar 10 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 128 (7.03%)	4 / 65 (6.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 128 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 128 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 128 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal obstruction			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 128 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 128 (0.78%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
subjects affected / exposed	1 / 128 (0.78%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-serious adverse events	Seladelpar 10 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 128 (51.56%)	40 / 65 (61.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 128 (3.13%)	4 / 65 (6.15%)	
occurrences (all)	4	4	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 128 (7.81%)	1 / 65 (1.54%)	
occurrences (all)	13	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 128 (3.91%)	4 / 65 (6.15%)	
occurrences (all)	5	4	
Fatigue			
subjects affected / exposed	8 / 128 (6.25%)	4 / 65 (6.15%)	
occurrences (all)	8	4	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 128 (0.78%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 128 (6.25%)	2 / 65 (3.08%)	
occurrences (all)	10	2	
Abdominal pain			
subjects affected / exposed	9 / 128 (7.03%)	1 / 65 (1.54%)	
occurrences (all)	10	1	
Nausea			
subjects affected / exposed	8 / 128 (6.25%)	3 / 65 (4.62%)	
occurrences (all)	9	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 128 (4.69%)	10 / 65 (15.38%)	
occurrences (all)	6	10	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	8 / 128 (6.25%)	4 / 65 (6.15%)	
occurrences (all)	8	4	
Infections and infestations			
Covid-19			
subjects affected / exposed	23 / 128 (17.97%)	9 / 65 (13.85%)	
occurrences (all)	24	9	
Upper respiratory tract infection			
subjects affected / exposed	1 / 128 (0.78%)	6 / 65 (9.23%)	
occurrences (all)	1	6	
Urinary tract infection			
subjects affected / exposed	4 / 128 (3.13%)	4 / 65 (6.15%)	
occurrences (all)	6	4	
Pharyngitis			
subjects affected / exposed	4 / 128 (3.13%)	5 / 65 (7.69%)	
occurrences (all)	5	5	
Nasopharyngitis			
subjects affected / exposed	7 / 128 (5.47%)	5 / 65 (7.69%)	
occurrences (all)	8	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2020	<p>Amendment 1, dated 01 December 2020, had the following key changes:</p> <p>Removed the statement that ursodeoxycholic acid (UDCA) was not considered a study drug for the AE reporting purposes. The change was made based on a recommendation from the United States Food and Drug Administration (US FDA) to avoid potential misunderstandings regarding reporting of safety events.</p> <p>Clarified which women must use contraception per Clinical Studies Facilitation Arm Recommendations related to contraception and pregnancy testing in clinical studies (Version 1.1, 21 September 2020).</p> <p>Added the following additional individual participant stopping criteria:</p> <p>Grade 3 events and above not already described by the safety monitoring criteria and related to study drug: any participant who experienced a Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 event that was considered possibly or probably related to study drug, was to be discontinued from study drug.</p> <p>Grade 4 events not already described by the safety monitoring criteria and not related to study drug: Any participant was to be considered for discontinuation from study drug. The Investigator, in consultation with the Sponsor's Medical Monitor, could consider the specific medical nature of the event, the causality assessment, and the possible outcome of the event.</p> <p>Added additional overall study stopping criteria in Section 12; these were to be assessed by the Data safety monitoring board (DSMB):</p> <p>Three participants develop the same Grade 3 CTCAE attributed to study drug</p> <p>Two participants develop any Grade 4 CTCAE attributed to study drug</p> <p>One participant develops a Grade 5 CTCAE</p> <p>Clarified the threshold of abnormal eosinophilia (absolute count > 1× upper limit of normal (ULN)) in Drug-induced liver injury (DILI) criteria for participants with normal baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and DILI criteria for participants with abnormal baseline ALT and AST.</p>
30 June 2021	<p>Amendment 2, dated 30 June 2021, had the following key changes:</p> <p>Removed the requirement of having at least 24 participants to participate in pharmacokinetic (PK) sample collection for the evaluation of seladelpar and its metabolites plasma concentration based on recommendations from the FDA. The intention was to allow all participants to be invited to participate in PK sample collection to support the planned exposure-response analysis. The PK sample collection schedule was revised from Months 1 and 3 to Months 3 and 12, and the number of PK blood samples to be collected was revised from 2 to 3.</p> <p>Added the following 2 exclusion criteria and updated the list of prohibited medications.</p> <p>Immunosuppressant therapies (eg, cyclosporine, tacrolimus, anti-Tumor Necrosis Factor (TNF), or other immunosuppressive biologics).</p> <p>Other medications affecting liver or GI functions, such as absorption of medication or the Roux-en-Y gastric bypass procedure could be prohibited and should be discussed with the Medical Monitor on a case-by-case basis.</p> <p>Added text to allow use of liver biopsy tissues collected within 6 months prior to Screening to ease the burden from participants.</p> <p>Outcomes related to adverse events (AEs) and definitions for action taken with study medication were revised to align with the Clinical Data Interchange Standards Consortium definitions.</p>

09 February 2022	<p>Amendment 3, dated 09 February 2022, had the following key changes:</p> <p>The estimated glomerular filtration rate (eGFR) Inclusion Criterion 5e was revised to > 45 mL/min/1.73m² from >60 mL/min/1.73m² after review by the Food and Drug Administration (FDA) of results from the seladelpar renal impairment study.</p> <p>Added a note in Inclusion Criterion 5 that prothrombin time, INR, and platelets could be performed locally at the Screening Visit, if deemed necessary by the Investigator after consultation with the Medical Monitor in cases in which centrally read samples were deemed invalid.</p> <p>Changed the washout period for use of prior obeticholic acid (OCA) and fibrate from 3 months to 6 weeks in Exclusion Criterion 9 to more accurately reflect the washout period that spanned 5 half-lives per each drug's half-life.</p> <p>Added Exclusion Criterion 17: Active coronavirus disease-2019 (COVID-19) infection during screening.</p> <p>The Safety Follow-up Window for subjects who were not enrolled in the long-term study (ASSURE) was reduced from 1 month (±7 days) to 14 (+3) days after last study drug dose based on the long-term safety of seladelpar in subjects with PBC and the half-life of seladelpar.</p> <p>The Screening and Run-in Period windows were revised to align with sites' average time to schedule screening assessments and to provide clarity.</p> <p>Clarified the text regarding which procedures participants should follow after discontinuation of study treatment on study and added a new section of annual follow-up for primary biliary cholangitis (PBC) outcomes assessment.</p> <p>Added that ascites and encephalopathy information should be collected during the physical examination at specified timepoints to allow for Child-Pugh (CP) score calculation.</p> <p>Updated the guideline for management of pancreatitis (Pancreatic Safety Criteria for Study Drug Interruption or Stopping Rules) based on recommendations from the United States (US) FDA.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported