



Clinical trial results:

An 8-week, dose ranging, open label, randomized, Phase 2 study with a 44-week extension, to evaluate the safety and efficacy of MBX-8025 in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response to or intolerance to ursodeoxycholic acid (UDCA).

Summary

EudraCT number	2016-002996-91
Trial protocol	DE GB
Global end of trial date	08 July 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	CB8025-21629
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02955602
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., 001 5102938800, mstanden@cymabay.com
Scientific contact	Alexandra (Sasha) Steinberg, CymaBay Therapeutics, Inc., 001 5102938800, asteinberg@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	30 July 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and efficacy of seladelpar 2 mg, 5 mg and 10 mg over 8 weeks of treatment in subjects of primary biliary cholangitis (PBC) as measured by the mean percent change from baseline in serum alkaline phosphatase (ALP) levels. After completion of the 8-week initial treatment period, subjects entered a 44-week open-label extension period for a total of up to 52 weeks of treatment. During the extension period subjects took seladelpar orally once daily for up to 52 weeks. The 2 mg group was started in order to define the lower dose range for efficacy after review of initial treatment period results for the 5 mg and the 10 mg groups.

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	01 November 2016
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	Canada: 6
Country: Number of subjects enrolled	United States: 82
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Germany: 11
Worldwide total number of subjects	119
EEA total number of subjects	31

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)	90
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 33 sites in the Canada, Germany, United Kingdom, and United States between 28 November 2016 and 08 July 2019.

Pre-assignment

Screening details:

A total of 192 subjects were screened of which 121 subjects randomized (2 subjects were not treated) into study and 71 were screen failures. Subjects were randomized to the 5 and 10 mg treatment groups for entry to the 8-week initial treatment period study, while those in the 2 mg treatment group entered after being sequentially assigned their dose

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Seladelpar 2 mg

Arm description:

Subjects received two seladelpar 1 mg capsules orally once daily for 8 weeks with a 44-week extension period. Dose up-titration for efficacy reasons could be made after 12 weeks of treatment up to 10 mg.

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

Dosage and administration details:

Seladelpar capsules taken once a day (QD) orally in initial treatment period and dose adjusted as necessary in the extension period. Dose up-titration up to 10 mg for efficacy reasons could be made after 12 weeks of treatment.

Arm title	Seladelpar 5 mg
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Arm description:

Subjects were randomized to receive one seladelpar 5 mg capsule orally once daily for 8 weeks with a 44-week extension period. Dose up-titration to 10 mg for efficacy reasons could be made after 12 weeks of treatment.

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

Dosage and administration details:

Seladelpar capsules taken QD orally in initial treatment period and dose adjusted as necessary in the extension period. Dose up-titration for efficacy reasons could be made after 12 weeks of treatment to up to 10 mg.

Arm title	Seladelpar 10 mg
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Arm description:

Subjects were randomized to receive one seladelpar 10 mg capsule orally once daily for 8 weeks with a 44-week extension period.

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

Dosage and administration details:

Seladelpar capsules taken QD orally in initial treatment period and dose adjusted as necessary in the extension period

Number of subjects in period 1	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg
Started	11	53	55
Completed	10	46	49
Not completed	1	7	6
Consent withdrawn by subject	1	3	2
Adverse event, non-fatal	-	3	-
Study entry with violation of protocol	-	-	3
Confirmed Paget's Disease	-	1	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Seladelpar 2 mg
Reporting group description:	
Subjects received two seladelpar 1 mg capsules orally once daily for 8 weeks with a 44-week extension period. Dose up-titration for efficacy reasons could be made after 12 weeks of treatment up to 10 mg.	
Reporting group title	Seladelpar 5 mg
Reporting group description:	
Subjects were randomized to receive one seladelpar 5 mg capsule orally once daily for 8 weeks with a 44-week extension period. Dose up-titration to 10 mg for efficacy reasons could be made after 12 weeks of treatment.	
Reporting group title	Seladelpar 10 mg
Reporting group description:	
Subjects were randomized to receive one seladelpar 10 mg capsule orally once daily for 8 weeks with a 44-week extension period.	

Reporting group values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg
Number of subjects	11	53	55
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)	8	41	41
From 65-84 years	3	12	14
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.2	57.5	57.4
standard deviation	± 9.6	± 8.1	± 9.7
Gender categorical			
Units: Subjects			
Female	11	51	50
Male	0	2	5
Race			
Units: Subjects			
White	10	50	49
Black or African-American	0	1	3
Asian	0	2	1
American Indian or Alaska native	0	0	1
Native Hawaiian or other Pacific Islander	0	0	0
Other	1	0	0
Multiple	0	0	1

Reporting group values	Total		
Number of subjects	119		
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)	90		
From 65-84 years	29		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	112		
Male	7		
Race			
Units: Subjects			
White	109		
Black or African-American	4		
Asian	3		
American Indian or Alaska native	1		
Native Hawaiian or other Pacific Islander	0		
Other	1		
Multiple	1		

End points

End points reporting groups

Reporting group title	Seladelpar 2 mg
Reporting group description: Subjects received two seladelpar 1 mg capsules orally once daily for 8 weeks with a 44-week extension period. Dose up-titration for efficacy reasons could be made after 12 weeks of treatment up to 10 mg.	
Reporting group title	Seladelpar 5 mg
Reporting group description: Subjects were randomized to receive one seladelpar 5 mg capsule orally once daily for 8 weeks with a 44-week extension period. Dose up-titration to 10 mg for efficacy reasons could be made after 12 weeks of treatment.	
Reporting group title	Seladelpar 10 mg
Reporting group description: Subjects were randomized to receive one seladelpar 10 mg capsule orally once daily for 8 weeks with a 44-week extension period.	

Primary: Relative Change from Baseline in Serum Alkaline Phosphatase (ALP) Levels at Week 8 (Endpoint)

End point title	Relative Change from Baseline in Serum Alkaline Phosphatase (ALP) Levels at Week 8 (Endpoint)
End point description: Relative change from baseline is in serum ALP levels at Week 8 (endpoint). The modified Intent-to-Treat (mITT) analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints	
End point type	Primary
End point timeframe: Week 8 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percent Change				
arithmetic mean (standard deviation)				
Percent change (n= 11, 47, 51)	-26.06 (± 9.15)	-33.38 (± 17.81)	-41.42 (± 13.05)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1, 5 mg vs 2 mg
Statistical analysis description: The analyses will assess the change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2	

mg and 5 mg treatment groups after 8 weeks of treatment

Comparison groups	Seladelpar 2 mg v Seladelpar 5 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2242
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2, 2 mg vs 10 mg
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Statistical analysis description:

The analyses will assess the change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2 mg and 10 mg treatment groups after 8 weeks of treatment.

Comparison groups	Seladelpar 2 mg v Seladelpar 10 mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0021
Method	ANCOVA

Statistical analysis title	Statistical Analysis 3, 5 mg vs 10 mg
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Statistical analysis description:

The analyses will assess the change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 5 mg and 10 mg treatment groups after 8 weeks of treatment.

Comparison groups	Seladelpar 5 mg v Seladelpar 10 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0024
Method	ANCOVA

Secondary: Absolute Change in Serum Alkaline Phosphatase (ALP) Levels from Baseline to Weeks 12 and 52 (Endpoint)

End point title	Absolute Change in Serum Alkaline Phosphatase (ALP) Levels from Baseline to Weeks 12 and 52 (Endpoint)
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End point description:

Absolute change in ALP from baseline to Weeks 12 and 52

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

n_i denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Absolute Change				
arithmetic mean (standard deviation)				
Absolute Change at Week 12 (n= 11, 46, 49)	-68.318 (± 63.276)	-135.902 (± 150.954)	-127.867 (± 60.284)	
Absolute Change at Week 52 (n= 10, 42, 48)	-101.150 (± 107.956)	-158.310 (± 143.668)	-133.760 (± 76.151)	

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change from Baseline in Serum Alkaline Phosphatase (ALP) Levels at Weeks 12 and 52 (Endpoint)

End point title	Relative Change from Baseline in Serum Alkaline Phosphatase (ALP) Levels at Weeks 12 and 52 (Endpoint)
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End point description:

Mean percent change in ALP from baseline to Weeks 12 and 52 (Endpoint)

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percent Change				
arithmetic mean (standard deviation)				
Percent Change at Week 12 (n= 11, 47, 51)	-22.56 (± 13.92)	-34.49 (± 20.62)	-43.20 (± 12.39)	
Percent Change at Week 52 (n= 11, 45, 49)	-32.72 (± 22.48)	-40.09 (± 24.23)	-44.19 (± 15.52)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1, 5 mg vs 2 mg (12 weeks)
Statistical analysis description:	
The analyses will assess the percent change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2 mg and 5 mg treatment groups after 12 weeks of treatment.	
Comparison groups	Seladelpar 2 mg v Seladelpar 5 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0493
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2, 2 mg vs 10 mg (12 weeks)
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Statistical analysis description:

The analyses will assess the percent change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2 mg and 10 mg treatment groups after 12 weeks of treatment.

Comparison groups	Seladelpar 10 mg v Seladelpar 2 mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0003
Method	ANCOVA

Statistical analysis title	Statistical Analysis 3, 5 mg vs 10 mg (12 weeks)
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Statistical analysis description:

The analyses will assess the percent change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 5 mg vs 10 mg treatment groups after 12 weeks of treatment.

Comparison groups	Seladelpar 5 mg v Seladelpar 10 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0053
Method	ANCOVA

Statistical analysis title	Statistical Analysis 4, 2 mg vs 5 mg (52 weeks)
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Statistical analysis description:

The analyses will assess the percent change from baseline in each treatment group and will assess the

hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2 mg and 5 mg treatment groups after 52 weeks of treatment.

Comparison groups	Seladelpar 2 mg v Seladelpar 5 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3466
Method	ANCOVA

Statistical analysis title

Statistical Analysis 5, 2 mg vs 10 mg (52 weeks)

Statistical analysis description:

The analyses will assess the percent change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 2 mg vs 10 mg treatment groups after 52 weeks of treatment.

Comparison groups	Seladelpar 2 mg v Seladelpar 10 mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0949
Method	ANCOVA

Statistical analysis title

Statistical Analysis 6, 5 mg vs 10 mg (52 weeks)

Statistical analysis description:

The analyses will assess the percent change from baseline in each treatment group and will assess the hypothesis that there are no differences in the percent change in ALP serum level between seladelpar 5 mg vs 10 mg treatment groups after 52 weeks of treatment.

Comparison groups	Seladelpar 5 mg v Seladelpar 10 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.251
Method	ANCOVA

Secondary: Percentage of Subjects with Response Defined by Composite Risk Scores (ALP < 1.67 x Upper Limit of Normal [ULN] at Endpoint, Total Bilirubin [BIL] Within Normal Limits at Endpoint, and Greater Than Equal To [≥] 15% ALP Reduction from Baseline to Endpoint

End point title	Percentage of Subjects with Response Defined by Composite Risk Scores (ALP < 1.67 x Upper Limit of Normal [ULN] at Endpoint, Total Bilirubin [BIL] Within Normal Limits at Endpoint, and Greater Than Equal To [≥] 15% ALP Reduction from Baseline to Endpoint
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End point description:

Reporting was done for percentage of subjects with response defined by Composite Risk Scores (ALP Less than [$<$] 1.67 x ULN at endpoint, Total BIL within normal limits at endpoint, and \geq 15% ALP reduction from baseline to Endpoint).

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. The mITT analysis was

performed in a manner similar to primary endpoint.
n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
12 Weeks and 52 Weeks	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Week 12 (n= 11, 47, 51)	45.5	48.9	66.7	
Week 52 (n= 11, 45, 49)	63.6	53.3	67.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response Based on PARIS I Risk Score at Weeks 12 and 52 (Endpoint)

End point title	Percentage of Subjects with Response Based on PARIS I Risk Score at Weeks 12 and 52 (Endpoint)
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End point description:

Percentage of subjects with response based on Paris I risk score was defined as ALP less than or equal to (\leq) 3x ULN and aspartate aminotransferase (AST) less than or equal to (\leq) 2 x ULN and Total Bilirubin \leq 1 mg/dL.

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
At Weeks 12, 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Week 12 (n=9, 35, 37)	81.8	76.1	75.5	
Week 52 (n=9, 34, 38)	90	81.0	79.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response Based on PARIS II Risk Score at Weeks 12 and 52 (Endpoint)

End point title	Percentage of Subjects with Response Based on PARIS II Risk Score at Weeks 12 and 52 (Endpoint)
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End point description:

Percentage of subjects with response based on Paris II risk score was defined as $ALP \leq 1.5 \times ULN$ and $AST \leq 1.5 \times ULN$ and Total Bilirubin ≤ 1 mg/dL.

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
At Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Week 12 (n=4, 17, 29)	36.4	37.0	59.2	
Week 52 (n=5, 23, 29)	50.0	54.8	60.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response Based on Toronto I Risk Score at Weeks 12 and 52 (Endpoint)

End point title	Percentage of Subjects with Response Based on Toronto I Risk Score at Weeks 12 and 52 (Endpoint)
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End point description:

Percentage of subjects with response based on Toronto I risk score defined as $ALP \leq 1.67 \times ULN$. The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

At Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Week 12 (n=7, 24, 40)	63.6	51.1	78.4	
Week 52 (n=7, 26, 35)	63.6	57.8	71.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response Based on Barcelona Risk Score at Weeks 12 and 52 (Endpoint)

End point title	Percentage of Subjects with Response Based on Barcelona Risk Score at Weeks 12 and 52 (Endpoint)
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End point description:

Percentage of subjects with response based on Barcelona risk scores was defined as Normalization of ALP or a Decrease of ALP $\geq 40\%$. The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. . n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

At Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Week 12 (n=1, 20, 32)	9.1	42.6	62.7	
Week 52 (n=5, 30, 32)	45.5	66.7	65.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response Based on Rotterdam Risk Score at

Weeks 12 and 52 (Endpoint)

End point title	Percentage of Subjects with Response Based on Rotterdam Risk Score at Weeks 12 and 52 (Endpoint)
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End point description:

Percentage of subjects with response based on Rotterdam risk scores was defined in terms of populations of early stage (normal Total Bilirubin and normal Albumin), moderately advanced stage (either abnormal Albumin or abnormal Total Bilirubin), and advanced stages (both abnormal Albumin and abnormal Total Bilirubin).

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

At Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Percentage of subjects				
number (not applicable)				
Early Stage (12 Weeks, n=11, 36, 42)	100	82.6	81.6	
Early Stage (52 weeks, n=10, 36, 42)	100	85.7	87.5	
Moderately Advanced Stage (12 weeks, n=0, 7, 9)	0	15.2	18.4	
Moderately Advanced Stage (52 weeks, n=0, 3, 5)	0	7.1	18.4	
Advanced Stage (12 weeks, n=0, 1, 0)	0	2.2	0	
Advanced Stage (52 weeks, n=0, 3, 1)	0	7.1	2.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total bilirubin (TB) Levels at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Total bilirubin (TB) Levels at Weeks 12 and 52 (Endpoint)
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End point description:

Change from baseline in TB levels at endpoint is being reported.

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 46, 49)	-0.010 (± 0.121)	-0.055 (± 0.161)	-0.067 (± 0.199)	
Week 52 (n= 10, 42, 48)	0.002 (± 0.152)	-0.028 (± 0.263)	-0.068 (± 0.190)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Aspartate Aminotransferase (AST) Levels at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Aspartate Aminotransferase (AST) Levels at Weeks 12 and 52 (Endpoint)
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End point description:

Change from baseline in AST levels at endpoint was reported. The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12, 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: U/L				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 46, 49)	-2.50 (± 16.72)	-1.13 (± 24.28)	-3.35 (± 10.55)	
Week 52 (n= 10, 42, 48)	-7.05 (± 10.50)	-6.18 (± 13.98)	-6.14 (± 9.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Alanine Aminotransferase (ALT) Levels at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Alanine Aminotransferase (ALT) Levels
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End point description:

Change from baseline in ALT levels at endpoint was reported. The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: U/L				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 46, 49)	-5.59 (± 16.07)	-10.48 (± 21.41)	-10.87 (± 20.25)	
Week 52 (n= 10, 42, 48)	-14.30 (± 25.12)	-17.29 (± 17.46)	-15.32 (± 13.89)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Gamma-glutamyl Transferase (GGT) Levels at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Gamma-glutamyl Transferase (GGT) Levels at Weeks 12 and 52 (Endpoint)
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End point description:

Change from baseline in GGT levels at endpoint was reported. The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: U/L				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 46, 49)	-43.68 (± 56.87)	-75.35 (± 87.57)	-80.82 (± 109.06)	
Week 52 (n= 10, 42, 48)	-78.60 (± 81.59)	-91.37 (± 102.23)	-88.08 (± 122.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Model for End-stage Liver Disease (MELD) score at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Model for End-stage Liver Disease (MELD) score at Weeks 12 and 52 (Endpoint)
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End point description:

The prognostic model for estimating disease severity and survival was utilized for subjects by assessing the Model for End-stage Liver Disease (MELD) score. To calculate the MELD score, samples for creatinine, bilirubin, international normalized ratio (INR), and sodium values were taken as specified in assessment schedule. The MELD scores were calculated as per following formulae:

MELD(i) score = $10 \times (0.957 \times \ln[\text{creatinine, mg/dL}] + 0.378 \times \ln[\text{bilirubin, mg/dL}] + 1.120 \times \ln[\text{INR}] + 0.643)$.

If MELD(i) is less than or equal to 11 then MELD score = MELD(i).

If MELD(i) is greater than 11 then MELD score = MELD(i) + $(1.32 \times (137 - (Na)) - (0.033 \times \text{MELD(i)} \times (137 - Na)))$

The mITT analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

mITT, included population; n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 46, 48)	-0.3 (± 1.6)	0.1 (± 1.2)	0.1 (± 1.0)	
Week 52 (n= 10, 42, 48)	-0.7 (± 1.6)	0.3 (± 1.1)	0.2 (± 1.2)	

Statistical analyses

Secondary: Change from Baseline in Global PBC Study Group (GLOBE) score at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Global PBC Study Group (GLOBE) score at Weeks 12 and 52 (Endpoint)
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End point description:

The Global PBC Study Group (GLOBE) score was assessed using the validated tool to accurately stratify patients into high- and low- risk for liver transplantation or death at 12 months of ursodeoxycholic acid (UDCA) treatment. Samples for bilirubin, ALP, albumin, and platelet count determination were used as per specifications to calculate the GLOBE score. Formula used : $(0.044378 \times \text{age} + 0.93982 \times \ln[\text{total bilirubin}/\text{ULN}] + [0.335648 \times \ln(\text{alkaline phosphatase}/\text{ULN})] - 2.266708 \times \text{albumin} / \text{LLN} - 0.002581 \times \text{platelet count per } 10^9/\text{L}) + 1.216865$.

The modified Intent-to-Treat (mITT) analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

mITT, included population; n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
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End point timeframe:

Weeks 12 and 52 (Endpoint)

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	53	55	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (n= 10, 43, 46)	-0.079 (± 0.260)	-0.292 (± 0.304)	-0.346 (± 0.269)	
Week 52 (n= 9, 37, 43)	-0.180 (± 0.217)	-0.271 (± 0.354)	-0.404 (± 0.298)	

Statistical analyses

No statistical analyses for this end point

Secondary: Risk as Assessed by United Kingdom-Primary Biliary Cholangitis (UK-PBC) Score at Weeks 12 and 52 (Endpoint)

End point title	Risk as Assessed by United Kingdom-Primary Biliary Cholangitis (UK-PBC) Score at Weeks 12 and 52 (Endpoint)
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End point description:

The UK-PBC Risk Score at endpoint is defined by the mean percentage risk that a PBC patient treated with ursodeoxycholic acid (UDCA) would develop liver failure requiring liver transplantation in 5, 10 and 15 years from diagnosis. Formula used for UK-PBC risk score = $1 - 0.982 \cdot \exp(0.0287854 \cdot (\text{AP}_{12} \times \text{ULN} - 1.722136304) - 0.0422873 \cdot ((\text{TA}_{12} \times \text{ULN}/10)^{-1}) - 8.675729006) + 1.4199 \cdot (\ln(\text{BIL}_{12} \times \text{ULN}/10) + 2.709607778) - 1.960303 \cdot (\text{Albumin} \times \text{LLN} - 1.17673001) - 0.4161954 \cdot (\text{Platelet} \times \text{LLN} - 1.873564875))$. Where, Baseline survivor function = 0.982, 0.941, and 0.893 for 5 years, 10 years and 15 years respectively. AP₁₂, TA₁₂ and BIL₁₂ refers to the AP, transaminases (ALT, AST), and total bilirubin assessments, respectively.

The modified Intent-to-Treat (mITT) analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment.

mITT, included population; n, denotes number of subjects evaluable for timepoint

End point type	Secondary
End point timeframe:	
Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Units on a scale				
arithmetic mean (standard deviation)				
5 years (week 12, n= 11, 44, 48)	1.3929 (± 0.6976)	2.2553 (± 2.5145)	1.8124 (± 1.7267)	
5 years (week 52, n= 10, 40, 47)	1.3145 (± 0.7704)	2.3485 (± 3.4325)	1.7244 (± 1.6121)	
10 years (week 12, n= 11, 44, 48)	4.5705 (± 2.2479)	7.1229 (± 7.4904)	5.8293 (± 5.3605)	
10 years (week 52, n= 10, 40, 47)	4.3128 (± 2.4649)	7.2322 (± 9.5794)	5.5607 (± 5.0092)	
15 years (week 12, n= 11, 44, 48)	8.3008 (± 3.9932)	12.4002 (± 12.1785)	10.3469 (± 9.1269)	
15 years (week 52, n= 10, 40, 47)	7.8325 (± 4.3413)	12.3028 (± 14.5701)	9.9008 (± 8.5396)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pruritus as Assessed by Visual Analogue Scale (VAS) Total Score at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Pruritus as Assessed by Visual Analogue Scale (VAS) Total Score at Weeks 12 and 52 (Endpoint)
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End point description:

VAS is the commonly used graphic tool for self-reporting of pruritus intensity in patients. VAS is a simple to use, validated, reliable and widely applicable tool that does not determine the impact of pruritus to quality of life. It comprises of a 100-mm horizontal line labelled as "no symptom" on left end and "worst imaginable symptom" on right end. Based on the intensity of the itch patient is instructed to draw a vertical line on the horizontal scale having a range [VAS values (unit: mm) ranging from 0 to 100, where 0 represents "no itching" and 100 "worst possible itching"]. The modified Intent-to-Treat (mITT) analysis set included all randomized subjects with confirmed PBC who received at least one study drug dose and had at least one post baseline ALP evaluation on treatment. mITT, included population; n, denotes number of subjects evaluable for the respective timepoints

End point type	Secondary
End point timeframe:	
Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (n= 11, 45, 49)	-3.7 (± 6.4)	-5.5 (± 25.0)	-12.3 (± 22.3)	
Week 52 (n= 10, 42, 48)	-3.3 (± 11.7)	-9.6 (± 22.5)	-16.5 (± 23.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Primary Biliary Cholangitis-40 (PBC-40) Quality of Life Questionnaire Scores at Weeks 12 and 52 (Endpoint)

End point title	Change from Baseline in Primary Biliary Cholangitis-40 (PBC-40) Quality of Life Questionnaire Scores at Weeks 12 and 52 (Endpoint)
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End point description:

The PBC-40 QoL questionnaire is a disease-specific health-related tool developed for measuring the psychometric profile in PBC patients. It has 10 domains and a 43 questions relevant to PBC, including Cognitive, Social, Emotional Function, Fatigue, Itch, and Other Symptoms. Questions in domains: 1) digestion and diet (questions 1-3); 2) experiences (questions 4-7); 3) itching (questions 8-10); 4) fatigue (questions 11-18); 5) effort and planning (questions 19-21); 6) memory and concentration (questions 22-27); 7) affects to you as person (questions 28-33); 8) affects to your social life (questions 34-37); 9) overall impact on your life (questions 38-40); 10) general health and well-being (questions A-C).

Within a domain, items are scored from 1 to 5 and the individual item scores are summed to give a total domain score. High scores represent high impact and low scores low impact of PBC on QoL.

mITT, included population; n, number of subjects evaluable at respective timepoint

End point type	Secondary
End point timeframe:	
Weeks 12 and 52 (Endpoint)	

End point values	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	49	52	
Units: Units on a scale				
arithmetic mean (standard deviation)				
General Symptoms	1.9 (± 2.7)	-0.7 (± 5.1)	-0.5 (± 3.6)	
Itch	-0.4 (± 2.0)	-0.5 (± 3.4)	-0.8 (± 3.1)	
Fatigue	-1.5 (± 6.1)	-2.1 (± 10.4)	-3.0 (± 5.2)	
Cognitive Function	-0.9 (± 2.4)	-0.6 (± 5.7)	-0.7 (± 2.8)	
Social	0.8 (± 2.8)	-0.5 (± 7.9)	-1.0 (± 6.3)	
Emotional	-0.9 (± 1.6)	-1.0 (± 2.6)	-0.8 (± 2.1)	
General Symptoms, Week 12 (n= 11, 45, 49)	1.9 (± 2.7)	-0.7 (± 5.1)	-0.5 (± 3.6)	
General Symptoms, Week 52 (n= 10, 42, 48)	0.3 (± 2.4)	-1.4 (± 4.4)	-0.1 (± 4.4)	

Itch, Week 12 (n= 11, 45, 49)	-0.4 (± 2.0)	-0.5 (± 3.4)	-0.8 (± 3.1)	
Itch, Week 52 (n= 10, 42, 48)	0.4 (± 2.7)	-1.3 (± 3.2)	-1.4 (± 3.7)	
Fatigue, Week 12 (n= 11, 45, 49)	-1.5 (± 6.1)	-2.1 (± 10.4)	-3.0 (± 5.2)	
Fatigue, Week 52 (n= 10, 42, 48)	-1.2 (± 7.8)	-3.0 (± 8.5)	-3.4 (± 6.3)	
Cognitive Function, Week 12 (n= 11, 45, 49)	-0.9 (± 2.4)	-0.6 (± 5.7)	-0.7 (± 2.8)	
Cognitive Function, Week 52 (n= 10, 42, 48)	-0.7 (± 7.6)	-1.4 (± 5.3)	-0.6 (± 2.5)	
Social, Week 12 (n= 11, 44, 49)	0.8 (± 2.8)	-0.5 (± 7.9)	-1.0 (± 6.3)	
Social, Week 52 (n= 10, 42, 48)	-3.3 (± 5.2)	-1.6 (± 7.2)	-1.6 (± 6.2)	
Emotional, Week 12 (n= 11, 44, 48)	-0.9 (± 1.6)	-1.0 (± 2.6)	-0.8 (± 2.1)	
Emotional, Week 52 (n= 10, 42, 47)	-2.1 (± 2.3)	-1.3 (± 2.7)	0.9 (± 2.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to week 56

Adverse event reporting additional description:

Adverse events

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Seladelpar 2 mg
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Reporting group description:

Subjects received seladelpar 2 milligram (mg) capsules orally once daily for 8 weeks with a 44-week extension period. Subjects entered the 44-week extension on their assigned dose. The dose was up-titrated after safety and efficacy data review of the first 8 weeks of treatment. During the extension, a subject's dose may have been re-adjusted for safety or efficacy reasons. The 2 mg group was started after safety and efficacy review of the 5 mg and the 10 mg groups was completed.

Reporting group title	Seladelpar 10 mg
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Reporting group description:

Subjects were randomized to receive seladelpar 10 milligram (mg) capsules orally once daily for 8 weeks with a 44-week extension period. Subjects entered the 44-week extension on their assigned dose. The dose was up- or down-titrated after safety and efficacy data review of the first 8 weeks of treatment. During the extension, a subject's dose may have been re-adjusted for safety or efficacy reasons.

Reporting group title	Seladelpar 5 mg
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Reporting group description:

Subjects were randomized to receive seladelpar 5 milligram (mg) capsules orally once daily for 8 weeks with a 44-week extension period. Subjects entered the 44-week extension on their assigned dose. The dose was up- or down-titrated after safety and efficacy data review of the first 8 weeks of treatment. During the extension, a subject's dose may have been re-adjusted for safety or efficacy reasons.

Serious adverse events	Seladelpar 2 mg	Seladelpar 10 mg	Seladelpar 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	5 / 55 (9.09%)	8 / 53 (15.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			

subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 55 (0.00%)	0 / 53 (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
Angina pectoris			
subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	0 / 53 (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
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	0 / 53 (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
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyonephrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	0 / 53 (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
Syncope			

subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 55 (1.82%)	0 / 53 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 55 (0.00%)	1 / 53 (1.89%)
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: 5 %

Non-serious adverse events	Seladelpar 2 mg	Seladelpar 10 mg	Seladelpar 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	47 / 55 (85.45%)	45 / 53 (84.91%)
Injury, poisoning and procedural complications			
Diarrhoea			
subjects affected / exposed	4 / 11 (36.36%)	9 / 55 (16.36%)	7 / 53 (13.21%)
occurrences (all)	4	9	7
Nausea			
subjects affected / exposed	4 / 11 (36.36%)	6 / 55 (10.91%)	9 / 53 (16.98%)
occurrences (all)	8	6	11
Abdominal pain upper			

subjects affected / exposed	3 / 11 (27.27%)	5 / 55 (9.09%)	7 / 53 (13.21%)
occurrences (all)	3	5	8
Vomiting			
subjects affected / exposed	3 / 11 (27.27%)	5 / 55 (9.09%)	4 / 53 (7.55%)
occurrences (all)	3	5	6
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 11 (9.09%)	5 / 55 (9.09%)	5 / 53 (9.43%)
occurrences (all)	1	5	7
Abdominal distension			
subjects affected / exposed	2 / 11 (18.18%)	4 / 55 (7.27%)	4 / 53 (7.55%)
occurrences (all)	2	4	4
Abdominal pain			
subjects affected / exposed	3 / 11 (27.27%)	3 / 55 (5.45%)	3 / 53 (5.66%)
occurrences (all)	3	3	3
Dry mouth			
subjects affected / exposed	2 / 11 (18.18%)	4 / 55 (7.27%)	2 / 53 (3.77%)
occurrences (all)	2	4	2
Dyspepsia			
subjects affected / exposed	3 / 11 (27.27%)	1 / 55 (1.82%)	2 / 53 (3.77%)
occurrences (all)	3	1	4
Urinary tract infection			
subjects affected / exposed	1 / 11 (9.09%)	8 / 55 (14.55%)	8 / 53 (15.09%)
occurrences (all)	2	12	11
Nasopharyngitis			
subjects affected / exposed	4 / 11 (36.36%)	6 / 55 (10.91%)	5 / 53 (9.43%)
occurrences (all)	5	9	7
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	3 / 55 (5.45%)	5 / 53 (9.43%)
occurrences (all)	1	3	6
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	2 / 55 (3.64%)	5 / 53 (9.43%)
occurrences (all)	0	2	5
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 55 (5.45%)	3 / 53 (5.66%)
occurrences (all)	0	3	3
Pruritus			

subjects affected / exposed	6 / 11 (54.55%)	12 / 55 (21.82%)	11 / 53 (20.75%)
occurrences (all)	9	12	13
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	7 / 55 (12.73%)	6 / 53 (11.32%)
occurrences (all)	1	8	6
Back pain			
subjects affected / exposed	3 / 11 (27.27%)	3 / 55 (5.45%)	5 / 53 (9.43%)
occurrences (all)	3	3	5
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 55 (3.64%)	5 / 53 (9.43%)
occurrences (all)	0	2	6
Muscle spasms			
subjects affected / exposed	1 / 11 (9.09%)	2 / 55 (3.64%)	3 / 53 (5.66%)
occurrences (all)	1	2	6
Musculoskeletal pain			
subjects affected / exposed	1 / 11 (9.09%)	4 / 55 (7.27%)	1 / 53 (1.89%)
occurrences (all)	1	5	1
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	6 / 55 (10.91%)	9 / 53 (16.98%)
occurrences (all)	3	6	10
Headache			
subjects affected / exposed	2 / 11 (18.18%)	3 / 55 (5.45%)	6 / 53 (11.32%)
occurrences (all)	5	3	9
Dizziness			
subjects affected / exposed	2 / 11 (18.18%)	3 / 55 (5.45%)	5 / 53 (9.43%)
occurrences (all)	2	3	5
Cough			
subjects affected / exposed	2 / 11 (18.18%)	3 / 55 (5.45%)	4 / 53 (7.55%)
occurrences (all)	2	3	4
Oropharyngeal pain			
subjects affected / exposed	2 / 11 (18.18%)	4 / 55 (7.27%)	1 / 53 (1.89%)
occurrences (all)	2	4	2
Dry eye			
subjects affected / exposed	2 / 11 (18.18%)	4 / 55 (7.27%)	1 / 53 (1.89%)
occurrences (all)	2	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2017	<ul style="list-style-type: none">•Enrollment in the 5 and 10 mg dose groups was changed from ~12 to ~18 subjects each. Subjects in the 2 mg (n ~ 6) and 20 mg (n ~ 12) dose groups were to be registered in the study.•Because of the level of activity observed in the 5 and 10 mg dose groups at Interim Analysis 1, the 2 mg dose group was added and the next highest dose was decreased from 25 mg to 20 mg to limit exposure to seladelpar.•Dose titration options for the extension period were changed from 5, 10, and 25 mg to 1, 2, 5, 10, 15, and 20 mg.•microRNA-122 was added as a biomarker of liver disease.
25 April 2017	<ul style="list-style-type: none">•After Interim Analysis 2, the extension period was changed from 18 to 44 weeks, and the treatment period was extended from 26 to 52 weeks. The total study duration (8 weeks' initial treatment + extension period + 4 weeks' follow-up) was extended from 30 to 56 weeks.•An exclusion criterion was added: total bilirubin > ULN and albumin < LLN with the exception of subjects with Gilbert's syndrome. Subjects with Gilbert's syndrome were to be excluded if direct bilirubin was >ULN.•During the extension period, dose up-titration to above 10 mg could not be performed until interim analysis results were available and the 20 mg dose group was initiated.•Barcelona PBC response criteria were added to outcome measures.•Prohibited systemic steroids were specified as long term (>2 weeks).•Review of medical history was to include history of liver related symptoms.•Physical examinations were to include evaluation of liver related symptoms.•A post-dose adjustment visit was added for subjects whose dose was adjusted at any time during the extension period.•Prothrombin time was removed from laboratory evaluations.•Subjects who withdrew from the study could be replaced.
17 July 2017	<ul style="list-style-type: none">•During the extension period, dose up-titration to above 10 mg was prohibited until interim analysis results were available.•The time for the second 24-hour PK determination was changed from after 2 weeks of treatment to after 12 weeks of treatment.•The size of the 2 mg dose group was changed from ~6 to up to 18 subjects, and the size of the 5 and 10 mg dose groups was changed from ~18 to ~49 subjects each. The size of the 20 mg dose group remained ~12 subjects.•The number of subjects undergoing 24-hour PK determinations was changed from ~3 to up to 6 subjects receiving 2 mg, from ~6 to up to 12 receiving 5 mg, from ~6 to up to 12 receiving 10 mg, and from ~6 to up to 12 receiving 20 mg.•Prohibited systemic steroids were specified as long term (>2 weeks).•Review of medical history was to include history of liver related symptoms.•Physical examinations were to include evaluation of liver related symptoms.•A post-dose adjustment visit was added for subjects whose dose was adjusted at any time during the extension period.

20 July 2017	<ul style="list-style-type: none"> •The 20 mg dose was removed. •Dose up-titration to 15 mg could take place only within 26 weeks of treatment. Beyond 26 weeks the highest dose was to be 10 mg. •The time for the second 24-hour PK determination was changed from after 2 weeks of treatment to after 12 weeks of treatment. •The size of the 2 mg dose group was changed from ~6 to up to 18 subjects, and the size of the 5 and 10 mg dose groups was changed from ~18 to ~49 subjects each. •The number of subjects undergoing 24-hour PK determinations was changed from ~3 to up to 6 subjects receiving 2 mg, from ~6 to up to 12 receiving 5 mg, and from ~6 to up to 12 receiving 10 mg.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported