Clinical trial results:
A 12-week, double-blind, randomized, placebo-controlled, Phase 2 study to evaluate the effects of two doses of MBX-8025 in subjects with Primary Biliary Cirrhosis (PBC) and an inadequate response to ursodeoxycholic acid (UDCA).

Summary

EudraCT number	2015-002698-39
Trial protocol	GB DE PL
Global end of trial date	01 July 2016

Results information

Result version number	v1 (current)
This version publication date	26 July 2017
First version publication date	26 July 2017
Summary attachment (see zip file)	Synopsis (cb8025-21528-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	CB8025-21528

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02609048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CymaBay Therapeutics, Inc.
Sponsor organisation address	7999 Gateway Blvd, Suite 130, Newark, United States, CA94560
Public contact	Karen Benson, CymaBay Therapeutics, Inc. , Kbenson@cymabay.com
Scientific contact	Pol Boudes, CymaBay Therapeutics, Inc. , Pboudes@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 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2016
Global end of trial reached?	Yes
Global end of trial date	01 July 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of seladelpar on alkaline phosphatase (AP) levels.

Protection of trial subjects:

Participation in the study is voluntary. Subjects can refuse to participate or stop at any time without stating a reason. Withdrawal will not affect access to other medical care to which the subject would otherwise be entitled.

Background therapy:

Ursodeoxycholic acid (UDCA) was continued to be taken by subjects in all treatment arms at the same dose during the study.

Evidence for comparator: -

Actual start date of recruitment	04 November 2015
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	Canada: 4
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	41
EEA total number of subjects	17

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)	35
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment period began in November 2015. On 26-May-16, the sponsor decided to terminate the study for safety and efficacy reasons.

Pre-assignment

Screening details:

Subjects are male or female with diagnosed PBC by at least two of the following criteria: History of AP above ULN for at least 6 months; Positive AMA titers or positive PBC-specific antinuclear antibodies; documented liver biopsy result consistent with PBC. Subjects are on a stable and recommended dose of UDCA for 12 months and have AP ≥ 1.67 ×ULN.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline / seladelpar 50 mg

Arm description:

4 weeks Baseline Period / seladelpar 50 mg

Arm type	Baseline evaluations
Investigational medicinal product name	Seladelpar 50 mg
Investigational medicinal product code	MBX-8025 50 mg
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Not applicable

Arm title	Baseline / seladelpar 200 mg

Arm description:

4 weeks Baseline Period / seladelpar 200 mg

Arm type	Baseline evaluations
Investigational medicinal product name	Seladelpar 200 mg
Investigational medicinal product code	MBX-8025 200 mg
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Not applicable

Arm title	Baseline / placebo

Arm description:

4 weeks Baseline Period / placebo

Arm type	Baseline evaluations

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

Dosage and administration details:

Not applicable

Number of subjects in period 1	Baseline / seladelpar 50 mg	Baseline / seladelpar 200 mg	Baseline / placebo
Started	14	13	14
Completed	13	12	13
Not completed	1	1	1
Adverse event, non-fatal	-	1	-
Administrative decision by investigator/sponsor	1	-	1

Period 2

Period 2 title	Double blind treatment and follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	50 mg

Arm description:

12-weeks treatment period with seladelpar 50 mg daily, followed by 2 week follow-up period

Arm type	Experimental
Investigational medicinal product name	Seladelpar 50 mg
Investigational medicinal product code	MBX-8025 50 mg
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Seladelpar 50 mg taken orally once a day

Arm title	200 mg

Arm description:

12-weeks treatment period with seladelpar 200 mg daily, followed by 2 week follow-up period

Arm type	Experimental

Investigational medicinal product name	Seladelpar 200 mg
Investigational medicinal product code	MBX-8025 200 mg
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Seladelpar 200 mg taken orally once a day

Arm title	placebo

Arm description:

12-weeks treatment period with placebo daily, followed by 2 week follow-up period

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:

Placebo taken orally once a day

Number of subjects in period 2	50 mg	200 mg	placebo
Started	13	12	13
Completed	4	2	4
Not completed	9	10	9
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	3	-
Early termination of the study	9	6	9

Baseline characteristics

Reporting groups	
Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Adults (18-64 years)	35	35	
From 65-84 years	6	6	
Gender categorical Units: Subjects			
Female	39	39	
Male	2	2	

End points

End points reporting groups

Reporting group title	Baseline / seladelpar 50 mg
Reporting group description: 4 weeks Baseline Period / seladelpar 50 mg	
Reporting group title	Baseline / seladelpar 200 mg
Reporting group description: 4 weeks Baseline Period / seladelpar 200 mg	
Reporting group title	Baseline / placebo
Reporting group description: 4 weeks Baseline Period / placebo	
Reporting group title	50 mg
Reporting group description: 12-weeks treatment period with seladelpar 50 mg daily, followed by 2 week follow-up period	
Reporting group title	200 mg
Reporting group description: 12-weeks treatment period with seladelpar 200 mg daily, followed by 2 week follow-up period	
Reporting group title	placebo
Reporting group description: 12-weeks treatment period with placebo daily, followed by 2 week follow-up period	

Primary: To evaluate the effect of seladelpar on AP levels

End point title	To evaluate the effect of seladelpar on AP levels
End point description:	
End point type	Primary
End point timeframe: End of treatment - Week 12	

End point values	50 mg	200 mg	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	10	12	
Units: LS mean percentage change from Baseline				
number (not applicable)	-53.21	-62.83	-1.84	

Statistical analyses

Statistical analysis title	effect of seladelpar on AP levels
Statistical analysis description: ANCOVA model	
Comparison groups	placebo v 50 mg v 200 mg

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA

Notes:

[1] - LS mean difference 50 mg vs. placebo: P < 0.0001. LS mean difference 200 mg vs. placebo: P < 0.0001. LS mean difference 50 mg vs. 200 mg: P = 0.1167.

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
An AE will be recorded any time after the time of signed ICF and captured until the end-of-study visit.	
Adverse event reporting additional description:	
Please see attached synopsis	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Justification: Please see attached synopsis

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2015	The protocol was amended on 4 September 2015 to create Version 3.0. The main changes to the protocol were as follows: - Tightened the requirements for contraceptive use during the study, including requiring the use of contraception for 90 days after the last dose of study medication because the effect of MBX8025 on pregnant women and fetuses has not been characterized. - Introduced stratification by geographic region in the efficacy analyses.
12 October 2015	The protocol was amended on 12 October 2015 to create Version 4.0. The main changes to the protocol were as follows: - Reporting of the severity of AEs was updated to reflect the use of NCI CTCAE Version 4. - Serum creatinine above the ULN was added to the study exclusion criteria because the target population for this study is early-stage PBC subjects. In early stages of PBC, patients have normal serum creatinine levels. - The current use of fibrates, including fenofibrates or simvastatin was added to the study exclusion criteria because of their potential to confound the primary efficacy analysis. - ECGs were moved to be performed 60-90 minutes after dosing to coincide with the time of the maximum plasma MBX-8025 concentration. Changes specific to the UK were made to Protocol Version 4.0 on 22 October 2015 to create Version 4.1 per the request of regulatory authorities. The main UK-specific changes to the protocol were as follows: - Added serum pregnancy tests for women of childbearing potential during the baseline period (within 2 weeks of Visit 2) and at each visit during the double-blind treatment period. - Specified that female subjects who became pregnant during the study were to be discontinued from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

26 May 2016	On 23 May 2016, a total of 3 subjects had experienced Grade 3 alanine aminotransferase (ALT) elevations. The study drug was unblinded for these cases and all 3 subjects were receiving seladelpar(1 receiving 50 mg and 2 receiving 200 mg). At the same time, based on concomitant decreases in GGT and 5'nucleotidase observed in the study overall (AP values were blinded during study), the proof-of-concept efficacy was demonstrated. As such, the Sponsor determined that there was no justification for continuing to expose subjects to seladelpar, and stopped and unblinded the study. An ad hoc DSMB meeting was held on 26-May-2016, at which the Sponsor informed the DSMB that the study had been stopped. On 27-May-2016, all active subjects were instructed to continue treatment with study medication until their next planned study visit. The last dose of study drug would be the day prior to this visit, and this visit was considered the end of treatment visit. Subjects were then to proceed, as planned in the original protocol, to a follow-up (off treatment) end of study visit, 2 weeks later.	-

Notes:

Limitations and caveats

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

Because the study was discontinued before its completion, the interpretation of the results is limited by the small sample size and some imbalance in baseline characteristics.

Notes: