



## 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 |
|-----------------------|--------------|

##### **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:

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### 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     |
| <b>Arm title</b>             | Placebo |

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.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Seladelpar |
|------------------|------------|

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 <sup>[1]</sup>                     |
| 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 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 <sup>[2]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

End point timeframe:

First dose date up to last dose (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)                |                 |                 |  |  |
| 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

### 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 <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

End point timeframe:

First dose date up to last dose plus 30 days (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)           |                 |                 |  |  |
| TEAEs                             | 84.6            | 86.7            |  |  |
| Serious TEAEs                     | 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 |
|-----------------|-----------------------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 <sup>[4]</sup> |
| 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 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Seladelpar 10 mg |
|-----------------------|------------------|

Reporting group description:

Patients who received Seladelpar 10 mg

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

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          |  |

| <b>Non-serious adverse events</b>                     | 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 &gt; 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 &gt; 45 mL/min/1.73m<sup>2</sup> from &gt;60 mL/min/1.73m<sup>2</sup> 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