



## Clinical trial results:

### A Phase Ib, Multicenter, Open-Label, 6-Week Study With a 48-Week Extension to Investigate the Pharmacokinetics, Safety, and Tolerability of Balovaptan in Children Ages 2-4 Years With Autism Spectrum Disorder

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-000989-38 |
| Trial protocol           | ES             |
| Global end of trial date | 06 May 2020    |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 07 October 2020 |
| First version publication date | 07 October 2020 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WP40877 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04049578 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                    |
|------------------------------|----------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Hoffmann-La Roche                                                                                  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                 |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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? | Yes |

Notes:

## Results analysis stage

|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 06 May 2020 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 06 May 2020 |
| Was the trial ended prematurely?                     | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the pharmacokinetics, safety, and tolerability of 4 mg balovaptan once a day administered for 6 weeks to children 2-4 years old with Autism Spectrum Disorder.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 19 December 2019 |
| 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 | United States: 2 |
| Worldwide total number of subjects   | 2                |
| EEA total number of subjects         | 0                |

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)                     | 2 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 0 |
| From 65 to 84 years                       | 0 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants in this study included children 2-4 years old with autism spectrum disorder (ASD).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Participants were to receive an oral dose of balovaptan once a day (QD) for a 6-week treatment period, followed by an optional extension period of 48 weeks.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Balovaptan         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Dispersible tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Balovaptan dispersible tablet was administered once a day (QD) orally.

| Number of subjects in period 1 | Balovaptan |
|--------------------------------|------------|
| Started                        | 2          |
| Completed                      | 1          |
| Not completed                  | 1          |
| Physician decision             | 1          |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Balovaptan |
|-----------------------|------------|

Reporting group description:

Participants were to receive an oral dose of balovaptan once a day (QD) for a 6-week treatment period, followed by an optional extension period of 48 weeks.

| Reporting group values                             | Balovaptan | Total |  |
|----------------------------------------------------|------------|-------|--|
| Number of subjects                                 | 2          | 2     |  |
| Age categorical                                    |            |       |  |
| Units: Subjects                                    |            |       |  |
| In utero                                           | 0          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0          | 0     |  |
| Newborns (0-27 days)                               | 0          | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0          | 0     |  |
| Children (2-11 years)                              | 2          | 2     |  |
| Adolescents (12-17 years)                          | 0          | 0     |  |
| Adults (18-64 years)                               | 0          | 0     |  |
| From 65-84 years                                   | 0          | 0     |  |
| 85 years and over                                  | 0          | 0     |  |
| Age Continuous                                     |            |       |  |
| Units: years                                       |            |       |  |
| arithmetic mean                                    | 3.45       |       |  |
| standard deviation                                 | ± 0.78     | -     |  |
| Sex: Female, Male                                  |            |       |  |
| Units: Participants                                |            |       |  |
| Female                                             | 0          | 0     |  |
| Male                                               | 2          | 2     |  |
| Race (NIH/OMB)                                     |            |       |  |
| Units: Subjects                                    |            |       |  |
| American Indian or Alaska Native                   | 0          | 0     |  |
| Asian                                              | 0          | 0     |  |
| Native Hawaiian or Other Pacific Islander          | 0          | 0     |  |
| Black or African American                          | 0          | 0     |  |
| White                                              | 2          | 2     |  |
| More than one race                                 | 0          | 0     |  |
| Unknown or Not Reported                            | 0          | 0     |  |
| Ethnicity (NIH/OMB)                                |            |       |  |
| Units: Subjects                                    |            |       |  |
| Hispanic or Latino                                 | 1          | 1     |  |
| Not Hispanic or Latino                             | 1          | 1     |  |
| Unknown or Not Reported                            | 0          | 0     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                              |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Reporting group title                                                                                                                                                                        | Balovaptan |
| Reporting group description:<br>Participants were to receive an oral dose of balovaptan once a day (QD) for a 6-week treatment period, followed by an optional extension period of 48 weeks. |            |

### Primary: Area Under the Curve at Steady State (AUCss) of Balovaptan

|                        |                                                                           |
|------------------------|---------------------------------------------------------------------------|
| End point title        | Area Under the Curve at Steady State (AUCss) of Balovaptan <sup>[1]</sup> |
| End point description: |                                                                           |

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

Notes:

[1] - 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 analysis for this end point.

| End point values                     | Balovaptan       |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup> |  |  |  |
| Units: day*ug/mL                     |                  |  |  |  |
| arithmetic mean (standard deviation) | ( )              |  |  |  |

Notes:

[2] - Due to low enrollment number, analysis are not provided to protect participant confidentiality.

### Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration of Balovaptan

|                        |                                                   |
|------------------------|---------------------------------------------------|
| End point title        | Plasma Concentration of Balovaptan <sup>[3]</sup> |
| End point description: |                                                   |

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

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 analysis for this end point.

|                                                     |                  |  |  |  |
|-----------------------------------------------------|------------------|--|--|--|
| <b>End point values</b>                             | Balovaptan       |  |  |  |
| Subject group type                                  | Reporting group  |  |  |  |
| Number of subjects analysed                         | 0 <sup>[4]</sup> |  |  |  |
| Units: ng/mL                                        |                  |  |  |  |
| geometric mean (geometric coefficient of variation) | ( )              |  |  |  |

Notes:

[4] - Due to low enrollment, number analysis are not provided to protect participant confidentiality.

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration of M2 Metabolite, as Applicable

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Plasma Concentration of M2 Metabolite, as Applicable <sup>[5]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

Notes:

[5] - 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 analysis for this end point.

|                                                     |                  |  |  |  |
|-----------------------------------------------------|------------------|--|--|--|
| <b>End point values</b>                             | Balovaptan       |  |  |  |
| Subject group type                                  | Reporting group  |  |  |  |
| Number of subjects analysed                         | 0 <sup>[6]</sup> |  |  |  |
| Units: ng/mL                                        |                  |  |  |  |
| geometric mean (geometric coefficient of variation) | ( )              |  |  |  |

Notes:

[6] - Due to low enrollment number, analysis are not provided to protect participant confidentiality.

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration of M3 Metabolite

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Plasma Concentration of M3 Metabolite <sup>[7]</sup> |
|-----------------|------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

Notes:

[7] - 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 analysis for this end point.

|                                                     |                  |  |  |  |
|-----------------------------------------------------|------------------|--|--|--|
| <b>End point values</b>                             | Balovaptan       |  |  |  |
| Subject group type                                  | Reporting group  |  |  |  |
| Number of subjects analysed                         | 0 <sup>[8]</sup> |  |  |  |
| Units: ng/mL                                        |                  |  |  |  |
| geometric mean (geometric coefficient of variation) | ()               |  |  |  |

Notes:

[8] - Due to low enrollment number, analysis are not provided to protect participant confidentiality.

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration Ratio of M2 to Balovaptan, as Applicable

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | Plasma Concentration Ratio of M2 to Balovaptan, as |
|-----------------|----------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

Notes:

[9] - 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 analysis for this end point.

|                                                     |                   |  |  |  |
|-----------------------------------------------------|-------------------|--|--|--|
| <b>End point values</b>                             | Balovaptan        |  |  |  |
| Subject group type                                  | Reporting group   |  |  |  |
| Number of subjects analysed                         | 0 <sup>[10]</sup> |  |  |  |
| Units: ng/mL                                        |                   |  |  |  |
| geometric mean (geometric coefficient of variation) | ()                |  |  |  |

Notes:

[10] - Due to low enrollment number, analysis are not provided to protect participant confidentiality.

## Statistical analyses

No statistical analyses for this end point

### Primary: Plasma Concentration Ratio of M3 to Balovaptan

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Plasma Concentration Ratio of M3 to Balovaptan <sup>[11]</sup> |
|-----------------|----------------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose, 2, 4, 6 hours postdose at Week 2; predose at Week 6; predose at Week 12; predose at Week 24, predose at Week 54

Notes:

[11] - 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 analysis for this end point.

|                                                     |                   |  |  |  |
|-----------------------------------------------------|-------------------|--|--|--|
| <b>End point values</b>                             | Balovaptan        |  |  |  |
| Subject group type                                  | Reporting group   |  |  |  |
| Number of subjects analysed                         | 0 <sup>[12]</sup> |  |  |  |
| Units: ng/mL                                        |                   |  |  |  |
| geometric mean (geometric coefficient of variation) | ()                |  |  |  |

Notes:

[12] - Due to low enrollment number, analysis are not provided to protect participant confidentiality.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Adverse Events

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Number of Participants With Adverse Events |
|-----------------|--------------------------------------------|

End point description:

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

End point timeframe:

Up to approximately week 20

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Balovaptan      |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 2               |  |  |  |
| Units: Participants         |                 |  |  |  |
| number (not applicable)     | 2               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first study drug to the data cutoff date: 6 May 2020 (up to approximately 20 weeks)

Adverse event reporting additional description:

The safety population is defined as patients who received any amount of study treatment.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Balovaptan |
|-----------------------|------------|

Reporting group description:

Participants were to receive an oral dose of balovaptan once a day (QD) for a 6-week treatment period, followed by an optional extension period of 48 weeks.

| Serious adverse events                            | Balovaptan    |  |  |
|---------------------------------------------------|---------------|--|--|
| Total subjects affected by serious adverse events |               |  |  |
| subjects affected / exposed                       | 0 / 2 (0.00%) |  |  |
| number of deaths (all causes)                     | 0             |  |  |
| number of deaths resulting from adverse events    |               |  |  |

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

| Non-serious adverse events                            | Balovaptan      |  |  |
|-------------------------------------------------------|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 2 / 2 (100.00%) |  |  |
| Investigations                                        |                 |  |  |
| Blood thyroid stimulating hormone increased           |                 |  |  |
| subjects affected / exposed                           | 1 / 2 (50.00%)  |  |  |
| occurrences (all)                                     | 1               |  |  |
| Vascular disorders                                    |                 |  |  |
| Haematoma                                             |                 |  |  |
| subjects affected / exposed                           | 1 / 2 (50.00%)  |  |  |
| occurrences (all)                                     | 1               |  |  |
| Nervous system disorders                              |                 |  |  |

|                                                                                                                |                     |  |  |
|----------------------------------------------------------------------------------------------------------------|---------------------|--|--|
| Psychomotor hyperactivity<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 2 (50.00%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)   | 1 / 2 (50.00%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>Abnormal weight gain<br>subjects affected / exposed<br>occurrences (all) | 1 / 2 (50.00%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study was terminated. Recent analysis of Phase II balovaptan data in paediatric ASD did not support the continuation of this study. No new safety concerns were identified. |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes: