



## Clinical trial results:

### A Randomized, Double-blind, Placebo-controlled, Multi-center, 2-part, Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of RGH-706 in Prader-Willi Syndrome

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2021-004262-35 |
| Trial protocol           | ES CZ IT       |
| Global end of trial date | 10 April 2024  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 June 2025 |
| First version publication date | 11 June 2025 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | RGH-706-003 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                    |
|------------------------------------|--------------------|
| ISRCTN number                      | -                  |
| ClinicalTrials.gov id (NCT number) | NCT05322096        |
| WHO universal trial number (UTN)   | -                  |
| Other trial identifiers            | IND Number: 154209 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Gedeon Richter Plc.   |
| Sponsor organisation address | Gyömrői út 19-21, Budapest, Hungary, H-1103   |
| Public contact               | Head of Global Regulatory CMC & Operation, Gedeon Richter Plc., +36 204162804, ra.ctarichter@richter.hu |
| Scientific contact           | Information Scientific Service, Gedeon Richter Plc., +36 15057032, medinfo@richter.hu                   |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 01 October 2024 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 10 April 2024   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 10 April 2024   |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The objectives were:

- To explore short-term efficacy of RGH706 on hyperphagia in patients with Prader-Willi syndrome (PWS)
- To explore the effect of RGH-706 on body weight and biomarkers
- To explore pharmacokinetics (PK), safety, and tolerability of RGH-706 in patients with PWS
- To explore the effect of RGH-706 on caregiver burden and on caregiver and clinician global impressions of severity and change

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its most recent update, and the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guideline. The study was also conducted in accordance with local legal and regulatory requirements of the countries involved, and with standard operating procedures in place.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 22 September 2022 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 3 Months          |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Spain: 18        |
| Country: Number of subjects enrolled | France: 3        |
| Country: Number of subjects enrolled | Italy: 10        |
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects   | 39               |
| EEA total number of subjects         | 31               |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 39 |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients were screened for their eligibility to participate in the study during the screening period. The primary caregiver was screened to ascertain his/her commitment to complete all study assessments during the study.

A total of 70 patients were screened during the study.

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | Overall (overall period) |
| Is this the baseline period? | Yes                      |
| Allocation method            | Randomised - controlled  |
| Blinding used                | Double blind             |
| Roles blinded                | Subject, Investigator    |

Blinding implementation details:

The study included a single-blind placebo run-in period followed by a double-blind treatment period.

- Single-blind (patient/caregiver) placebo was dispensed to the eligible patients orally once daily for 2 weeks during the run-in period.

- At the start of the double-blind (patient/caregiver and investigator/study personnel) treatment period, the investigator reconfirmed patients' eligibility based on screening results and treatment compliance during the run-in period.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | RGH-706 |

Arm description: -

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | RGH-706       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

22.5 mg once daily for 4 weeks

5 identical RGH-706 capsules/day: 2.5 mg (4 capsules) and 12.5 mg (1 capsule)

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

Arm description: -

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

Dosage and administration details:

Placebo once daily for 4 weeks

5 identical placebo capsules/day

| <b>Number of subjects in period 1</b> | RGH-706 | Placebo |
|---------------------------------------|---------|---------|
| Started                               | 21      | 18      |
| Completed                             | 20      | 18      |
| Not completed                         | 1       | 0       |
| Lost to follow-up                     | 1       | -       |

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | RGH-706 |
|-----------------------|---------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

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

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values                             | RGH-706 | Placebo | Total |
|--|---------|---------|-------|
| Number of subjects                                 | 21      | 18      | 39    |
| Age categorical                                    |         |         |       |
| Units: Subjects                                    |         |         |       |
| In utero   | 0       | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0       | 0     |
| Newborns (0-27 days)                               | 0       | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0       | 0       | 0     |
| Children (2-11 years)                              | 0       | 0       | 0     |
| Adolescents (12-17 years)                          | 0       | 0       | 0     |
| Adults (18-64 years)                               | 21      | 18      | 39    |
| From 65-84 years                                   | 0       | 0       | 0     |
| 85 years and over                                  | 0       | 0       | 0     |
| Age continuous                                     |         |         |       |
| Units: years                                       |         |         |       |
| arithmetic mean                                    | 30.1    | 26.1    |       |
| standard deviation                                 | ± 8.76  | ± 6.93  | -     |
| Gender categorical                                 |         |         |       |
| Units: Subjects                                    |         |         |       |
| Female   | 9       | 11      | 20    |
| Male   | 12      | 7       | 19    |

## End points

### End points reporting groups

|                              |         |
|------------------------------|---------|
| Reporting group title        | RGH-706 |
| Reporting group description: | -       |
| Reporting group title        | Placebo |
| Reporting group description: | -       |

### Primary: Change from Baseline in the 9item HQCT Total Score at Visit 5

|                        |  |
|------------------------|--|
| End point title        | Change from Baseline in the 9item HQCT Total Score at Visit 5  |
| End point description: | Hyperphagia Questionnaire for Clinical Trials [HQ-CT]<br>The HQ-CT is a questionnaire designed to measure symptoms of food-related preoccupations, problems, and behaviors. It was administered electronically via an electronic handheld device.<br>9-item-level responses (which ranged from 0 to 4) for a maximum score of 36. Higher scores represent increased hyperphagia. |
| End point type         | Primary  |
| End point timeframe:   | from Baseline to Visit 5 (after a 4 weeks treatment period)  |

| End point values                    | RGH-706              | Placebo              |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 21                   | 18                   |  |  |
| Units: HQ-CT Total Score            |                      |                      |  |  |
| least squares mean (standard error) | -2.10 ( $\pm$ 1.514) | -0.11 ( $\pm$ 1.695) |  |  |

### Statistical analyses

|   |                       |
|---|-----------------------|
| Statistical analysis title              | LS Mean Difference    |
| Comparison groups                       | Placebo v RGH-706     |
| Number of subjects included in analysis | 39                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[1]</sup>  |
| P-value                                 | = 0.3295              |
| Method                                  | ANCOVA                |
| Parameter estimate                      | Mean difference (net) |
| Point estimate                          | -2                    |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -6.1                  |
| upper limit                             | 2.1                   |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.02                       |

Notes:

[1] - LS means, SEs, 95% CI and p-values are from an ANCOVA model on the response variable change from baseline in 9-item HQ-CT total score with fixed factors for treatment arm and geographical location and a covariate for baseline 9-item HQ-CT total score.

Difference is calculated as LS Mean in RGH-706 22.5 mg – LS Mean in Placebo.

### Primary: Absolute change from baseline in body weight at each visit

|                 |  |
|-----------------|--|
| End point title | Absolute change from baseline in body weight at each visit |
|-----------------|--|

End point description:

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

End point timeframe:

From baseline at each visit

| End point values                    | RGH-706         | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 21              | 18              |  |  |
| Units: kg                           |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Visit 4 (Day 28)                    | 0.09 (± 0.279)  | 0.41 (± 0.313)  |  |  |
| Visit 5 (Day 42)                    | -0.29 (± 0.497) | 1.16 (± 0.512)  |  |  |
| Visit 6 (Day 56)                    | -0.08 (± 0.474) | 0.35 (± 0.505)  |  |  |
| Visit 7 (Day 98)                    | 1.47 (± 0.483)  | 0.95 (± 0.524)  |  |  |
| Visit 8 (Day 133)                   | 1.75 (± 0.519)  | 1.48 (± 0.552)  |  |  |

### Statistical analyses

|                            |                    |
|----------------------------|--------------------|
| Statistical analysis title | LS Mean Difference |
|----------------------------|--------------------|

Statistical analysis description:

From baseline to End of treatment

|   |                       |
|---|-----------------------|
| Comparison groups                       | RGH-706 v Placebo     |
| Number of subjects included in analysis | 39                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[2]</sup>  |
| P-value                                 | = 0.0456              |
| Method                                  | ANCOVA                |
| Parameter estimate                      | Mean difference (net) |
| Point estimate                          | -1.38                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | -2.73                 |
| upper limit                             | -0.03                 |



|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.664                      |

Notes:

[2] - LS means, SEs, 95% CI and p-values are from an ANCOVA model on the response variable change from baseline in body weight with fixed factors for treatment arm and geographical location and a covariate for baseline body weight value.

Difference is calculated as LS Mean in RGH-706 22.5 mg – LS Mean in Placebo.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline to the end of the trial.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Safety set - Placebo Run-in |
|-----------------------|-----------------------------|

Reporting group description: -

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Safety set - RGH-706 |
|-----------------------|----------------------|

Reporting group description:

The number of patients with at least one TEAE for this group in the overall trial is 12.

However, the number of Subjects affected by non-serious adverse events reported below is 5 in order to avoid validation errors; as the information reported in this record represents the Treatment-emergent Adverse Events by Preferred Term Reported for  $\geq 2$  Patients in Overall Population (Safety Set).

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Safety set - Placebo |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events                            | Safety set - Placebo Run-in | Safety set - RGH-706 | Safety set - Placebo |
|---|-----------------------------|----------------------|----------------------|
| Total subjects affected by serious adverse events |                             |                      |                      |
| subjects affected / exposed                       | 0 / 2 (0.00%)               | 0 / 21 (0.00%)       | 0 / 18 (0.00%)       |
| number of deaths (all causes)                     | 0                           | 0                    | 0                    |
| number of deaths resulting from adverse events    | 0                           | 0                    | 0                    |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events                            | Safety set - Placebo Run-in | Safety set - RGH-706 | Safety set - Placebo |
|---|-----------------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events |                             |                      |                      |
| subjects affected / exposed                           | 1 / 2 (50.00%)              | 5 / 21 (23.81%)      | 13 / 18 (72.22%)     |
| Injury, poisoning and procedural complications        |                             |                      |                      |
| Contusion   |                             |                      |                      |
| subjects affected / exposed                           | 0 / 2 (0.00%)               | 1 / 21 (4.76%)       | 1 / 18 (5.56%)       |
| occurrences (all)                                     | 0                           | 1                    | 1                    |
| Fall  |                             |                      |                      |
| subjects affected / exposed                           | 0 / 2 (0.00%)               | 1 / 21 (4.76%)       | 1 / 18 (5.56%)       |
| occurrences (all)                                     | 0                           | 1                    | 1                    |

|   |  |   |  |
|---|--|---|--|
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)   | 0 / 2 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   | 2 / 18 (11.11%)<br>2   |
| Nervous system disorders<br>Somnolence<br>subjects affected / exposed<br>occurrences (all)  | 1 / 2 (50.00%)<br>1  | 0 / 21 (0.00%)<br>0   | 2 / 18 (11.11%)<br>2   |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 2 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   | 2 / 18 (11.11%)<br>2   |
| Psychiatric disorders<br>Dermatillomania<br>subjects affected / exposed<br>occurrences (all)<br><br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Behaviour disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 2 (0.00%)<br>0<br><br>0 / 2 (0.00%)<br>0<br><br>0 / 2 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0<br><br>0 / 21 (0.00%)<br>0<br><br>0 / 21 (0.00%)<br>0 | 3 / 18 (16.67%)<br>3<br><br>2 / 18 (11.11%)<br>2<br><br>2 / 18 (11.11%)<br>2 |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 2 (0.00%)<br>0   | 1 / 21 (4.76%)<br>1   | 1 / 18 (5.56%)<br>1  |
| Infections and infestations<br>Cellulitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 2 (0.00%)<br>0   | 2 / 21 (9.52%)<br>2   | 0 / 18 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Hyperphagia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 2 (0.00%)<br>0   | 0 / 21 (0.00%)<br>0   | 2 / 18 (11.11%)<br>2   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 14 December 2021 | Protocol Version 1.1 – Global <ul style="list-style-type: none"><li>• Age of male and female patients enrolled in the study was changed from <math>\geq 16</math> years to <math>\geq 17</math> years at screening</li></ul>   |
| 16 December 2021 | Protocol Version 2.0 – Global <ul style="list-style-type: none"><li>• An additional study visit was included in Part B of the study</li><li>• Every week or every 2 weeks phone calls in Parts A and B starting from Study Day 7 <math>\pm 1</math> (where personal attendance visits were not required) were included</li><li>• Contraception measures for male patients with female partners of childbearing potential were included</li><li>• Text on C-SSRS was updated</li><li>• Follow-up thyroid function tests at end of study visit were included</li><li>• Thyroid function tests were moved from metabolic biomarkers under secondary endpoints to safety endpoints</li><li>• The study visits for Part B were updated</li><li>• Study schema was revised</li><li>• The metabolic biomarkers leptin, ghrelin, and adiponectin were moved from secondary objectives/endpoints to exploratory objective/endpoint</li></ul>  |
| 09 November 2022 | Protocol Version 3.0 – USA/ Protocol Version 3.1 – EU <ul style="list-style-type: none"><li>• Addition of requirement of informed consent by legally authorized representative and an assent by the adult patients who were not able to provide informed consent</li><li>• The PK endpoint was described in detail in synopsis and protocol main body and time windows for collection of PK sample were added to protocol main body and Appendix 5 Schedule of Assessments.</li><li>• Clarification added that no nonclinical data from Prader-Willi-specific animal models were available</li><li>• The process to manage delayed reporting of SAEs and COVID-19 crisis was described</li><li>• Appendix 2: Clinical Laboratory Evaluations and Appendix 5 Schedule of Assessments were revised</li><li>• Added a section on SRC and its role</li><li>• Instances that mentioned 'Covance' were updated to 'Labcorp' on the Title Page, Section 7.2.2, and Appendix 3</li></ul> |
| 24 March 2023    | Protocol Version 4.0 – USA/ Protocol Version 4.1 – EU <ul style="list-style-type: none"><li>• Revisions were made in inclusion criteria and exclusion criteria</li><li>• Reconfirmation of eligibility of the patients at Visit 3</li><li>• Revisions for better clarity regarding retesting and added the possibility to rescreen patients one time</li><li>• Clarification added regarding administration of HQ-CT at screening visit</li><li>• Revision of concomitant medication section and clarification regarding timeframe for prohibited medication</li><li>• Clarification added regarding time window for collection of predose PK sample at Visit 5 in Part A and Visit 7 in Part B prior to on-site dosing</li><li>• Clarification added regarding study drug storage conditions</li><li>• Revisions in visit windows for Visits 7 and 8 in Part A and Visit 8 in Part B</li></ul>  |
| 14 December 2023 | Protocol Version 5.0 – USA/ Protocol Version 5.1 – EU <ul style="list-style-type: none"><li>• Part B of the study was removed</li><li>• The sample size of the study was reduced</li><li>• The study design, objectives, and endpoints were revised to reflect removal of Part B from the study</li></ul>  |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported