# An adaptive, randomized, double-blind, placebo-controlled, single and multiple ascending dose study to examine the safety, tolerability, pharmacokinetics, pharmacodynamics and food effect of RGH-338 in healthy male volunteers.

Published: 20-02-2020
Last updated: 15-05-2024

To investigate the safety and tolerability, and to characterise the pharmacokinetics (PK) of RGH-338 in healthy subjects

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Developmental disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55280

**Source**
ToetsingOnline

**Brief title**
First-in-Human study of RGH-338

### Condition

- Developmental disorders NEC

**Synonym**
Autism spectrum disorder

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Gedeon Richter Plc.
**Source(s) of monetary or material Support:** Pharmaceutical Industry

## Intervention

**Keyword:** Autism, FIH, GABAB receptor, PAM

## Outcome measures

### Primary outcome

Tolerability / safety endpoints

Safety: vital signs, 12-lead safety ECG, physical examination, laboratory safety tests (routine haematology, biochemistry, urinalysis and coagulation), C-SSRS, concomitant medication and adverse events.

Tolerability: adverse events.

Pharmacokinetic endpoints

The following pharmacokinetic parameters of RGH-338 will be determined as applicable

Part 1: Cmax, Tmax, AUC0-t, AUC0-24, AUCinf, MRT, CL/F, VZ/F, t1/2.

Part 2: Cmax, Tmax, AUC0-t, AUC0-24, AUCinf, MRT, CL/F, VZ/F, t1/2

Part 3: For the first day of multiple dosing: Cmax, Tmax and AUCtau. For the last day of multiple dosing: Cmax, Tmax, Cmin, Cavg, AUC0-t, AUCtau, AUCinf, MRT, CL/F, V/F, t1/2, Fluctuation%, Rac.

Renal clearance and the cumulative amount of RGH-338 excreted in urine will be determined, if applicable.

### Secondary outcome

Pharmacodynamic endpoints

Part 1:

1. Heart rate corrected QT interval measured with 12-lead Holter ECG for precision QT analysis.

2. Changes in subjective sleep pattern assessed with Leeds Sleep Evaluation Questionnaire (LSEQ).

3. The NeuroCart CNS battery test will include the following core assessments to characterize RGH-338*s pharmacodynamic profile in SAD.

4. Dynamo hand-held dynamography (HHD)

5. Plasma growth hormone levels.

Part 3:

1. Heart rate corrected QT interval measured with 12-lead Holter ECG for precision QT analysis.

2. Changes in subjective sleep pattern assessed with Leeds Sleep Evaluation Questionnaire (LSEQ)

3. Polysomnography (PSG) will include, among others, the following parameters for analysis:

4. The NeuroCart CNS battery test consists of several assessments to characterize the pharmacodynamic profile of RGH-338 in parts 1 and 3.

5. The PainCart battery test (in Part 3) consists of several assessments to characterize the effect of RGH-338 on nociceptive (pain) detection and tolerance threshold

6. Dynamo hand-held dynamography (HHD)

7. Plasma growth hormone as a peripheral neuroendocrine biomarker for GABAB

receptor engagement.

# Study description

### Background summary

Autism spectrum disorder (ASD) is a neurodevelopmental condition that is typically recognized during the first 2-3 years of life but may not become fully manifested until social demands exceed limited capacities or may be masked by learned strategies in later life. The core symptoms of ASD include impaired socio-communicational and social interaction skills as well as repetitive behaviour and restricted thinking.

Recent human imaging data in ASD demonstrate reduced GABA-ergic neurotransmission with preservation normal gamma-aminobutyric acid (GABA) levels2. This is most likely the functional consequence of reduced GABA receptor expression despite a seemingly conserved GABA production. Under such conditions, a positive allosteric modulation (PAM) approach where a molecular partner (endogenous GABA) is needed for enhancing receptor activation is expected to boost GABA-ergic neurotransmission, and as a consequence, may reduce ASD-related symptoms. Specifically, a number of clinical, post mortem, and preclinical findings suggest that stimulation of the GABAB receptor may be relevant for treatment of the core symptoms of ASD.

The novel proprietary drug candidate RGH-338 is a potent, orally active and selective PAM of the GABAB receptor discovered and developed at Gedeon Richter Plc. for the treatment of ASD. RGH-338 has nanomolar affinity to a PAM binding site of the human recombinant and rat native GABAB receptors.
RGH-338 showed significant improvement in several endpoints of social behavior including social play, social approach-avoidance, and social recognition memory at the dose of 0.05 mg/kg and above in the prenatal valproic acid (VPA) model, a widely accepted disease model of ASD.

The results of preclinical studies suggest that RGH-338 has the potential to effectively alleviate the socio-communicational deficits, together with some of the associated symptoms of individuals with ASD with a satisfactory safety profile. All these data together support to proceed to investigation of the compound in humans. Additionally, enhancing GABA receptor function may have therapeutic benefit in treating other conditions, such as chronic pain.

### Study objective

To investigate the safety and tolerability, and to characterise the

pharmacokinetics (PK) of RGH-338 in healthy subjects

## Study design

The study will be conducted in three parts in healthy male participants:Part 1 SAD, Part 2 Food Effect, and Part 3 MAD.
Part 1 will evaluate single-ascending doses (SAD) of RGH-338 following an overnight fast using a single-dose, double-blind, randomized, placebo-controlled, dose-escalating design.
Part 2 will be an open-label, randomized, two-way crossover study to assess the effect of food on RGH-338 pharmacokinetics. Part 2 is intended to start following review of sufficient interim safety, tolerability, pharmacokinetic and pharmacodynamic data from Part 1. All subjects will receive one dose of RGH 338 after an overnight fast and another dose of RGH 338 after consumption of a high-fat breakfast, on two different occasions separated by a washout period of at least 2 weeks (or 5 times the half-life of RGH-338 determined in Part 1, whichever is longer.).
Part 3 will evaluate multiple-ascending doses of RGH-338 in healthy male volunteers.

## Intervention

RGH-338 or placebo (oral tablets) , starting dose of 0.05 mg in cohort 1 of Part 1, subsequent dose levels are to be determined following satisfactory review of the safety, tolerability, pharmacodynamic and pharmacokinetic data from previous cohorts.

## Study burden and risks

This phase 1 trial has been designed to mitigate the known risks associated with GABA potentiators as a class in general and the potential risks based on the nonclinical toxicity data RGH- 338 in particular. As this trial will be conducted in healthy male subjects, there is no expected clinical benefit to trial participants. The principal mitigations for these potential risks include the maintenance of an appropriate safety margin based on nonclinical study drug exposure, appropriate selection of the trial population, prespecified safety monitoring procedures, and the selection of the trial facility, where close monitoring can be performed and rapid institution of appropriate care canbe given. The potential risks associated with GABAB receptor potentiators as a class and the potential risk based on nonclinical toxicity data can be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical trial.

In addition to the potential risks associated with study drug administration, there is minimal risk associated with trial procedures including scheduled, periodic phlebotomy (limited to < 500 mL), pain tests and non-invasive

procedures including vital sign assessments, electrocardiograms (ECGs), and PD assessments. Overall, the benefit-risk profile is considered appropriate for this trial.

# Contacts

**Public**
Gedeon Richter Plc.

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Healthy male volunteers.
2. Aged 18*45 years (inclusive).
3. A body mass index (Quetelet index) in the range 18.5 * 30.0 kg/m2 (inclusive) as measured at screening.

### Exclusion criteria

1. Clinically relevant abnormal history, physical finding,12-lead safety ECG, or laboratory value at screening that could interfere with the objectives of the trial or the safety of the volunteer.
2. Family history of seizures or a clinically significant psychiatric disorder.
5. Risk of suicide, as judged by an Investigator, based upon available source information * including the C-SSRS or family history of suicide * indicating current suicidal ideation or a history of active suicidal ideation or suicide attempts.
28. Positive SARS-CoV-2 PCR analysis prior to first dosing.
29. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (such as disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy).
30. Participants indicating pain tests intolerable at screening. Participants achieving tolerance at >80% of maximum input intensity for cold pressor and electrical pain tests are to be excluded. If pressure pain test tolerance is >80% of maximum input intensity they may be enrolled as per PI judgement.

## Study design

### Design

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| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 12-03-2020 |
| Enrollment: | 200 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | RGH-338 |
| Generic name: | NA |

## Ethics review

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| Approved WMO Date: | 20-02-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 26-03-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-05-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 14-09-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-10-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-11-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

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| Approved WMO Date: | 17-04-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 06-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-06-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

ID: 23656
Source: Nationaal Trial Register
Title:

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2019-004694-15-NL |
| CCMO | NL72621.056.20 |
| OMON | NL-OMON23656 |