First-in-Human study of RGH-338

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Investigate the safety and tolerability, and to characterize the pharmacokinetics (PK) of RGH-338 in healthy subjects

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23656

Bron
Nationaal Trial Register

Verkorte titel
CHDR1943

Aandoening

Autism spectrum disorder

Ondersteuning

Primaire sponsor: Gedeon Richter Plc.
Overige ondersteuning: Sponsor

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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: Cmax, Tmax, AUC0-t, AUC0-24 and AUCtau will be determined for the first day of multiple dosing. For the last day of multiple
dosing Cmax, Tmax, Cmin, Cavg, AUC0-t, AUCtau, AUC0-24, AUCinf, MRT, CL/F, V/F, t1/2 and Fluctuation% will be calculated.
Renal clearance and the cumulative amount of RGH-338 excreted in urine will be determined, if applicable.

Toelichting onderzoek

Achtergrond van het onderzoek

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 gammaaminobutyric
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.

Doel van het onderzoek

Investigate the safety and tolerability, and to characterize the pharmacokinetics (PK) of RGH-338 in healthy subjects

Onderzoeksopzet

Baseline till EOS

Onderzoeksproduct en/of interventie

RGH-338 or placebo (oral tablets)

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.
4. Healthy as determined by a responsible physician, based on medical, surgical and psychiatric history at screening, and physical examination, vital signs, clinical laboratory tests

and 12-lead safety ECG at both screening and admission.
5. Non-smokers or subjects who have not smoked (or used any nicotine products) for at least 3 months before screening; negative cotinine test at screening and admission.
6. Agree to use effective contraception method and agree to not donate sperm, and not have their partner become pregnant or contact with sperm, throughout the study and for up to 3 months after the last administration of the IMP.
7. Agree not to donate blood or blood products during the study and for up to 3 months after the administration of the trial medication.
8. Sufficient intelligence to understand the nature of the trial and any hazards of participating in it, as judged by the Investigator. Ability to communicate satisfactorily with the Investigator and to participate in, and comply with the requirements of, the entire trial.
9. Willingness to give written consent to participate after reading the information and consent form, and after having the opportunity to discuss the trial with the Investigator or their delegate.
10. Willingness to give written consent to have data entered into “Verified Clinical Trials”.
11. Agree to avoid sunbathing or using a sunbed during the trial.
12. Agree to avoid any strenuous exercise from screening until follow-up.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Clinically relevant abnormal history, physical finding,12-lead safety ECG 12-lead safety ECG (e.g. PQ/PR interval > 210 ms , presence of Left Bundle Branch Block (LBBB), AV Block (second degree or higher), or a permanent pacemaker or implantable cardioverter defibrillator [ICD]), 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.
3. Personal history or presence of epilepsy, seizures, recent head trauma, severe head injury, unexplained blackouts, childhood febrile seizures, chronic pain or any other clinically significant chronic neurological condition or any clinically significant psychiatric disorder (including but not limited to diagnosed anxiety disorders or depression).
4. (Parts 1 and 3) History or current significant ophthalmologic or neurologic condition that would adversely affect the eye movement assessments.
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.
6. Diagnosis or suspicions of any sleep disorder in the last 6 months or current complaints of sleep disturbance or daytime symptoms attributable to unsatisfactory sleep. Shift workers (those whose routine work hours overlap with the typical sleep period).
7. Clinically relevant history or presence of respiratory, gastrointestinal (including lactose intolerance), renal, hepatic (including Gilbert’s syndrome), haematological, lymphatic, cardiovascular (including recurrent orthostatic hypotension, syncope, vasovagal attacks), musculoskeletal (including clinically relevant history or presence of muscular disorder), genitourinary, immunological, dermatological, connective tissue diseases or disorders sufficient to invalidate the volunteer’s participation in the trial or make it unnecessarily

hazardous.
8. QTc values measured at screening visit greater than 450 ms or lower than 340 ms on 12-lead ECG, using Fridericia's formula (QTcF) for correction. Triplicate measurements will be made at screening and predose, and any out-of-range reading on mean QTcF higher than 450 ms (M) will lead to exclusion.
9. Family history of long QT syndrome or sudden death.
10. Surgical history (e.g. stomach bypass) or medical condition that might affect absorption of medicines.
11. A history of any kind of hypersensitivity (eg. Drugs/excipients) or allergic reactions to any of the inactive ingredients contained in the active or placebo drug products, including compounds related to RGH-338.
12. Abnormal vital signs at screening or admission, after 5 minutes of rest in supine position, outside the following ranges:
-systolic blood pressure 90–140 mmHg;
-diastolic blood pressure 50–90 mmHg;
-pulse rate 45–100 beats/minute;
-tympanic temperature 35.4–37.8 °C;
-respiratory rate 8-20 breaths/min.
Borderline values (i.e. values that are above or below the criterion's defined range with 5 mmHg for blood pressure, 5 beats/min for pulse rate and 0.2 °C for body temperature) have to be repeated. Subjects can be included if the repeat value is within the range or still in the borderline range but deemed not clinically significant by the Investigator. For all other out of range vitals one repeat is allowed.
13. Clinically significant elevated values at screening or admission of AST, ALT or alkaline phosphatase (AP) ≥1.5 × ULN; bilirubin exceeding ULN.
14. Creatinine clearance <90 mL/min, according to the CKD-EPI formula. One repeat is allowed.
15. Presence or history of drug or alcohol use disorder (including abuse and dependence) in the last 5 years, or intake of more than 21 units of alcohol weekly; positive alcohol breath test or evidence of drug abuse on urine testing at screening or admission.
16. Caffeine intake of more than 6 cups of coffee, or equivalent (> 600 mg caffeine), daily.
17. Acute gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea, heartburn) within 1 week before the first dose of trial medication.
18. Any condition predisposing the volunteer to electrolyte imbalances (e.g. altered nutritional states, vomiting, anorexia nervosa, etc.) within 1 week before the first dose of trial medication.
19. Acute infection (e.g. influenza) or known inflammatory process within 1 week before the first dose of trial medication.
20. Use of a prescription medicine (including psycho-active medication, or medications known to have CNS effects) within 30 days before the first dose of trial medication, unless agreed by the Investigator and the Sponsor.
21. Use of an over-the-counter medicine herbal remedy, multi-vitamin preparation or any other products likely to interfere with the safety of the subject or interpretation of the data within 7 days of the first dose of trial medication. Acetaminophen [paracetamol] use is exclusionary if more than 2,000 mg is taken on any day during the 7 days before admission, or it was taken more than 3 days during the 7 days before admission.
22. Receipt of an investigational drug as part of another clinical trial within 3 months (or 5

halflives, whichever is longer) before admission to this study; in the follow-up period of another clinical trial at the time of screening. Have previously received RGH-338.
23. Received a strong CYP3A4 inhibitor (e.g. clarithromycin, itraconazole, or ketoconazole) or inducers (e.g. rifampicin) within 30 days before the first dose of trial medication.
24. Positive test for hepatitis B, hepatitis C or HIV.
25. Donated and/or received any blood or blood products or blood loss of more than 500 mL (e.g. through surgery) within 3 months before screening.
26. For Part 3 only: Contraindication to conduct TMS-EMG-EEG (including, but not restricted to, a history of epilepsy or febrile seizures, having metal objects in brain or skull, having a cochlear implant or implanted deep brain stimulator, resting motor threshold (rMT) of more than 75% of the maximum stimulator output) as measured using TMS-EMG during screening.
27. Unsuitable veins for cannulation and/or repeated venepuncture.
28. Any other condition that, in the Investigator's opinion, might indicate that the subject is unsuitable for the study (e.g. information provided by the General Practitioner, if available).
29. Positive SARS-CoV-2 PCR analysis prior to first dosing.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	09-03-2020
Aantal proefpersonen:	200
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Toelichting
N.a.

Ethische beoordeling

Positief advies

Datum:	28-09-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 55280
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8930
CCMO	NL72621.056.20
OMON	NL-OMON55280

Resultaten

Samenvatting resultaten
N.a.