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Clonazepam in patients with ARID1B-related intellectual disability

Submission date
06/09/2022

Recruitment status
No longer recruiting

Registration date
07/09/2022

Overall study status
Completed

Last Edited
02/01/2025

Condition category
Mental and Behavioural Disorders

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol

Background and study aims
Intellectual disability (ID) is one of the most frequent neurodevelopmental disorders and affects up to 2-3% of the population. Mutations in ARID1B are found to be the most frequent cause of ID, explaining about 1% of the patients. Besides non-specific ID, ARID1B mutations have been identified in a high proportion (>50%) of patients with a clinical diagnosis of Coffin-Siris syndrome. This condition is characterized by delayed development, abnormalities of the fifth (pinky) fingers or toes, and characteristic facial features that are described as coarse. Although there are no good estimates of incidence and prevalence, ~50 patients with ARID1B mutations are currently known in the LUMC's expertise center. Worldwide the largest group of described patients consists of 143. Except for supporting therapies such as physiotherapy and speech therapy, no treatment options are available for ARID1B patients.

Clonazepam (Rivotril) is a well-known and safe drug used to treat epilepsy in children and adults and occasionally for behavioral problems. Studies in laboratory animals indicate that clonazepam may be effective in the condition ARID1B-related intellectual disability. Plasma sampling is not desirable in the ARID1B patient population, therefore we will first establish the relations between clonazepam plasma concentrations and saliva in healthy volunteers in Part A. Such correlation was previously established for diazepam.
The study will continue with Part B, a two-way crossover study evaluating the effects of clonazepam in patients with ARID1B-related intellectual disability. We will do this by conducting a number of questionnaires and performing neurological tests after the use of clonazepam.

Who can participate?
Part A: 20 Healthy male or female volunteers
Part B: 20 ARID1B patients.

What does the study involve?
Part A. Open label study in 20 healthy volunteers where pharmacokinetics of clonazepam will be measured in paired plasma and saliva samples.
Part B. Two-way cross over, placebo-controlled randomized study in patients with ARID1B-related intellectual disability. Each period will be 22 days and periods will be separated by a three-week washout. Patients will be monitored in the clinic for 5 hours for safety, PK, and

biomarker effects on day 1 and 22 in both periods. Between those days, patients remain at home and fill in questionnaires and wear digital technologies.

What are the benefits and risks of participating?
Potential benefit consists of improvement of behaviour and/or cognitive function. The burden consist of potential experience of side effects of clonazepam, and the burden of the non-invasive study procedures. The study is group related since treatment effects on ARID1B-related intellectual disability can only be assessed by treating patients with this disease.

Where is the study run from?
Centre for Human Drug Research (The Netherlands)

When is the study starting and how long is it expected to run for?
February 2020 to June 2022

Who is funding the study?
CHDR and ZonMW (The Netherlands)

Who is the main contact?
R. (Rob) Zuiker, MD, PhD, Principal Investigator, clintrials@chdr.nl

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2019-003558-98

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CHDR1939

Study information

Scientific Title
Randomized, double-blind, placebo-controlled, two way crossover, single centre study evaluating the acute and chronic effect of clonazepam on cognitive tests and patient-reported outcome measures in patients with ARID1B-related intellectual disability

Acronym
CARE study

Study objectives
Clonazepam administration has acute beneficial effects on neurocognitive tests and multiple-doses clonazepam has beneficial effects on behaviour and cognitive function in ARID1B patients as measured by the ABC and CGI-I scale.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/02/2020, Stichting Beoordeling Ethiek Biomedisch Onderzoek (stichting BEBO, Dr. Nassaulaan 109401 HK ASSEN, The Netherlands; +31592405871; info@stbebo.nl), ref: NL71395.056.19

Study design
Open-label study followed by a two-way cross over placebo-controlled randomized study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
ARID1B-related intellectual disability

Interventions
Part A (open-label study)
• Clonazepam (Rivotril) droplets for oral use, solution 2.5 mg/ml, dissolved in lemonade. Dose: 0.5 mg or 1 mg, both administered to 50% of subjects.

Part B (randomised cross-over study)
• Active medication. Clonazepam (Rivotril) droplets for oral use, solution 2.5 mg/ml, dissolved in lemonade, tea or juice.
• Placebo: dissolved in lemonade, tea or juice

Study drug or placebo during part B will be administered to the subjects as follows:
- Day 1-3: Starting dose is 0.005 mg/kg, twice daily (max 0.5 mg, twice daily)
- Day 4-6: 0.01 mg/kg, twice daily (max 0.5 mg, twice daily)
- Day 7-22: 0.015 mg/kg, twice daily (max 0.5 mg, twice daily)
At the end of the study period, clonazepam will be tapered by decreasing the daily dose by 0.01 mg/kg/day every three days.

The randomization code was generated by a study-independent statistician on-site. The randomization code was unblinded/broken and made available for data analysis only after study closure. The randomization code was kept strictly confidential. Sealed individual randomization codes, per subject and per treatment, were placed in a sealed envelope containing the labelled 'emergency decoding envelopes' and kept in a safe cabinet on-site.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Clonazepam

Primary outcome measure
1. Pharmacokinetic endpoints
Part A: serum and saliva at baseline, 0.5h, 1h, 2h, 4h, 6h, 8h, 24h and 48h post-dose. Part B: saliva only at baseline, 4.5h n 5h post-dose on Day 1 and Day 22 for study periods 1 en 2.
1.1. The maximum serum concentration, Cmax
1.2. The time to reach maximum serum concentration, tmax
1.3. The terminal disposition rate constant (λz) with the respective half-life, t½
1.4. The area under the serum concentration-time curve from zero to infinity, AUC0-inf
1.5. The area under the serum concentration-time curve from zero to t of the last measured
1.6. concentration above the limit of quantification, AUC0-last
1.7. Clearance, Cl
1.8. Volume of distribution, Vz

2. Trial@home endpoints (Part B) performed at home from Day 1-Day 22 for study periods 1 and 2: Continuous physical activity, heart rate and sleep monitoring, as well as twice-weekly finger tapping, adaptive tracking and animal fluency.
2.1. Physical activity (daily)
2.2. Sleep (duration, %light sleep, amount of times woken up) (daily)
2.3. Heart rate (daily)
2.4. Daily symptom scores (daily)
2.5. Tapping frequency, adaptive tracking, animal fluency (twice-weekly)

3. Pharmacodynamic endpoints (Part B) at baseline, 1h, 3h, 5h post-dose on Day 1 and Day 22 for study periods 1 en 2.

3.1. NeuroCart
3.2. Adaptive Tracking
3.3. Animal fluency test
3.4. Body Sway
3.5. Saccadic Eye Movements
3.6. Smooth Pursuit Eye Movements
3.7. Tapping frequency

4. Questionnaires (Part B) at baseline at Day 1 and Day 22 for study periods 1 en 2.
4.1. ABC questionnaire (parents, teacher)
4.2. Clinician's Global Impression of improvement (CGI-I)

5. Tolerability / safety endpoints
5.1. Adverse events at dosing, 1h, 3h and 5h post-dose, evaluation by phone at Day 3 and Day 6 and when needed.
5.2. Vital signs measurements at baseline
5.3. General physical examination findings on indication during the study

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
10/02/2020

Completion date
03/06/2022

Eligibility

Key inclusion criteria
Part A: healthy volunteers
1. Healthy male or female volunteers aged 18-30 years.
2. Informed consent provided by volunteer.

Part B: ARID1B patients.
1. Informed consent provided by both parents, or the legal guardian prior to any study mandated procedure.
2. Known mutation in ARID1B.
3. Assent provided by the participant.
4. Aged 6 years or older.

Participant type(s)
Mixed

Age group
Mixed

Lower age limit
6 Years

Upper age limit

30 Years

Sex
Both

Target number of participants
40

Total final enrolment
36

Key exclusion criteria
Part A: healthy volunteers
1. Disorder that could interfere with saliva production.
2. Known hypersensitivity to clonazepam, other benzodiazepines or other excipients of the study medication.
3. Treatment with another investigational drug within 3 months prior to screening or more than 4 times a year.
4. History or clinical evidence of any disease and/or existence of a surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion of the study drug.
5. History of severe respiratory problems or severe liver- or renal insufficiency.
6. Other medical or psychosocial condition or history making the participant unsuitable for participation.
7. History or clinical evidence of alcoholism within the 3-year period prior to screening (i.e. regular use of more than 21 units of alcohol/week).
8. Clinically significant findings on physical examination.
9. Medications with a strong influence on CYP3A4 metabolism.
10. Clinically meaningful blood loss (including blood donation), or a transfusion of any blood product within 12 weeks before screening.

Part B: ARID1B patients.
1. Clear indication of not wanting to participate during the study.
2. Use of benzodiazepines or any other medication or drug with the potential to influence study related endpoints in the investigator’s opinion (including e.g. CYP3A4-related drugs).
3. Known hypersensitivity to clonazepam, other benzodiazepines or other excipients of the study medication.
4. History of severe respiratory problems or severe liver- or renal insufficiency.
5. Other medical or psychosocial condition or history making the participant unsuitable for participation as determined by the treating physician or general practitioner.

Date of first enrolment
10/02/2022

Date of final enrolment
03/05/2022

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
Zernikedreef 8
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Sponsor information

Organisation
Centre for Human Drug Research

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Sponsor type
Research organisation

Website
https://chdr.nl/

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Research organisation

Funder Name
Center for Human Drug Research

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
03/06/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other files	Adverse Events Listing	04/08/2022	30/01/2023	No	No
Other files	Demographics and Baseline Characteristics	04/08/2022	30/01/2023	No	No
Other files	Statistical appendix ABC data	18/01/2023	30/01/2023	No	No
Other files	Statistical appendix CGI data	18/01/2023	30/01/2023	No	No
Other files	Statistical appendix Drug concentration data	19/10/2022	30/01/2023	No	No
Other files	Statistical appendix Drug concentration data individual subjects	05/10/2022	30/01/2023	No	No
Other files	Study Participants and Safety Data	04/08/2022	30/01/2023	No	No
Other files	Subject Disposition	04/08/2022	30/01/2023	No	No
Protocol file	version 6	21/01/2022	30/01/2023	No	No
Results article		01/05/2022	30/01/2023	Yes	No

Dataset	Excel	24/02/2023	27/02/2023	No	No
Other files	Analysis of pharmacodynamic parameters	16/12/2022	11/09/2023	No	No
Results article		31/12/2024	02/01/2025	Yes	No