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

Published: 08-01-2020
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* To test the hypothesis that clonazepam administration has acute beneficial effects compared to placebo on body sway, adaptive tracking, smooth eye pursuit, tapping frequency and the animal fluency test.* To test the hypothesis that multiple-doses...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON52899

Source
ToetsingOnline

Brief title
Clonazepam in ARID1B Evaluation (CARE study)

Condition

- Mental impairment disorders

Synonym
ARID1B syndrome, ARID1B-related intellectual disability

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR-sponsored study

Intervention

Keyword: ARID1B, clonazepam, cognitive tests

Outcome measures

Primary outcome

Pharmacokinetic endpoints

Part A: serum and saliva. Part B: saliva only.

* The maximum serum concentration, Cmax

* The time to reach maximum serum concentration, tmax

* The terminal disposition rate constant (*z) with the respective half-life, t*

* The area under the serum concentration-time curve from zero to infinity,

AUC0-inf

* The area under the serum concentration-time curve from zero to t of the last

measured concentration above the limit of quantification, AUC0-last

* Clearance, Cl

* Volume of distribution, Vz

Trial@home endpoints

* Physical activity

* Sleep (duration, %light sleep, amount of times woken up)

* Heart rate

* Daily symptom scores

* Tapping frequency, adaptive tracking, animal fluency (twice-weekly)

Pharmacodynamic endpoints

* NeuroCart

o Adaptive Tracking

o Animal fluency test

o Body Sway

o Saccadic Eye Movements

o Smooth Pursuit Eye Movements

o Tapping frequency

* Questionnaires

o ABC questionnaire (parents, teacher)

o Clinician*s Global Impression of improvement (CGI-I)

Tolerability / safety endpoints

* Adverse events

* Vital signs measurements

* General physical examination findings

Secondary outcome

NA

Study description

Background summary

Clonazepam is a registered and safe drug which is being used for the treatment of epilepsy. Preclinical experiments show that clonazepam rescues some of the preclinical phenotypes in ARID1B +/- mice. There is currently no treatment for ARID1B-related intellectual disability. The aim of this study is to assess the efficacy and safety of clonazepam in patients with ARID1B-related intellectual disability.

Study objective

* To test the hypothesis that clonazepam administration has acute beneficial effects compared to placebo on body sway, adaptive tracking, smooth eye pursuit, tapping frequency and the animal fluency test.
* To test the hypothesis that multiple-doses clonazepam has beneficial effects compared to placebo on behaviour and cognitive function in ARID1B patients as measured by the ABC, and CGI-I scale.
* Assess safety and tolerability of clonazepam in ARID1B patients.
* To explore the feasibility of using saliva PK to predict plasma PK
* To assess the potential of at-home neurocognitive tests for the evaluation of treatment effects in children with neurodevelopmental disorders.
* To assess and compare the difference in predictive capability between linear and nonlinear (NONMEM) regression of the saliva:plasma relationship.

Study design

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.

Intervention

Clonazepam and placebo

Study burden and risks

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Part A, correlation blood-saliva PK.
* Healthy male or female volunteers aged 18-30 years
* Informed consent provided by volunteer

Part B: ARID1B patients.
* Informed consent provided by both parents, or the legal guardian prior to any study mandated procedure.

* Known mutation in ARID1B
* Assent provided by the participant.
* Aged 6 years or older

Exclusion criteria

Part A, healthy volunteers
* Disorder that could interfere with saliva production.
* Known hypersensitivity to clonazepam, other benzodiazepines or other excipients of the study medication.
* Treatment with another investigational drug within 3 months prior to screening or more than 4 times a year.
* 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.
* History of severe respiratory problems or severe liver- or renal insufficiency.
* Other medical or psychosocial history making the participant unsuitable for participation as determined by the treating paediatrician.
* 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).
* Clinically significant findings on physical examination.
* Medications with a strong influence on CYP3A4 metabolism
* Clinically meaningful blood loss (including blood donation), or a transfusion of any blood product within 12 weeks before screening.
* Subjects with a BMI > 30 and/or cardiovascular, respiratory or immune system disorders

Part B: ARID1B patients.
* Clear indication of not wanting to participate during the study
* 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).
* Known hypersensitivity to clonazepam, other benzodiazepines or other excipients of the study medication.
* History of severe respiratory problems or severe liver- or renal insufficiency.
* Other medical or psychosocial history making the participant unsuitable for participation as determined by the treating paediatrician.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-07-2020
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	clonazepam
Generic name:	clonazepam
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	10-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	03-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2022
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: 29120
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-003558-98-NL
CCMO	NL71395.056.19
OMON	NL-OMON29120