Guanabenz in VWM

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24121

Source
Nationaal Trial Register

Brief title
VWM1

Health condition

Vanishing White Matter (VWM)

Childhood ataxia with central nervous system hypomyelination (CACH)

Sponsors and support

Primary sponsor: Amsterdam University Medical Centers, location VUmc, De Boelelaan 1117, 1081HV Amsterdam
Source(s) of monetary or material Support: Spinoza award
ZonMw
European Leukodystrophy Association
Nederlandse Hersenstichting
Private donations

Intervention

Outcome measures

Primary outcome

• All adverse events and serious adverse events collected from the start of study treatment until the end of the study, applying the most recent version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, 27-Nov-2017), as well as applying:
- Scales to specifically monitor the 2 most important adverse events in children (daytime drowsiness and headache): the PDSS and the Faces Pain Scale to grade headache.
- A scale to grade the impact of adverse events on daily life.

Secondary outcome

• Guanabenz PK parameters in plasma, such as maximum plasma concentration (Cmax), area under the plasma concentration-time curve (AUC), half-life, and predicted trough concentration (Ctrough) at steady state
• Quantitative brain MRI parameters: Diffusion Tensor Imaging (DTI), Chemical Shift Imaging (CSI), Neurite Orientation Dispersion and Density Imaging (NODDI), Myelin Water Fraction Imaging (MWFI)
• Clinical parameters: Health Utility Index (HUI), Euro-Quality of Life Instrument 5D, 5 levels (EQ-5D-5L), Euro-Quality of Life Instrument 5D, 5 levels (EQ-5D-Y), Vineland Adaptive Behavior Scales, 3rd edition (Vineland-3), Gross Motor Function Measure (GMFM), Leiter International Performance Scale (LIPS), Gross Motor Function Classification for Metachromatic Leukodystrophy (GMFC-MLD), Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Expressive Language Function Classification for Metachromatic Leukodystrophy (ELFC-MLD), Communication Function Classification System (CFCS) and Eating and Drinking Ability Classification System (EDACS)
• Overall survival

Study description

Background summary

Rationale:
Vanishing white matter (VWM) is a rare and devastating leukodystrophy (genetic brain white matter disorder). The incidence in The Netherlands is approximately 1 per 100,000 live births; the prevalence is approximately 1.2 per million inhabitants. The disease course is variable with age of onset being a key factor. Patients with a disease onset before the age of 6 years represent the majority of the cases (~70%) and have a fast disease course with rapid neurological decline and short life expectancy. The disease course is more variable and often more protracted (but still fatal) for patients with a disease onset from the age of 6 years onwards. Such patients may survive for a few years to several decades. There is no known effective treatment for VWM.
The VWM genetic defect leads to an abnormal activation of the integrated stress response (ISR). Guanabenz is an alpha2-adrenergic antihypertensive drug with proven safety in adults. Evidence also supports safe use in children aged 12 years and older. Recently, guanabenz has been shown to impact the ISR and currently is the only registered drug with a known

effect on the ISR. The ameliorating effect of guanabenz on VWM has been substantiated in a VWM mouse model representative for the human disease.

Study objectives
Primary objective
• To evaluate the safety and tolerability profile of guanabenz in pediatric patients with VWM.
Secondary objectives
• To evaluate the pharmacokinetic (PK) profile of guanabenz in pediatric patients with VWM.
• To evaluate how quantitative MRI parameters relevant to brain white matter integrity change over time in pediatric patients with VWM receiving guanabenz.
• To evaluate how quality of life and disability change over time in pediatric patients with VWM receiving guanabenz as compared to historical controls.
• To evaluate overall survival in pediatric patients with VWM receiving guanabenz as compared to historical controls.
Exploratory objectives
• To perform exploratory PK-covariate and PK/pharmacodynamic (PD) analyses.
• To perform exploratory biomarker analyses in blood and cerebrospinal fluid (CSF).

Study design:
This is an open-label, non-randomized study with historical control group, in which patients will receive guanabenz in addition to their usual standard of care. Patients will be titrated to the guanabenz study dose while carefully being monitored for adverse events. A minimum of 20 and a maximum of 40 VWM patients is planned to be enrolled. Every 6 months after the start of the study, an independent Data Safety Monitoring Board (DSMB) commissioned for this study will review all safety and PK data available at that time. The study will continue per DSMB recommendation.
Historical controls (N=296) are available and will be matched as much as possible to the study population based on age at disease onset and disease duration at study entry.

Study population:
Patients with genetically proven VWM and a brain MRI compatible with the diagnosis are eligible if they have a disease onset below the age of 6 years, are still able to stand up and walk at least 10 steps with or without light support of one hand, and have a maximum disease duration of 8 years at study entry.

Intervention:
The investigational medicinal product (IMP) is guanabenz ([(2,6-dichlorobenzylidene)amino] guanidine monoacetate), which was marketed in the United States and Europe for treatment of hypertension in adults. Depending on the individual tolerability and safety profile, patients will be titrated to the highest tolerated dose, with a target dose of 2 mg/kg/day, a minimum dose of 1 mg/kg/day and a maximum dose of 10 mg/kg/day, given orally in a single dose before sleep for a duration of at least 1 year. All patients will remain in the trial till the end, with a trial duration of 4 years. So, the duration of the intervention will depend on the time of entry during the trial.

Study endpoints:
1. Primary endpoint

• All adverse events and serious adverse events collected from the start of study treatment until the end of the study, applying the most recent version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, 27-Nov-2017), as well as applying:
- Scales to specifically monitor the 2 most important adverse events in children (daytime drowsiness and headache): the Pediatric Daytime Sleepiness Scale (PDSS) and the Faces Pain Scale to grade headache.
- A scale to grade the impact of adverse events on daily life.
2. Secondary endpoints
• Guanabenz PK parameters in plasma, such as maximum concentration (Cmax), area under the concentration-time curve (AUC), half-life, and predicted trough concentration (Ctrough) at steady state
• Quantitative brain MRI parameters: Diffusion Tensor Imaging (DTI), Chemical Shift Imaging (CSI), Neurite Orientation Dispersion and Density Imaging (NODDI), Myelin Water Fraction Imaging (MWFI)
• Clinical parameters: Health Utility Index (HUI), Euro-Quality of Life Instrument 5D, 5 levels (EQ-5D-5L), Euro-Quality of Life Instrument 5D, 5 levels (EQ-5D-Y), Vineland Adaptive Behavior Scales, 3rd edition (Vineland-3), Gross Motor Function Measure (GMFM), Leiter International Performance Scale (LIPS), Gross Motor Function Classification for Metachromatic Leukodystrophy (GMFC-MLD), Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Expressive Language Function Classification for Metachromatic Leukodystrophy (ELFC-MLD), Communication Function Classification System (CFCS) and Eating and Drinking Ability Classification System (EDACS)
• Overall survival
3. Exploratory endpoints
• The relationship between guanabenz PK and safety/efficacy-related biomarkers, such as blood pressure, heart rate and MRI-based quantitative (continuous) markers of change in brain white matter integrity, in an exploratory PK/PD analysis.
• Exploratory search for biomarkers in body fluids.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Based on (1) the effect of guanabenz on the ISR, (2) results of previous studies using guanabenz in nonclinical models of human neurodegenerative disorders characterized by abnormal activation of the ISR, and (3) results of a guanabenz study in a mutant mouse model that is representative of human VWM disease, guanabenz may ameliorate VWM in patients.
As by far most VWM patients have an early childhood disease onset, the present study cannot be conducted without participation of patients belonging to this group. The strongest beneficial effects of guanabenz on the neurological phenotype are expected to occur in children with severe disease, early in the disease course, when the brain white matter is still relatively intact.
In addition to the intake of guanabenz, the burden of study participation includes:
• Regular (every 3 months) control visits to the study site for physical and neurological examinations, 10-step walk test, body temperature, blood pressure and heart rate measurements, and capillary blood draws (blood spots on filter paper) for monitoring guanabenz intake and PK assessments.

• If travel is not possible or considered high risk because of the COVID-19 pandemic, the control visits, except for the first visit at 3 months, the annual visits and the last visit, can be replaced by video consultations, which allow global assessment of the physical and neurological condition of the child and the 10-step walk test. Body temperature, blood pressure and heart rate measurements will then be obtained through a local physician (general practitioner or pediatrician). The capillary blood draws for blood spots on filter paper can be performed by the patient's parents/legal guardians or the local physician. The parents/legal guardians will receive instructions on how to obtain and send the blood spots to the study site.
• Brain MRI scans (annually). The MRI procedures will take place under superficial anesthesia aiming at spontaneous respiration. At the sites participating in this study, annual MRI scans under superficial anesthesia are routine practice for patients with a leukodystrophy, including VWM.
• Blood sampling for monitoring guanabenz intake, PK assessments, safety laboratory testing and biomarker analyses. All samples but one will be collected from the intravenous infusion line placed for propofol anesthesia during the MRI assessments. Only at 3 months a separate vena puncture is needed for safety laboratory testing (this visit cannot be replaced by a video consultation).
• CSF sampling for biomarker analyses when the patient is under anesthesia for MRI.
• Annual assessments (by standard questionnaires and scales) of quality of life and disability (these visits cannot be replaced by a video consultation).
Evidence suggests that adverse reactions to guanabenz are dose-related. Patients will be titrated to their highest tolerated dose (target dose: 2 mg/kg/day; minimum: 1 mg/kg/day; maximum: 10 mg/kg/day) while carefully being monitored for adverse events. Given the relatively short half-life of guanabenz (6 hours), adverse reactions are expected to subside rapidly after a dose reduction.

Study objective

Guanabenz is a safe and tolerable drug in young children en it ameliorates the disease course in patients with VWM

Study design

1 year, 2 years, 3 years, 4 years

Intervention

Guanabenz

[(2,6-dichlorobenzylidene)amino] guanidine monoacetate

Contacts

Public
Amsterdam University Medical Centers, location VU University Medical Center
Marjo S. van der Knaap

31 20 4441130
Scientific
Amsterdam University Medical Centers, location VU University Medical Center
Marjo S. van der Knaap

31 20 4441130

Eligibility criteria

Inclusion criteria

1. Each patient’s parents/legal guardians must sign an informed consent form (ICF) indicating that they understand the purpose of and procedures required for this study, are willing for their child to participate in the study and attend all scheduled assessments (on site or by video consultation as indicated per protocol), and are willing and able to comply with all study-related procedures, including maintaining contact with the site for at least 1 year, and adhere to the prohibitions and restrictions as specified in the protocol.
Note: For each patient, both parents/legal guardians must give written consent.
2. Male or female who has a maximum disease duration of 8 years.
3. Genetically proven VWM with 2 clinically relevant mutations in one of the EIF2B1-5 genes and a brain MRI compatible with the diagnosis.
4. Disease onset before the age of 6 years.
5. Able to stand up and walk at least 10 steps with or without light support of one hand.
6. Lives within reasonable travel distance from Amsterdam.

Exclusion criteria

1. Clinically asymptomatic.
2. Comorbidity with another genetic defect.
3. Presence of an unrelated serious condition (eg, developmental anomaly, cardiac, liver or kidney disease).
4. Participation in another clinical study with therapeutic intervention.
5. Unable or unwilling to come to the study site as required by the protocol.
6. Unable to undergo MRI due to metal-containing implants, such as cochlea implant, neurostimulator or pacemaker.
7. Family situation in which adherence to the study medication or follow-up procedures

cannot be guaranteed.
8. Known allergy or hypersensitivity to guanabenz or to any of the other components of the formulation used in this study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2021
Enrollment:	30
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
Individual participant data that underlie the results reported in this article (text, tables, figures, and appendices) will be available after deidentification. Study protocol, statistical analysis plan, and analytic code will be available beginning 3 months and ending 5 years following article publication to researchers who provide a methodologically sound proposal. Analyses applied are those to achieve aims in the approved proposal. Proposals should be directed to ms.vanderknaap@amsterdamumc.nl. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at https://www.vumc.com/departments/center-for-children-with-white-matter-disorders.htm.

Ethics review

Positive opinion

Date:	16-09-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
NTR-new	NL7260
NTR-old	NTR7482
Other	2017-001438-25 : EudraCT

Study results