

A first trial of Guanabenz in Vanishing White Matter

The Center for Childhood White Matter Disorders (CCWMD, <https://www.vumc.com/departments/center-for-children-with-white-matter-disorders.htm>) at the Amsterdam University Medical Centers (Amsterdam UMC), location VU University medical center (VUmc) is planning to conduct a clinical trial in children with Vanishing White Matter (VWM). Location Academic Medical Center (AMC) is a participating center and the trial can also be executed there. In this trial, we want to evaluate whether a drug called Guanabenz is effective in slowing progression, stabilizing or even improving the brain white matter abnormalities in VWM.

Guanabenz is an old and well-known medicine that has been used for decades for the treatment of high blood pressure. It has been approved by the FDA, the American medicines agency. Given the mechanism of action of Guanabenz, we estimated it likely to be beneficial in VWM. We have laboratory mice with VWM and have treated them with Guanabenz. The results indicate that long-term high-dose Guanabenz treatment ameliorates VWM in these mice and leads to both important improvement of motor function and amelioration of brain pathology (for further information, see <https://onlinelibrary.wiley.com/doi/epdf/10.1111/nan.12411>). Because we have shown previously that the disease mechanism of VWM and the mode of action of Guanabenz are the same in mice and patients, our expectation is that long-term treatment with high doses of Guanabenz could also be beneficial in patients with VWM. However, mice are different from humans and the effect of Guanabenz in humans with VWM still has to be investigated. As Guanabenz has been used for years by adults for treatment of high blood pressure and has proven to be safe in this patient population, and research also supports the safe use of Guanabenz in teenagers, we want to treat children with VWM with Guanabenz.

Who can take part in the trial?

A patient is eligible for participation in the trial if he/she meets the following criteria:

- genetically proven VWM
- brain MRI abnormalities consistent with VWM
- at the time of study entry, a maximum disease duration of 8 years
- VWM disease started before the age of 6 years
- able to stand up and walk at least 10 steps, with or without some support
- not suffering from another significant disease (eg, heart, liver or kidney disease)
- not participating in another medical-scientific study
- able to undergo MRI examination (ie, no presence of metal-containing implants, such as cochlea implant, neurostimulator or pacemaker)
- living within reasonable travel distance from Amsterdam

When all of these eligibility criteria are met, we can start the process of evaluating whether the child can participate in the trial.

Parents/guardians or treating physicians can contact us to discuss whether the child can participate in the trial. To start the process, we would first need clinical information, results of the genetic test confirming VWM, and the MRIs of the child. Feel free to contact us at TreatVWM@amsterdamumc.nl.

What does taking part in the trial mean?

The primary aim of the trial is to evaluate the safety, tolerability and pharmacokinetics (what the body does to a drug) of Guanabenz when given to young children with VWM. In addition, the trial will investigate whether treatment with Guanabenz has a potential beneficial effect on VWM. All children in the trial will receive Guanabenz in addition to their standard medical care. Because there are no biomarkers in body fluids known in VWM that allow monitoring of the disease, we will also use the study to search for suitable biomarkers.

The duration of the trial will be at least 1 year but may be extended to 3 or 4 years, depending on how fast the planned number of 20 patients can be enrolled in the study. Guanabenz must be taken once daily, in the evening, during the whole trial period. All children in the trial will also undergo various tests; these are briefly described below (see *Timeline*).

The trial will take place at VUmc or AMC in Amsterdam. This means that children who participate in the trial must come to Amsterdam for control visits.

Timeline

- Contact with the CCWMD in Amsterdam.
- Screening for eligibility at VUmc or AMC in Amsterdam, including physical and neurological examination.
- If it is confirmed that the patient is a suitable candidate and parents/caregivers consent for participation, the patient will undergo a brain MRI (under light anesthesia) and the investigator will fill out several standard questionnaires to evaluate quality of life and disability. Motor and cognitive function will also be assessed. Before, during and after the MRI procedure, blood samples will be collected at regular intervals. The blood samples will be collected from a vein and by finger pricks. The blood sampling from a vein will be done via the infusion line of the MRI anesthetic; there will be no extra needle sticks for this. During anesthesia a lumbar puncture (spinal tap) will also be performed for biomarker searches.
- Guanabenz treatment will be started at a low dose in a day-care setting at the Department of Pediatrics at VUmc or AMC. The dose will be increased every 3 days (or more slowly, depending on side effects) and body temperature, blood pressure, heart rate, and side effects will be carefully monitored. As soon as the study dose is reached and Guanabenz is well tolerated, the patient can go home.
- Every 3 months a control visit will take place at VUmc or AMC to check for possible side effects and use of other medications, and to perform physical and neurological examinations, body temperature, blood pressure and heart rate measurements, and blood sampling (from a vein on one occasion and by finger pricks at other occasions – all without anesthesia).
- If traveling to Amsterdam is too risky or impossible due to the COVID-19 pandemic, visits may be replaced by video consultations, which allow assessment of the general physical and neurological condition of the patient. We will ask the parents/caregivers to have their local general practitioner or pediatrician to measure body temperature, blood pressure and heart rate. We will also ask the parents/caregivers to obtain a blood spot by finger prick or to have this done by the local general practitioner or pediatrician. The parents/caregivers will then be asked to send us the blood spot in a return envelope. Only the first 3-monthly control visit cannot be replaced by a video consultation, because of the blood sampling from a vein at that visit. The yearly visits with extensive testing must also take place in Amsterdam.
- In addition, parents/caregivers will be asked to keep a diary to document information on the patient's ability to walk, occurrence of side effects, and use of other medications during the study. The diary will be provided by the investigator.
- After 1 year of study treatment, the brain MRI (under light anesthesia and including blood draws and a spinal tap), the standard questionnaires to evaluate quality of life and disability, and the assessment of motor and cognitive function will be repeated. If the patient remains in the study for more than 1 year, MRIs (under light anesthesia and including blood draws and a spinal tap), questionnaire collection and the assessment of motor and cognitive function will be repeated annually.

The study-related visits will partly replace the regular follow-up visits of the patient and partly are additional.

To our knowledge, this will be the first trial in which guanabenz is used in young children. The safety of Guanabenz will therefore be carefully monitored throughout the entire study. As it is still unclear whether young children will tolerate higher doses of Guanabenz, dose titration will take place under intensive supervision.

Possible side effects of Guanabenz

In the treatment of high blood pressure, the main side effects of Guanabenz are drowsiness, dry mouth and headache. To avoid daytime sleepiness as much as possible, Guanabenz will be taken once a day before sleep in the current study. Blood pressure may be lowered; this is not dangerous, but may lead to complaints such as dizziness, feeling of weakness and feeling tired. In adults dizziness is common, but this has not been reported in children. Because in the current study, the Guanabenz dose used is higher than for high blood pressure, we expect all side effects to be more common. If side effects are present, they generally disappear when the dose of the drug is lowered or drug intake is discontinued. Patients usually get accustomed to the drug and side effects will disappear.

Additional information

More information about the trial can be found in the documents available on this page.

For more information about VUmc and AMC, refer to www.vumc.com and www.amc.nl.

How to contact us?

You can contact us, preferably by e-mail: TreatVWM@amsterdamumc.nl.