E1/E2: Subject information for participation in medical scientific research

A first trial of Guanabenz in Vanishing White Matter

Official title: A study to explore the safety, tolerability, pharmacokinetic profile, and potential efficacy of Guanabenz in patients with early-childhood onset Vanishing White Matter (VWM)

Introduction

Dear Sir/Madam,

You are asked to take part in a medical-scientific study. Participation is voluntary. Participation requires your written consent. You have received this letter, because you have a child or are the legal guardian of a child with a disease called “Vanishing White Matter” (in brief “VWM”). In both cases the child will be referred to as "your child”. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves. Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document, for additional information. You may also discuss it with your partner, friends or family. Additional information about participating in a study can be found in the enclosed general brochure on medical research (**Appendix A**).

1. General information

This study is being carried out by the Amsterdam University Medical Centers (Amsterdam UMC), location VU University medical center (VUmc), The Netherlands. Location Academic Medical Center (AMC) is a participating center and the study can also be executed there. For this study, 20 to 30 young children with VWM from different countries in northwest Europe (within reasonable travel distance from Amsterdam, where control visits will take place) are required. Approximately 3 children from the Netherlands are expected to participate. The Central Committee on Research involving Human Subjects (CCMO) has approved this study. General information about the assessment of research can be found in the general brochure on medical research (**Appendix A**).

2. Purpose of the study

The purpose of this study is to investigate how safe and effective the drug Guanabenz is for the treatment of VWM in young children. The study will also evaluate the pharmacokinetics of Guanabenz (what the body does to the drug) when given to young children. Guanabenz cannot yet be prescribed for VWM by doctors outside the scope of this study. The effect of Guanabenz will be investigated in this study by comparing the disease course of Guanabenz-treated patients with untreated patients in the past. In the context of this study, blood and cerebrospinal fluid (the fluid that surrounds the brain and spinal cord) will also be collected to allow a search for body fluid biomarkers that are suitable to monitor the disease course.

3. Background of the study

VWM is a serious brain disorder that mainly affects young children. The disease mostly starts before the age of 6 years. Children lose motor function, become wheelchair-dependent, and often die after several years. No treatment is currently available.

At Amsterdam UMC, we work at developing treatment. 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. Based on how Guanabenz works, we started to think it might be beneficial in VWM. We have laboratory mice with VWM and have therefore 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. 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.

Because 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 with high blood pressure, we want to treat children with VWM with Guanabenz.

The dose of Guanabenz to treat high blood pressure is lower than the dose that we used to treat VWM in mice. In terms of side effects, we do not know whether children tolerate the Guanabenz dose needed to impact their disease. We aim at the highest individually tolerated dose for each child in the study. The most important side effect of Guanabenz is drowsiness. To avoid daytime drowsiness, Guanabenz will be given once a day in the evening, before bedtime. Based on literature and results from our mouse studies, we expect 1 milligram per kilogram per day to be the lowest dose that might have a beneficial effect in children with VWM, but a dose of at least 2 milligram per kilogram per day is preferable. For this study, the maximum dose is 10 milligram per kilogram per day. This higher dose has not been used in humans before, but long-term treatment (2 years) with this higher dose did not lead to toxicity in rodents. As this is the first study with Guanabenz in young children and a higher dose will be used, the safety of Guanabenz will be carefully monitored throughout the entire study. The initial dose titration to the maximum tolerated dose will take place under intensive supervision at VUmc or AMC in Amsterdam, The Netherlands. In addition, all 3-monthly follow-up visits will be at VUmc or AMC in Amsterdam or by video consultation as described under “Visits and Tests” in Chapter 4 below.

At present, no body fluid biomarkers are available for VWM to monitor the disease. A body fluid biomarker is a substance that can be measured in blood or in cerebrospinal fluid and indicates improvement or worsening of the disease. Such biomarkers would greatly facilitate disease monitoring and future therapeutic trials. Therefore, in the context of this study, blood and cerebrospinal fluid will be collected to allow a search for suitable body fluid biomarkers for VWM.

4. What participation involves

Your child's participation will last 1 to up to 4 years, depending on how fast the planned number of 20 to 30 patients can be enrolled in the study.

Screening

We will first evaluate whether your child may participate. The investigator will do a physical examination. The investigator will also ask you about your child's medical history. The study entry criteria will be assessed to evaluate your child's suitability for the study. A summary of the study entry criteria is provided in **Appendix B**.

Treatment

We will treat your child with Guanabenz for 1 to 4 years. In order to avoid side effects, we will start at a low dose (0.5 milligram per kilogram body weight) and increase the dose slowly until the maximum tolerated dose has been reached. As long as there are significant side effects, you and your child will stay in the Ronald McDonald house next to the VUmc or AMC in Amsterdam, so that we can see your child frequently and check the blood pressure and heart rate. When the maximum tolerated dose has been reached and there are no side effects, you and your child can go home.

Visits and tests

The first study visit will take approximately 3 to 5 weeks. You and your child will stay in the Ronald McDonald house next to the VUmc or AMC in Amsterdam. The following will take place:

- screening procedures
- baseline MRI of the brain under light anesthesia
- blood will repeatedly be taken from the infusion line of the anesthetic to investigate how the body treats Guanabenz ('pharmacokinetics')
- blood will be obtained during anesthesia for routine safety laboratory testing
- blood and cerebrospinal fluid (by spinal tap, also called lumbar puncture) will be obtained during anesthesia for biomarker studies
- completion of quality of life and disability questionnaires, and assessment of motor and cognitive performance
- dose titration of Guanabenz under intensive supervision

This study requires that your child will visit the VUmc or AMC in Amsterdam every 3 months. A visit will take 2 to 3 hours. The following will take place:

- physical and neurological examination
- body temperature, blood pressure and heart rate measurements
- 10-step walk test
- blood sampling by a finger prick for blood spots on filter paper. This is to check if Guanabenz is well absorbed in the blood stream. At the first follow-up visit at 3 months, blood will be drawn from a vein without anesthesia to check for side effects.

If traveling to Amsterdam is too risky or impossible due to the COVID-19 pandemic, the 3-monthly control visits can be replaced by video consultations, which allow assessment of

the general physical and neurological condition of your child and the 10-step walk test. We will then ask you to have your local general practitioner or pediatrician to measure body temperature, blood pressure and heart rate. The blood spot may be obtained either by yourself at home or by your local general practitioner or pediatrician. If you will perform the blood spot yourself, we will provide you with instructions, also on paper. We will ask you 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 draw from a vein for routine laboratory testing at that visit.

Once every year your child will be extensively examined. A visit will take 3 days. You and your child will stay in the Ronald McDonald house next to the VUmc or AMC in Amsterdam. The following will take place:

- physical and neurological examination
- body temperature, blood pressure and heart rate measurements
- 10-step walk test
- completion of quality of life and disability questionnaires, and assessment of motor and cognitive performance
- MRI of the brain under light anesthesia
- blood will repeatedly be taken from the infusion line of the anesthetic to investigate how the body treats Guanabenz (‘pharmacokinetics’)
- blood will be obtained during anesthesia to check for side effects
- blood and cerebrospinal fluid (by lumbar puncture) will be obtained during anesthesia for biomarker studies

These yearly visits **cannot** be replaced by video consultations and must be performed in Amsterdam.

You will be asked to keep a patient diary throughout the study, in which you must document information about your child's ability to stand up and walk, the occurrence of side effects, the occurrence of illnesses, and the use of other medications during the study.

Appendix C describes what procedures will take place during each visit. **Appendix D** provides information about MRI under anesthesia.

Other than standard care

Usually your child may visit his/her doctor for follow-up for VWM every 6 or 12 months. The study-related visits will partly replace these regular visits and partly are additional. At VUmc and AMC, completing quality of life and disability questionnaires and an annual MRI of the brain under anesthesia are part of the standard care for VWM. The finger pricks every 3 months and the blood sampling at the first follow-up visit are additional. In addition, the annual collection of blood and cerebrospinal fluid (the latter by lumbar puncture) during the anesthesia for MRI and the assessment of motor and cognitive performance are extra. Keeping a diary is also additional.

5. What is expected of you

In order to carry out the study properly and for your child's safety, it is important that you follow the study instructions. The study instructions require that you:

- give your child Guanabenz once daily during the entire study in the evening at bedtime (the only exceptions are the days before and of the MRI during the study visit in Amsterdam; then follow the instructions of the study staff).
- do not stop Guanabenz abruptly, because side effects may occur that would remain absent when your child stopped Guanabenz slowly.
- do not participate with your child in another medical-scientific study.
- keep appointments for visits or video consultations.
- bring with you all empty and unused Guanabenz packages to Amsterdam.
- send all empty and unused Guanabenz packages, as well as the blood spot, to Amsterdam, if the visit is replaced by a video consultation.
- have your child carry the participant card for the study with him/her (**Appendix E**). This card states that your child is participating in this study. It also states whom to contact in the event of an emergency. Show this card if you visit any doctor.
- have made adequate arrangements for the local medical care of your child at home. We will inform all relevant doctors of your child (general practitioner, pediatrician, neurologist or other) of your child's participation in the study. We are available for consultation at any time through the pediatric neurologist on call for the Amsterdam UMC.

It is important that you contact the investigator:

- before you child starts using other medicines. Even if they are homeopathic or natural remedies, vitamins and/or over-the-counter medicines.
- if your child is admitted to hospital or is going for treatment there.
- if your child suddenly develops any health problems.
- if you no longer want to participate in the study.
- if your contact details change.

6. Possible side effects and other discomforts

Study medication

The use of Guanabenz is associated with several uncertainties. The evidence that Guanabenz has an ameliorating effect on VWM comes from studies in VWM mice, which may not be replicated in human patients. It is likely that a higher Guanabenz dose is needed to impact VWM and it is uncertain whether this dose is tolerated by children with VWM. Because Guanabenz side effects wear off, we start with a low dose and slowly increase it. It is important to realize that Guanabenz side effects probably manifest soon, while possible beneficial effects may take months before they become apparent or only consist of lack of further decline, hampering the decision on continuing or stopping study participation.

It is essential that you know what the side effects of Guanabenz may be. The following side effects were common in teenagers treated with Guanabenz for high blood pressure (in 1 in 10 teenagers or more):

- drowsiness
- headache
- dry mouth

Guanabenz is an antihypertensive drug and lowered blood pressure may cause a feeling of weakness or dizziness. These were sometimes observed in adults, but not in children.

Guanabenz may also have side effects that are still unknown.

We expect all side effects to be more common in the current study than observed in the treatment of high blood pressure, because the Guanabenz dose used is higher. You should immediately contact the investigator if your child develops bothersome side effects or in case of any suspicion or doubt about side effects of Guanabenz.

Make sure that your child does not stop Guanabenz abruptly; there may side effects that would remain absent when your child would stop slowly (eg, high blood pressure). If Guanabenz treatment needs to be stopped, this will be done in 4 steps taking 2 weeks under twice daily checking of the blood pressure and heart rate. In the case of a significant rise of blood pressure, the tapering of Guanabenz will be slowed.

Procedures

Drawing blood may be painful or cause some bruising. We will take approximately 45 milliliter blood from your child in the first year of the study and approximately 21 milliliter in every consecutive year. If needed, an additional 21 milliliter may be taken at the last visit. These amounts do not cause any problems in children.

Collection of blood from the intravenous infusion line and cerebrospinal fluid by lumbar puncture during anesthesia does not cause pain or anxiety. Some children experience headaches and nausea in the days following the lumbar puncture, which will be treated with bed rest and if necessary anti-pain and anti-nausea medication.

MRI does not cause side effects.

Anesthesia comes with a small risk, such as breathing problems and allergic reaction to the anesthetic drug. To keep the risk at a minimum, we will aim at using light anesthesia, so that your child will breathe spontaneously with a larynx mask, but without intubation.

We use Propofol (not Sevoflurane) as anesthetic, because Sevoflurane activates the cell stress response, while Propofol inhibits the cell stress response. In VWM, the basic defect is in the cell stress response and situations activating the response may cause worsening in VWM. So, Propofol is safer in patients with VWM

The anesthetic (Propofol) may cause side effects.

- The following side effects occur frequently (1 in 10 people or more) during anesthesia:
    - a feeling of pain at the site of the infusion (while the injection is being given, before falling asleep)

  - low blood pressure
  - changes in breathing pattern
  - slow heartbeat
- The following side effects occur frequently (1 in 10 people or more) after anesthesia (when waking up or thereafter):
  - feeling sick (nausea), being sick (vomiting)
  - headache

These side effects will be monitored and treated as needed.

7. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. Participation may have consequences for the quality of life for you and your child. We mention points that are relevant for you to consider.

First, no treatment is currently available for the disease itself. VWM is a serious disease, leading to progressive handicap and possibly death. An important benefit of the study is that it is a first contribution to insight into therapy development for this disease.

In Chapter 3 above, we explain that Guanabenz may ameliorate VWM and make that your child is less severely disabled with Guanabenz treatment than it would have been without, but we also stress that we do not know that for sure. The available evidence for a beneficial effect of Guanabenz comes from studies in mice and mice are different from humans. The effect of Guanabenz in patients with VWM still has to be determined. That is the subject of the current study.

The severity of VWM is associated with considerable risks, and these risks do not simply disappear with Guanabenz treatment. Also with Guanabenz, your child's disease can worsen at any time during the study. Deteriorations and death are part of VWM. We do not know whether Guanabenz can prevent this. If deterioration occurs, we would like to hear that from you immediately. We therefore ask you to follow the standard precautions that help avoid rapid deteriorations (see **Appendix F**).

Disadvantages of participation in the study may be:

- possible side effects of Guanabenz
- possible discomforts of the evaluations in the study
- possible discomforts of travelling to Amsterdam

Participation in the study also means:

- additional time
- instructions you need to follow

All these aspects have been described above under points 4, 5 and 6.

8. Resistance of your child

Your child may resist (refuse to cooperate) during the study. The investigator will then have to stop the study immediately. It is difficult to describe what exactly resistance is. Before the start of the study you will be given an explanation of what is considered resistance; this will

be documented in the medical/research files. The investigator will follow the Code of Conduct on resistance of minors.

9. If you do not want to participate or you want to stop participating in the study

It is up to you to decide whether or not to participate in the study. Participation is voluntary. If you do not want to participate, your child will be treated as usual for VWM.

If you do participate in the study, you can always change your mind and decide to stop, at any time during the study. Your child will then be treated as usual for VWM. You do not have to say why you are stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study. If you want, body fluids collected can be destroyed.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

10. End of the study

Your participation in the study stops when:

- you have completed all the visits according to **Appendix C**.
- you choose to stop.
- the end of the entire study has been reached.
- the investigator considers it best for your child to stop.
- VUmc (the sponsor of the study), the government or the CCMO decides to stop the study.

The study is concluded once all the participants have completed the study.
The medication your child has used during the study will be available once the study has ended. The investigator will discuss the options for further medical care with you.
After processing the data, the investigator will inform you about the most important results of the study. This will happen about 1 to 3 years after your child's participation.

11. Usage and storage of your child's data and body fluids

Your child's personal data and body fluids (blood and cerebrospinal fluid) will be collected, used and stored for this study. This concerns data such as your child's name, address, date of birth and data about your child's health. The collection, use and storage of your child's data and body fluids are required to answer the questions asked in this study and to publish the results. We ask your permission for the use and storage of your child's data and body fluids.

You and your child's personal data, such as name, address and contact details, will be provided to the Ronald McDonald house. We ask your permission for this.

Confidentiality of your child's data and body fluids

To protect your child's privacy, his/her data and body fluids will be given a code. Your child's name and other information that can directly identify your child, will be omitted. Data can only be traced back to your child with the encryption key. The encryption key remains safely

stored in the local research institute. The data and body fluids will only contain the code, not your child's name or other data with which he/she can be identified. The data cannot be traced back to your child in reports and publications about the study.

Access to your child's data for verification
Some people can access all your child's data at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to your child's data for review are: the committee that monitors the safety of the study, a monitor working for the sponsor of the study (VUmc) or who has been hired by the sponsor, and national and international supervisory authorities, for example, the Healthcare and Youth Inspectorate. They will keep your child's data confidential. We ask you to consent to this access.

Retention period of your child's data and body fluids
Your child's data collected during the study must be kept for a minimum period of 25 years at VUmc.

Your child's body fluids will be kept for the duration of the study in order to be able to perform the analyses in connection with this study.

Storage and use of data and body fluids for other research
VWM is a very rare disease; patient data and material are scarce. Your child's data and body fluid samples may also be of importance for further scientific research by us or others in the field of VWM or other leukodystrophies. We therefore ask your permission to share your child's body fluids with other researchers or "Clinical Research Organizations" (CROs) for studies on VWM or other leukodystrophies. We may ask a CRO to manage, under our control, the body fluid samples and thus make sure that studies of other researchers or companies on the subject of VWM or other leukodystrophies are coordinated and executed. In this way, research can be facilitated and accelerated, while we keep control over the body fluid samples entrusted to us. To this end, we would like to store your child's data and body fluids for 50 years. You can indicate on the consent form whether or not you agree with this. If you do not agree with this, you can still participate in the current study.

Information about unexpected findings
During this study, something may be found by chance that is not important to the study, but may be important to you. If this is important for your child's health, you will be informed by the investigator. You can then discuss with your doctor or specialist what needs to be done. You also consent to this.

Withdrawing consent
You can withdraw your consent to the use of your child's personal data at any time. This applies to this study. The study data collected until the moment you withdraw consent will still be used in the study. Your child's body fluids will be destroyed after your consent has been withdrawn. If measurements have already been made with those body fluids, then this data will still be used.

More information about your rights when processing data

For general information about your child's rights when processing his/her personal data, you can consult the website of the Dutch Data Protection Authority or the website of VUmc (https://www.vumc.nl/privacy-en-cookies.htm).

If you have questions about your child's rights, please contact the person responsible for the processing of your child's personal data. For this study, that is VUmc. See **Appendix G** for contact details.

If you have questions or complaints about the processing of your child's personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of VUmc (see **Appendix G** for contact details) or the Dutch Data Protection Authority.

Registration of the study

Information about this study is included in a list of medical-scientific studies, namely: www.trialregister.nl/. It does not contain any information that can be traced to your child. After the study, the website may display a summary of the results of this study. You can find this study under number NTR7482.

12. Study subject insurance

Insurance has been taken out for everyone participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. **Appendix H** contains more information about the insurance and the exclusions. It also tells you to whom damage should be reported.

It is important that VWM itself may cause deterioration and death, independent of the study. If your child experiences a deterioration related to VWM, the expenses must be covered by your child's regular health insurance. Before entering the trial, we need evidence that health insurance for the disease of your child is adequate. What you can do to prevent such deteriorations as much as possible, is described in **Appendix F**.

13. Will my child's GP and/or treating specialist and/or pharmacist be informed if my child participates?

We will always send your child's GP, treating specialist and pharmacist a letter or email to let them know that your child is participating in the study. This is for your child's own safety. If you do not agree to this, your child cannot participate in this study. If necessary, we may contact your child's GP and/or treating specialist, for example about your child's medical history or about medications that he/she uses.

14. No compensation for participation

Guanabenz, the additional tests and the additional visits for the study are free of charge for you. You will not be paid for your child's participation in this study.

You will be fully reimbursed for your additional travel costs, travel insurance and stay at the Ronald McDonald house.

15. Any questions?

If you have any questions, please contact the study team. If you would like any independent advice about participation in this study, you may contact Dr. M. Finken. Dr. Finken knows about the study but is not involved in it.

If you have any complaints about the study, you can discuss this with the investigator or treating specialist. If you prefer not to do this, you may contact the complaints' committee at VUmc. All the relevant details can be found in **Appendix G**, Contact Details.

16. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation of your child in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form (**Appendix I**). By your written permission you indicate that you have understood the information and consent to participation of your child in the study. Both you and the investigator will receive a signed copy of the consent form.

Thank you for your attention.

17. Appendices to this information

A. Medical Scientific Research Brochure. General Information for Study Subjects (March 2017)*
B. Study entry criteria
C. Overview/description of study procedures
D. Information on MRI under anesthesia
E. Patient card
F. Guidelines to avoid rapid deteriorations in VWM
G. Contact details
H. Insurance information
I. Parent or guardian informed consent form

* To be handed out separately with this information letter.

Appendix B. Study entry criteria

In order to be eligible for study participation, your child must meet **all** of the following criteria:

1. Genetically proven VWM.
2. Brain MRI abnormalities consistent with VWM.
3. At the time of study entry, a maximum disease duration of 8 years.
4. Clinical symptoms of VWM disease before the age of 6 years.
5. Able to stand up and walk at least 10 steps with or without the support of one hand.
6. Living within reasonable travel distance from Amsterdam, The Netherlands.

If **any** of the following criteria are met, your child **cannot** participate in the study:

1. Your child has no clinical symptoms.
2. Your child is suffering from another genetic disease.
3. Your child is suffering from another significant disease (eg, heart, liver or kidney disease).
4. Your child is participating in another medical-scientific study.
5. You and your child are unable or unwilling to come to Amsterdam, The Netherlands, as required by the study.
6. Unable to undergo MRI due to metal-containing implants, such as cochlea implant, neurostimulator or pacemaker.
7. You are in a family situation where adherence to the study treatment or follow-up procedures cannot be guaranteed.
8. Your child has a known allergy or hypersensitivity to the study treatment.

Appendix C. Overview/description of study procedures

	Scheduled Visits at VUmc or AMC in Amsterdam																	
	First Study Year					Second Study Year				Third Study Year*				Fourth Study Year *				Last study visit**
Visit Number (Month)	**1 (0)**	**2 (3)**	**3 (6)**	**4 (9)**	**5 (12)**	**6 (15)**	**7 (18)**	**8 (21)**	**9 (24)**	**10 (27)**	**11 (30)**	**12 (33)**	**13 (36)**	**14 (39)**	**15 (42)**	**16 (45)**	**17 (48)**	
Visit may be replaced by a video consultation.	no	no	yes	yes	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes	yes	no	no
Screening procedures	●																	
Reach study dose	●																	
Physical/neurological examination, incl. height and body weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Ability to walk (10-step walk test)		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Brain imaging (MRI)	●				●				●				●				●	● ***
Questionnaires and motor and cognitive tests	●				●				●				●				●	● ***
Patient diary review and instructions	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling:																		
- From a vein ****	●	●			●				●				●				●	● ***
- By finger prick	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	● ***
Body temperature, blood pressure and heart rate measurements	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Biomarkers (blood and cerebrospinal fluid sample)	●				●				●				●				●	● ***

* It is at present unknown how fast the planned number of 20 to 30 patients can be enrolled in the study and it is therefore unknown how many years the study will take.
** The last study visit takes place when the study is ended.
*** This assessment will only take place if the previous MRI was performed at least 6 months ago.
**** All blood sampling from a vein, except at Visit 2, will take place via the infusion line of the MRI anesthetic.

Appendix D. Information on MRI under anesthesia

Magnetic Resonance Imaging (MRI), or nuclear spin tomography, is a method to see what happens inside the body. The radiologist can use MRI to visualize what is going on in the body without the need for surgery and without the use of X-rays. MRI provides information that cannot be obtained in any other way. The research is painless and there are no side effects.

How does MRI work?
MRI uses magnetic fields and radio waves. During the examination, your child is placed in a magnetic field. The hydrogen atoms in the body are aligned in this field and therefore respond to the radio signals from the MRI system. The hydrogen atoms become small transmitters themselves, the signals of which can again be collected, arranged and converted into an image of the examined parts of the body via a computer.

Preparation
The investigator will tell you where and at what time you and your child must check in.
Your child must be under fasting condition. An instruction for this will be given by the anesthesiologist who has seen your child. After the MRI examination, your child is taken to the recovery room. As soon as your child is well awake, and when all other assessments for the study visit have been completed, you and your child can go home.

Diet
In general, your child does not need to follow a diet or special guidelines for an MRI study. An exception to this is an MRI under anesthesia, for which your child must be under fasting condition.

Regulations
Because the MRI research is disturbed by metal objects, these may not enter the research area. It is not allowed to wear clothing with metal buttons, buckles, and/or press studs. Eye makeup should be removed, as it also contains metals.
The following items may not enter the magnetic space:

- jewelry
- watch
- hearing aids
- coins (small change)
- credit cards (contain magnetic code)
- other metal objects

The MRI study
The MRI study takes place in a room that is shielded from outside radio waves. Your child lies on an examination table that is pushed into the magnet of the device during the examination. The MRI examination is not painful. The loud, monotonous sound comes from

switching the radio coils. They are normal sounds in an MRI study. The examination takes about an hour.

Aftercare

After the MRI, your child is taken to the recovery room and allowed to wake up. You can stay in the recovery room with your child. After permission from the investigator, and when all other assessments for the study visit have been completed, your child can go home.

Questions

If you have any questions, please contact the investigator or the pediatrics outpatient clinic.

Outpatient department of pediatrics
Reception L
telephone +31 (0)20 444 0872, for nursing questions between 9.00-10.00 and 15.00-16.00 hours
telephone +31 (0)20 566 7508, +31 (0)20 444 1130, or +31 (0)20 566 9111 for other questions

Appendix E. Patient card

Patient Name

Date of Birth

This patient is participating in a study on treatment of 'Vanishing White Matter' (VWM), a rare disease affecting the white matter of the brain.

Protocol ID: VWM1

Study medication: Guanabenz.

The following medications should not be taken during the course of this study: antihypertensives.

In case of an emergency, please contact the investigators:

- Dr. Renate Verbeek, pediatric neurologist, phone: +31 (0)20 5669111 / 5667508, treatVWM@amsterdamumc.nl
- Drs. Marije Voermans, trial coordinator, phone: + 31 (0)20 5669111 / 5667508, m.m.voermans@amsterdamumc.nl
- Prof. dr. Marjo S. van der Knaap, pediatric neurologist, phone: +31 (0)20 5669111 / 5667508, ms.vanderknaap@amsterdamumc.nl
- Dr. Nicole I. Wolf, pediatric neurologist, phone: +31 (0)20 5669111 / 5667508, n.wolf@amsterdamumc.nl
- Pediatric neurologist on call: +31 (0)20 5669111

Appendix F. Guidelines to avoid rapid deteriorations in VWM

Rapid deteriorations have a negative impact on the disease course in VWM. The most important provoking factor is febrile infection (infections that are associated with high body temperature or fever). Examples are common cold, pneumonia, flu, and bladder infection. Minor head trauma, such as bumping the head and a fall, may also provoke rapid deteriorations.

It is important to avoid rapid deteriorations as much as possible.

1. Infections need to be avoided as much as possible.
    a. Close contact with other sick children should be avoided. This measure should be applied in moderation because patients with VWM should go to school as much as possible and not become socially isolated.
    b. Your child should receive all vaccinations, including flu vaccination. From the moment of vaccination until several days thereafter your child should receive antipyretics to avoid fever. Antipyretics are medications used to lower body temperature when a fever is present. Examples are paracetamol and ibuprofen.
    c. Some VWM patients have frequent respiratory tract infections during winter. If your child has this problem, he/she can best be put on low-dose maintenance antibiotics from fall till spring. Fragile patients should use the maintenance antibiotics the year round.
2. Infections should be treated with antibiotics. Contact your GP or the investigator immediately when your child develops an infection (eg, common cold, pneumonia, flu, bladder infection).
3. It is best to keep your child’s body temperature below 38 or 38.5 degrees Celsius. Antipyretics (eg, paracetamol and ibuprofen) should be used to prevent or treat the fever. In case of doubt, contact your GP or the investigator.
4. Minor traumas of daily activities are hardly avoidable. It is best to wear a helmet during outdoor activities and sports. Contact sports must be avoided.
5. Major surgical procedures are major stressors for the body and should be avoided.

Appendix G: Contact details

Principal investigator:	Prof. Dr. M.S. van der Knaap, pediatric neurologist; Amsterdam UMC T: +31 (0)20 4441130 or +31 (0)20 5667508 E: ms.vanderknaap@amsterdamumc.nl
Coordinating investigator:	Dr. N.I. Wolf, pediatric neurologist; Amsterdam UMC T: +31 (0)20 4441130 or +31 (0)20 5667508 E: n.wolf@amsterdamumc.nl
Investigator executing the trial:	Dr. R.J. Verbeek, pediatric neurologist; Amsterdam UMC T: +31 (0)20 4441130 or +31 (0)20 5667508 E: r.verbeek1@amsterdamumc.nl
Trial coordinator:	Drs. M.M.C. Voermans, Amsterdam UMC T: +31 (0)20 5667508 E: m.m.voermans@amsterdamumc.nl
Independent expert:	Dr. M. Finken, pediatric endocrinologist; VUmc T: +31 (0)20 4441130 E: m.finken@amsterdamumc.nl
Pediatric neurologist on call Amsterdam UMC	T: +31 (0)20 5669111
Complaints committee:	Servicecentrum Patiënt & Zorgverlener; VUmc T: +31 (0)20 4440700 / 4443555 E: zorgsupport@vumc.nl
Data Protection Officer:	Dr. M. Paardekooper; VUmc T: +31 (0)20 4441717 E: michel.paardekooper@amsterdamumc.nl www.vumc.nl/privacy-en-cookies.htm

Appendix H: Insurance information VUmc

Insurance has been taken out by the sponsor VUmc for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within 4 years of the end of your child's participation in the study. You must notify the insurance company about the damage within those 4 years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.
This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree is listed on the website of the Central Committee on Research Involving Human Subjects www.ccmo.nl (see "Library" and then "Legislation and regulations").

In the event of damage, please contact the insurance company directly.

Insurance company:	Centramed
Name:	Onderlinge Waarborgmaarschappij Centramed B.A.
Address:	Maria Montessorilaan 9, 2719 DB Zoetermeer, The Netherlands
Telephone number:	+31 (0)70 301 70 70
E-mail:	info@centramed.nl
Policy number:	624.529.204

The insurance offers a cover of up to €650,000 per study subject and €5,000,000 for the entire study and €7,500,000 annually for all studies from the same sponsor.

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your child's health that would also have occurred if he/she had not participated in the study;
- damage resulting from not or not entirely following directions or instructions;
- damage to descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

Appendix I. Parent or guardian informed consent form

A first trial of Guanabenz in Vanishing White Matter

I have been asked to consent to my child participating in this medical-scientific study:

Name of study subject (child): Date of birth __ / __ / __

- I have read the subject information form for the parents/guardians. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether I want my child to participate.
- I know that participation is voluntary. I know that I may decide at any time that I do not want my child to participate after all or to withdraw my child from the study. I do not need to give a reason for this.
- I give permission for my child's GP and/or treating specialist to be informed about my child's participation in this study and to inform them about possible effects and side effects.
- I give permission for information to be requested from my child's GP and/or treating specialist.
- I give permission for the collection and use of my child's data and body fluids (blood and cerebrospinal fluid) to answer the research question in this study.
- I know that some people may have access to all data of my child to verify the study. These people are listed in the information sheet. I consent to the inspection by them.
- I agree that my child's GP and/or treating specialist will be informed of coincidental findings that (may) be of interest for my child's health.
- I □ **do**
  □ **do not**
  consent to keeping my child's personal data longer (50 years) and to use them for future research in the field of my child's condition or related conditions.
- I □ **do**
  □ **do not**
  consent to keeping my child's body fluids for 50 years and to use them for future research in the field of my child's condition or related conditions.
- I □ **do**
  □ **do not**
  consent to sharing my child's personal data and body fluids with other researchers or "Clinical Research Organizations" (CROs) for research on my child's condition or related conditions.

- I □ **do**
  □ **do not**
  consent to being contacted again after this study for a follow-up study.
- I agree to my child's participation in this study.

Parent/guardian name:

Signature: Date:__ / __ / __

Parent/guardian name:

Signature: Date:__ / __ / __

I declare that I have fully informed the abovementioned person(s) about the study referred to.

If information becomes available during the study that could affect the parent's or guardian's consent, I will notify him/her about this in good time.

Name of investigator (or his/her representative):

Signature: Date:__ / __ / __

Additional information was given by:

Name:

Job title:

Signature: Date: __ / __ / __

The parent or guardian will receive the full information sheet, together with a signed copy of the consent form.