Emma Kinderziekenhuis
Amsterdam UMC

Amsterdam UMC
University Medical Centers

Vanishing white matter

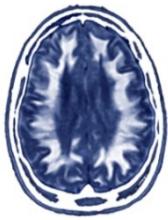
Guanabenz trial

FORUM

Second meeting December 9, 2021

vrije Universiteit amsterdam

Amsterdam Leukodystrophy Center



Amsterdam Neuroscience

CNCR

Forum & the trial team

- Representatives of patients and families:
  - ELA: Guy Alba and Elise Saunier
  - VWM Family Foundations: Brett Hollberg and Allyson + Nick Buck
  - ULF: Donna Skwirut
  - VKS: Hanka Dekker

- Representatives of the trial: Renate Verbeek (sub-I), Marije Voermans (trial coordinator), Marjo van der Knaap (PI)

Refresh:
Why Guanabenz?

Molecular mechanisms of VWM

- The genes *EIF2B1–EIF2B5* encode the α–ε subunits of an enzyme called eIF2B
- eIF2B is essential for translation of DNA into protein
- eIF2B is central in regulating the rate of protein synthesis, especially for downregulating the synthesis during activation of the integrated stress response (ISR)
- The ISR is a protective response of cells to physical stresses like fever and viral infections

- VWM is caused by mutations in the genes *EIF2B1–EIF2B5*
- Mutations decrease eIF2B activity and with that they cause a constitutive activation of the ISR, so in VWM the ISR is always activated, also when there is no stress
- In VWM, the ISR is specifically activated in brain white matter cells
- There is growing evidence that inhibiting the activated ISR is beneficial in VWM

Guanabenz

- Guanabenz is an old α2 adrenergic antihypertensive drug, FDA- and EMA-approved, used since the seventies/eighties
- Safe in chronic use in patients ≥12 years, no long-term adverse effects known
- Most frequent side-effect in adolescents and adults: drowsiness
- Side-effects are dose-dependent and wear off

- Guanabenz also inhibits the ISR
- It ameliorates the disease in VWM mouse models: better motor performance, ameliorated brain pathology and reduced ISR activation in brain white matter cells

- International, monocenter (Amsterdam) open-label clinical trial with Guanabenz in patients with VWM, overall trial duration 4 years
- Inclusion criteria:
  - Onset < 6 years
  - Disease duration ≤ 8 years
  - Ambulant

Update on the Guanabenz trial December 1, 2021

Inclusion in the trial

- The first participant was included at May 31, 2021
- In total 8 patients are in the trial on December 1, 2021

- Patient characteristics of the children on Guanabenz (n=8)
  - Sex: 5 males, 3 females
  - Age at entering the trial: median 6 years, range 2-11 years
  - Disease duration at the time of inclusion: median 5 years, range 1-8 years

- The inclusion is ahead of schedule; it is expected that inclusion of 30-40 patients will be finished in 2 years

Tolerability and efficacy of Guanabenz

- Currently, 8 children are treated with Guanabenz
- They are titrated to the maximum tolerated dose in 4-6 weeks in Amsterdam
- During titration, children experience temporary side-effects (next slide)
- At the follow-up visits at 3 months (n=4) and 6 months (n=1), all patients tolerated Guanabenz and did not experience major side-effects
- None of the patients experienced neurological deterioration until now

- Efficacy as measured by clinical outcome, quantitative brain MRI parameters and potential biomarkers has to be awaited
- Longer follow-up is needed to determine efficacy of Guanabenz

Side-effects of Guanabenz

- 4 main categories of side-effects have been observed during the titration phase

1. Sleepiness and drowsiness (expected)
   - present in all children (n=8)
2. Other α2 adrenergic effects (expected):
   - dry mouth (n=8)
   - feeling unsteady (n=8)
3. Gastrointestinal effects (less expected):
   - constipation (n=3)
   - nauseau and vomitting (n=2)
4. Psychological effects (unexpected):
   - unexplainable sad feelings, moodiness (n=8)
   - vivid dreams and nightmares (n=8)
   - visual or tactile hallucinations (n=3)

- Sometimes temporarily extra medication needed
- Side-effects resolve gradually over the weeks (at home)

Pharmacokinetics of Guanabenz

- Pharmacokinetics:
  - first blood samples for measuring the levels of Guanabenz are under analysis
  - preliminary results show that the Guanabenz levels in the blood are in line with predicted values

- Pharmacodynamics:
  - blood pressure and heart rate show a variability that does not change during the titration phase
  - no substantial effect of Guanabenz on blood pressure

Data and Safety Monitoring Board (DSMB)

- The first DSMB meeting took place on November 25, 2021
- There were no queries or concerns regarding the execution and safety of the trial
- Permission was given to continue the trial in its present form
- The next meeting will be in 6 months (after the first trial year)