



# Vanishing white matter

Guanabenz trial  
FORUM

Fifth meeting 18-Nov-2024



European  
Reference  
Network

for rare or low prevalence  
complex diseases

 Network  
Neurological Diseases  
(ERN-RND)

# Forum & trial team

- Representatives of patients and families:
  - ELA: Guy Alba and Audrey Boyer
  - 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 coördinator), Marjo van der Knaap (PI)

# Update November 2024

- This trial includes patient with DNA- and MRI-confirmed VWM, disease onset  $\leq 6$  years and disease duration  $\leq 8$  years; patients must be able to walk at least 10 steps without support or with light support of one hand
- The first participant was included at May 31, 2021
- In total 33 patients are included; inclusion ended at 31 May, 2024
- 2 drop outs (1. disbalance between intensity of the trial and mild neurological deficit of the child and 2. personal circumstances)
- 31 patients are currently treated with Guanabenz in adequate doses
- Patient characteristics
  - 21 boys, 10 girls
  - At start trial: median age of 5 years (range 2-12 years) and median disease duration of 2 years (range 2 months-8 years)
  - Achieved Guanabenz dose: 1.0 – 1.7 mg/kg/day (minimum dose  $\geq 1$  mg/kg/day)
- Trial end date: 31 May 2025, after 4 years

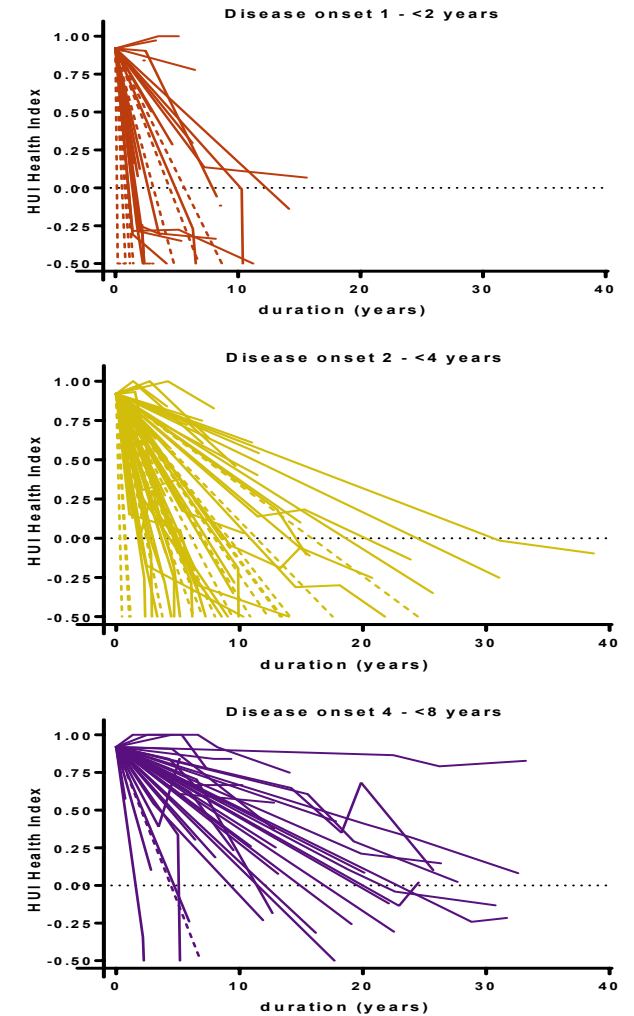
# Side-effects of Guanabenz

- Most important side-effects (all  $\alpha$ 2-adrenergic):
  - Nervous system: tiredness, feeling unsteady, tremor
  - Gastrointestinal disorders: dry mouth, constipation, nausea, vomiting
  - Psychiatric disorders: sad feelings/moodiness, vivid dreams/nightmares, hallucinations (visual/tactile), hyperactivity
- Side-effects mainly seen in the titration phase
- After the titration phase, Guanabenz is tolerated without important side-effects in most children; they are able to resume their daily routines
- Two exceptions: one child has behavioral issues and sometimes hallucinations; one child has become very inactive, with decreased school performance; relationship with Guanabenz unclear

# Effects of Guanabenz

- Clinical course:
  - Sometimes still decline in younger children, who typically have an aggressive disease course, **but no massive declines and no deaths**
  - In the older children, who typically have milder disease course, mostly stability observed
- Majority of VWM children and parents report positive effects on well being and stamina:
  - Children feel more confident
  - They have more energy
  - They are less ill during episodes of fever or cold with faster recovery
- This disease course differs from what was seen in the natural history study; based on the natural history study we would expect some children to have a rapid and massive decline and some children to die.
- Definitive analysis will follow at the end of the trial: comparison with untreated historical controls

## Natural history study



Hui 1.00 is normal, HUI -0,5 is death

## Data and Safety Monitoring Board (DSMB)

- The sixth DSMB meeting took place on July 1st, 2024
- There were no queries or concerns regarding the conduction and safety of the trial
- Permission was given to continue the trial in its present form

# Future plans: development outline



## Completed steps

- **Pre-clinical research**
- **Patent US & EU, Canada pending**
- **Orphan designation**
- **Phase I/II trial completed soon**
- **Positive results of fertility analysis & clinical observations**

## Next steps

- **Product development: ongoing in Ofichem / Ofimedicine**
- **Long term extension trial (4 yr): to be submitted for ethics approval soon**
- Protocol assistance for EMA submission
- Regulatory development
- Marketing authorization
- Distribution in different parts of the world
- Aim: reasonable pricing taking the economic status of patients into account
- Total budget required € 6,135,960; we acquired € 5,725,960, so € 410,000 still uncovered: donations welcome!