Tralesinidase alfa (AX 250) enzyme replacement therapy for Sanfilippo Syndrome Type B

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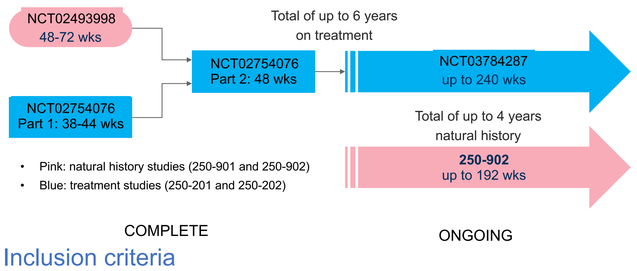
Introduction and Objectives

- Sanfilippo syndrome type B (mucopolysaccharidosis IIIB; MPS IIIB) is a lysosomal storage disorder caused by α-N-acetylglucosaminidase (NAGLU) enzyme deficiency, which leads to heparan sulfate (HS) accumulation in brain and other organs
- Patients typically present between 1 and 4 years of age with speech and/or developmental impairment. Hyperactivity, aggression, loss of fear, impulsivity, anxiety, hearing loss and sleep disorders predominate over the next several years.
- Progressive dementia and loss of motor function occur by the late first or early second decade of life and lead to death by the late second or early third decade.
- Visceral signs such as hepatosplenomegaly, coarse facies and hirsutism are common.
- We present treatment and safety data from 22 patients treated for up to 4 ½ years with weekly intracerebroventricular (ICV) administration of tralesinidase alfa (AX 250) enzyme replacement therapy in NCT02754076 and extension study NCT03784287.

Study design



- Pink: natural history studies (250-901 and 250-902)
- Blue: treatment studies (250-201 and 250-202)

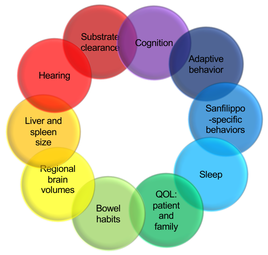
Inclusion criteria

- Signs and symptoms of Sanfilippo B
- Deficient NAGLU activity at screening
- ≥1 and < 11 years of age (NCT02754076, Part 1), completion of Part 1 or observational study NCT02493998 (NCT02754076, Part 2), and completion of NCT02493998 (NCT03784287)

Exclusion criteria

- Other neurological illness that could cause cognitive decline
- Stem cell, gene therapy or prior ERT for Sanfilippo B
- Requirement for ventilator support
- Contraindications to neurosurgery or MRI
- History of poorly-controlled seizure disorder
- Hydrocephalus or ventriculoperitoneal shunts

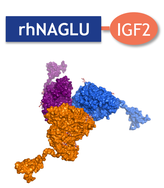
Endpoints

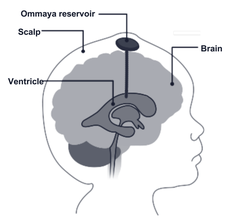


Assessment schedule

- NCT02754076
  - Every 12 weeks: cognitive function (BSID-III or KABC-II) and behavior assessment (VABS-II and Sanfilippo Behavior Rating Scale)
  - Every 24 weeks: heparan sulfate non-reducing end (HS-NRE) levels, abdominal and brain volumetric MRI imaging, hearing function (brainstem auditory evoked responses), sleep (Children's Sleep Habits Questionnaire) and quality of life measures (Infant/Toddler Quality of Life and Pediatric Quality of Life Family Impact Module)
- NCT03784287 – same as NCT02754076 for first 96 weeks, then assessment frequency halved (Q12W goes to Q24W and Q24W goes to Q48W)

Intracerebroventricular administration of tralesinidase alfa ERT

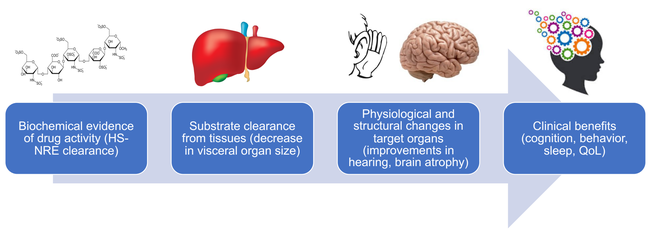




- Novel fusion of recombinant human alpha-N-acetylglucosaminidase (rhNAGLU) and insulin-like growth factor 2 (IGF2)
- IGF2 tag enhances cellular uptake and lysosomal targeting while minimizing off-target effects
- Administered via Ommaya reservoir – technique used for over 50 years
- Bypasses the blood-brain barrier
- Infusion time 5-10 minutes
- 300 mg ICV weekly

Treatment goals and expected sequence of events

- Effective treatments will slow (good), stabilize (better) or reverse (best) disease symptom progression



Results

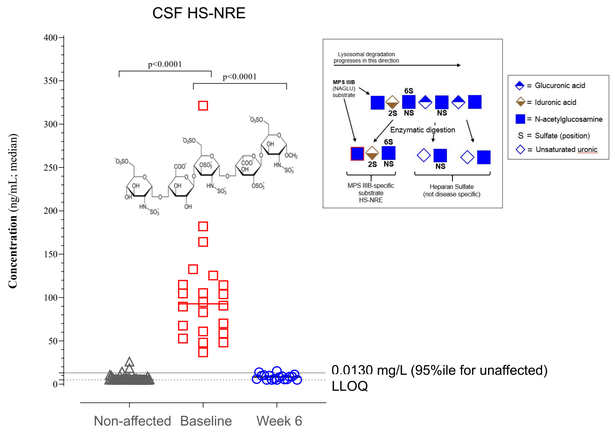
Baseline characteristics

Study	N	Mean age ± SD (mo) (range)	# (%) pts < 6 y/o	% male
NCT02754076	22	61.6 ± 24.0 (24.8 – 117.6)	19 (86%)	59%
NCT03784287	20	74.1 ± 25.3 (35.9 – 137.6)	9 (45%)	65%

CSF HS-NRE

- HS-NRE is specific for Sanfilippo B
- Normalization of CSF HS-NRE is prerequisite for and likely predictive of maximal clinical benefits
- CSF HS-NRE is normalized by Week 6 of treatment in all patients (N = 22)

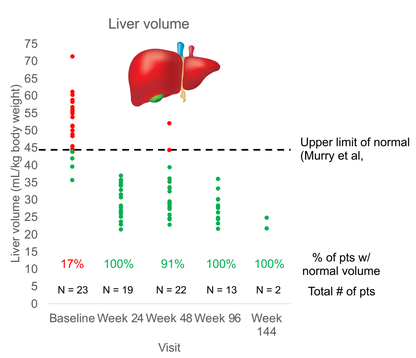
Biochemical evidence of drug activity (HS-NRE clearance)



Liver volume (MRI)

- Liver volumes normalized to body weight were supranormal in 18/22 patients at Baseline
  - Demonstrates that subclinical hepatosplenomegaly is nearly universal in young Sanfilippo B patients
- After 24 weeks of treatment (first time point examined), liver volume normalizes in the majority of patients, and this is maintained out to 3 years on treatment
- Demonstrates that ICV tralesinidase alfa clears HS-NRE throughout the body

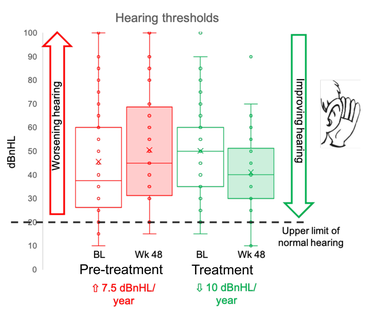
Substrate clearance from tissues (decrease in visceral organ size)



Hearing

- Baseline hearing impairment is common in the study population
  - Medical history: 5/22 patients (23%)
  - Hearing aids: 2/22 patients (9%)
- Hearing thresholds (BAER)
  - Natural history: worsened (increased) 7.5 dBnHL from Baseline to Week 48 (N = 19)
  - Treatment: improved (decreased) 10.0 dBnHL from Baseline to Week 48 (N = 19)
- 1 of 2 treated patients no longer uses hearing aids

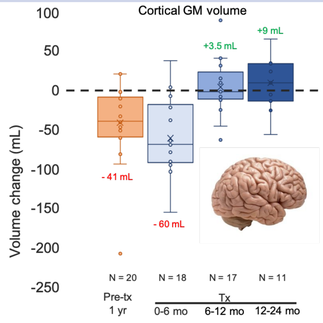
Physiological and structural changes in target organs (improvements in hearing, brain atrophy)



Cortical gray matter volume (MRI)

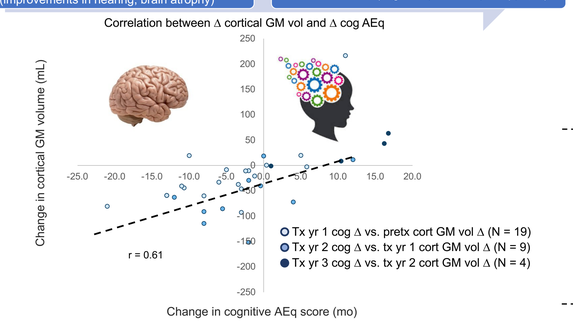
- Natural history: cortical gray matter volume decreases ~41mL/yr
- Treatment
  - Baseline - Week 24: loss accelerates to ~60 mL, likely representing rapid HS-NRE clearance from the brain
  - Week 24 – 48: gain of ~3.5 mL
  - Week 48 – 96: gain of ~9 mL

Physiological and structural changes in target organs (improvements in hearing, brain atrophy)



- Cortical gray matter volume changes predict subsequent changes in cognitive function

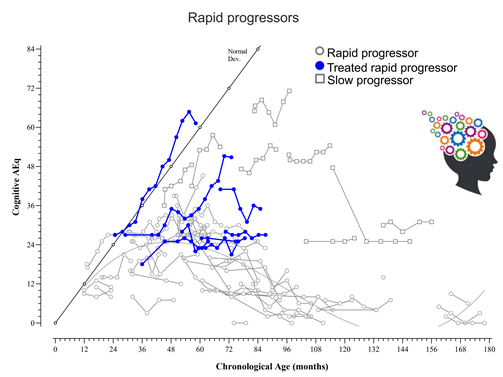
Physiological and structural changes in target organs (improvements in hearing, brain atrophy) → Clinical benefits (cognition, behavior, sleep, QoL)



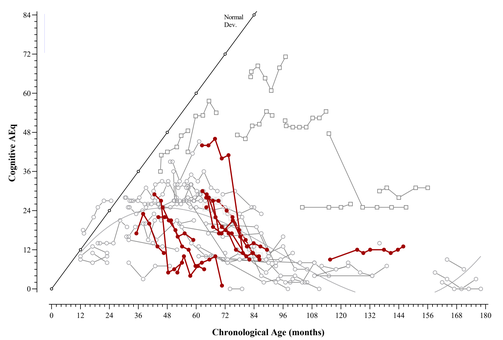
Cognitive function (AEq) – BSID-III and KABC-II

- Rapid progressors
  - Natural history
    - Peak function at 3 – 6 years followed by rapid loss of cognitive skills
    - Some patients decline prior to age 6 years
  - Treatment
    - 39% (7/18) of treated rapid progressors are stable or outperform predicted natural history trajectory over at least 2 years of treatment
      - 3 of these patients were ≤ 36 months of age at treatment initiation

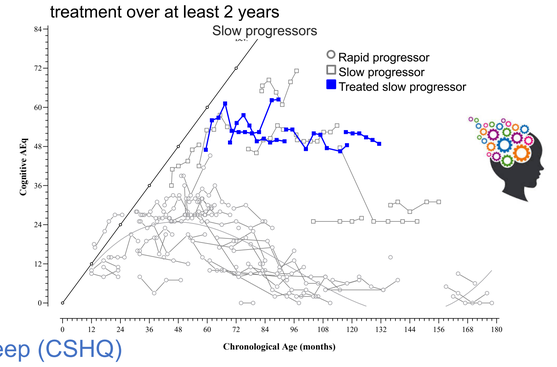
Clinical benefits (cognition, behavior, sleep, QoL)



- 61% (11/18) of treated rapid progressors followed predicted natural history trajectories despite treatment
  - Only 1 patient was ≤ 36 months of age at treatment initiation

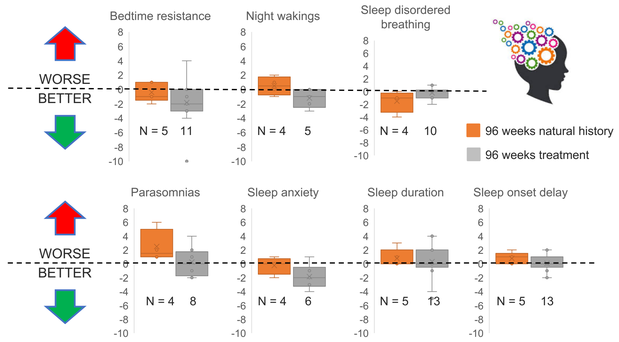


- Slow progressors (~10% of the affected population)
  - Natural history
    - All achieve cognitive function >48 months AEq
    - Cognitive AEq below normal but can increase past 6 years of age
    - Decline occurs after 10+ years of age
  - Treatment
    - 100% (4/4) of slow progressors have stable cognitive function on treatment over at least 2 years



Sleep (CSHQ)

- Children's Sleep Habits Questionnaire includes a series of items encompassing major sleep complaints
  - Higher scores indicate greater dysfunction
- Preliminary data on limited number of patients suggests that change from Baseline to Week 96 was directionally better on treatment than natural history



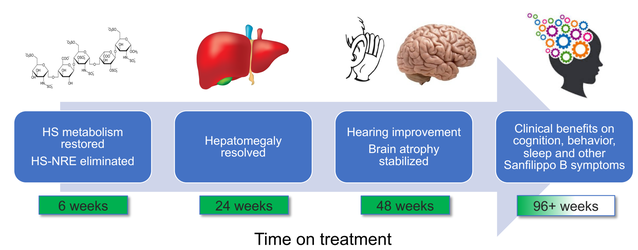
Safety

- AEs and SAEs are consistent with mode of administration and ERTs in general

Combined Safety Profile	
Safety population	22
Total doses administered	>2311 (~96% of scheduled)
Longest exposure to date	>4 years
Drug-related AEs	<10% of doses ~94% CTCAE grade 1 or 2 Most common (68% of total): fever, headache, vomiting
Drug-related SAEs (15 total)	<1% of doses CTCAE grade 2 or 3 Most common (53% of total): CSF pleocytosis
Device-related SAEs (16 total)	<1% of doses CTCAE grade 1 – 3 Most common (69% of total): infection, malfunction
Treatment discontinuations (6 total)	AE-related (4), withdrawal of consent (2)

Summary

- Tralesinidase alfa treatment rapidly normalizes CSF HS-NRE, demonstrating correction of enzyme deficiency
- Liver size normalizes within 6 months of treatment initiation, demonstrating systemic drug delivery and clearance of pathogenic substrate
- Hearing improves on treatment
- Treatment-related increase in cortical gray matter volume in a neurodegenerative disease is unique and suggests reversal of underlying disease pathology
- Cognition improves or stabilizes in 50% of treated patients
- Preliminary data suggest improved sleep function after 2 years of treatment



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