THN391 – An Anti-fibrin Antibody Targeting Fibrin-Driven Inflammation in Early Alzheimer's Disease: Update from an Ongoing Phase 1b Study

Aaron B. Kantor[1], Tanja A. M. Hoffman[1], Sarah Kavanagh[1] Nuno Mendonca[1], Henk JMM Mutsaerts[2], Ellen Dicks[2], Frederik Barkhof[2,3], Khalid Abd-Elaziz[4,5], E (Jort) G.B. Vijverberg[2], Catherine Mummery[3], and Craig Ritchie[6,7]

[1]Therini Bio, Sacramento, CA ,USA; [2]Amsterdam UMC, Amsterdam, NLD; [3]University College London Hospitals, London, GBR; , [4]CTC Groningen, NLD, [5]University Medical Center Groningen, Groningen, NLD, [6]Scottish Brain Sciences Edinburgh, GBR [7]University of St Andrews, St Andrews, GBR

P4-01
Wed-0033

Abstract

Background
THN391 is a first-in-class high-affinity humanized monoclonal antibody, targeting the inflammatory epitope on fibrin to treat inflammatory neurodegenerative diseases (Kantor et al JNI 2025). At sites of vascular damage, conversion of fibrinogen to fibrin exposes a cryptic inflammatory epitope, γ377–395, which can bind complement receptors CD11b/c on microglia, macrophages, and dendritic cells, triggering a toxic inflammatory response. Anti-fibrin γ377–395 antibodies significantly reduce inflammation and neuronal damage in 5XFAD mice (Ryu et al Nat Imm 2018). THN391 was safe and well-tolerated in a Ph1a study in healthy adults with a half-life supporting monthly intravenous dosing and warranting further investigation in patients.

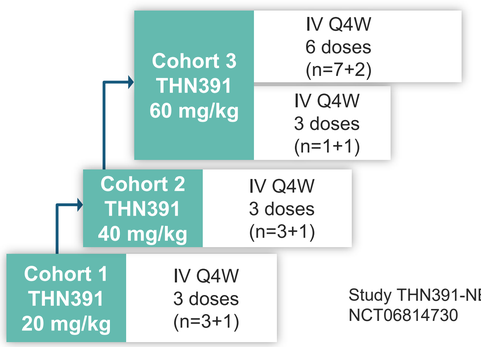
Methods
THN391-NEU-102 is a double-blind, randomized, placebo-controlled, Phase 1b study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of THN391 in individuals with early Alzheimer's disease (AD; mild cognitive impairment [MCI] and mild AD) and cerebral small vessel disease. APOε4 heterozygotes and homozygotes are allowed with dose cohorts escalating up to 60 mg/kg. Secondary objectives are immunogenicity and impact of THN391 on coagulation. Exploratory objectives include: 1) THN391 distribution in the CSF; 2) cognitive assessments; 3) white matter hyperintensity volume (ARIA-E), microbleeds and superficial siderosis (ARIA-H), hemodynamic parameters such as cerebral blood flow, vascular efficiency, and blood-brain barrier integrity proxies from arterial spin labeling, NODDI, and DCE MRI and 4) pharmacodynamic markers in the plasma and CSF, including fully validated assays for Aβ42/40, total Tau and p-Tau181, 217, 231, GFAP, and exploratory NULISAseq for neurodegenerative and inflammatory markers.

Results
THN391-NEU-102 is ongoing in the Netherlands and the United Kingdom. Dosing has been completed for 2 cohorts at 20 and 40 mg/kg Q4W x3 and a 60 mg/kg cohort is ongoing. The interim results of Phase 1b study showed that THN391 is safe and well tolerated in patients up to a dose of 40mg/kg at Day 120. Trial design, endpoints, and progress will be discussed.

Conclusions
This ongoing Phase 1b study will further characterize the safety profile, pharmacokinetics, coagulation effects, and CSF exposure of THN391 in early AD, including in APOEε4 homozygotes, and will explore pharmacodynamic signals using integrated biomarker, imaging, and cognitive assessments.

Ongoing Phase 1b

Multiple Ascending Dose (MAD)



Study THN391-NEU-102, NCT06814730

Study Design

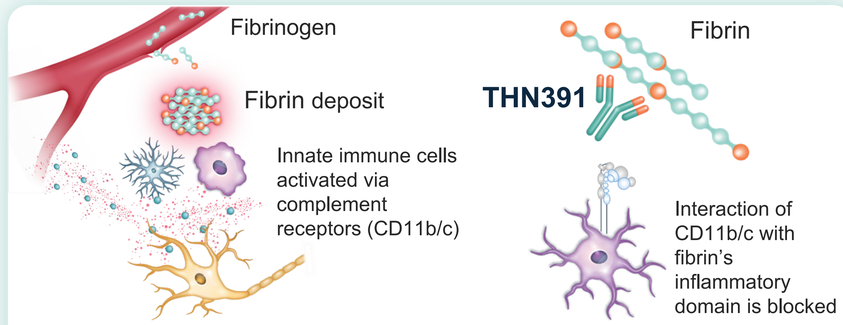
- Diagnosis of Early Alzheimer's Disease (MCI or mild AD)
- Mini Mental State Examination (MMSE) score ≥20 and ≤28 at screening
- Ages 60-85, male and female
- AD confirmed by amyloid testing
- APOE4 carriers, including homozygotes, eligible
- Diagnosed with cSVD based on findings from a pre-study MRI (Fazekas score ≥ 1) or other evidence of vascular risk, such as hypertension
- N=19
- 4 sites in the UK, Neth`erlands
- 5 months follow-up

Key Endpoints

PRIMARY	• Safety, tolerability, incidence of AEs and SAEs PK (AD population with cSVD: many would be ineligible for anti-amyloid therapies or at risk for ARIA) • THN391 serum concentration and PK parameters
SECONDARY AND EXPLORATORY	• THN391 concentration in CSF • Immunogenicity, occurrence of anti-drug antibodies to THN391 • Impact on coagulation, aPTT, PT, etc • Pharmacodynamic biomarkers in plasma/serum & CSF to detect early signal of efficacy • Structural and functional imaging with ASL and DCE MRI • Digital cognitive assessments

Fibrin is central to innate immune cell-mediated inflammation

- Loss of vascular integrity results in fibrin deposition
- Fibrin inflammatory epitope binds to the complement receptors, CD11b and CD11c, on macrophage, microglia, etc. and triggers immune cell-mediated inflammation
- Blocking the inflammatory epitope with antibodies is protective in animal models of Alzheimer's disease, multiple sclerosis and retinal diseases
- THN391 is a pure antagonist with LALA mutations in the CH2 domain to minimize FcγR and C1q mediated effector functions



Damage to Neurons
Fibrin deposits outside of blood vessels activate microglia-mediated inflammation, causing damage to neurons

Protection of Neurons
THN391 binds to the inflammatory epitope on fibrin and blocks activation of a toxic inflammatory cascade, protecting neurons

Phase 1b early AD trial progress

Enrollment complete, dosing ongoing

- Cohort 1 (20 mg/kg, 3 active:1 placebo) - 4 enrolled, dosing complete
- Cohort 2 (40 mg/kg, 3 active:1 placebo) - 4 enrolled, dosing complete
- Cohort 3 (60 mg/kg, 8 active:3 placebo) - 11 enrolled, dosing ongoing

Subjects (n=19)

- Gender: Female, 8 (42%), Male 11 (58%); Age: Median 73, Range 63-83
- Height: 173 ± 7.9 cm; Weight: 77.8 ± 12.1; BMI: Median 26.1, Range 18.4 – 31.9
- MMSE: Median 25, Range 20– 28; Fazekas: Fz1 = 8, Fz2 = 7, Fz3 = 4
- 16 of 19 patients have vascular risk factors, (e.g., hypertension, T2DM)

Safety

THN391 remains safe and well-tolerated

- Cohorts 1 and 2, through Day 120, (n=8)
- Most AEs were mild and resolved
- General disorders and administration site conditions were the most common AEs
- One bowel obstruction SAE reported in participant with a history of multiple abdominal surgeries, considered unrelated to study drug
- THN391 does not interfere with coagulation as measured by Prothrombin time (PT) activated partial thromboplastin time (aPTT), and PT-INR

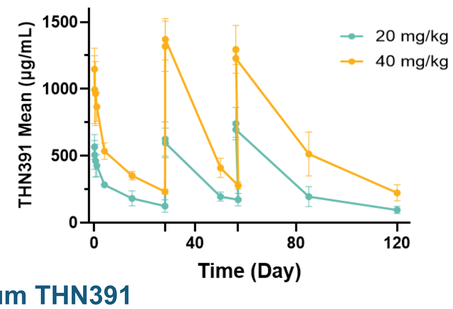
MRI assessment of ARIA

- 11 APOE4 heterozygotes (ε3/ε4) and 3 homozygotes (ε4/ε4)
- 16 of 19 patients have vascular involvement
- ARIA E and H assessed at screening and D22, D50, D120, and D248
- No evidence on ARIA E
- 60 mg/kg cohort: 1 observation of a microbleed, consistent with an elderly AD population, patient asymptomatic and continued dosing

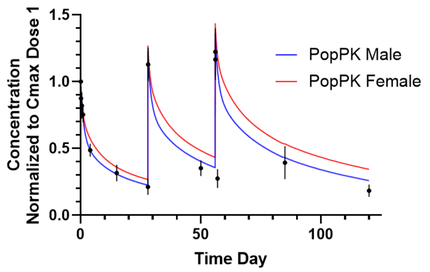
Pharmacokinetics

- PK of THN391 in AD subjects from Phase 1b matches popPK model of Phase 1a healthy volunteers at 20 and 40 mg/kg
- Dose proportional PK. Terminal half-life of 40 days supports monthly or longer dosing
- THN391 CSF:Serum ratio of ≈0.15–0.5% is consistent with other AD treatment antibodies
- mPBPK model predicts that THN391 will be effective at study doses

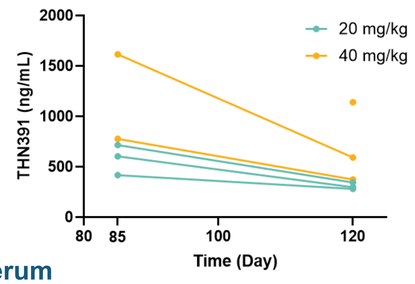
Serum THN391



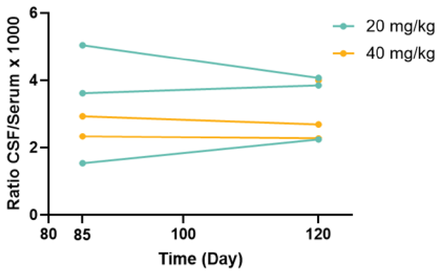
Normalized Serum THN391 compared to healthy subject popPK



CSF THN391



THN391 CSF:Serum ratio (x1000)



Conclusions

- THN391, a first-in-class therapeutic monoclonal antibody targeting the fibrin inflammatory epitope responsible for driving neuroinflammation, is currently in clinical development
- THN391 was safe and well-tolerated in healthy subjects following intravenous injection of single and multiple ascending doses up to 40 mg/kg in a Phase 1a study
- We have competed enrollment in a Phase 1b study of THN391 in subjects with early Alzheimer's disease in the Netherlands and United Kingdom
- THN391 remains safe and well-tolerated to date in all cohorts with MCI and early AD patients
- We have also initiated an open-label Phase 1b study of intravitreal THN391 in subjects with DME in Australia, NCT06701721, and plan to explore the clinical potential of THN391 alone and in combination with VEGF antagonists.

Acknowledgements
We thank our colleagues at Therini Bio, Gladstone Institutes, the clinical sites, our patients, and CROs for their many contributions leading to the development and clinical trials of fibrin targeting therapies

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