THN391 – A Novel, First-In-Class Anti-fibrin Antibody for Treatment of Inflammation in Alzheimer's Disease: An Ongoing Phase 1b Study for the Treatment of Early Alzheimer's Disease

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Abstract

Background: Inflammation and more recently, cerebral small disease have been recognized as critically important events in the onset and progression of Alzheimer's disease (AD). A large body of animal and clinical data has shown that fibrin is critical to the onset and progression of AD by triggering an inflammatory response that contributes to neuronal injury[1]. THN391 is a first-in-class high-affinity humanized monoclonal antibody, targeting the inflammatory γ377–395 epitope on fibrin that binds complement receptors CD11b/c on microglia, macrophages, and dendritic cells[1]. Innate immune cell binding to fibrin γ377–395 triggers an inflammatory response, resulting in neuronal damage and behavioral impairment in the 5XFAD mouse which is mediated by reactive oxidative species and the upregulation of neurotoxic chemokines and cytokines[2].

Anti-fibrin γ377–395 antibodies significantly reduce inflammation and neuronal damage in 5XFAD mice[2]. Currently approved anti-amyloid treatments for AD are modestly effective, and present safety risks, especially for patients who are ApoE4 homozygotes. Importantly, these agents do not target inflammation, an early and essential driver of disease. THN391 was safe and well-tolerated in a randomized, first-in-human, double-blind, placebo-controlled single and multiple ascending dose (SAD and MAD) trial in healthy subjects[3]. THN391 had no impact on coagulation and fibrinolysis, as measured by PT, aPTT, and rotational thromboelastometry (ROTEM). Population pharmacokinetic modeling shows that THN391 exhibits dose-proportional pharmacokinetics and a long terminal half-life supporting monthly or less frequent dosing. Based on these results, a Phase 1b study is ongoing in patients with early AD.

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 early Alzheimer's disease subjects. The study includes individuals with mild cognitive impairment (MCI) due to AD and individuals with mild AD who show progressive decline in 1 or more cognitive domains. ApoE4 heterozygotes and homozygotes are allowed. with subsequent dose cohorts escalating to at least 60 mg/kg. Primary objectives are safety and tolerability and THN391 pharmacokinetics. Secondary objectives are immunogenicity and impact of THN391 on coagulation. Exploratory objectives include:1) THN391 distribution in the CSF; 2) cognitive assessments including the Mini Mental State Examination (MMSE) and a digital battery of verbal, spatial memory and executive function, sensitive to change in response to treatment; 3) cerebral blood flow by arterial spin labeling MRI and blood-brain- barrier integrity by dynamic contrast-enhanced-MRI; and, 4) pharmacodynamic markers in the plasma and CSF, including fully validated assays for Aβ42/40, total Tau and p-Tau181, 217, 231 and exploratory NULISAseq for neurodegenerative and inflammatory markers.

Results: THN391-NEU-102 , "A Double-Blind, Randomized, Placebo-Controlled, Phase 1b Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of THN391 in Early Alzheimer's Disease Subjects," is ongoing-in the Netherlands and the United Kingdom. Trial design, endpoints and progress are discussed. THN391 remains safe and well-tolerated to date.

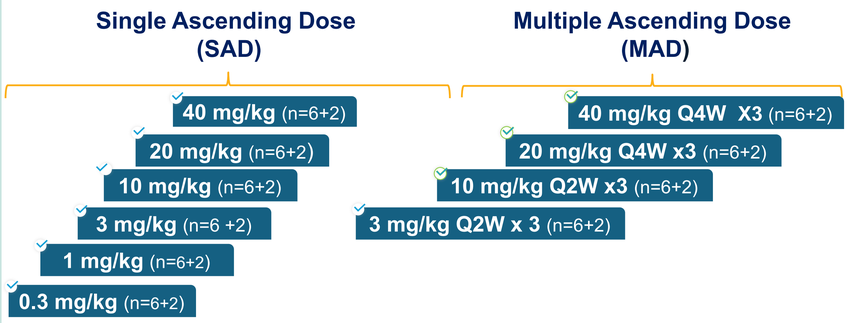
Conclusions:THN391, a first-in-class antibody targeting fibrin-induced inflammation, was found to be safe and well-tolerated in a Phase 1a study, with a half-life supporting monthly intravenous dosing. A Phase 1b study is ongoing in patients with early AD with ApoE4 homozygotes included. The study will assess safety, pharmacokinetics, early signals of efficacy based on CSF and plasma biomarkers of inflammation and disease progression, brain MRI, and cognition.

References

1 Kantor, A. B. *et al., J Prev Alzheimers Dis 10, 647-660 (2023)*
2 Ryu, J. K. *et al,. Nat Immunol* 19, 1212-1223 (2018)
3 Kantor, A. B. *et al,. AAIC 2025, Toronto*

Completed Phase 1a
Placebo-controlled safety trial in healthy volunteers

- THN391 was safe and well-tolerated
- No impact on coagulation
- PK supports monthly or longer dosing



- Intravenous injection
- Randomized, double-blind, placebo-controlled trial to assess the safety, tolerability, and PK of THN391

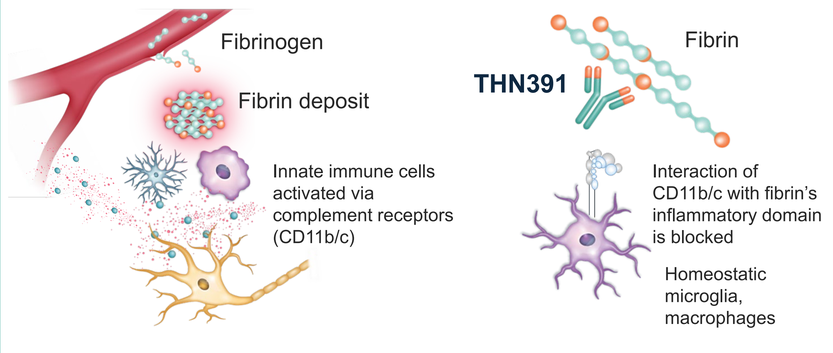
- **Safety**
  - No serious adverse events (SAEs)
  - Adverse events (AEs) were mild, mostly related to the infusion site and resolved without sequelae
  - No clinically significant changes observed in lab results, vital signs or ECG
  - THN391 had no impact on coagulation and fibrinolysis, as measured by PT, aPTT and ROTEM (rotational thromboelastometry)
  - THN391 did not induce anti-drug antibodies (ADA)

- **PK**
  - Population PK (popPK) model for THN391 following IV infusion using data for all cohorts
  - 3-compartment model with linear elimination and sex and body weight as covariates
  - THN391 concentration declined in a poly-exponential manner
  - Dose proportional PK
  - No indication of dose or time-dependent PK
  - Terminal half-life of 40 days supports monthly or longer dosing

- Study THN391-101, EudraCT 2022-003831-24

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



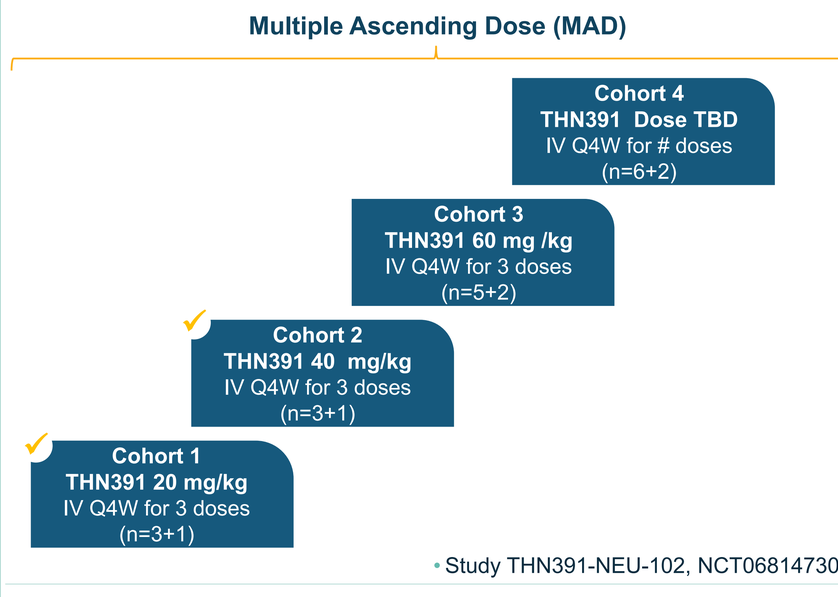
Damage to Neurons

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

Ongoing Phase 1b: Placebo-controlled trial in early Alzheimer's disease



- Study THN391-NEU-102, NCT06814730

SUBJECTS

- Male and female, age 65-85
- Diagnosis of Early Alzheimer's Disease (MCI or mild AD)
- Confirmed amyloid pathology
  - Historical or baseline CSF data: [Aβ]42/40 ratio, Elecsys® pTau181/Aβ42 ratio, or another regulatory approved assay
  - or historical amyloid PET imaging
- Mini Mental State Examination (MMSE) score ≥20 and ≤28 at screening
- Diagnosed with cSVD based on findings from a pre-study MRI (Fazekas score ≥ 1) or other evidence of vascular risk, such as hypertension
- APOE4 heterozygotes and homozygotes are allowed
- Moderate and severe dementia are excluded

ENDPOINTS

- **Primary**
  - Safety, tolerability, incidence of AEs and SAEs
  - THN391 serum concentration and PK parameters
- **Secondary**
  - Immunogenicity, occurrence of antidrug antibodies to THN391
  - Impact on coagulation, aPTT, PT, etc.
- **Exploratory**
  - THN391 concentrations in CSF
  - Pharmacodynamic effects of multiple doses of THN391 on markers related to blood brain barrier breakdown, neurodegeneration, astrocytic activity, microglial markers, and inflammatory proteins including cytokines and chemokines
  - Measures of cognition, including choice reaction time (CRT), spatial working memory (SWM), and delayed picture recognition (DPR)
  - Imaging measures, including, but not limited to, brain volume, measures of cerebral blood flow (ASL-MRI), and measures of blood brain barrier integrity (DCE-MRI)

Phase 1b early AD trial progress

Enrolment and dosing

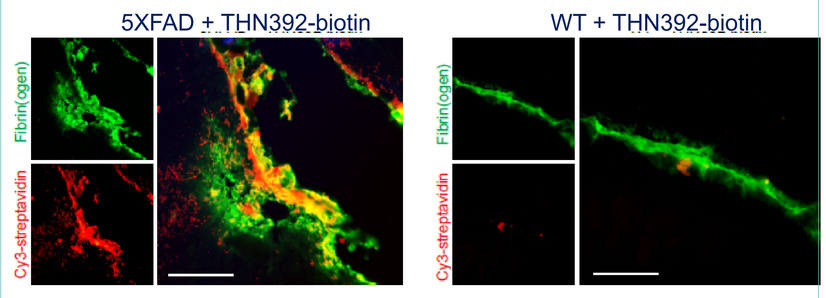
- Cohort 1 (20 mg/kg, 3 active:1 placebo) - 4 enrolled, dosing complete
- Cohort 2 (40 mg/kg, 3 active:1 placebo) - 4 enrolled, 1 or more doses each
- Cohort 3 (60 mg/kg, 5 active:2 placebo) - screening in progress

Safety

- THN391 remains safe and well-tolerated
  - All AEs were mild and resolved, and 2 possibly related to the drug
  - General disorders and administration site conditions were the most common AEs
- MRI assessment of ARIA
  - First 6 subjects: 4 are APO ε3/ε4 and 1 is APO ε4/ε4 (historical)
  - ARIA E and H assessed at screening and D22, D50, D120, and D248
  - No evidence on ARIA E or H based on the first 11 post-dose assessments

Target engagement in 5XFAD mice

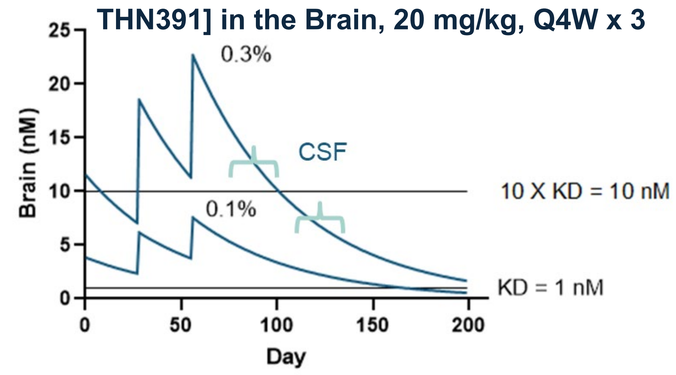
- The uptake of a murine version of THN391 was characterized in brain of 5XFAD mice, which model features of AD including neuroinflammation and fibrin deposition.
- THN392 spatially correlated with fibrin(ogen)-rich areas in both the cortex and hippocampus of 5XFAD mice
- THN392 was not detected in the parenchymal area of the cortex and hippocampus in aged-matched littermate controls



Modified from experiment with Jae Ryu in Kantor et al, manuscript in revision

PK modeling of effective dose

- Minimal physiologically based pharmacokinetic (PBPK) modeling informs on efficacious dose
- $T_{1/2}$ = 40 days
- Assume, brain penetration 0.1-0.3%
- Assume drug is effective when THN391 concentration in the brain is > KD or >10X KD
- A dose of 20 mg/kg is predicted to be effective



Planned first analysis

- Early exploration of a pharmacodynamic (PD) biomarker response
- Timing: Cohort 1 and 2 reach complete day 120
- Plasma and CSF PD biomarkers
  - Paired plasma – CSF collections at baseline, D85 and D120
  - Additional plasma time points
- Lumipulse validated assays
  - Plasma - Aß42, pTau217, pTau217/Aß42, GFAP
  - CSF - Aß42, Aß40, Total Tau, pTau181, Aβ42/Aβ40, pTau181/Aβ42, pTau181/tTau
- NULISAseq multiplex panels
  - Plasma and CSF
  - Inflammation panel (~250 markers)
  - CNS disease panel with fibrinogen (~120 markers)

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 initiated 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 the first two cohorts of early AD patients
- We have also initiated an open-label Phase 1b study of intravitreal THN391 in subjects with DME in Australia

- **Acknowledgements**

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