Safety, tolerability, and pharmacokinetics of single and multiple ascending doses of THN391, a monoclonal antibody targeting the fibrin inflammatory epitope: Phase 1a clinical trial results

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Abstract

Background
Currently approved treatments for AD do not target inflammation, an essential driver of disease. These treatments are modestly effective, and present safety risks, especially for patients who are ApoE4 homozygotes. THN391 is a first-in-class high-affinity humanized monoclonal antibody, targeting the inflammatory epitope on fibrin to treat inflammatory neurodegenerative diseases. At sites of vascular damage, conversion of the blood coagulation protein fibrinogen to fibrin exposes a cryptic inflammatory epitope, γ377–395, which can bind complement receptors CD11b/c on microglia, macrophages, and dendritic cells, triggering an inflammatory response. Anti-fibrin γ377–395 antibodies significantly reduce inflammation and neuronal damage in 5XFAD mice (Ryu et al 2018).

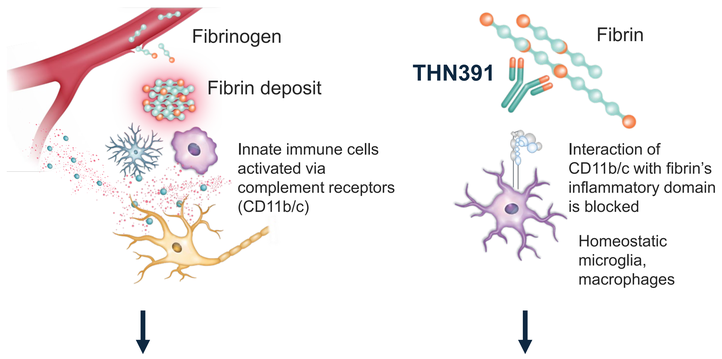
Methods
THN391 was evaluated in a randomized, double-blind, placebo-controlled trial to assess the safety, tolerability, and PK of single and multiple ascending doses (SAD and MAD) in healthy subjects. The SAD portion comprised 6 cohorts with 8 participants each (n=6 THN391 and n=2 placebo) receiving IV doses ranging from 0.3 to 40 mg/kg. MAD participants received 3 doses, initially Q2W at 3 and 10 mg/kg, then Q4W at 20 and 40 mg/kg. Safety assessments included rotational thromboelastometry (ROTEM) to evaluate any impact on coagulation and fibrinolysis.

Results
THN391 was safe and well-tolerated at all doses with no serious adverse events and only 5 adverse events which were mild, related to the infusion site and resolved without sequelae. There were 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. Population PK modeling indicates that THN391 exhibits dose proportional pharmacokinetics and a terminal half-life of 40 days, supporting monthly or less frequent dosing.

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 IV dosing. A Phase 1b study is planned in patients with early AD .ApoE4 homozygotes will be eligible. The study will assess safety, PK, early signals of efficacy based on CSF and plasma biomarkers of inflammation and disease progression, brain MRI (ASL and DCE-MRI) and cognition.

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



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

Summary of Treatment-Emergent Adverse Events SAD + MAD, N=80

- There were no serious adverse events
- Most reported TEAEs were mild, deemed not related to THN391, and resolved without sequelae

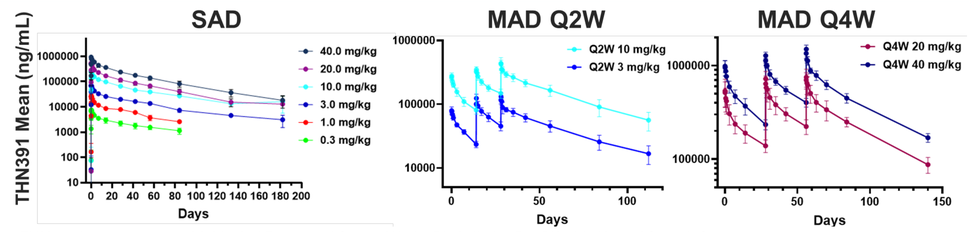
	SAD		MAD	
Category	THN391 N=36 E n (%)	Placebo N=12 E n (%)	THN391 N=24 E n (%)	Placebo N=8 E n (%)
Any TEAEs	88 28 (77.8)	29 9 (75.0)	53 20 (83.3)	19 8 (100.0)
TEAEs by relationship				
TEAEs related to study drug	4 4 (11.1)	1 1 (8.3)	0	0
TEAEs not related to study drug	84 28 (77.8)	28 9 (75.0)	53 20 (83.3)	19 8 (100.0)
TEAEs by severity				
Mild	86 28 (77.8)	29 9 (75.0)	53 20 (83.3)	19 8 (100.0)
Moderate	2 2 (5.6)	0	0	0
Severe	0	0	0	0
SAEs	0	0	0	0
AEs leading to study drug withdrawal	0	0	0	1 1 (12.5)
AEs leading to early termination	0	0	0	1 1 (12.5)

E=number of TEAEs; N=number of subjects exposed; n=number of subjects that experienced the TEAE

- General and site disorders: Drug, placebo — SAD 42%, 42%; MAD 46%, 63%
- Headache: Drug, placebo — SAD 25%; 17%; MAD 29%, 13%
- Nasopharyngitis: Drug, placebo — SAD 22%; 16%; MAD 29%, 13%

Pharmacokinetics

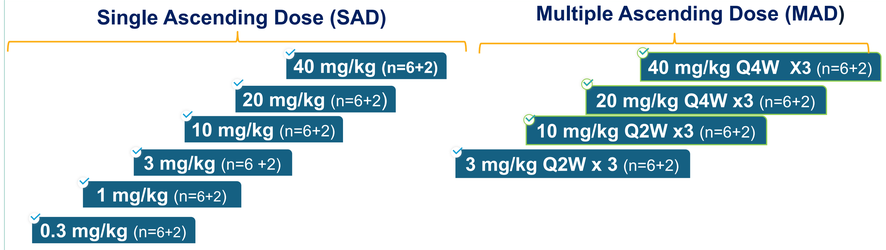
- Population PK (popPK) model for THN391 following IV infusing using data for all cohorts
- 3-compartment model with linear elimination and sex and body weight as covariates
- THN391 concentration declined in a poly-exponential manner
- Dose proportional PK. No indication of dose or time-dependent PK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



THN391 immunoassay with Mychal Feeny and Staton Wade, BioAgilytix; PopPK with Ahmed Saeed, Certara

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
- 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
- PK is dose proportional, linear, and supports monthly or longer dosing
- THN391 had no impact on coagulation and fibrinolysis, as measured by PT, aPTT and ROTEM

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

THN391 does not induce anti-drug antibodies (ADA)

- **THN391 has a clean immunogenicity profile**
- The presence or absence of anti-THN391 antibodies was accessed using a validated electrochemiluminescent bridging immunoassay
- ADA was evaluated using a 3-tier screening and confirmation procedure: screening (5% FPR [false positive rate]) confirmation (1% FPR), and titer (0.1% FPR)
- All samples were ADA negative in the SAD cohorts of 0.3 to 40 m/g/kg
- One sample, from 1 subject in the MAD 3 mg/kg cohort had an ADA titer of <5 at Day 113
- The <5 value means that the sample was below the titer cut-point of 1.26 normalized value when ran at the minimum required 5-fold dilution
- This is considered titer negative

THN391 does not interfere with coagulation

- **Standard laboratory coagulation assessments**
- Prothrombin time (PT) activated partial thromboplastin time (aPTT), D-dimer, thrombin time, and fibrinogen
- PT assess the extrinsic and common coagulation pathways
- aPTT assess the intrinsic and common coagulation pathways
- FIbrinogen is part of the common pathway
- No changes or trends of clinical significance were seen in coagulation parameters across all dosing cohorts

Exposure margin calculation for Phase 1b study in early Alzheimer's disease

- THN391 is safe and well-tolerated in NHP
- Safety exposure margin calculation using Phase 1a popPK and NHP popPK calculations
- NHP 26-week, weekly dosing study with a NOAEL of 100 mg/kg
- NHP 5-week weekly dosing study, with no THN391-related toxicological effects at 400 mg/kg
- Exposure margin supports dosing from 20 mg/kg to 60 mg/kg or higher

Human (Q4Wx3)			Exposure Margin NHP/Human			
Dose (mg/kg)	C_{max} µg/mL	AUC_{tau} h*µg/mL	100 mg/kg C_{max}	100 mg/kg AUC_{tau}	400 mg/kg C_{max}	400 mg/kg AUC_{tau}
20	703.7	237,200	7.7	10.7	26.6	53.2
40	1407	474,500	3.8	5.3	13.3	26.6
60	2111	711,700	2.6	3.6	8.8	17.7
80	2815	1,186,000	1.9	2.7	6.7	13.3

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

Multiple Ascending Dose (MAD)

Cohort 1
THN391 20 mg/kg
IV Q4W for 3 doses
(n=3+1)

Cohort 2
THN391 40 mg/kg
IV Q4W for 3 doses
(n=3+1)

Cohort 3
THN391 60 mg /kg
IV Q4W for 3 doses
(n=5+2)

Cohort 4
THN391 Dose TBD
IV Q4W for 3 doses
(n=5+2)

KEY ENDPOINTS

- **Primary:** Safety, tolerability, PK
- **Secondary:** Biological Activity
  - Immunogenicity
  - Impact on coagulation

EXPLORATORY BIOMARKERS

- Cognitive assessments
- Cerebral blood flow by arterial spin labeling MRI and BBB integrity by dynamic contrast-enhanced-MRI
- PD markers in the plasma and CSF, including fully validated assays for Aβ42/40, total Tau and p-Tau181, 217, 231 and exploratory NULISAseq for NEURO and INFLAM markers

SUBJECTS

- Mild cognitive impairment (MCI) due to AD
- Mild AD who show progressive decline in 1 or more cognitive domains
- Confirmed amyloid pathology
- ApoE4 heterozygotes and homozygotes are allowed
- Age 65-85
- Moderate and severe dementia excluded

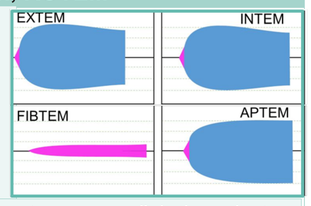
- Study THN391-NEU-102, NCT06814730

Summary of Demographics, SAD + MAD, N=80

Parameter	n (%)
Sex - n (%)	
Female	39 (48.8)
Male	41 (51.3)
Race - n (%)	
White	70 (87.5)
Black or African American	1 (1.3)
Asian	5 (6.3)
American Indian or Alaska Native	2 (2.5)
Native Hawaiian or Other Pacific Islander	0
Other	2 (2.5)
Ethnicity - n (%)	
Hispanic or Latino	4 (5.0)
Not Hispanic or Latino	76 (95.0)
Age (years)	
Mean (Std Dev)	31.7 (10.93)
Median (Min, Max)	28.0 (18, 55)
Weight (kg)	
Mean (Std Dev)	74.31 (11.098)
Median (Min, Max)	74.15 (51.3, 99.4)
Height (cm)	
Mean (Std Dev)	174.8 (8.71)
Median (Min, Max)	174 (150, 192)
BMI (kg/m^2)	
Mean (Std Dev)	24.27 (2.749)
Median (Min, Max)	23.85 (19.3, 30.8)

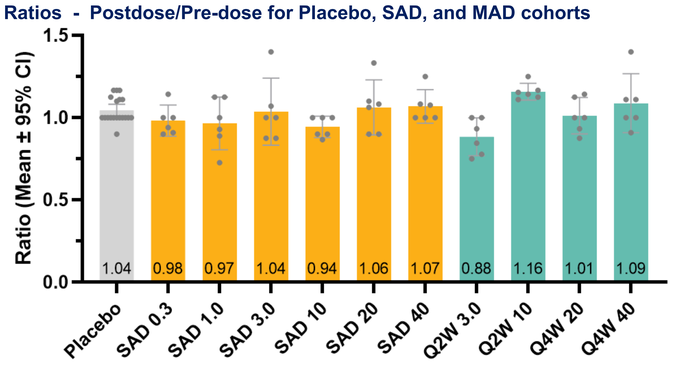
THN391 does not interfere with coagulation, ROTEM

- **Rotational thromboelastometry (ROTEM)**
- ROTEM sigma is a point-of-care cartridge-based thromboelastometry system for coagulation analysis
- Clotting start and firmness is continuously monitored
- Together, 4 separate assays, EXTEM, INTEM, FIBTEM and APTEN provide a comprehensive assessment
- The FIBTEM assay, which bocks platelet activation with Cytochalasin D, is especially sensitive to disruption in fibrin formation and polymerization



- No changes or trends of clinical significance were seen in all ROTEM parameters across all dosing cohorts
- No changes or trends of clinical significance were seen in the FIBTEM parameters across all dosing cohorts
- For example, clot firmness in the FIBTEM assay at 10 min (A10) is not affected by THN391: the Post dose/pre-dose ratios are all near 1

FIBTEM A10 Ratios - Postdose/Pre-dose for Placebo, SAD, and MAD cohorts



Pre-dose 1 hr before first IV infusion, Post dose 2hr after end of last dose, SAD Day 1, MAD Q2W day 29, MAD Q4W day 57
Placebo n=20, Each cohort n=6
Least Squares mean comparison vs placebo, with Dunnet multiple comparison test: Q2W 3.0 $p < 0.05$, all other NS
With Sarah Kavanagh

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
- We have also initiated an open-label Phase 1b study of intravitreal THN391 in subjects with DME in Australia
- **Acknowledgements**

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