THN391 – A Novel Anti-fibrin Antibody, Evaluated in an Ongoing Phase 1b Study for the Treatment of Diabetic Macular Edema

ARVO 2025
3785 - B0006

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Abstract

Purpose: Increased vascular permeability, deposition of blood-derived fibrin, and subsequent activation of innate immune cells is a central mechanism underlying vascular retinal diseases, including diabetic retinopathy (DR), diabetic macular edema (DME) and wet age-related macular edema (AMD). Proteolytic conversion of the blood coagulation protein fibrinogen to fibrin by thrombin exposes an inflammatory epitope, which activates microglia and macrophages by binding to CD11b/CD11c complement receptors, resulting in the release of cytokines and reactive oxygen species (ROS) and damage of retinal and vascular cells. THN391 is a first-in-class humanized antibody targeting this inflammatory epitope. It is effective in reducing neovascular lesions in animal models of laser-induced choroidal neovascularization (CNV) and streptozotocin (STZ) induced DR (Kantor et al, ARVO 2024) both of which contain fibrin deposits. Here we demonstrate fibrin deposition in human eyes with DR and Wet AMD and the advancement of THN391 to a Phase 1b study assessing safety, tolerability, and biological activity in DME.

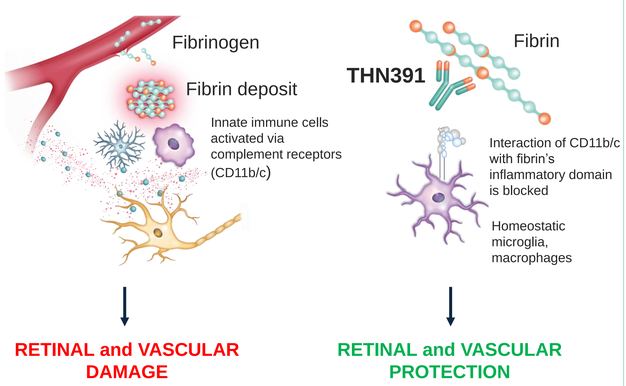
Methods: We performed immunohistochemical staining to show fibrin deposition (MAb 102-10) and macrophage/microglia accumulation (Iba1) and activation (iNOS) in eyes from patients with AMD and DR. We designed an open-label safety and tolerability study in ~21 patients with DME. Patients are sequentially assigned to 3 ascending doses of THN391 administered intravitreally every 4 weeks and followed for a total of 16 weeks. Assessments include ocular and systemic adverse events, Best Corrected Visual Acuity (BCVA), optical coherence tomography (OCT), fluorescein angiography, and OCT-angiography (OCTA). Exploratory assessments include measurement of macrophage-like cell densities with OCT-angiography.

Results: We show that human DR and wet AMD retinal tissues display high levels of fibrin deposition and associated increase in activation of innate immune cells. Study THN391-OPT-101, a Phase 1b Open-Label, Multiple Ascending Dose Study of the Safety, Tolerability, and Biological Activity of Intravitreal THN391 in Diabetic Macular Edema Secondary to Non-Proliferative Diabetic Retinopathy, is ongoing in Australia. Results are analyzed on an ongoing basis.

Conclusion: The presence of fibrin deposits in human DR and wet AMD eyes supports a role for THN391 in the treatment of vascular retinal diseases. A clinical development program to study the safety and efficacy of THN391 was initiated and preliminary results will be discussed when available.

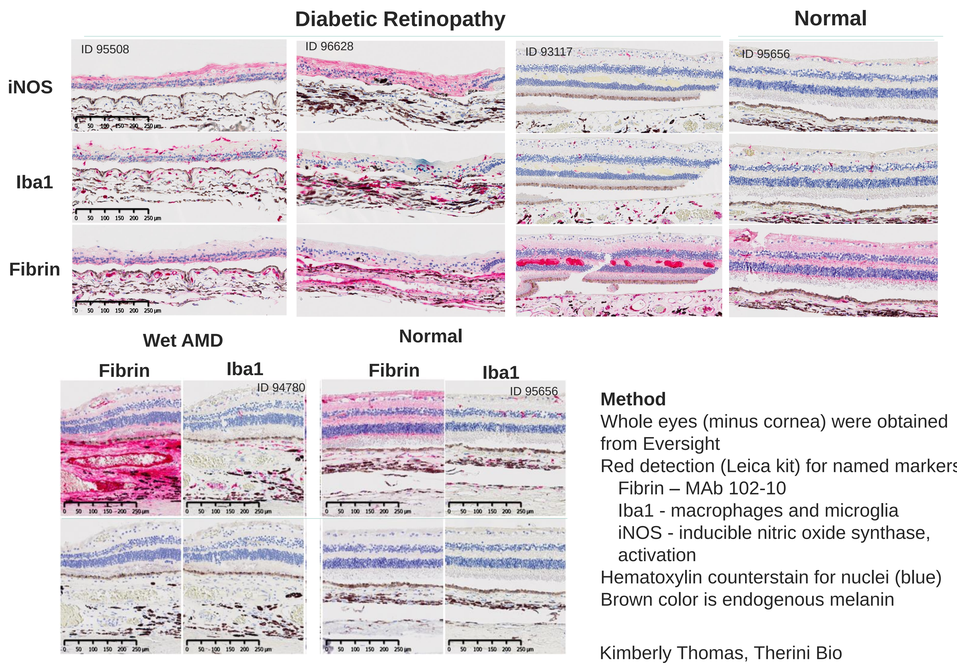
Fibrin is central to innate immune cell-mediated inflammation

- Loss of vascular integrity results in fibrin deposition
- Fibrin inflammatory epitope triggers immune cell-mediated inflammation
- Blocking the inflammatory epitope with antibodies is protective in animal models of retinal disease, Alzheimer's disease and multiple sclerosis



Diabetic retinopathy tissues display high levels of fibrin deposition and associated increase in activation of innate immune cells

- Fibrin deposition observed at high levels in the choroid of DR and wet AMD eyes
- Macrophage activation (iba1/iNOS) is present in DR and AMD eyes

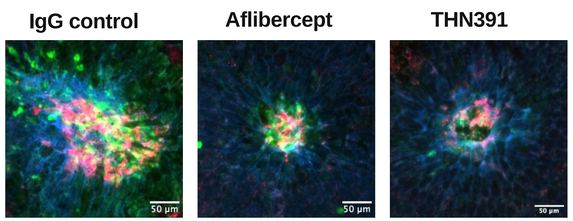


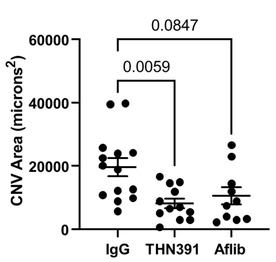
Method
Whole eyes (minus cornea) were obtained from Eversight
Red detection (Leica kit) for named markers
Fibrin – MAb 102-10
Iba1 - macrophages and microglia
iNOS - inducible nitric oxide synthase, activation
Hematoxylin counterstain for nuclei (blue)
Brown color is endogenous melanin

Kimberly Thomas, Therini Bio

THN391 reduces neovascular lesions in rodent models of wet AMD and diabetic retinopathy

- THN391 IVT injection reduces neovascular lesions in the rat LCNV model of wet AMD (Kantor et al, ARVO 2024)
- THN391 IP injection is effective in the mouse STZ model of DR (ARVO 2024)
- THN391 IVT injection reduces neovascular lesions in the mouse LCNV model of wet AMD (shown below)





CD31 (PECAM-1) – endothelial cells, vascular marker
IBA1- macrophage, microglia
Actin – cytoskeleton, angiogenesis

Method
C57/B6 mice (male) lasered in both eyes on Day 0
IVT injection within 30 minutes, IgG 13 µg/eye, THN391 13 µg/eye, Aflibercept 10 µg/eye (molar equivalent)
Flat mount immunofluorescence on day 7. Analysis for CNV size by masked grader

Patients with diabetic macular edema secondary to non-proliferative diabetic retinopathy

Multiple Ascending Dose (MAD)

Cohort 1
THN391 1.2 mg dose
IVT Q4W for 3 doses
(n=3)

Cohort 2
THN391 3.5 mg dose
IVT Q4W for 3 doses
(n=9)

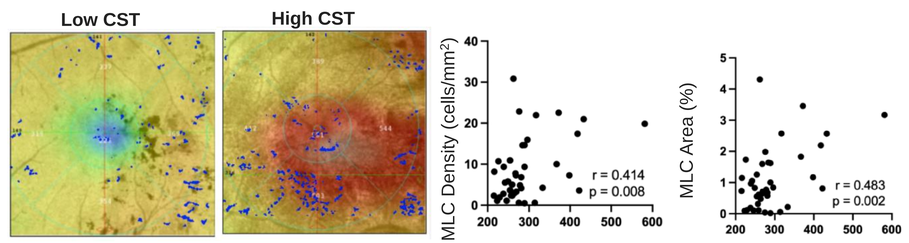
Cohort 3
THN391 10 mg dose
IVT Q4W for 3 doses
(n=9)

KEY ENDPOINTS
- **Primary:** Safety and tolerability
- **Secondary:** Biological Activity
  - Δ Central subfoveal thickness (SD-OCT)
  - Δ Visual acuity (BCVA)
  - Retinal anatomy: color fundus photographs, wide-field FA, OCT, and OCTA
  - **EXPLORATORY BIOMARKERS**
- Δ Macrophage-like cells (MLC) OCTA

SUBJECTS
- Center-involving macular edema associated with non-proliferative DR in the study eye
- BCVA between 70 and 35 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) testing (~20/40 to 20/200, inclusive, by Snellen chart)
- Central subfield thickness of ≥ 325 µM
- Treatment experienced and treatment naïve

Epiretinal macrophage-like cell density imaged with OCT-Angiography
A novel exploratory biomarker implemented in the Phase 1b ongoing study

MLC density and area correlate with DME severity



Representative overlays of MLCs (blue) on the macular thickness map
Thick to thin: white ►red ►yellow ►green ► blue

From Zhang et al., *Diagnostics*, (2022)

Conclusions

- We demonstrated the effectiveness of intravitreal THN391 in the rat and mouse laser-damage models of wet AMD and the mouse STZ model of DR
- DR tissues display high levels of fibrin deposits and associated increase in activation of innate immune cells
- THN391, a first-in-class therapeutic monoclonal antibody targeting the fibrin inflammatory epitope responsible for driving neuroinflammation, is currently in clinical development
- We have initiated an open-label Phase 1b study of intravitreal THN391 in subjects with DME in Australia, NCT06701721
- 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
- Macrophage-induced inflammation may exacerbate the clinical manifestations of DR, DME, and wet AMD as well as contribute to the resistance and/or loss of efficacy of the VEGF antagonists in retinal diseases. THN391 alone, or in combination with VEGF antagonists has the potential to improve treatment outcomes

Acknowledgements
We thank our colleagues at Therini Bio, the Lavine lab, the clinical sites, Novotech, and Voiant for their many contributions leading to the development of fibrin targeting therapies for retinal diseases and the implementation of this study.