Oral Formulation Development of the Anti-Angiogenesis Drug D-4517.2 to Treat Age-related Macular Degeneration (wet AMD) and Diabetic Macular Edema (DME)

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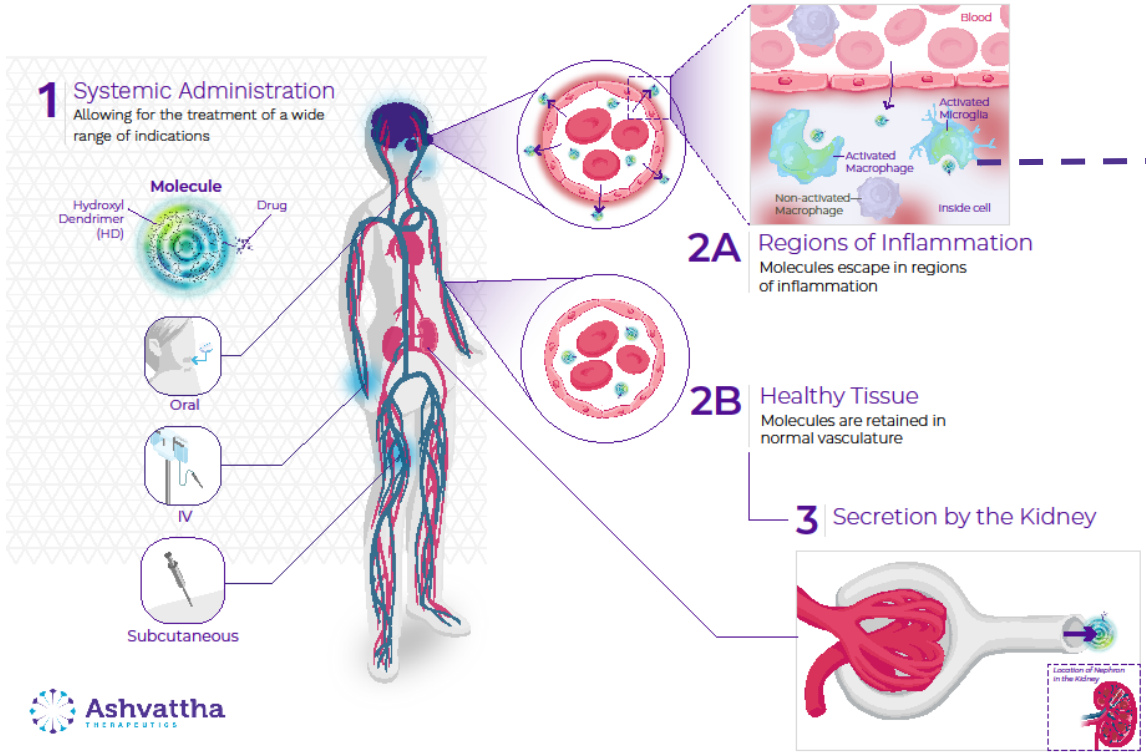
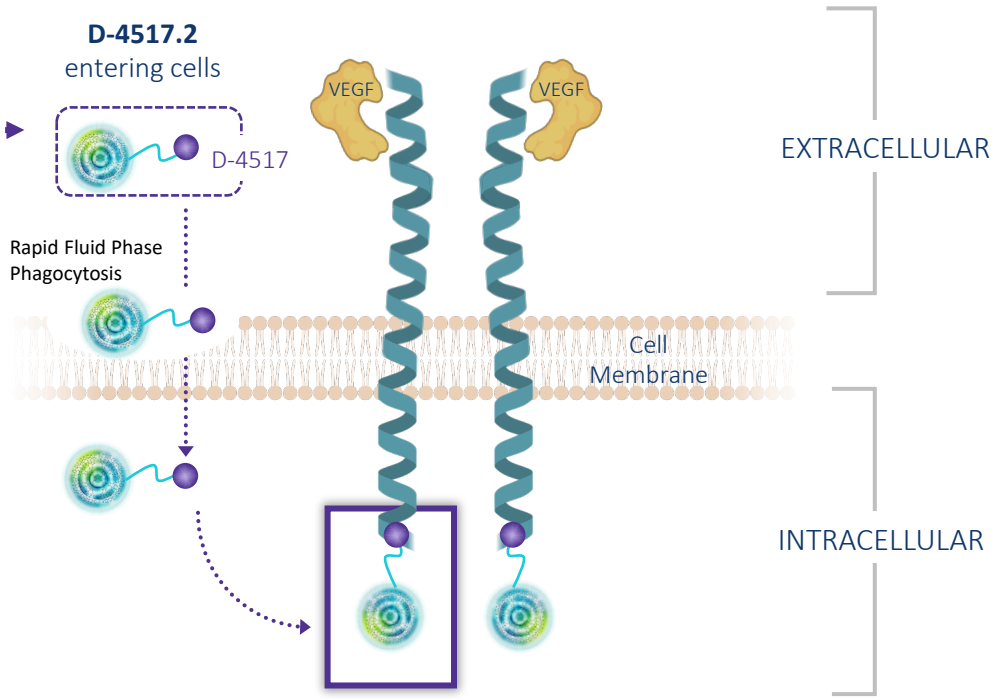
D-4517.2 is a new precision nanomedicine technology delivered subcutaneously to nAMD and DME patients

D-4517.2 inhibits vascular endothelial growth factor receptor tyrosine kinases selectively in activated microglia and hypertrophic retinal pigment epithelial (RPE) cells.

Cross the blood-retinal barrier and target activated cells



Shuts down VEGF expression and restores normal levels of signaling[1]



inhibits intracellular VEGFR1/2
(D-4517.2 stays in cells for up to 1 month)

1. Cleland et al, ARVO 2022, Poster F0181

Preclinical studies and clinical trials with D-4517.2

- Preclinical studies demonstrating that:
  - D-4517.2 crosses the blood-retinal barrier in rodents after systemic administration
  - D-4517.2 accumulates specifically in activated microglia and macrophages, and RPE cells
  - D-4517.2 demonstrates efficacy in 3 ocular models (CNV[1], *VLDLR*$^{-/-}$[2] and OIR)

- Completed 6- and 9-month GLP tox studies in rats and dogs (NOAEL allowing ~5-10-fold safety factor of maximum human dose at 2 mg/kg).

- In Phase I clinical trial, subcutaneous (SC) administration of D-4517.2 in healthy subjects was safe and well-tolerated at highest dose level tested, 2.0 mg/kg (**NCT05105607**).

- A Phase 2 clinical trial is ongoing in neovascular AMD (nAMD) and DME patients to explore the safety, pharmacodynamics, and durability of subcutaneous D-4517.2 compared to intravitreal aflibercept in nAMD and DME Patients (**NCT05387837**).

1. Cleland et al, ARVO 2021
2. Wu et al, ARVO 2023, Poster 3900 - B0180, April 26, 2023, from 10:30 AM to 12:30 PM

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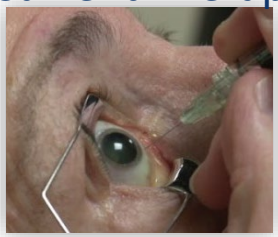
TEJAS: D-4517.2 Phase 2 Trial Overview

Current Therapy



D-4517.2

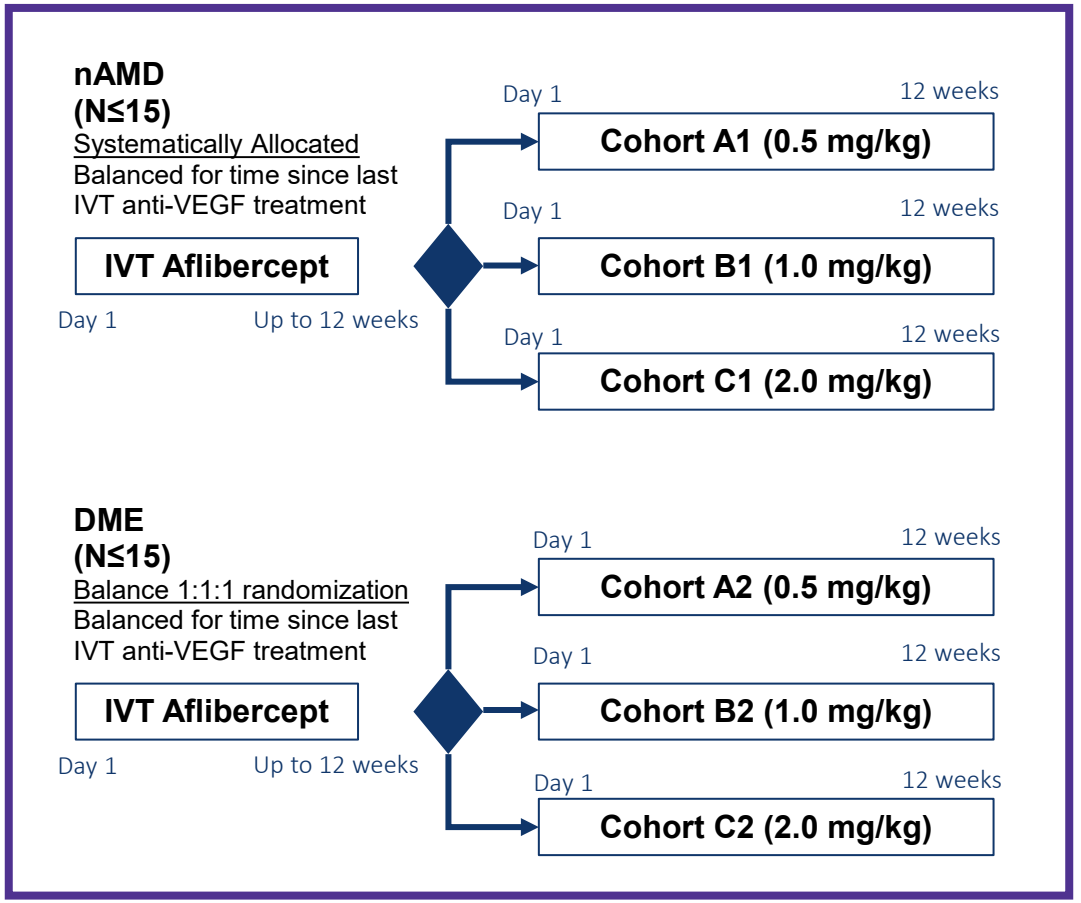
Target population: patients with nAMD or DME who respond to intravitreal anti-VEGF therapy (based on at least 3 doses) and who have been treated for ≤ 36 months.

Stage 1: single SC dose; 3 dose levels; intrasubject crossover comparison to aflibercept (N=30 subjects, LPI Q2 2023).

Stage 2: multiple doses over 9 months (N=270 subjects, FPI H1 2024); 2 dose levels with separate aflibercept arm (non-inferiority).

Endpoints: safety/tolerability (primary), amplitude/duration of subretinal fluid reduction/change in BCVA (secondary), change in CST/BCVA/drusen volume in fellow eye (exploratory).

Phase 2, Stage 1



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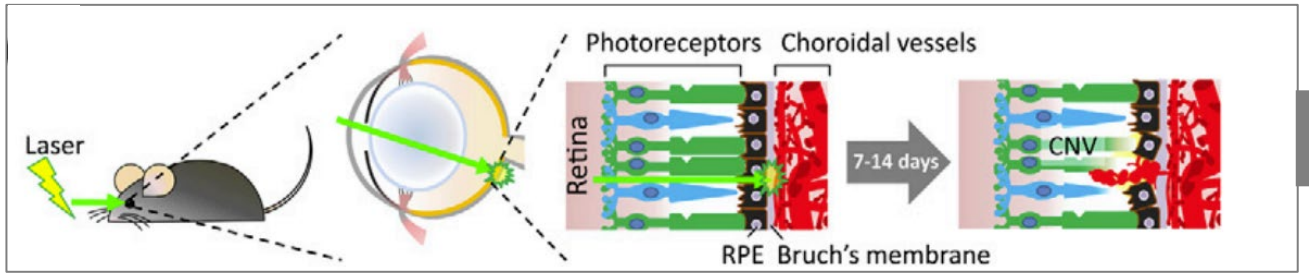
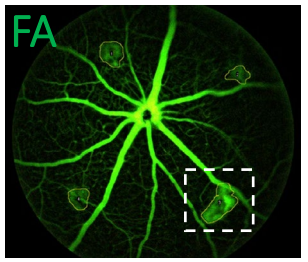
Single oral administration of D-4517.2 inhibits choroidal neovascular lesions in a laser-induced mouse model of CNV

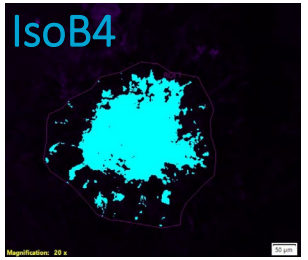
Laser-induced mouse model of CNV[1]



Readouts



Fluorescein angiography (vasculature leakage)



Isolectin-stained flat mount (neovascular lesion)

- Model: Laser-induced rupture of Bruch's membrane in both eyes of C57BL/6 mice (n=6-8/group).
- Treatment: single dose of D-4517.2 SC (40 µg), oral gavage at 2 dose levels (40 and 200 µg), and aflibercept IVT (1 µL, 40 µg).
- Treatment timing: 24 hours after laser injury.
- Endpoints: CNV lesion area with isolectin B4 staining of the RPE-choroid-sclera flat mounts and fluorescein angiograms (FA) 14 days after injury.
- Excipients for oral dosing: salcaprozate sodium (SNAC), disodium EDTA and sucrose laurate.

1. Liu et al, The FASEB Journal, 2017.

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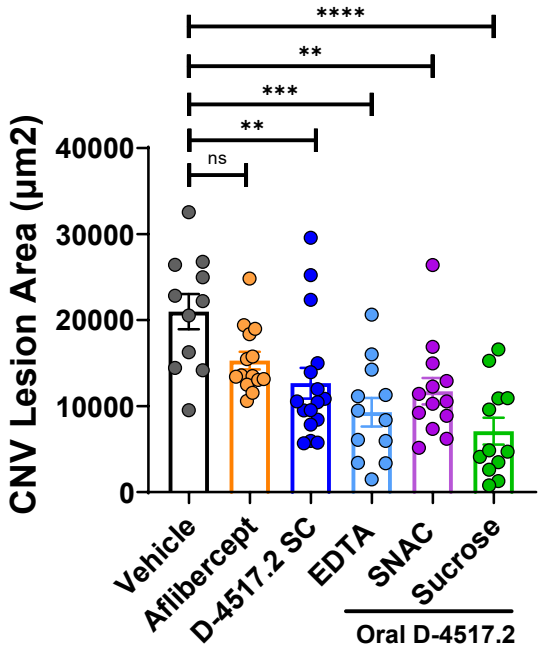
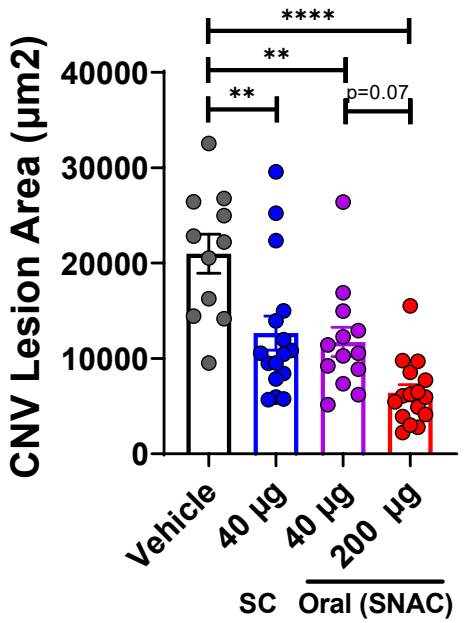
Single oral administration of D-4517.2 reduces CNV lesion area and vascular leakage in a laser-induced CNV mouse model

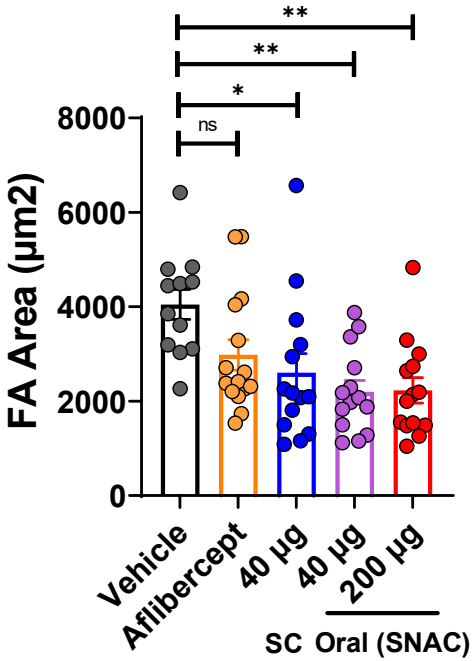
CNV lesion area at Day 14 (Isolectin B4 staining)



CNV lesion area at Day 14 (Isolectin B4 staining)



Vascular leakage at Day 14 (fluorescein angiogram)



- The CNV lesion area was significantly reduced by ~2-fold (**p<0.01) in mice treated with a single SC and oral dose of D-4517.2 (40 µg).
- D-4517.2 in SNAC significantly reduced both CNV lesion area and vascular leakage by ~2-fold (**p<0.01), suggesting comparable SC and oral bioavailability.

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Summary & Conclusions

- A single oral dose of D-4517.2 significantly reduced CNV lesions in mice to a level comparable to the subcutaneous administration of D-4517.2 and IVT aflibercept at a same mass dose.

- The reduction of the CNV lesions after oral administration of D-4517.2 was confirmed in *VLDLR*$^{-/-}$ mice by Elia Duh's lab[1].

- These preclinical studies support the development of D-4517.2 as a potentially safe and effective oral agent that can be administered chronically to nAMD and DME patients, eliminating the need for frequent IVT injections.

1. Wu et al, ARVO 2023, Poster 3900 - B0180, April 26, 2023, from 10:30 AM to 12:30 PM

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