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SUPRACHOROIDAL AVORALSTAT, A PLASMA KALLIKREIN INHIBITOR, STOPS VASCULAR LEAKAGE IN A WELL-ESTABLISHED RABBIT MODEL

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Disclosures

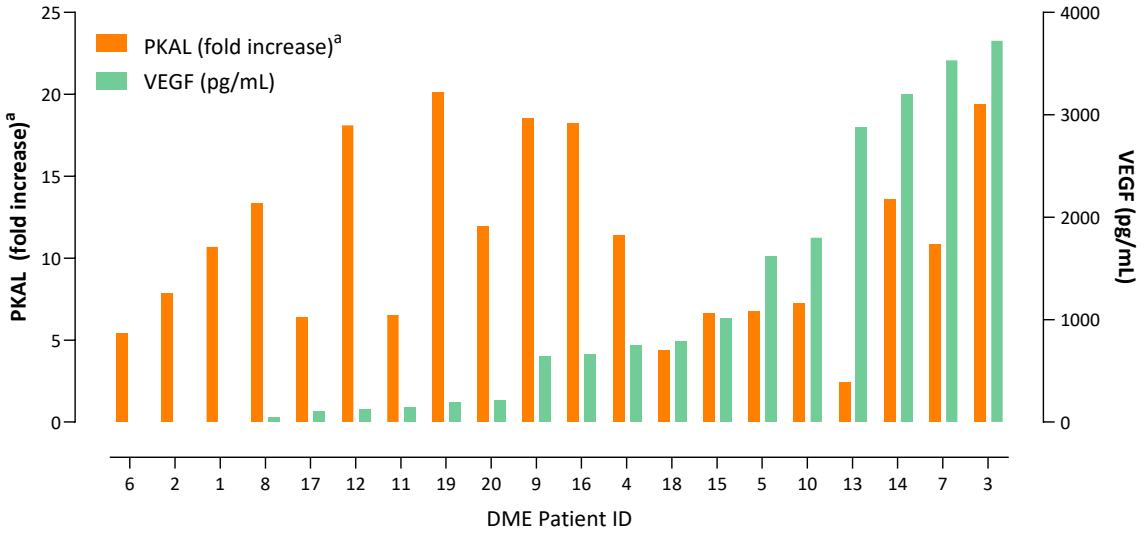
- **Dilsher Dhoot**: Consultant/Advisor for Alcon, Alimera Sciences, Allergan, Annexon, Apellis, Bayer, BioCryst, Coherus, EyePoint, Genentech, IvericBio, Novartis, Ocular Therapeutix, Optos, Outlook, Oxular, Regeneron, REGENXBIO, Roche, Santen.
- **Charles Wycoff:** Consultant for and has accepted grants, consulting fees, and/or contracts from 4DMT, AbbVie, Adverum, AffaMed, Aldeyra, Alexion, Alimera, Alkahest, Allgenesis, Amgen, Annexin, Annexon, Apellis, Ascidian, Asclepix, Astellas, Aviceda, Avirmax, Bayer, BioCryst Pharmaceuticals, Boehringer Ingelheim, Chengdu Origen, Clearside, Curacle, Eluminex, EyeBiotech, EyePoint, Genentech, GlaxoSmithKline, IONIS, iRENIX, Janssen, Kalaris, Kodiak, Kyoto DDD, Kyowa Kirin, Nanoscope, Neurotech, NGM, Novartis, Ocugen, Ocular Therapeutix, Oculis, OcuTerra, OliX, Opthea, Opus, Outlook Therapeutics, Oxular, Oxurion, Oyster Point, Perceive Bio, Pykus, Regeneron, REGENXBIO, Rezolute, Roche, Sandoz, Shanghai Henlius, Skyline, Stealth, UNITY, Verily, VH401. Member of an advisory board for Kato, Aerie, ASRS, Vit-Buckle Society. Stock options with InGel, Ollin, ONL, Osanni, Panther, PolyPhotonix, RecensMedical, TissueGen, Visgenx, Vitranu.
- **David Culp**: Consultant for and has accepted fees and/or contracts for preclinical contract research from BioCryst Pharmaceuticals.
- **Matthew Campbell**: Consultant for and receives research grants from BioCryst Pharmaceuticals.
- **Raj Maturi**: Consultant for BioCryst Pharmaceuticals. Received grants and/or contracts for sponsored research studies from Allergan, Genentech, Ophthea, Samsung Bioepis, Graybug, Santen, Thrombogenics, Gyroscope, Gemini, Boehringer Ingelheim, Allegro, Senju, Ribomic, NGM, Unity, Graybug, Clearside, Avecida, 4DMT, Ocular, Ocugen, Ocugenix, REGENXBIO. Has accepted consulting fees from Allegro, Allergan, Aviceda, Allgenesis, Eli Lilly, Dutch Ophthalmic, Novartis, Neurotech, Jaeb Center for Health Research, Unity, REGENXBIO. Member of an advisory board for Aviva, REGENXBIO.
- **John Michael Sauer**: Former employee of BioCryst Pharmaceuticals. Patent planned, issued, or pending for Avoralstat/DME provisional application field. Owner of AMGN stock.
- **Raluca Kubaszky, Aileen Morgan, and Donald S. Fong**: Employees of BioCryst Pharmaceuticals.

VEGF Inhibitors Not Fully Effective in DME

Plasma kallikrein (pKal) inhibition is an alternate approach for treating diabetic macular edema (DME)

- Persistent DME occurs in ~40% treated with VEGF (Protocol T)[1]
- Kallikrein-bradykinin system is one alternate pathway
- Elevated plasma kallikrein enzyme measured in DME vitreous samples[2]
- Previous trials failed due to insufficient kallikrein inhibition from
  - Insufficient dose
  - Poor retinal penetration

Elevated pKal in Vitreous of DME Patients



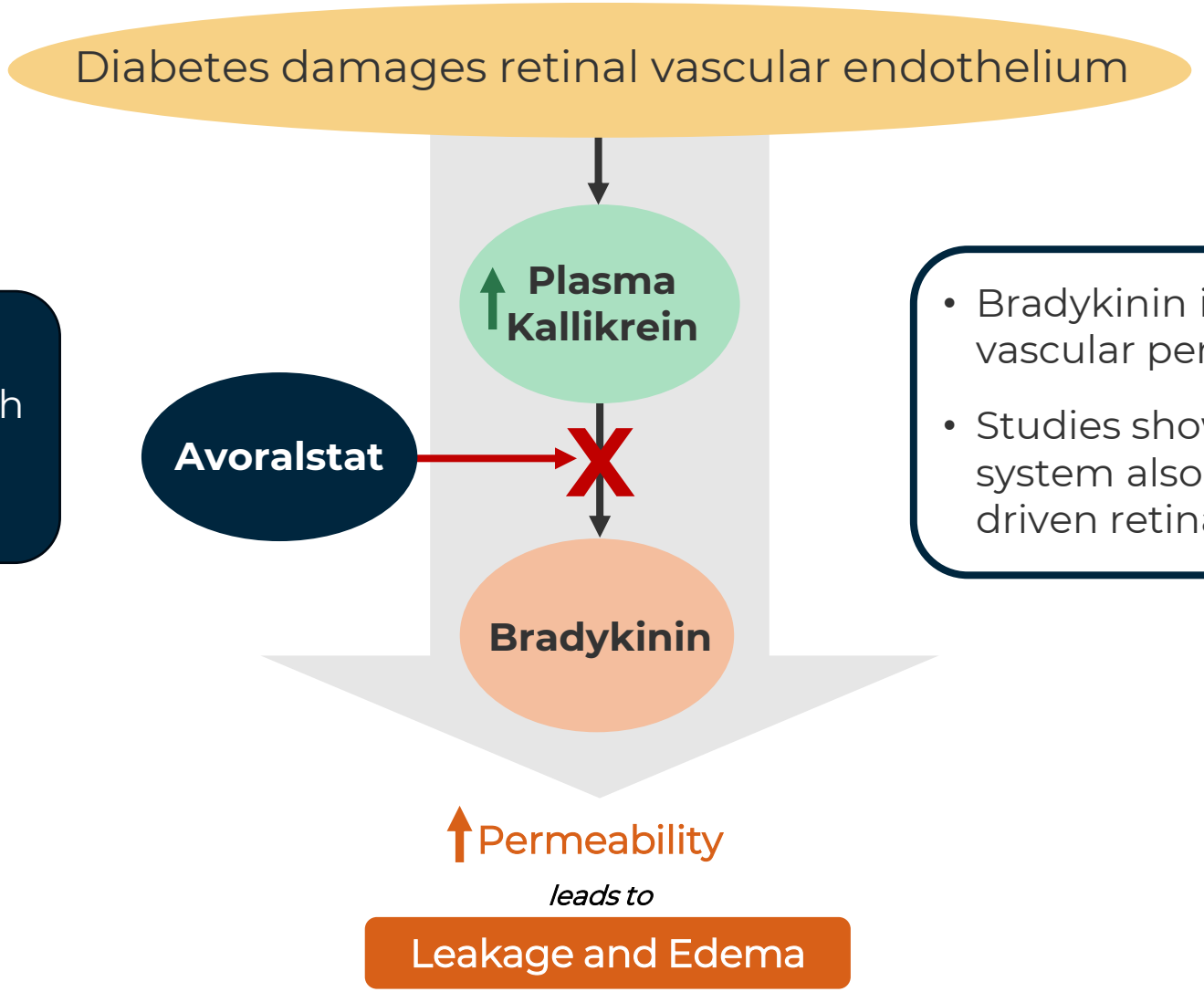
[a]Relative to mean of control subjects with macular hole

All DME patients in study showed elevated pKal, but only a subset had elevated VEGF relative to non-DME patients[2]

PKAL, Plasma Kallikrein; VEGF, Vascular Endothelial Growth Factor.
[1]Bressler et al. *JAMA Ophthalmol*. 2018;136(3):257-269
[2]Adapted and digitized from Kita et al. *Diabetes*. 2015;64(10):3588-3599

Kallikrein-Bradykinin is an Alternate Pathway in DME

Avoralstat could reduce edema by blocking bradykinin production



Avoralstat is a small molecule that can reach the retina from the suprachoroidal space

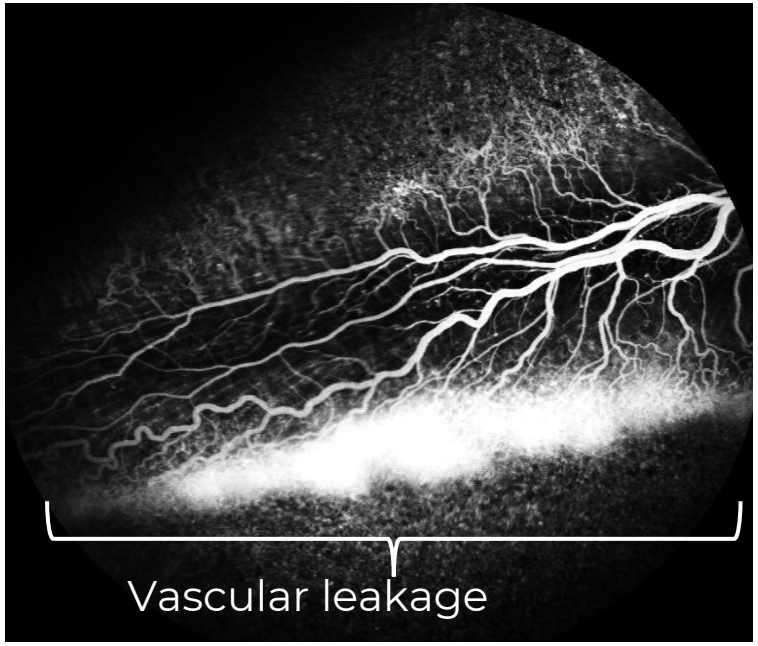
- Bradykinin is a known factor in vascular permeability/edema
- Studies show kallikrein-bradykinin system also mediates VEGF-driven retinal thickening[1]

DME, diabetic macular edema

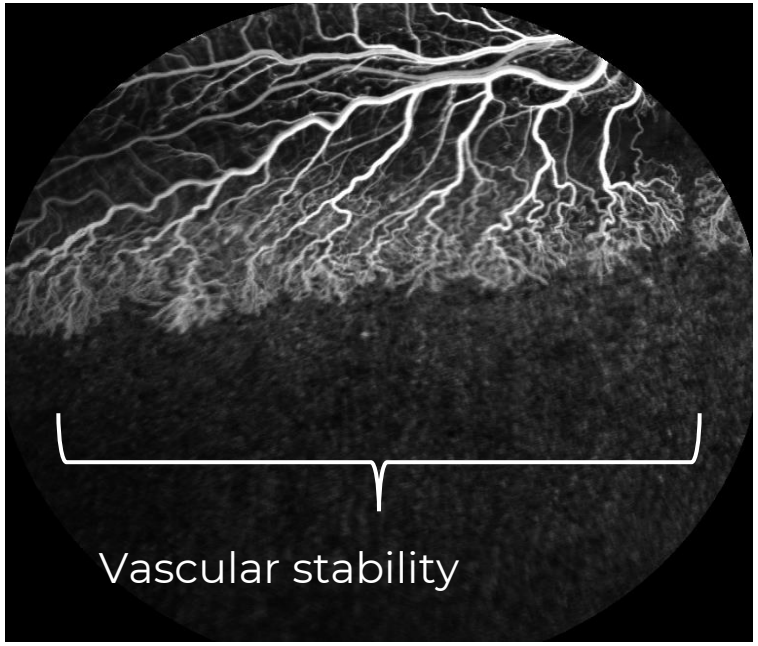
[1]Clermont et al. *Invest Ophthalmol Vis Sci.* 2016;57(6):2390-2399

Suprachoroidal Avoralstat Stops Retinal Leakage in DL-AAA Rabbit Model

Pre Dose

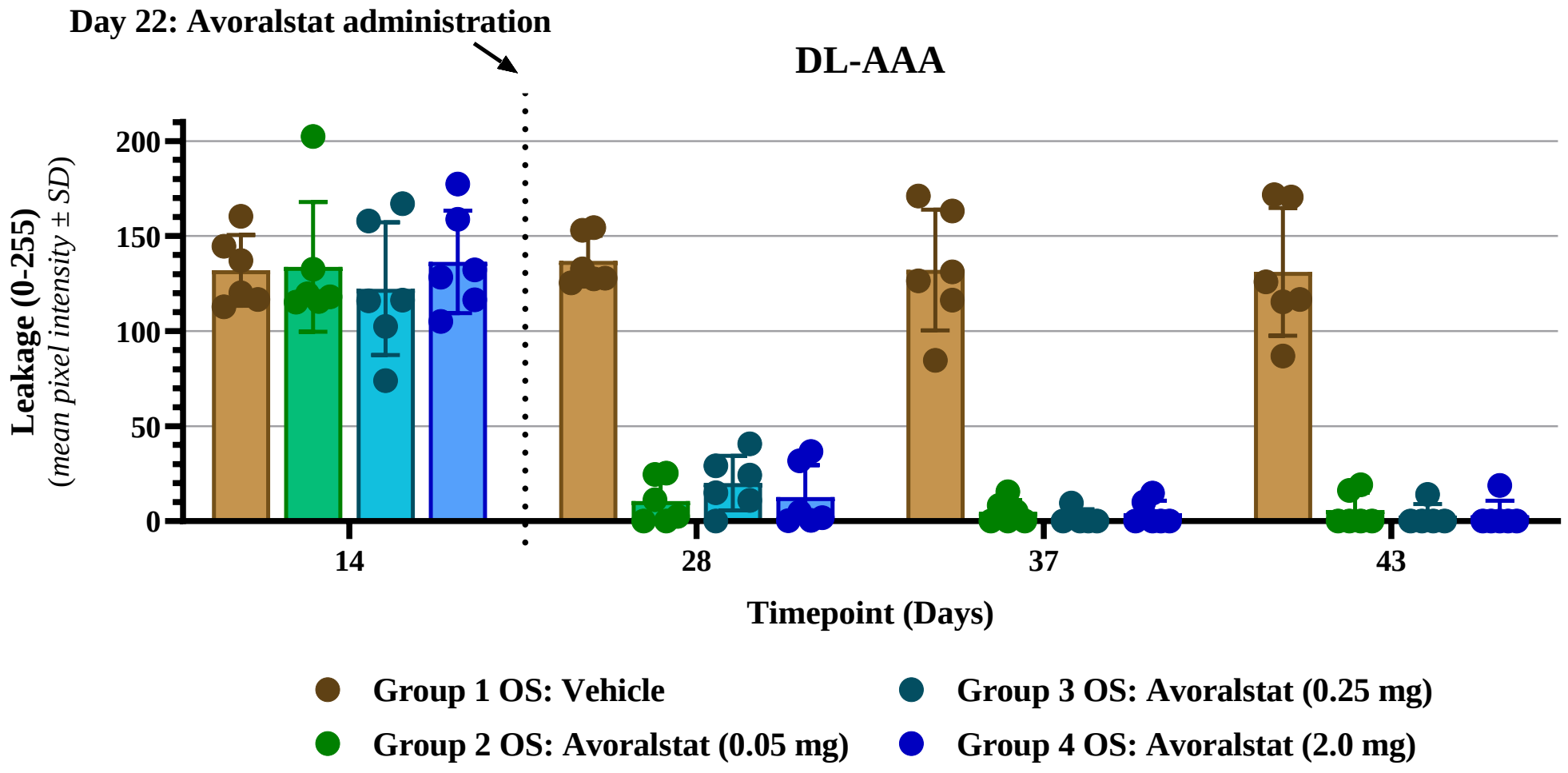


7 Days Post (2mg)



DL-AAA, DL-2-Aminoadipic Acid, glial cell toxin.

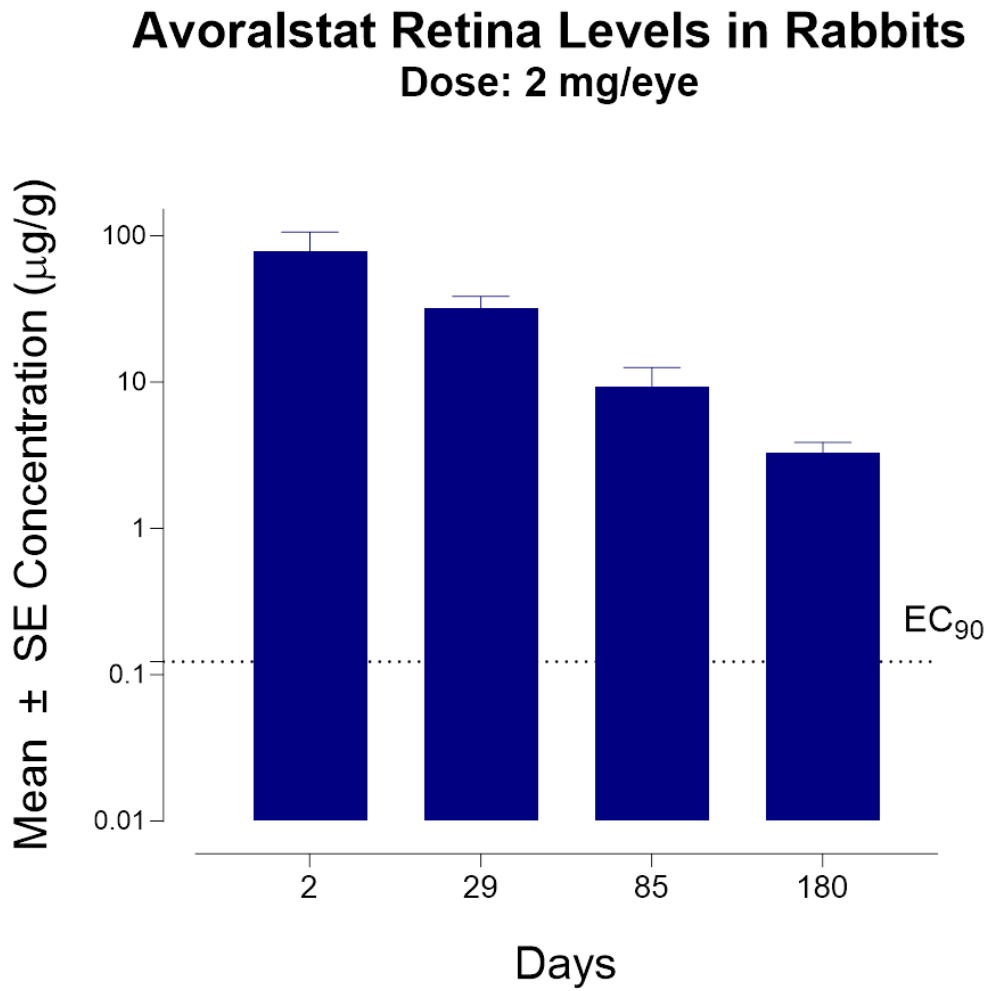
Resolution of Leakage by Quantitative Fluorescein Angiography



N=6 per group

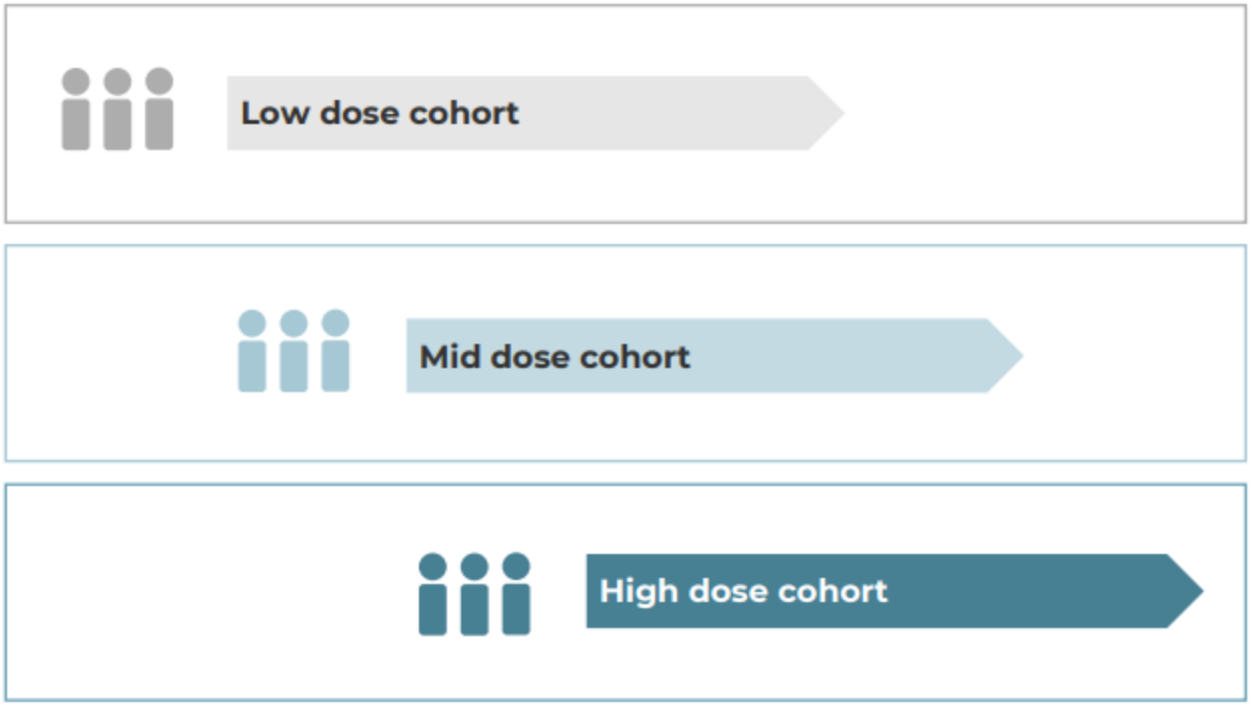
DL-AAA, DL-2-Aminoadipic Acid, glial cell toxin; OS, Left eye; SD, standard deviation.

Avoralstat Shows Durability in Rabbit Through 180 days



SE, standard error
EC_{90} The concentration of a drug that leads to 90% maximal response

Phase 1b Open-Label Study Design



- **Single dose**
- **24-week follow-up**
- **Data collected every 4 weeks**
  - Safety
  - Central subfield thickness
  - BCVA
- **Enrollment:**
  - Newly diagnosed patients
  - Patients previously treated with anti-VEGF

BCVA, Best Corrected Visual Acuity; VEGF, Vascular Endothelial Growth Factor.

Conclusions

- VEGF inhibitors are not effective in all DME patients and suggests alternate pathway
- Kallikrein-bradykinin pathway can lead to edema
- Avoralstat, by blocking kallikrein-bradykinin pathway, stops vascular leakage in rabbit model
- Suprachoroidal avoralstat has potential durability of 6 months
- Phase 1b study is recruiting DME patients in Australia

DME, diabetic macular edema; VEGF, Vascular Endothelial Growth Factor.

THANK YOU

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