Cascade PRODRUG™

CPD100

First in Class Hypoxia-Activated Therapy Targeting the Primary Drivers of Age-related Macular Degeneration (AMD)

Executive Summary

- Wet age-related macular degeneration (wet AMD) develops primarily from hypoxia-driven vascular endothelial growth factor ***(VEGF)*** upregulation and secretion by mononuclear phagocytes, leading to abnormal blood vessel growth ***(neovascularization)*** and leakage under the retina, **rapidly damaging central vision**

- Medicare spends >$4B per year on drugs to treat AMD-related neovascularization

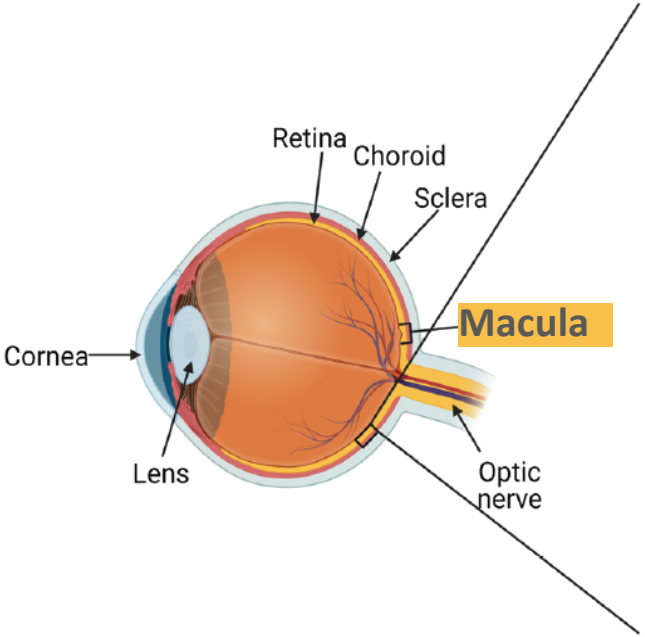
- CPD100 is activated under hypoxia to release vinblastine, which exerts dual anti-angiogenic effects:

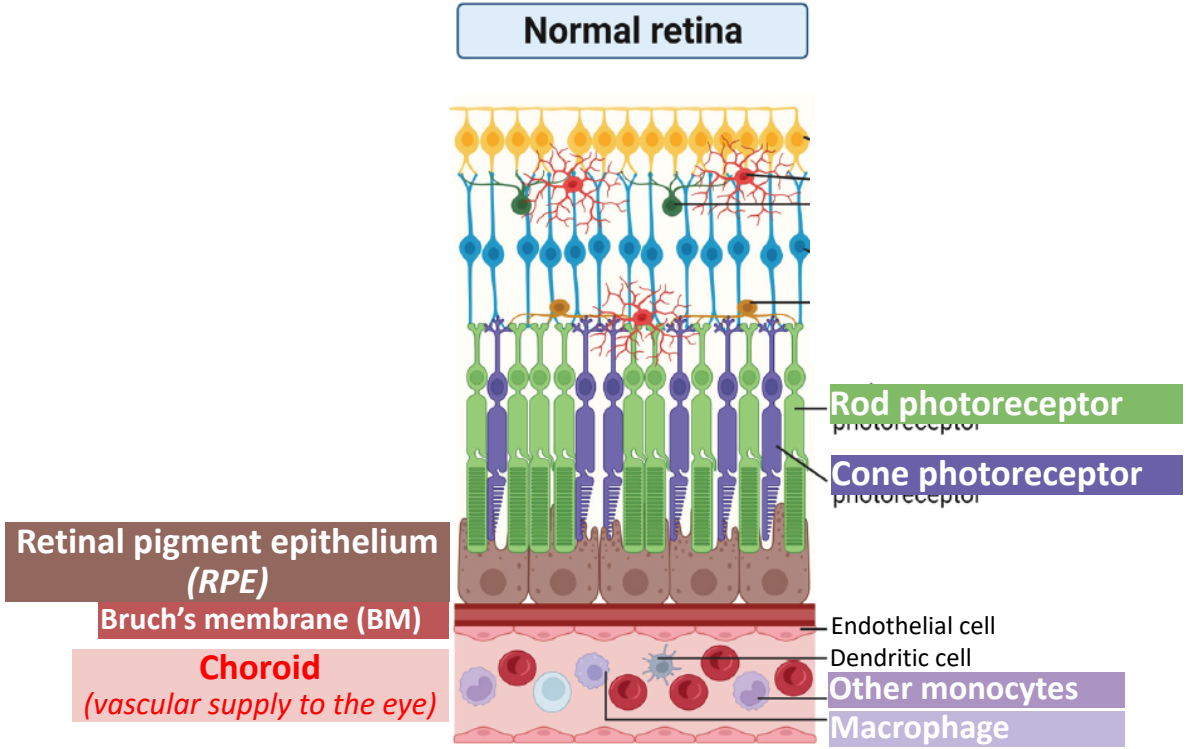
  i. Suppression of abnormal blood vessel growth,[1] and

  ii. Reduction of mononuclear phagocytes and other cells that stimulate excess VEGF production[2,3]

- Suprachoroidal administration of CPD100 has the potential to become the first targeted therapy to selectively inhibit angiogenesis in wet AMD through a dual mechanism of action

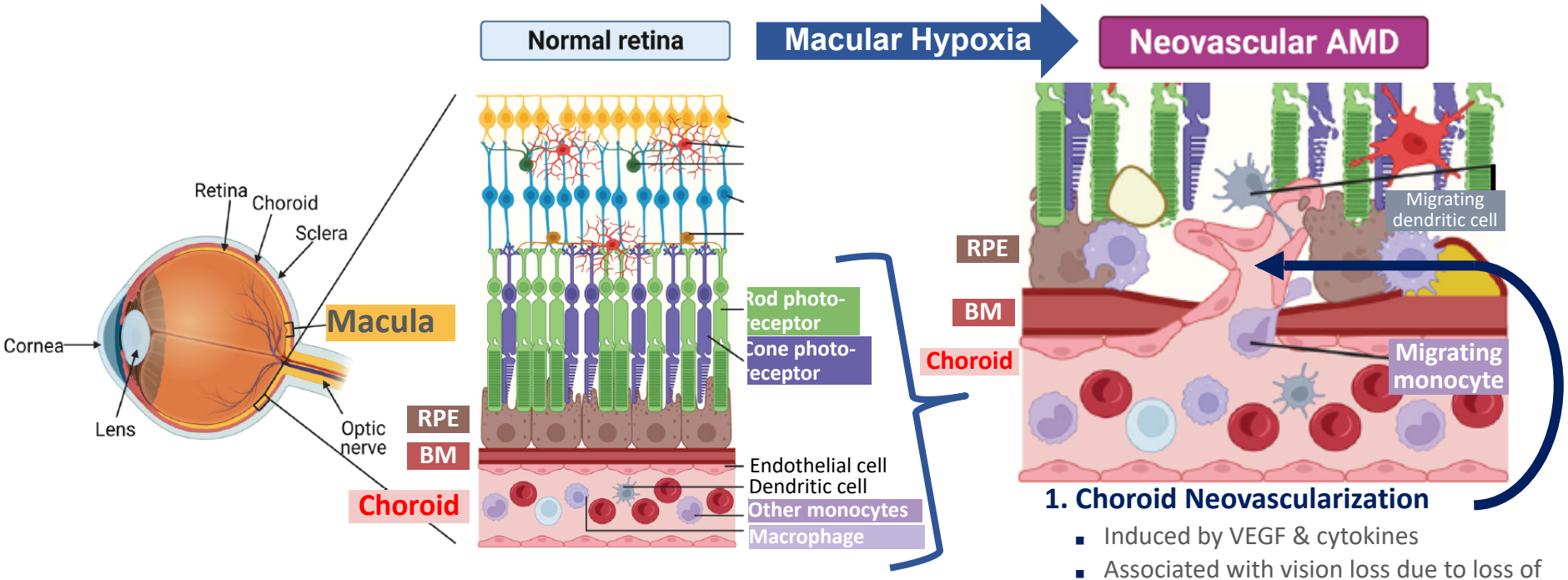
Normal Retina: Baseline in Younger Population[4-6]





Adapted from Wong JHC *et al., Frontiers in Neuroscience,* 2022.

Wet AMD: Evolution in the Ageing Eye[4-6]



1. Choroid Neovascularization

- Induced by VEGF & cytokines
- Associated with vision loss due to loss of photoreceptors, RPE, & BM

2. Para-Inflammation

- Mononuclear cells produce VEGF & other cytokines that promote neovascularization
- Damages RPE & BM

Adapted from Wong JHC *et al.*, *Frontiers in Neuroscience*, 2022.
RPE, retinal pigment epithelium; BM, Bruch's membrane

Wet AMD: High Burden, High Cost

- ~2M Americans affected; rapid, permanent central vision loss
- **Hypoxia → excess VEGF → choroid neovascularization + mononuclear migration** → vascular leakage [4]
- Medicare spends >$4B/year on anti-VEGF drugs, standard of care
- Current therapies are palliative, not disease modifying

2019 estimates for AMD prevalence in the US:

~20 million in population ≥ 40 years old

~ 10% (2 million) with wet AMD

A Large and Growing Market

- Intravitreal anti-VEGF therapy: $9.5B (2025) → $18.3B (2034)
- US represents 33–50% of global market
- Multiple blockbuster intravitreal-anti VEGF drugs (Eylea®, Lucentis®, Vabysmo®)
- Strong investor and pharma activity (e.g., EyeBio/Merck $1.3B upfront)

Intravitreal anti-VEGF therapy

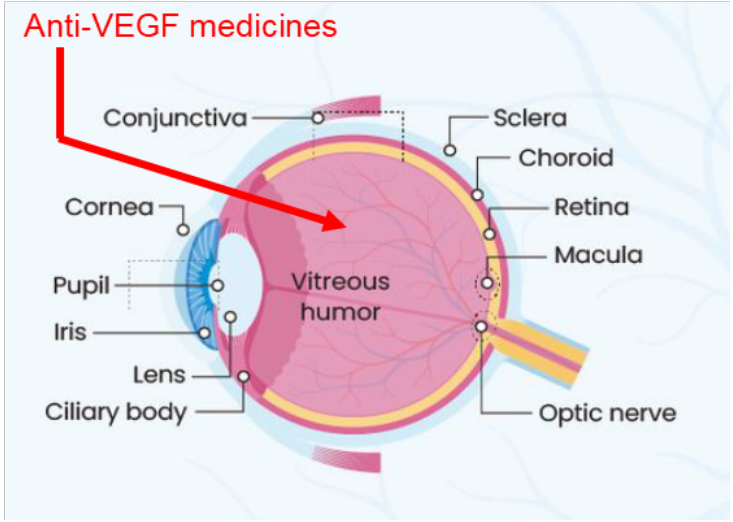
Standard of Care :

Eylea® ($9.5 B global in 2024[1])
Lucentis®, Vabysmo®, etc.

1. Includes retinal vascular conditions where VEGF-driven leakage and neovascularization are central, including wet AMD, diabetic macular edema (DME), diabetic retinopathy (DR) & macular edema following retinal vein occlusion (MEfRVO)

Limitations of Anti VEGF Therapies

- Require **intravitreal injections** with limited targeting to the retina and choroid *(painful)*
- Monthly loading + q2–4 month maintenance
- Do not address **hypoxia, direct action on growth of endothelial cells or on VEGF-producing immune cells**
- **Risks**: retinal tear, hemorrhage, cataract, uveitis, IOP elevation

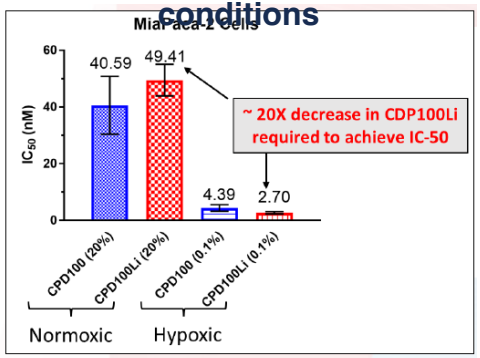


Source: https://www.drugdiscoverynews.com/a-new-type-of-injection-could-improve-eye-disease-treatment-16458
Illustration by Alisha Vroom

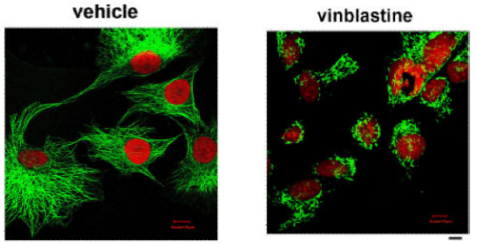
CPD100 (Vinblastine-N-Oxide)
First in Class Hypoxia-Activated Therapy for Wet AMD

- Targets **root causes** of wet AMD: new blood vessels and hypoxia-driven VEGF overproduction
- Releases **vinblastine** selectively in hypoxic tissue [7-9]
- Vinblastine (VBL) **destabilizes microtubules** and **stops cell division**
- **Potential dual mechanism in wet AMD**: blocks neovascularization + reduces VEGF-producing mononuclear phagocytes (M2)
- **Suprachoroidal delivery** for targeted, safer, more potentially durable therapy in the choroid

CPD100 is **more active** against cell cultures exposed to **hypoxic conditions**



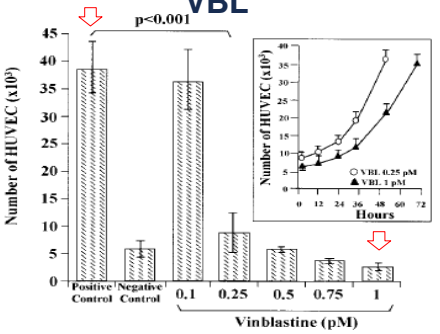
Vinblastine (VBL) **destabilizes microtubules** and **stops cell division**



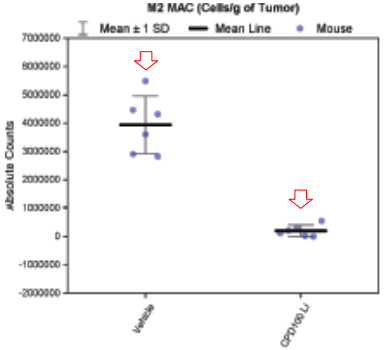
CPD100 Mechanism of Action

- **Vinblastine N-oxide** is a **prodrug** converted to vinblastine (VBL) only in hypoxic tissue
- **Endothelial cells** highly sensitive to VBL→ rapid shutdown of abnormal vessel growth[1]
- **Mononuclear phagocytes** (**M2**) reduced → upstream VEGF suppression[2-3]
- Potential for **more durable** and **more complete** disease control

Growth Inhibition of Endothelial Cells Exposed to VBL

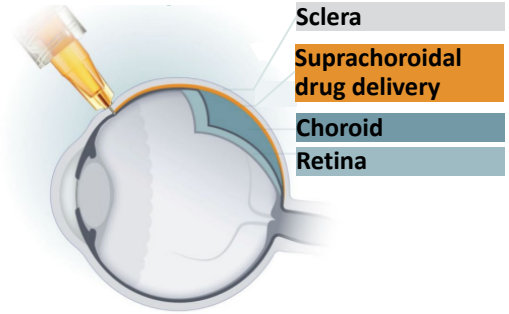


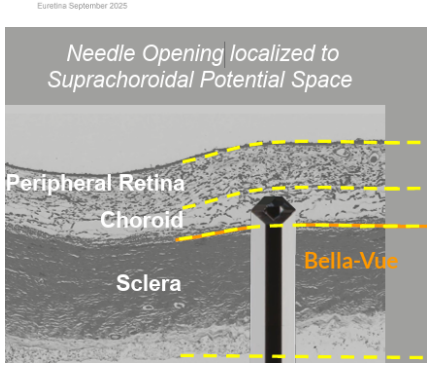
Reduction of M2 cells in Tumors Treated with CPD100



Suprachoroidal Delivery Advantage

- Direct access to **choroid**, the site of pathology
- Minimizes vitreous exposure and systemic toxicity
- FDA-cleared **micro-injection technology** (e.g., Bella-Vue / Uneedle) validated in AMD trials
- Enables **safer** and **more targeted** therapy to the choroid
- Growing clinical adoption of suprachoroidal injection





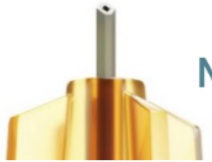
Mentink S – EURETINA 2025

CPD100 to Be Administered Suprachoroidally Using Bella-Vue (U-Needle) Microneedles

- Chosen for CPD100 — proven safety and precision in Phase 1/2a wet AMD trials (AXT107, N=15)[10]
- **Excellent safety & tolerability** — no adverse events, leakage, reflux, hemorrhage, or perforation[10]
- **Precision delivery** — Optical coherence tomography 1h post-injection confirmed full drug distribution[10]
- Easy and reliable to use — 100% user satisfaction; single microneedle length[10]

100% User satisfaction on

- Product Integrity
- Risk
- Ease of injection
- Reflux



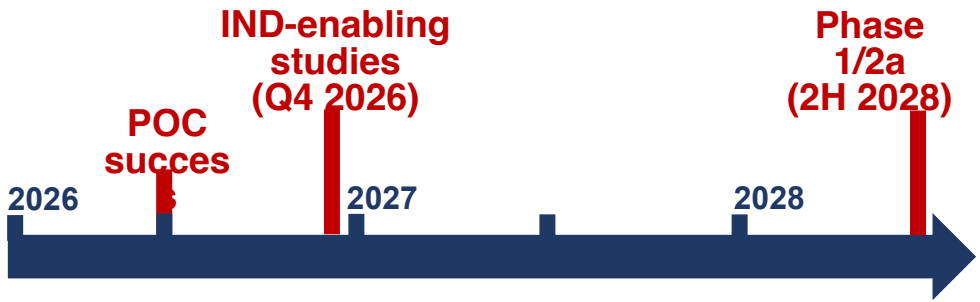
Single Microneedle Length !

Stopping Neovascularization with CPD100 in an Animal Model of Wet AMD Would Provide Proof-of-Concept (POC) of Cascade's Approach

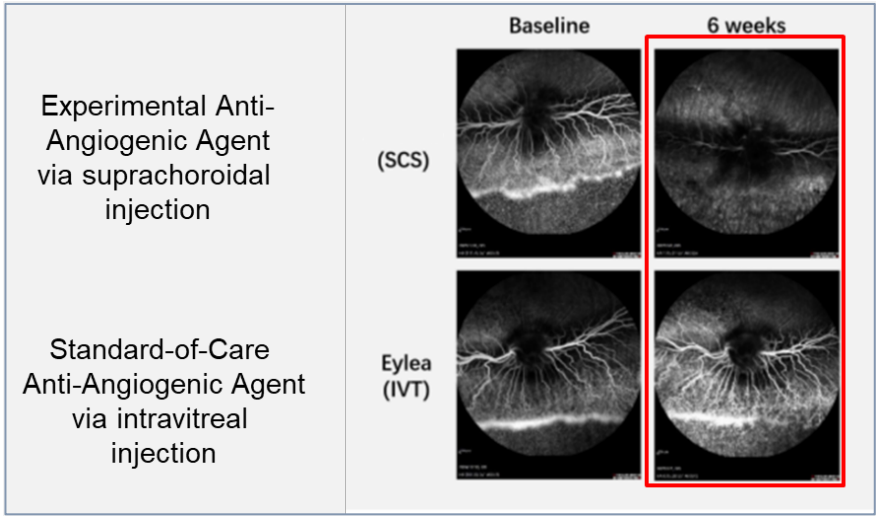
Rabbit POC (expected mid-2026) should be major inflection point

Quick and robust inhibition of neovascularization could translate into clinical benefits in humans, including:

- Reduction of leakage/edema (i.e., retinal drying)
- Faster and deeper recovery of vision



Representative **Example** of the Rapid Effect Expected with CPD100 vs. Standard of Care



Uneedle - PharmaLegacy Collaboration - Personal Communication

Commercial Opportunity for CPD100 in Wet AMD

- Wet AMD prevalence: **~2M US patients**
- **CPD100 advantages**:
  - **Only drug with dual MOA**: anti-neovascularization + anti-inflammatory
  - **Potential to improve vision** & decrease frequency of administration
  - Suprachoroidal administration avoids intravitreal morbidity
  - **Significant market opportunity** by mid-2030s

- **Expansion into other indications:**

Predominant Antiangiogenic Effect

  - Diabetic macular edema (DME)
  - Macular edema following retinal vein occlusion (MEfRVO)

Predominant Anti-Inflammatory Effect

  - Dry AMD – Geographic atrophy
  - Prior retinal transplantation in retinitis pigmentosa, AMD, etc.

Oncology

  - Retinoblastoma
  - Uveal melanoma (+ Ipilimumab)

Investment Opportunity

- **$750K** to complete rabbit POC & CMC kick-off campaign
- Part of **$3M convertible note**:
  20% discount or **$35M valuation cap**
  9% interest
- **+$8–10M** needed to reach IND submission
- **+$20M** needed to hire management & conduct Phase 1/2 study
- Strategy: position for **strategic exit or asset sale**
- Leadership & consultants with deep experience in **clinical development**, **ophthalmology, CMC, regulatory, BD**

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Q&A

AMD Has Emerged as One of the Most Attractive Opportunities for Investors & Pharma Licensing/Acquisition

- In 2025, IMARC estimated the total wet AMD market value to be $9.5 billion across the 7 Major Markets
  - The wet AMD market is anticipated to grow to a value of $18.3 billion in 2034
  - The US accounts for 1/3 to 1/2 of the market – a share that is expected to decline somewhat over the next 10 years
- Currently Medicare alone spends >$4B per year on anti-VEGF drugs — one of the largest chronic drug categories in Part B – with 50-55% of these patients having wet AMD
- These statistics have not been lost on investors, with venture capital actively funding wet AMD biology – including prior to clinical proof-of-concept
  - **EyeBio;** $130M Series A funded by Bain, Omega, Vertex, SV Health, Jeito, Samsara, MRL
  - **Ollin Biosciences;** $100M Series A funded by ARCH, Mubadala, Monograph
  - **Character Biosciences;** $93M Series B funded by aMoon, Luma Group, Bausch + Lomb, Jefferson
  - **PulseSight Therapeutics;** undisclosed Series A funding by Pureos BioVentures
  - **RevOpsis Therapeutics;** undisclosed seed funding by ExSight Ventures
- In parallel, established companies in the space have executed attractive licensing deals or acquisitions
  - **Adverum**/Lilly: $74M upfront company acquisition
  - **Coherus**/Sandoz: $170M upfront product acquisition
  - **EyeBio**/Merck: $1.3B upfront company acquisition
  - **RemeGen**/Santen: $35M for Asian license

CPD100 for Wet AMD: Alignment & Rationale

Rationale	Comment
Rapid path to commercialization	• Multiple value inflection points along this path
Lead candidate selected	• CPD100 (vinblastine N-oxide) is lead in wet AMD
Hypoxia-targeting MOA	• Reduced blood flow in choroidal layer of eye leads to chronic hypoxia • Hypoxia-induced VEGF leads to abnormal blood vessel growth characterized by wet AMD • CPD100 exerts a dual antiangiogenic effect
Low-dose vinblastine effects on HUVEC cells	• Suppresses abnormal blood vessel growth and reduces VEGF-producing cells (anti-angiogenic effect) • CPD100 preferential activation in hypoxia should improve therapeutic index of vinblastine warhead
Timeline to clinic	• Proof of concept in 2026, Phase 1 opportunity in early 2028
Significant market opportunity	• Multiple > $1 billion blockbuster products in wet AMD, US patient prevalence ~2 million • Potential use in other ophthalmic indications
Opportunity for 1st in class MOA	• No hypoxia-targeted therapies in clinic (sector dominated by anti-VEGF therapies) • No available wet AMD drugs for suprachoroidal administration
Suprachoroidal Delivery	• Ideal for antiangiogenic and immune-modulatory drug (local delivery at choroid, minimizing vitreous exposure & systemic tox) • Next generation micro-injection technology, FDA cleared and safe use in clinical trials of AMD

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