Addressing Optic Neuropathy Through Neuroinflammation Modulation and IOP Lowering with the ABCD Platform: A Polymedicine Approach to Glaucoma

Forward Looking Statements

- These slides contain “forward-looking statements.” Forward-looking statements are based on our current expectations of future events and are subject to risks and uncertainties that could cause actual results to differ materially and adversely from those in or implied by such forward-looking statements. For a discussion of risks and uncertainties and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our most recent Form 10-K, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. These forward-looking statements speak only as of the date hereof and Kodiak undertakes no obligation to update forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.
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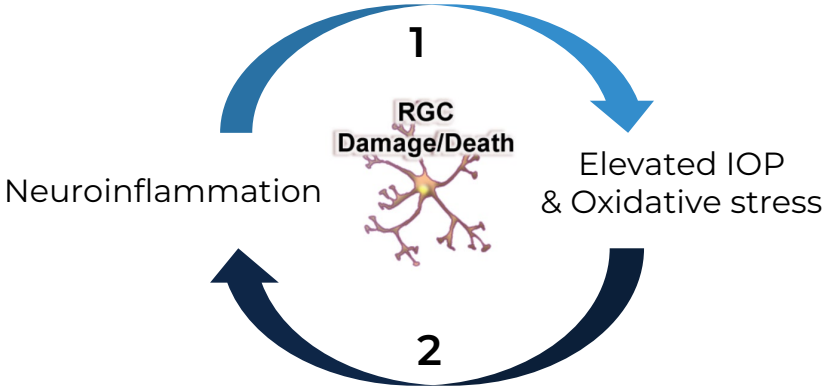
Glaucoma is an optic neuropathy driven by neuroinflammation: addressing IOP alone is no longer sufficient for effective treatment

- **Historically, glaucoma was thought to occur *due to* elevated IOP**
  - Raised IOP was thought to inflict damage on the ONH via mechanical stress
  - Reduction of IOP is known to mitigate glaucoma progression
- **However, data suggest that an IOP-independent mechanism is at play**
  - Many people with high IOP do not develop glaucoma
  - 30-40% of patients with glaucoma present with normal or low IOP. Many continue to experience vision loss due to glaucoma progression[1]

IOP: intraocular pressure; ONH: optic nerve head; RGC: retinal ganglion cell

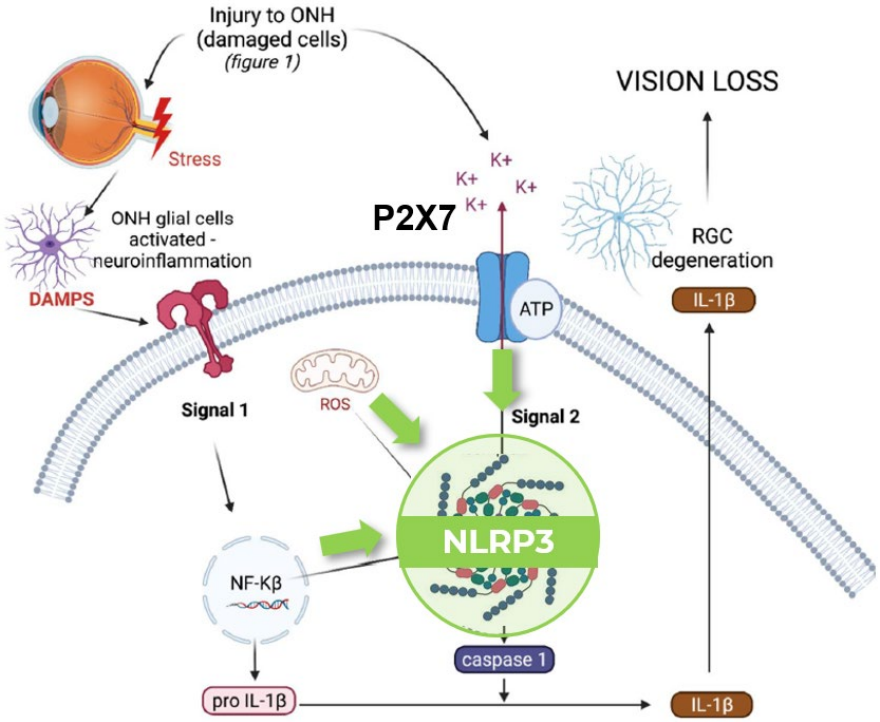
1. Coyle S, et al. Targeting the NLRP3 Inflammasome in Glaucoma. Biomolecules. 2021 Aug 19;11(8):1239. doi: 10.3390/biom11081239. PMID: 34439904; PMCID: PMC8393362. 2. Adornetto et al. Neur Regen Res 19

Recent studies show that neuroinflammation is the key driver of optic neuropathy in glaucoma[2]



- Current therapies focus on lowering IOP as it is the only modifiable risk factor
- **There is an unmet need to develop new therapies that target the underlying neuroinflammation that drives optic neuropathy**

The NLRP3 inflammasome complex is a key driver of neuroinflammation that results in optic neuropathy



The NLRP3 inflammasome drives retinal ganglion cell (RGC) degeneration and axon loss[1]

- First, stress to the optic nerve head activates the NF-κB pathway, upregulating NLRP3 and the production of pro-IL-1β
- Second, ATP from damaged cells or reactive oxygen species (ROS) result in NLRP3 inflammasome complex formation, activation of caspase-1, and IL-1β activation by cleavage, leading the RGC degeneration

1. Coyle S, et al. Targeting the NLRP3 Inflammasome in Glaucoma. Biomolecules. 2021 Aug 19;11(8):1239. doi: 10.3390/biom11081239. PMID: 34439904; PMCID: PMC8393362.

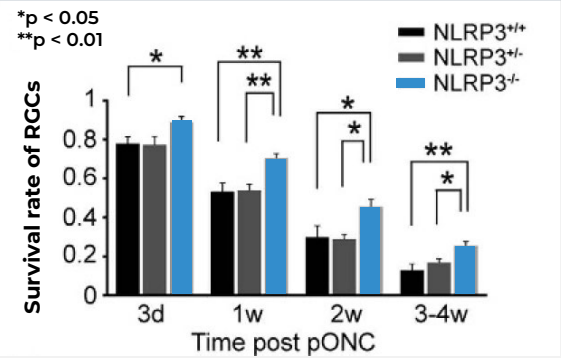
Evidence from animal models support NLRP3 inflammasome driving optic neuropathy, as evident by RGC degeneration and axon loss

- Following an optic nerve crush (pONC), NLRP3 was upregulated in retinal microglial cells. Activation of NLRP3-ASC inflammasome led to the up-regulation of caspase-1 and IL-1β

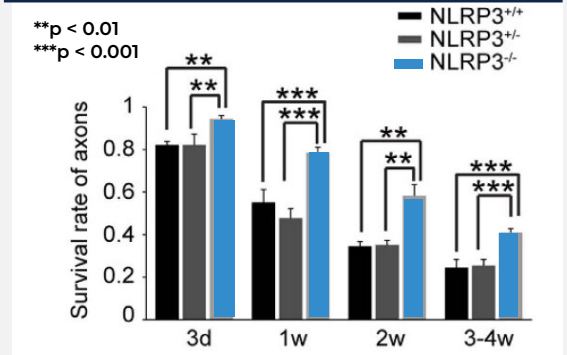
In NLRP3 knockout mice:

– Up-regulation of ASC, caspase-1, and IL-1β were all reduced, and RGC and axon loss was substantially reduced and delayed following pONC injury

More RGCs survived in NLRP3−/− mice than in controls



Survival rate of axons in NLRP3 -/- was much higher than in controls



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Puyang, Z., Feng, L., Chen, H. *et al.* Retinal Ganglion Cell Loss is Delayed Following Optic Nerve Crush in NLRP3 Knockout Mice. *Sci Rep* **6**, 20998 (2016). https://doi.org/10.1038/srep20998

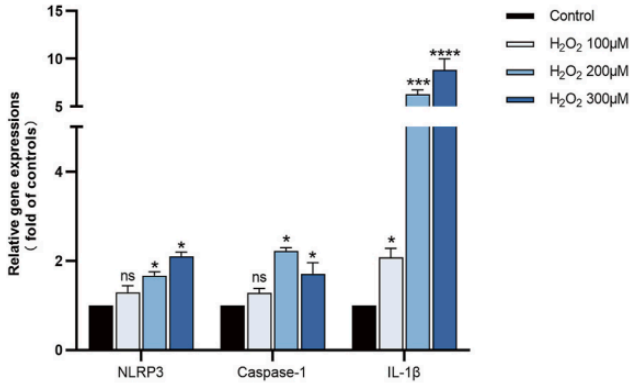
Inhibiting NLRP3 has demonstrated the potential to modulate the trabecular meshwork and lower IOP

- The trabecular meshwork (TM) plays a crucial role in maintaining the aqueous outflow pathway

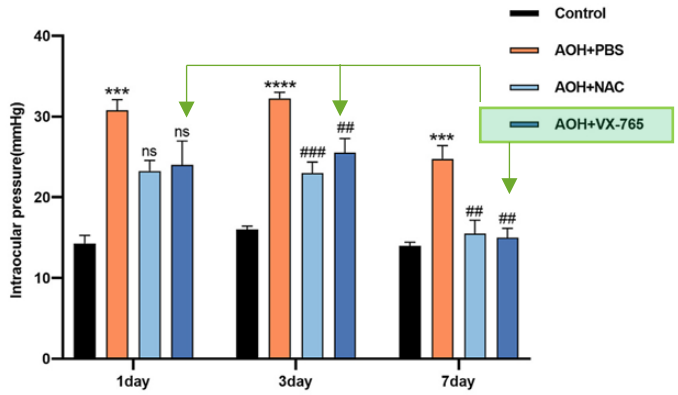
Preclinical studies demonstrated that inhibiting NLRP3/caspase-1 pathway protects the TM and lowered IOP

- Elevated levels of NLRP3 and Caspase-1 were found in TM samples from glaucoma patients
- Oxidative damage in human TM cells led to upregulation of NLRP3, caspase-1, and IL-1β, resulting in decreased cell viability
- Caspase-1 inhibitor VX-765 has been shown to protect TM cells from pyroptosis (cell death) and lowered IOP in rat acute ocular hypertension model

NLRP3, caspase-1 and IL1β mRNA levels are elevated in TM with oxidative stress



Treatment with VX-765 improved elevated IOP due to AOH

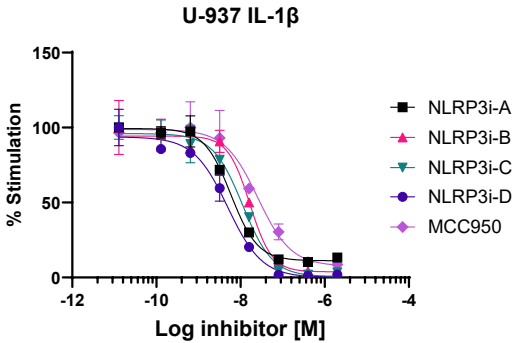


*P<0.05, **P<0.01, ***P<0.001 vs. control, ## P<0.01, ### P< 0.001 vs. AOH

Feng, Xiaomei et al. Role for NLRP3 inflammasome-mediated, Caspase1-dependent response in glaucomatous trabecular meshwork cell death and regulation of aqueous humor outflow. Heliyon, Volume 10, Issue 19, e38258

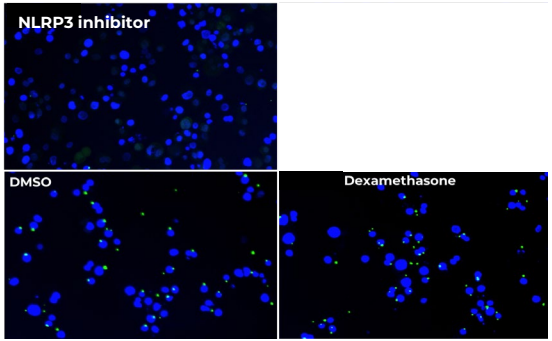
Kodiak's novel small molecule NLRP3 inhibitor candidates decrease IL-1β production and reduce inflammasome complex formation in preclinical studies

NLRP3 inhibitors decrease macrophage IL-1β production in multiple human macrophage lines*



* U937 cells were treated with NLRP3 inhibitors and nigericin activation to monitor IL-1b production

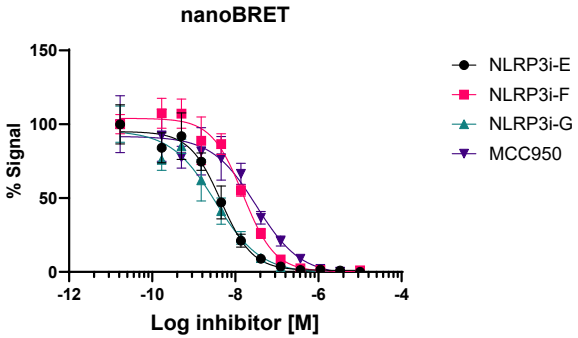
NLRP3 inhibitors reduce inflammasome complex formation



- NLRP3 inhibitors, but not the anti-inflammatory steroid dexamethasone, decreased detectable fusion protein complexes

THP-1 cells expressing GFP-ASC fusion protein were differentiated, primed, compound treated and activated (green)

Inhibitors directly affect NLRP3 molecular interactions†



† Compounds dose-dependently displace a small molecule tracer that promotes the inactivate conformation of NLRP3 in cells

https://kodiak.com/wp-content/uploads/sites/4/2024/05/22.-2024-ARVO-NLRP3-Cell-Assays.pdf
Kodiak Sciences. Investigative Ophthalmology & Visual Science June 2024, Vol.65, 2208.

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Challenges in intracellular NLRP3 inhibition: limitations of small molecule delivery to retinal and optic nerve targets using today's technology

Limitations of small molecule delivery

Eye drops

Poor patient compliance and insufficient drug concentration reaching target tissues, such as RGCs and the optic nerve

Orally

Poor ocular bioavailability and systemic side effects

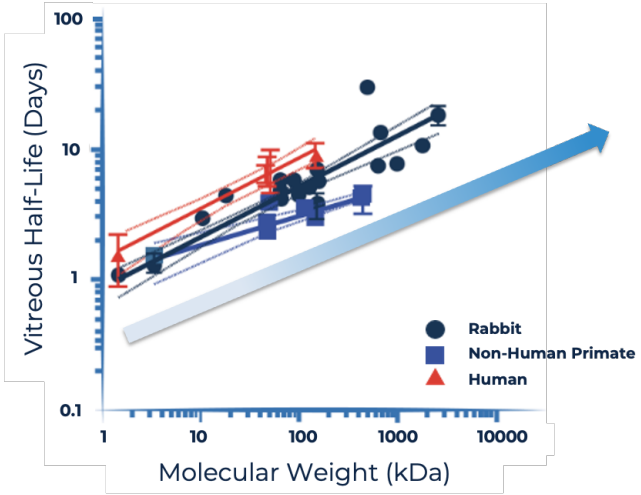
Intravitreally

Small molecules are cleared quickly from the eye, limiting their efficacy

What if we can create an intravitreally injected small molecule that does not clear the eye quickly?

- There is a strong positive correlation between ocular half-life and molecular size for intravitreally injected biologics

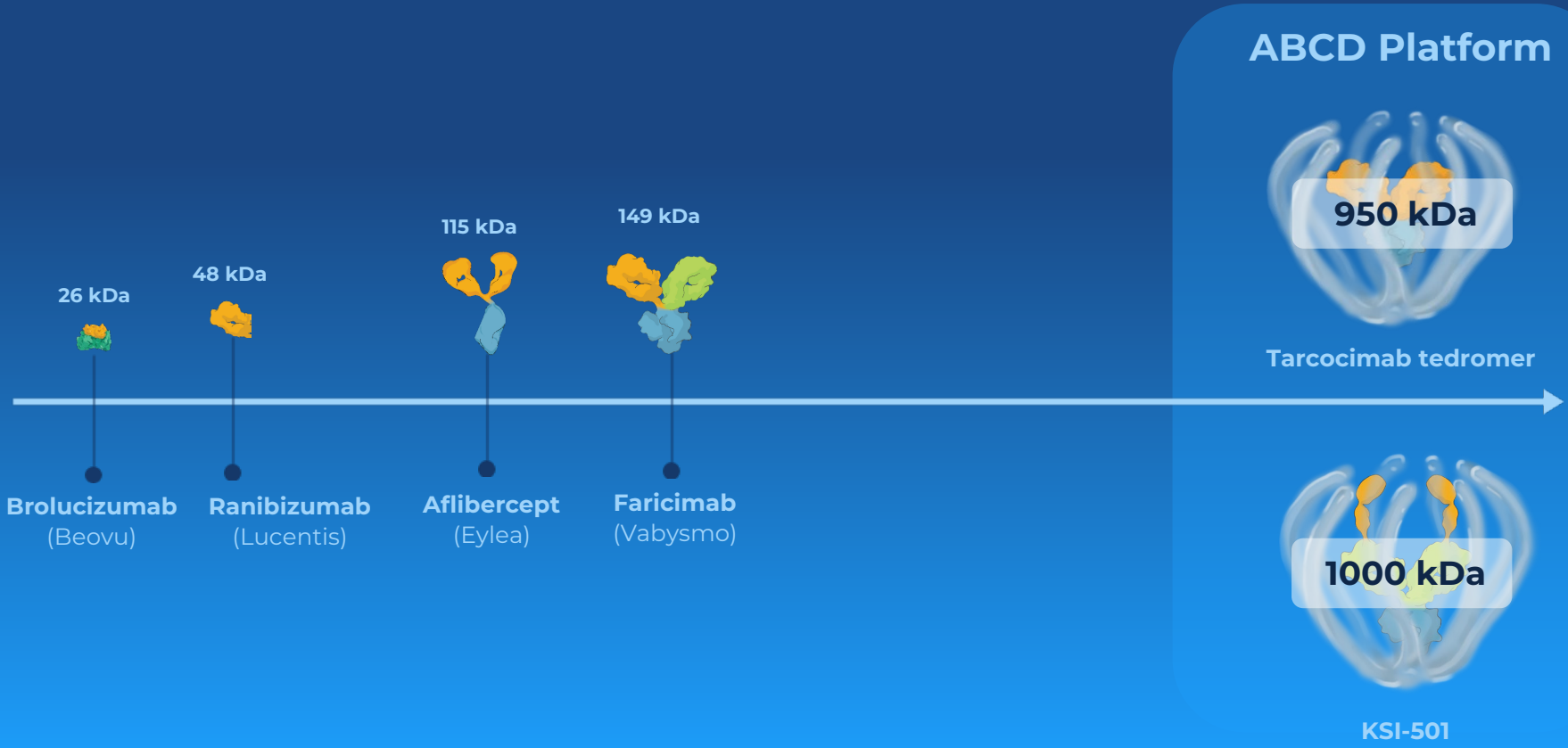
Relationship between ocular half-life and molecular weight (MW, kDa)[1]



1. Adapted from Crowell SR, et al. Trans Vis Sci Tech. 2019;8(6):1.

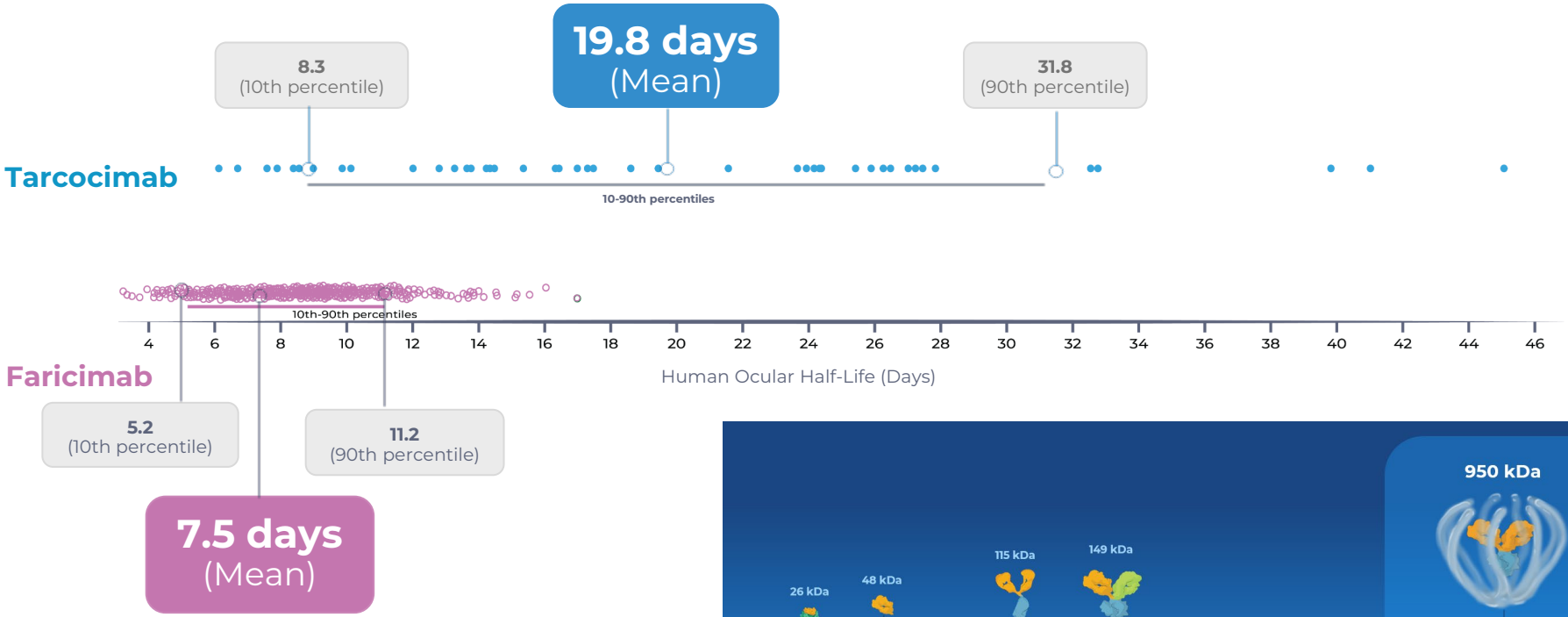
Data from Tarcocimab, Kodiak's lead ABCD Platform-Based Medicine in Clinic

Empowered for durability, Kodiak's high molecular weight ABCD Platform offers a unique approach to overcome the limitations of small molecule delivery to the eye



ABCD: Antibody Biopolymer Conjugate Drug

Tarcocimab and the ABCD Platform's high molecular weight increases its human ocular half-life, extending its therapeutic benefit in the eye



Each dot represents an individual patient.
VABYSMO™ (faricimab solution for injection) Prescribing Information. South San Francisco, USA: Genentech, Inc.
PK and ER of faricimab, Report # 1105763

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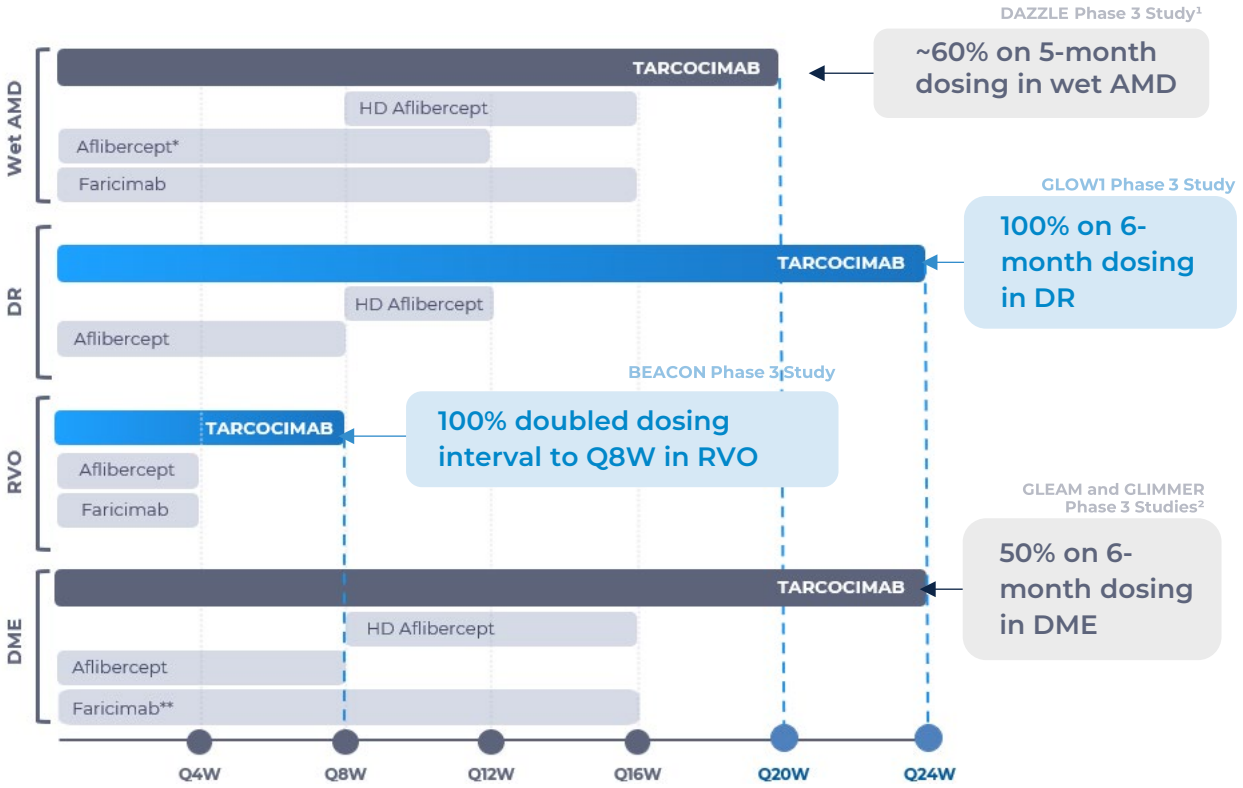
Tarcocimab consistently demonstrated extended durability in multiple retinal vascular diseases across its pivotal studies

- Durability remains a key unmet need in retinal vascular diseases
- **Tarcocimab and the ABCD Platform demonstrated extended durability** compared to today's approved therapies across multiple indications
- **Favorable safety profile also demonstrated with 2,500+ patient years of experience and >13,000 injections**

*Q12W after 1 year of effective therapy.
**Based on dosing interval at primary endpoint at year 1 in pivotal studies YOSEMITE and RHINE



1. Study did not meet primary endpoint believed to be due to the undertreatment of a minority of patients.
2. Studies did not meet primary endpoints due to an unforeseen increase in cataracts in tarcocimab-treated patients; Kodiak's enhanced formulation may mitigate this liability.

Applying the ABCD Platform to Glaucoma

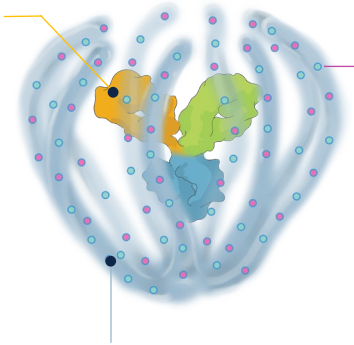
Kodiak's ABCD Platform is designed for targeted, high drug loading, multi-specific and tailored modulation of biological pathways

Antibody Biopolymer Conjugate Drug ("ABCD"):

A product platform enabling multi-mechanism therapies empowered for durability

Antibody or other Biologic

Any biologic can be conjugated to the biopolymer via a stable, site-specific linkage



Drug Cargo

Diverse APIs of varying biophysical properties are covalently embedded in the biopolymer and released over a designed-in time

Biopolymer

Engineered to make medicines last longer and extend their therapeutic benefit. Combines multiple APIs and can be tailored to meet a specific therapeutic goal. High molecular weight, optically clear and made of phosphorylcholine, the primary hydrophilic component of human cell membranes

Conjugates of diverse APIs +/- a biologic
Target both intracellular and extracellular pathways

High Drug Antibody Ratio ("DAR") medicines
Can include APIs with DAR of 10 up to >250

Tailored release of APIs
Release of API payloads enabled by pH modulation or enzymatic cleavage of linkers

Proven safety record of the ABC Platform
>2,500 patient years of experience in patients and >13,00 tarcocimab injections

A new combination of targeting, high drug loading, mixed API formats and tailored drug release – with applications in ophthalmic and systemic diseases

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The ABCD Platform is modular and each component can be customized to fit a specific therapeutic need

Antibody or Other Biologic

Antibody

Fusion Protein

Aptamer

Biopolymer

(Copolymer is customizable to match therapeutic need)

9-arm

- 10% drug loading
- 500 or 750kD
- DAR of 166 or 250

3-arm

- 3% or 10% drug loading
- 150 or 250kD
- DAR of 15 or 83
- +/- conjugation snout for conjugation to a biologic

Copolymers of variable sizes and percent loading

- Copolymer arm length and percent loading are both customizable

Drug Cargo

(Diverse payloads with varying biophysical properties)

Small molecules

Macrocycles

Peptides

Oligonucleotides

Each drug cargo has a customizable release rate (t½) of 5 days, 10 days, 20 days or 30 days

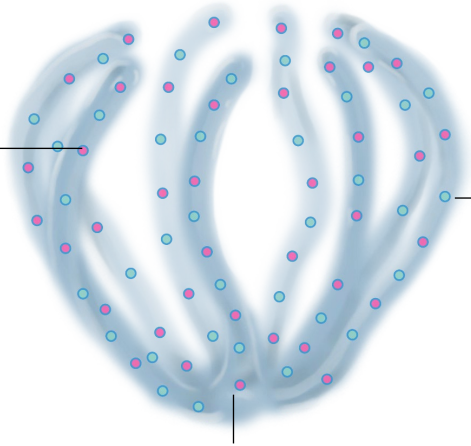
If you can imagine it, we can design it and manufacture it

A single molecule designed to target NLRP3, the driver of neuroinflammation that causes optic neuropathy, and elevated IOP simultaneously

Glaucoma "Duet": Biopolymer with 2 Small Molecules
NLRP3 inhibitor + IOP lowering agent

Disease Modifying NLRP3 Inhibitor

Targets the underlying neuroinflammation that drives optic neuropathy. May also provide additional IOP lowering effects through TM modulation



IOP Lowering Small Molecule

Extended Durability

A high molecular weight, phosphorylcholine-based biopolymer that enables extended ocular residence time for the potential of a **quarterly dosed intravitreal therapy**

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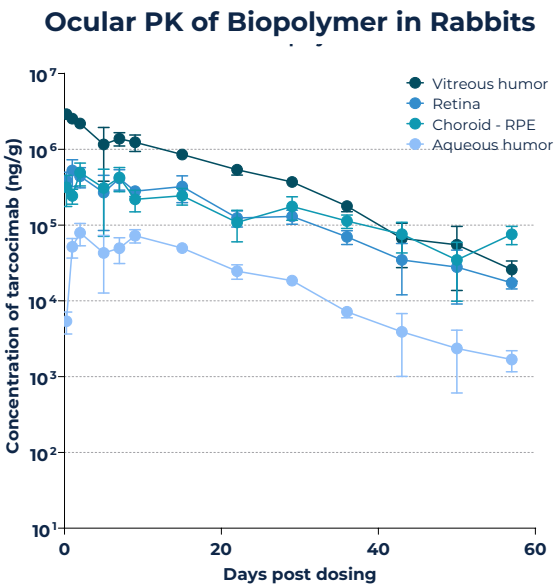
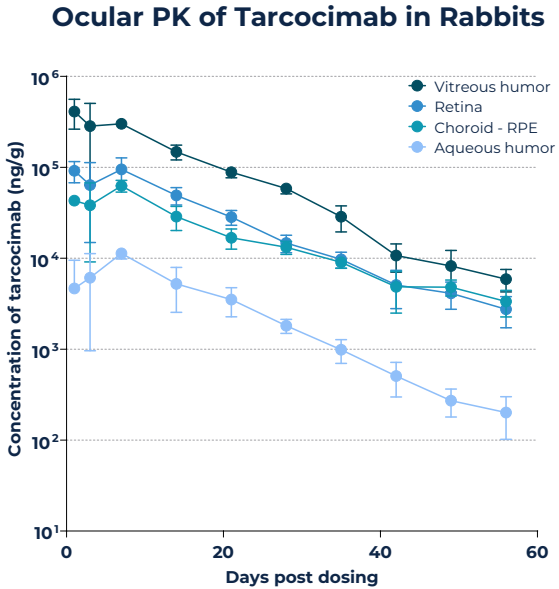
Administered via intravitreal injection

Biopolymer selection for glaucoma duet: choosing a biopolymer with similar size to that used in tarcocimab, demonstrating comparable ocular half-life and pharmacokinetics

Biopolymer Alone



Biopolymer + Antibody



Rabbit Ocular Half-Life

Biopolymer	Tarcocimab
11.6	11.1*

(Days)

*Translates to a human ocular half-life mean of ~20 days

In summary, ABCD Platform-based glaucoma “duet” is designed to address 4 key attributes needed in a next-generation glaucoma therapy

Design attributes of the ABCD Platform-based glaucoma “duet”

Neuroprotective

- Glaucoma is an optic neuropathy driven by neuroinflammation
- The **NLRP3 inhibitor** targets the NLRP3 inflammasome complex that drives neuroinflammation causing optic neuropathy

+

Reduces IOP

- The **IOP lowering agent** addresses the IOP elevation stressor
- The NLRP3 inhibitor demonstrates the potential to provide *additional* IOP reduction effects

+

Durable

- The ABCD Platform has a **high molecular weight to increase its ocular half-life**, providing potential for a quarterly dosed intravitreal therapy
- Tarcocimab, an ABC Platform-derived biologic, demonstrated a strong durability profile across multiple pivotal studies

+

Safe

- Tarcocimab and the ABCD Platform have demonstrated a **favorable safety profile across multiple pivotal studies (>13,000 intravitreal injections)**