KHK4951
(Tivozanib eye-drops for retinal diseases)

R&D Day, Kirin Holdings

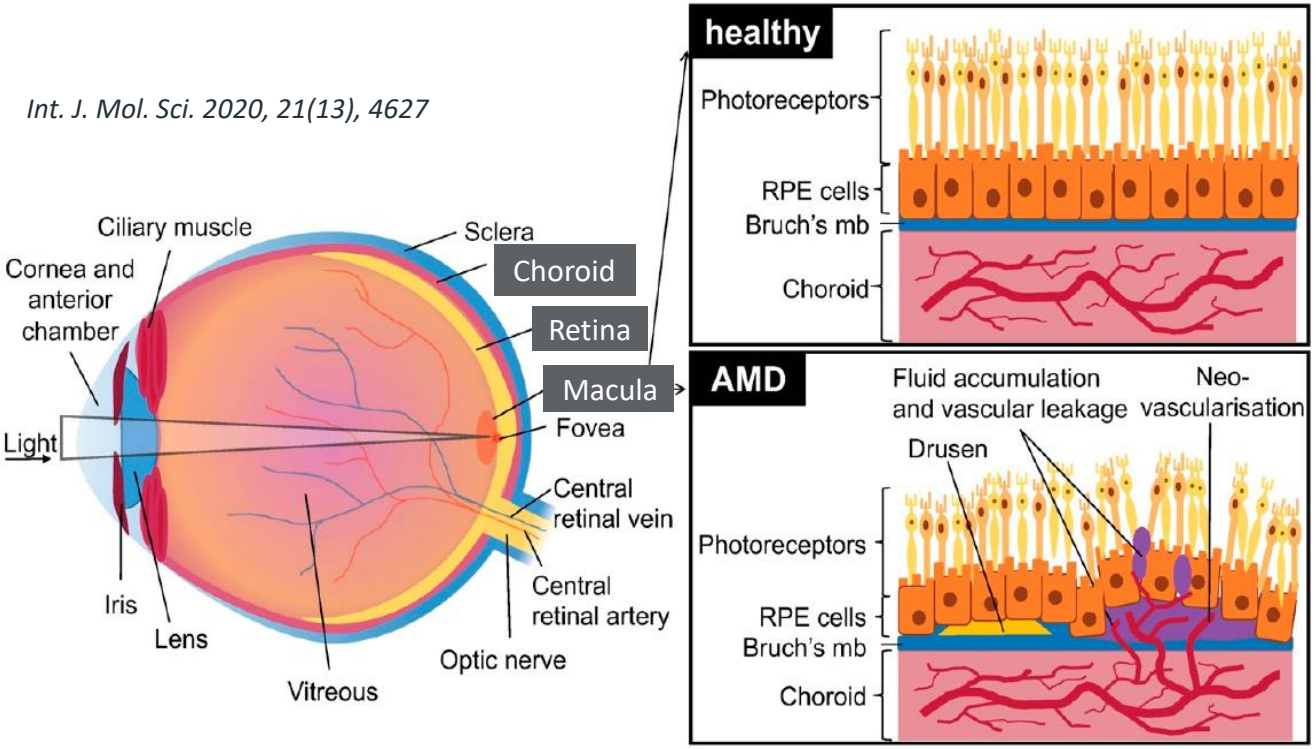
Dec 17th, 2025

Target indications

Neovascular age-related macular degeneration (nAMD)

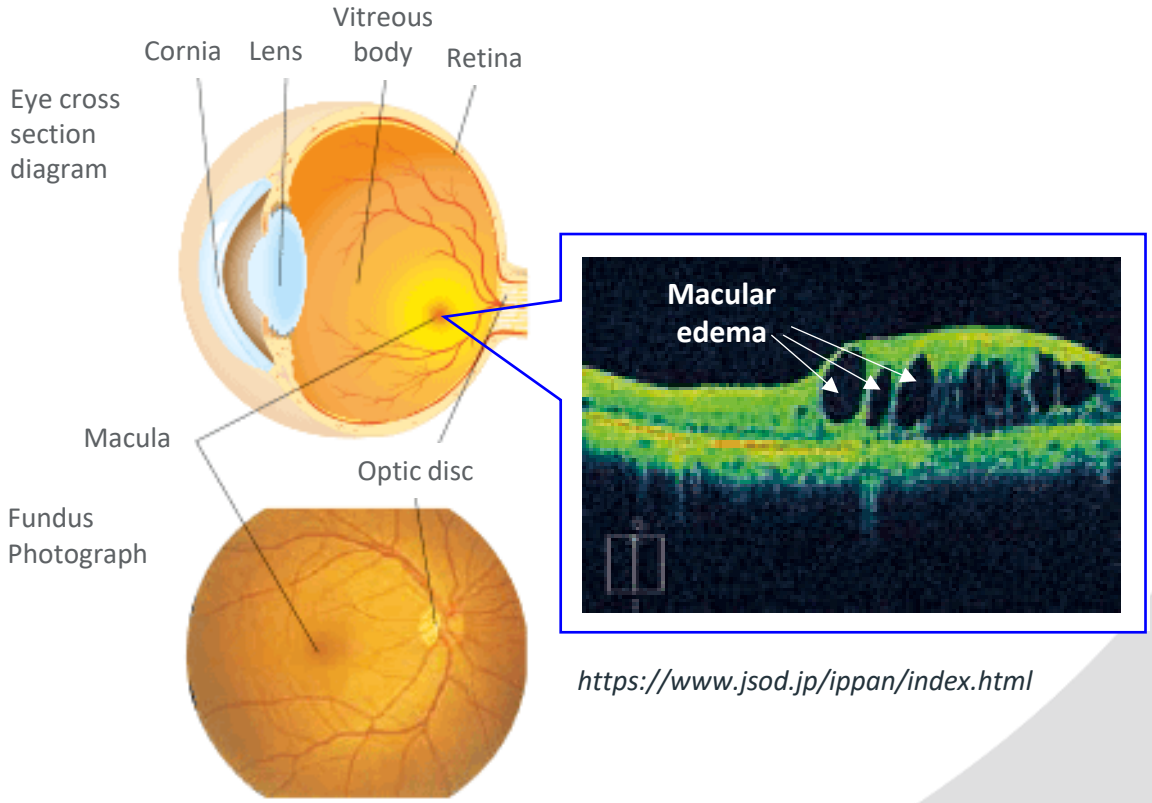
- Abnormal choroidal neovascularization damages the macular tissue leading to reduction of vision.
- VEGF[1] overexpression is a major cause of the disease.
- The number of patients treated by anti-VEGF drugs : ~260K Japan, ~1.87M global.

Int. J. Mol. Sci. 2020, 21(13), 4627



Diabetic macular edema (DME)

- Hyperglycemia elevates VEGF[1] and other inflammatory cytokine leading to damage of retinal vessels, macular edema and finally reduction of vision.
- The number of patients treated by anti-VEGF drugs: ~150K Japan, ~1.53M global.



https://www.jsod.jp/ippan/index.html

1. Vascular endothelial growth factor

Unmet medical needs in nAMD and DME

Standard of Care: Intravitreal injection of anti-VEGF drugs

- Invasive administration route
- Frequent hospital visits and surgeries for intravitreal injections are significant treatment burden for patients.
- Some doctors and patients are unable to perform or receive intravitreal injections of anti-VEGF drugs.

Lancet 2012; 379: 1728–38

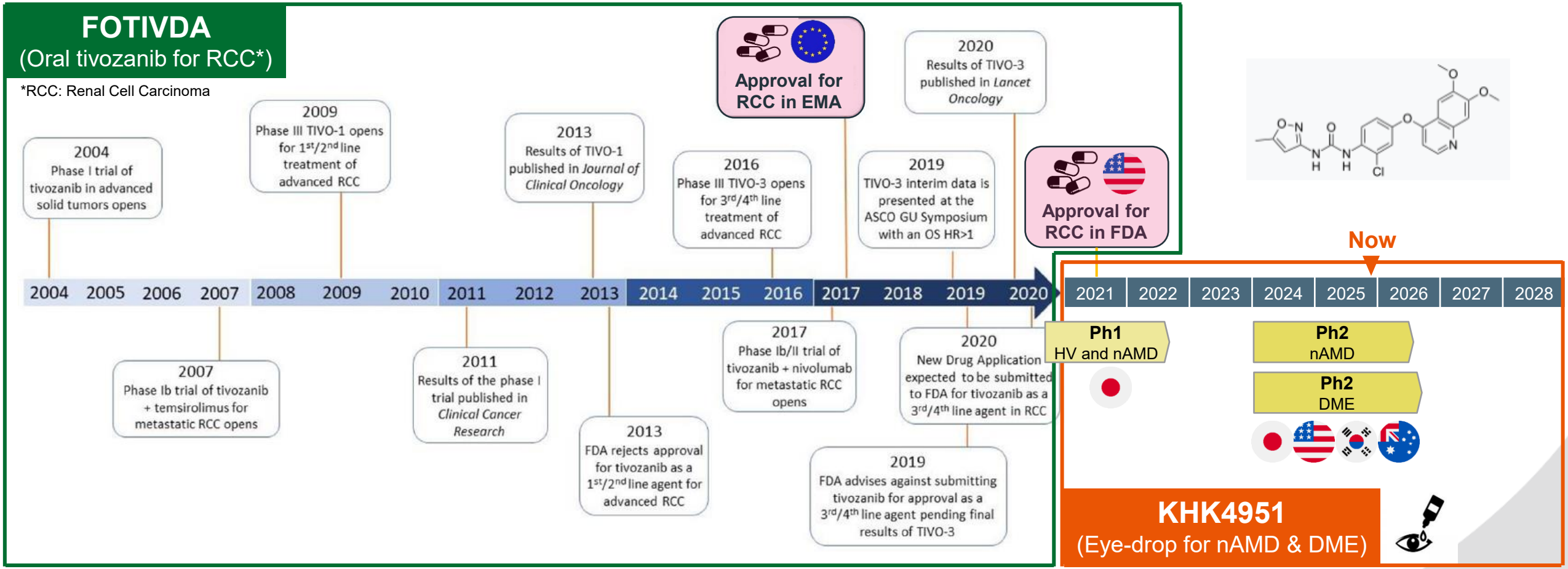
nAMD patient journey mapping by IDEA Pharma (2023)

Tivozanib's development history

- Tivozanib is a potent small molecule VEGFR inhibitor originated by Kyowa Kirin.
- Kyowa Kirin licensed the US and EU rights to AVEO oncology in 2006, and tivozanib has been in the market in RCC.
- Kyowa Kirin licensed back the non-oncology field right (including ophthalmology) from AVEO oncology in 2019 and is developing KHK4951 as "nano-crystalized tivozanib eye-drops" in the retina diseases.

FOTIVDA
(Oral tivozanib for RCC*)

*RCC: Renal Cell Carcinoma

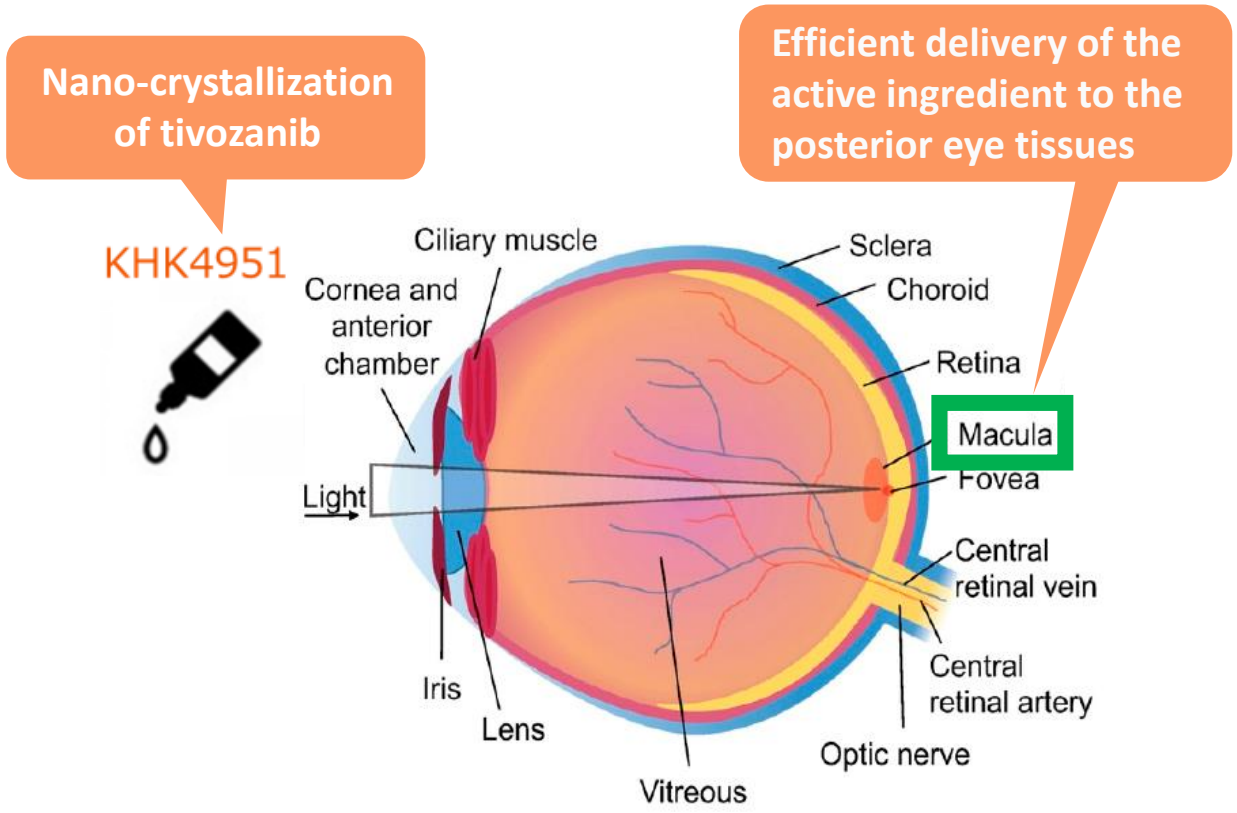


Ther Adv Med Oncol, 2020, 12: 1–9

KHK4951: Nano-crystallized tivozanib eye-drops

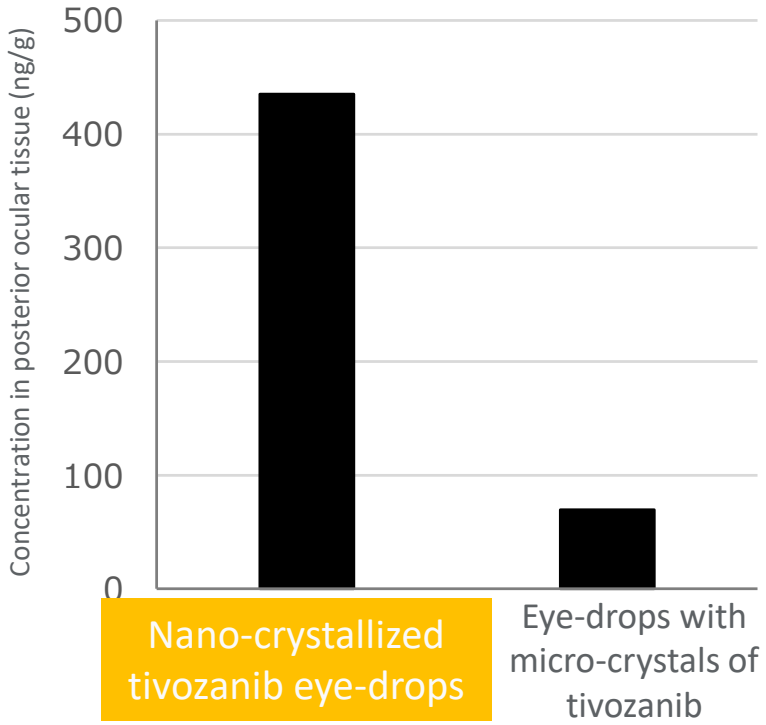
Nano-crystallized tivozanib eye-drops efficiently delivers the active ingredient to the posterior segment of the eye.

Drug concept



Rat ocular PK study results

Tivozanib concentration in the posterior ocular tissue after the administration of the same amounts of tivozanib to rats.



Phase 1 study : Study Design

Subjects

- Healthy volunteers and nAMD patients

Primary endpoints

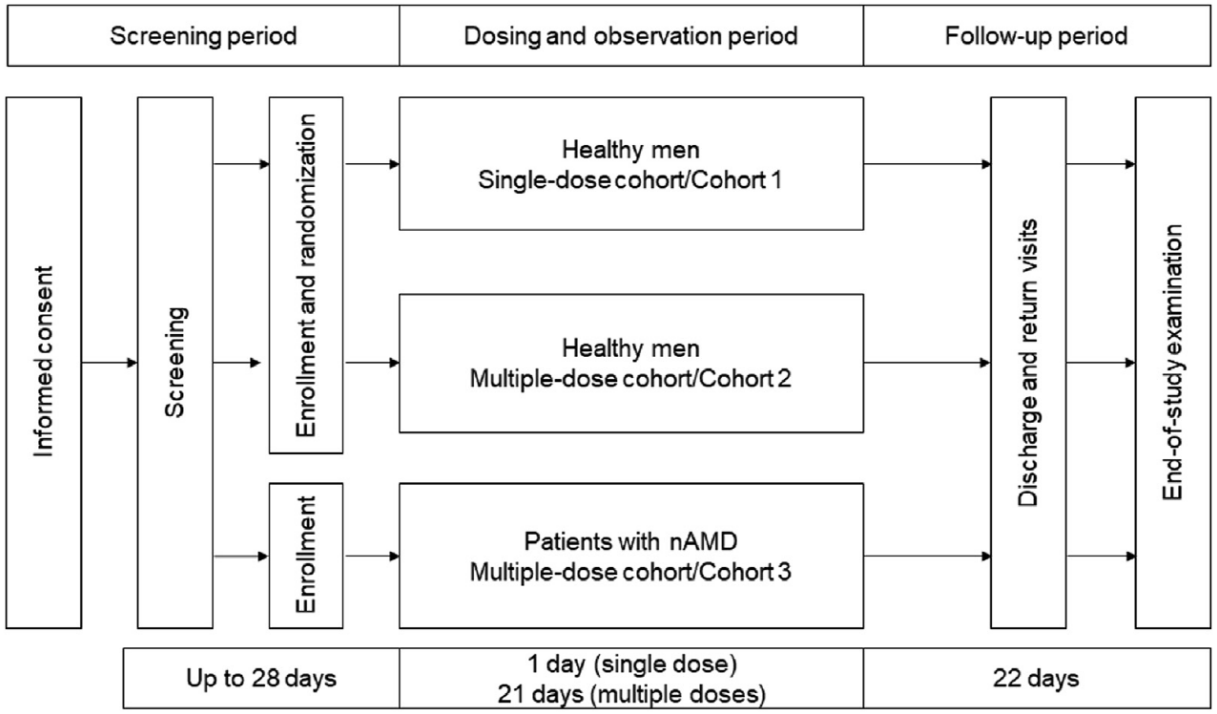
- Safety and tolerability

Secondary endpoints

- Pharmacokinetics and clinical signs in short-term repeated administration

Study Design

Figure 1. Study design. nAMD = neovascular age-related macular degeneration.

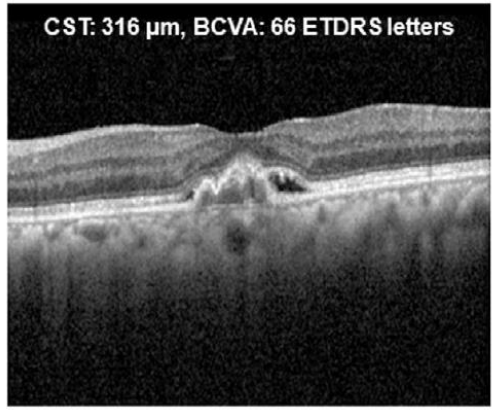


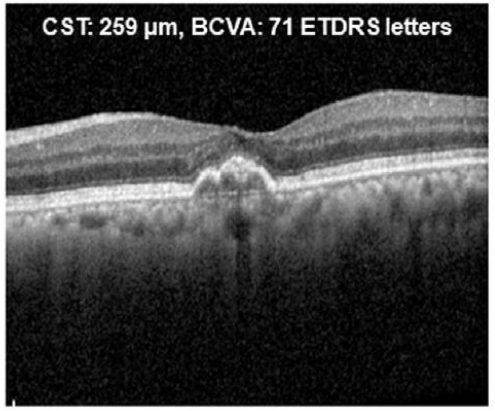
Ophthalmology Science 2024;4:100553

Phase 1 study: Anatomical improvement of the retinal tissues

In some nAMD patients, 3 weeks of KHK4951 treatment reduced or eliminated retinal edema.

Patient C (Cohort 3 Step 1)

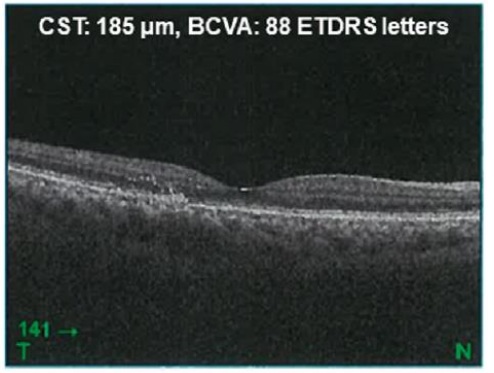




Patient D (Cohort 3 Step 2)

Enrollment (Day 1)

Day 22

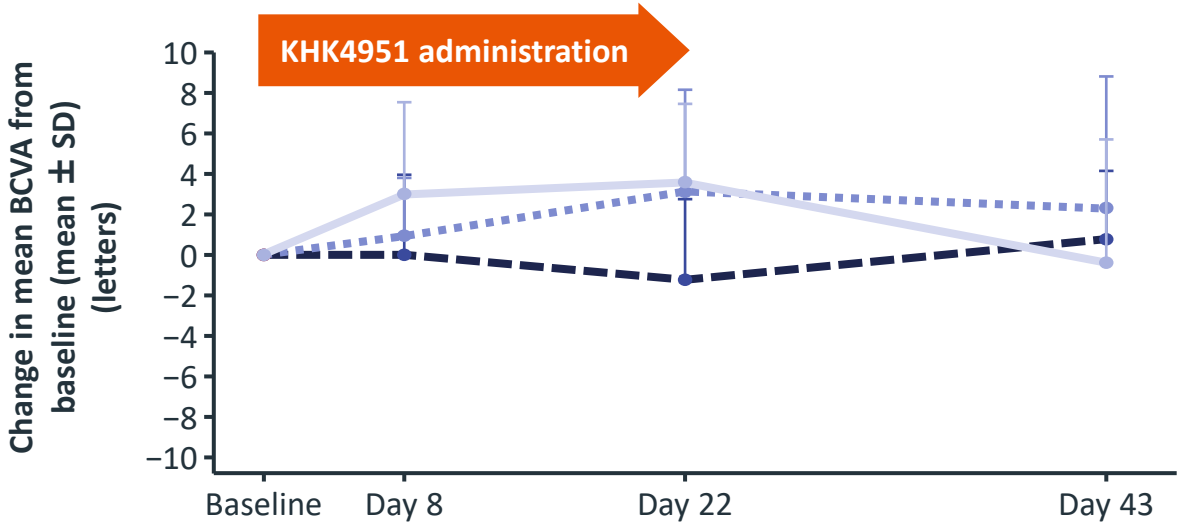


Day 43

Ophthalmology Science 2024;4:100553

Phase 1 study : Best Corrected Visual Acuity (BCVA)

In 3-week administration of tivozanib eye drops, mean BCVA was maintained .



	Mean BCVA baseline (letters)	Mean BCVA change at Day 22 (letters)
0.5 w/v%, 1 drop	61.6 ± 16.17	+3.6 ± 3.87
1.0 w/v%, 1 drop	75.2 ± 13.66	+3.1 ± 5.00
1.0 w/v%, 2 drops	76.2 ± 10.59	−1.3 ± 4.03

Ophthalmology Science 2024;4:100553

The latest article on pipeline for nAMD published Oct, 2024

KHK4951 is listed as “only one eye-drop drug” in the latest new horizons for nAMD.

The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

REVIEW ARTICLE OPEN

Check for updates

Exploring new horizons in neovascular age-related macular degeneration: novel mechanisms of action and future therapeutic avenues

Jonathan D. Shirian[1,2], Priya Shukla[1,2,3] and Rishi P. Singh[2,3,4,5]✉

Table 2. Future therapeutic agents.

Class	Name	Structure	Target	Method of delivery
Gene therapy	RGX-314	AAV8 vector expressing a ranibizumab like Fab	VEGF-A	Subretinal/Suprachoroidal
	Ixoberogene soroparvovec (Ixo-vec)	AAV.7m8 vector encoding the aflibercept protein	VEGF-A, VEGF-B, PGF	IVT Injection
	4D-150	AAV vector (R100) expressing both aflibercept and a VEGF-C inhibitory miRNA	VEGF-A, VEGF-B, VEGF-C, PGF	IVT Injection
Anti-VEGF related	OPT-302	Recombinant fusion “trap” protein consisting of three extracellular ligand-binding domains of VEGFR-3	VEGF-C and VEGF-D	IVT Injection
	BI 836880	Bispecific nanobody®	VEGF-A, Ang-2	IVT Injection
	Tarcocimab tedromer (KSI-301)	IgG1 anti-VEGF antibody biopolymer conjugate	VEGF-A	IVT Injection
Tyrosine kinase inhibitor	EYP-1901	Selective tyrosine kinase inhibitor	VEGF-A, VEGF-B, VEGF-C, PDGF	IVT Injection
	OTX-TKI	Small molecule tyrosine kinase inhibitor	VEGFR-1, 2, and 3	Intravitreal bioresorbable hydrogel implant
	CLS-AX	Small molecule tyrosine kinase inhibitor	VEGFR-1, 2, and 3	Suprachoroidal space microinjector
	KHK4951	Small molecule tyrosine kinase inhibitor	VEGFR-1, 2, and 3	Eye drop
Other	UBX1325	Small molecule inhibitor	Bcl-xL	IVT Injection
	Restoret (EYE103)	Tri-specific Wnt agonist antibody	VEGFR-1, 2, and 3	IVT Injection

Exploring new horizons in neovascular age-related macular degeneration: novel mechanisms of action and future therapeutic avenues | Eye

KHK4951: Aiming to deliver life-changing value

- Kyowa Kirin is developing KHK4951 (nano-crystallized tivozanib eye-drops) to deliver life-changing value for nAMD and DME patients.
- As of December 2025, global Phase 2 trials for nAMD and DME are in progress.

As of October 30th , 2025

Diseases under development*1	Development status	Total addressable market*3	No. of Patients*4
Neovascular age-related macular degeneration (nAMD)	P2 (JP, US)	¥500Bn-¥1Tn	3810K
Diabetic macular edema (DME)	P2 (JP, US)	¥500Bn-¥1Tn	3470K

*1 Expected indications as of the date of this document; indications may ultimately differ to expectations due status of approvals from regulatory authorities. *2 Expected year of first approval. *3 Expected total addressable market estimated by Kyowa Kirin, which is the sum of all products for the indications shown in *1, not projected sales or the Company's targets. **Colored areas represent estimates for global, and the rest are for Japan.** *4 Total number of estimated patients by Kyowa Kirin. **Colored areas represent in-house estimates for global, and the rest are in-house estimates for Japan.**