D. Western Therapeutics Institute (DWTI) | 4576

Sponsored Research
April 5, 2024

Sessa Investment Research

Flurry of pipeline activity in 2023

Commenced dosing of H-1337 in US P2b trials, orphan drug designation for dual formula DW-1002 (US), and DWR-2206 (Japan)

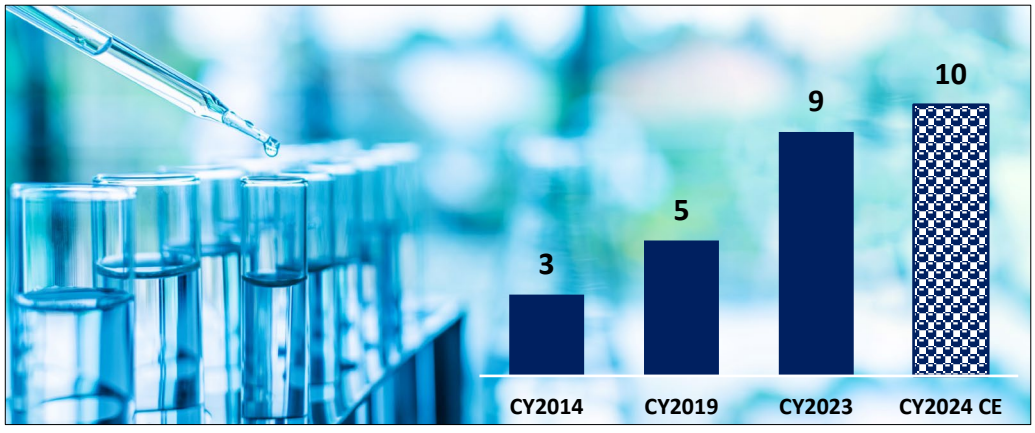
SUMMARY

- Major milestones with high expectations coming in the next 2-3 years: 1) Phase IIb US trials for H-1337 as "first choice as a second-line Glaucoma drug" for patients who do not respond to PGs, 2) 2024 application/approval and 2025 launch of DW-1002 in Japan, 2023 application and 2024 approval/launch in China, as well as orphan drug designation for combination formula MembraneBlue-Dual® (DW-1002 + trypan blue) in the US, 3) in Japan, start P2 clinical trials in 2024, P3 trials in late 2025 though 2026, and normal schedule application for approval for regenerative cell-therapy DWR-2206 in 2027, and 4) an amended application for approval of DW-5LBT lidocaine patch for treatment of neuropathic pain after shingles in the US was re-submitted in Jan- 2024, the FDA setting a target action date in Jul-2024.

- On 8/29/23, DWTI announced that H-1337 dosing has commenced in P2b clinical trials in the US, signaling deployment of R&D expense is set to ramp up. For DWTI, which originally focused on drug discovery and early out-licensing, H-1337 is the first foray into late-stage clinical development. Similar to Ripasudil, H-1337 facilitates drainage of aqueous humor through the trabecular meshwork and Schlemm's canal, and it has demonstrated a "strong and long-lasting IOP pressure-lowering effect." DWTI estimates the target market for 1) patients who do not respond to first-line drugs such as PGs, and 2) patients who receive multiple drugs and suffer side effects, is up to a maximum 40% of the estimated US Glaucoma treatment market of $3 billion ($1.2bn).

- The revised DWR-2206 plan aims to submit an IND (Investigational New Drug) application and start P2 trials in 2024, start P3 trials in late 2025 though 2026, and submit an NDA (New Drug Application) on normal development schedule in 2027. A clinical trial plan notification was submitted on March 27, and P2 trials will begin after a 30-day investigation by PDMA. FY24/12 R&D includes preparations toward H-1337 US P3 (still undecided), DWR-2206 Japan P2, and DW-5LBT milestone pmt.

DWTI No. of Drug Candidate Compounds in the Development Pipeline



Source: compiled by SIR from "Details of the Business Plan and Growth Potential" annual IR presentation materials.

Full Report

Focus Points:

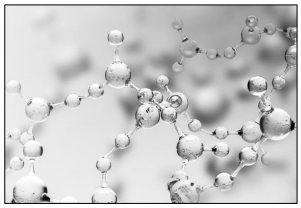
Drug discovery bio-venture with strengths in the kinase inhibitor mechanism and treatments for ophthalmic diseases such as glaucoma and ocular hypertension. Business model expanded to include in-license development and joint discovery/development.

Key Indicators	
Share price (4/4)	120
YH (23/1/25)	305
YL (24/2/16)	115
10YH (15/6/4)	1,140
10YL (24/2/16)	115
Shrs out. (mn shrs)	32.128
Mkt cap (¥ bn)	3.855
Equity ratio (12/31)	53.9%
24.12 P/S (CE)	9.6x
23.12 P/B (act)	3.01x

6M price chart (daily)

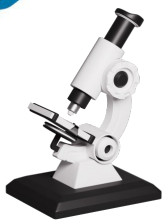
Chris Schreiber CFA
Company Specialist
research@sessapartners.co.jp

DWTI Group Head Office and R&D Labs



Japan Innovative Therapeutics

Rohto Research Village Kyoto



DWTI

Nagoya Head Office

Mie University Faculty of Medicine R&D Lab

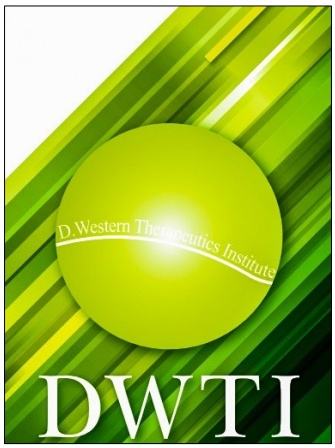
Source: compiled by SIR from company IR materials.

President and CEO
Yuichi Hidaka

DWTI Group Corporate Profile

	Details
Company Name	D. Western Therapeutics Institute, Inc.
Business Field	Discovery and development of new drugs
Established	February 26, 1999
Share Capital	831 million yen (as of December 31, 2023)
Head Office	1-18-11 Nishiki, Naka-ku, Nagoya, Aichi Prefecture, Japan 〒460-0003
Founder	Hiroyoshi Hidaka, MD, PhD
R&D Laboratory	Institute of Human Research Promotion and Drug Development,Mie University Faculty of Medicine, Room 432, University Research Hall, Mie University, 2-174 Edobashi, Tsu City, Mie Prefecture, Japan 〒514-8507
Employees	DWTI: 19, JIT: 2 (as of December 31, 2023), total 32 including executive officers
Group Subsidiary	Japan Innovative Therapeutics, Inc. (consolidated subsidiary)

Source: company website.



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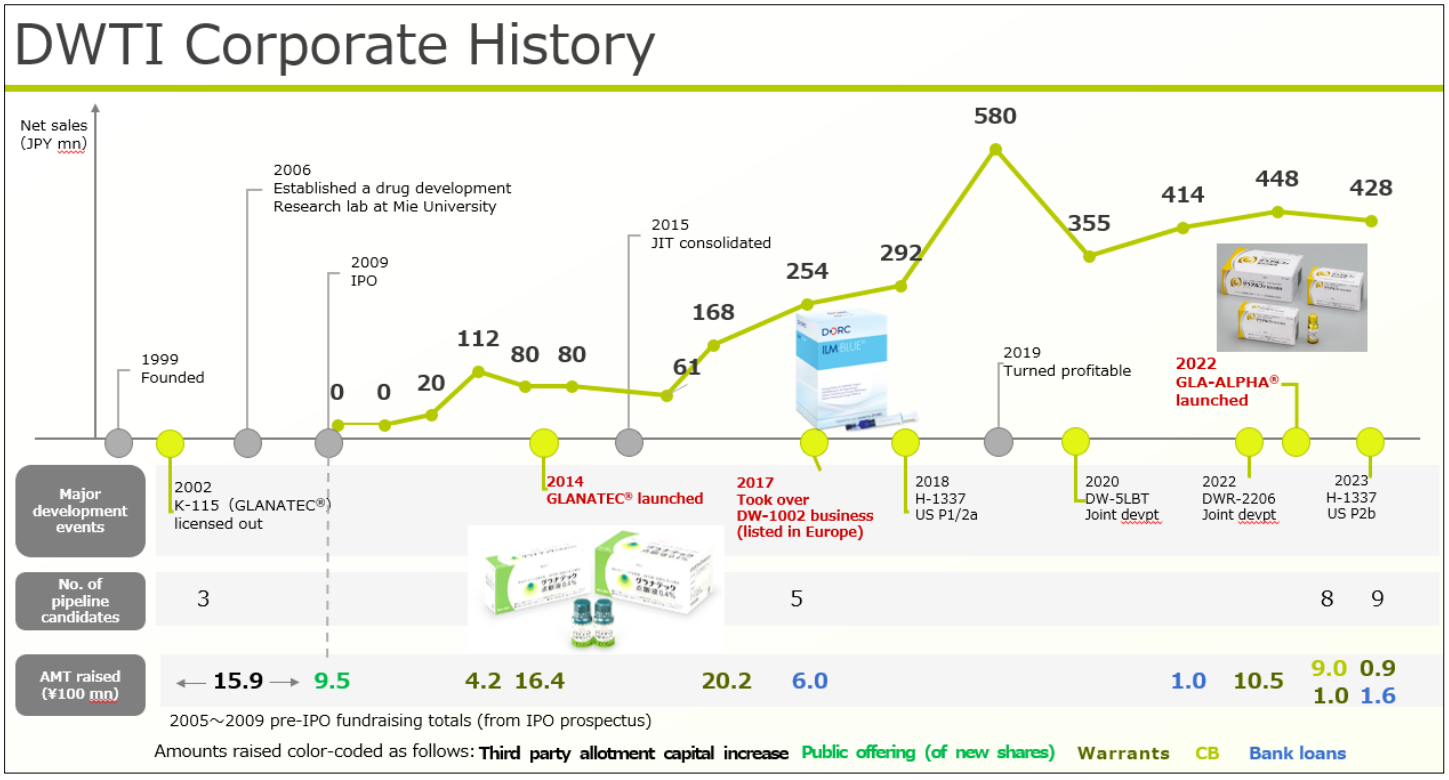
DWTI

❶ BUSINESS

Part 1: Business model evolution, strengths, origin story – corporate history

DWTI (pronounced do-tee) is a drug discovery biotech venture originating from Mie University, focusing on the development of therapeutic drugs for eye diseases. Founded on the principle of "Delivering innovative new drugs from Japan to patients worldwide," the DWTI Group has been engaged in research and development of drug candidates based on proprietary science and technology obtained from research on protein kinase inhibitor development since its establishment. Lead compounds that are candidates for development are selected from the compound library accumulated over decades, optimized using efficient drug design capabilities, and the mechanism of action is clarified using the "Drug-Western method" to determine the target. The original business model focused on out-licensing in-house developed products to pharmaceutical companies at an early stage of development to generate revenue.

However, since it generally takes a decade for a drug candidate to be approved, with huge R&D cost and low probability of success, and steady red ink in the early stage of development with low revenues, following the successful launch of GLANATEC® in 2014, management reached a strategic turning point, shifting away from specializing in fundamental research to focus on internal development and license acquisition. In Part ❶ we examine DWTI's origin story, strengths including 3 drug creation engines used in drug discovery, evolution of its business model to include in-license product development and joint product development (toward steady expansion and diversification of its development pipeline), and key events and milestones in DWTI's corporate history.



Source: excerpt from annual IR reference document "Business Plan and Growth Potential."

DWTI

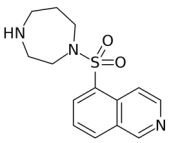
DWTI origin story – pioneer in kinase inhibitor drug discovery

DWTI founder, Dr. Hiroyoshi Hidaka, worked as a doctor after graduating from medical school, and experienced a certain level of satisfaction as his patients recovered. But after deep deliberation, he felt that discovering new drugs might have a greater contribution to the health of many patients overall. While teaching at universities, he continued his studies in pharmacology, and was involved in developing two drugs with two pharma companies which reached successful commercialization. This instilled a desire to develop effective drugs with his own company, so he founded D. Western Therapeutics Institute in February 1999 as a biotech venture company for the purpose of new drug discovery R&D and development.

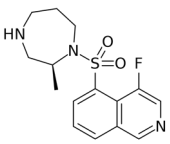
Hiroyoshi Hidaka, MD, PhD
DWTI Founder

Dr. Hidaka was involved in development of the world's first kinase inhibitor Fasudil hydrochloride (HA-1077), which is a ROCK kinase inhibitor. After approval in 1995 in Japan and China, it has been used for the treatment of cerebral vasospasm following subarachnoid hemorrhage. It has also been found to be effective for the treatment of pulmonary hypertension. Fasudil derivative Ripasudil hydrochloride hydrate (K-115) is used to treat glaucoma and ocular hypertension.

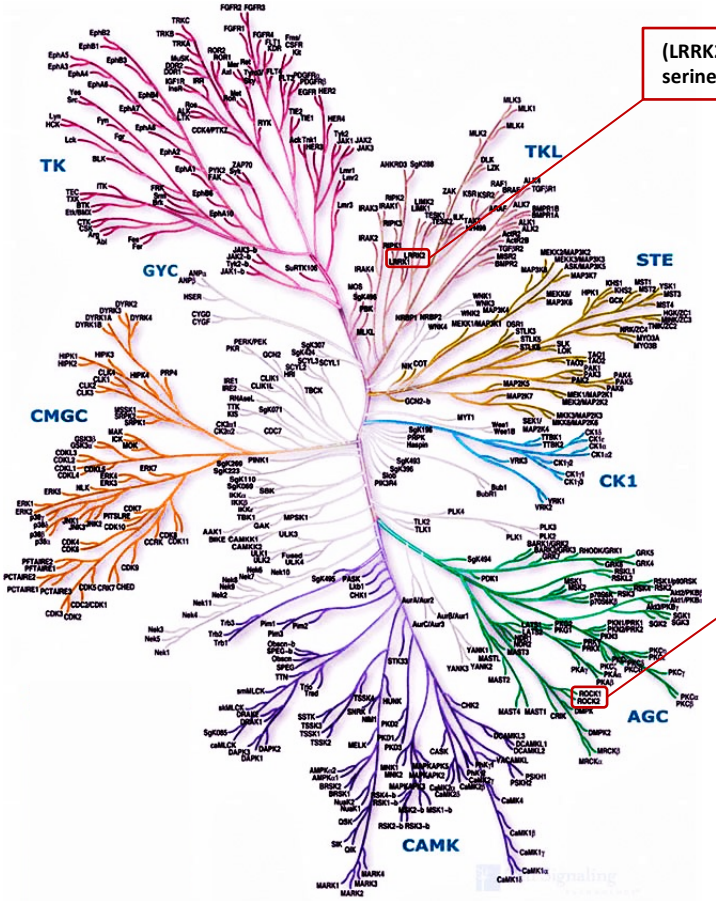
Fasudil
hydrochloride
molecule skeletal
formula



Ripasudil
hydrochloride
hydrate molecule
skeletal formula



Human Protein Kinases Overview (classified by groups based on sequence similarity)



(LRRK2) Leucine-rich repeat serine/threonine-protein kinase

DWTI's H-1337 currently under development in the US is an LRRK2 multi-kinase inhibitor indicated for treating glaucoma and ocular hypertension

(ROCK1) Rho-associated coiled-coil-containing protein kinase

DWTI's K-115 Ripasudil (GLANATEC® ophthalmic solution 0.4%) is a ROCK1 kinase inhibitor

Source: image reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

The Human Kinome and kinase inhibitors used as therapeutic agents

According to Wikipedia, a kinase inhibitor is a type of enzyme inhibitor that blocks the action of one or more protein kinases. Protein kinases are enzymes that add a phosphate (PO_4) group to a protein to modulate its function.

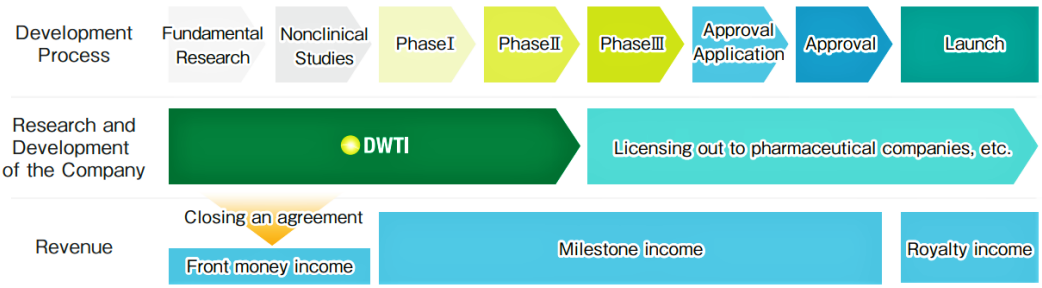
Phosphorylation regulates many biological processes, and kinase inhibitors can be used to treat diseases due to hyperactive protein kinases (including mutant or overexpressed kinases in cancer) or to modulate cell functions to overcome other disease drivers.

The human kinome contains 518 protein kinases that comprise 1.7% of human genes, 478 eukaryotic protein kinases (ePKs), and 40 atypical protein kinases (aPKs) which lack sequence similarity to the ePK domain.

Drug discovery and development business: evolution to 3 business models

Since its founding as a bio-venture, DWTI has been positioned in the upstream of drug discovery and development business, concentrating management resources on drug creation and licensing out the new drug candidate compound at an early stage. This first basic business model is depicted in the graphic below. Revenue streams from this business are comprised of: ① initial lump-sum payment on concluding the license-out contract, ② milestone income to be received at certain milestones as clinical trials progress, and ③ royalty income at a fixed percentage (margin) of sales after the drug is launched. As mentioned earlier, R&D expense is high during an early period with no income, so this model allows the company to focus management resources on its strength in R&D technology and steady efforts to continue to expand the development pipeline.

Initial basic business model: drug discovery and early out-licensing



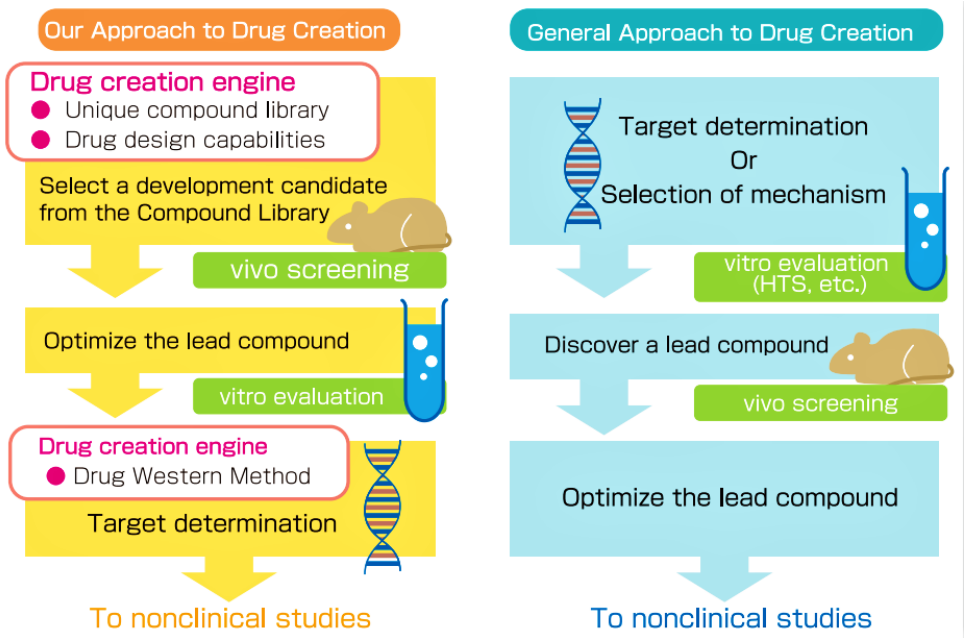
Source: company website

The basic steps in DWTI's fundamental research and uncovering the mechanism of action (MOA) for a new drug candidate compound are: ① utilizing the unique drug creation engine, synthesize a new material from a seed compound and repeat screening so as to demonstrate its effect in the target disease to create a candidate for a beneficial treatment, ② utilizing the drug creation engine, explore a binding protein for the new drug candidate compound and uncover its mechanism of action, and ③ obtain a patent for the new drug candidate compound.

As highlighted on the previous page, DWTI has technical expertise in protein kinase inhibitors, and DWTI's approach to drug creation shown in the graphic on the top of the following page is based on 3 drug creation engines: ① extensive library of protein kinase inhibitor seed compounds accumulated over several decades, ② drug design capabilities based on the founder's previous involvement in drug development projects with major pharma companies and accumulated extensive molecular pharmacological data and analysis based on intracellular signal transduction research, and ③ the Drug-Western Method, which is used to examine to which protein an administered drug binds in the body (identifying the target).

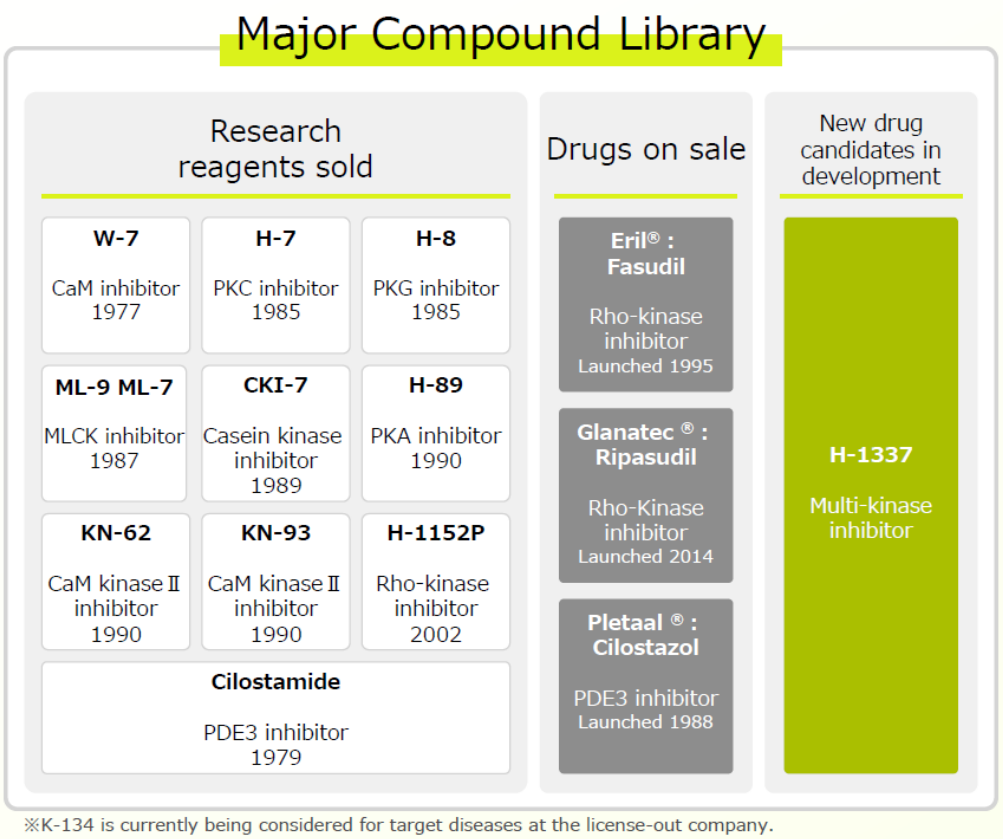
3 drug creation engines:
- Compound library
- Design capabilities
- Drug-Western Method

DWTI approach to drug creation based on 3 drug creation engines



Source: company website

Highlights from DWTI's extensive compound library accumulated over decades

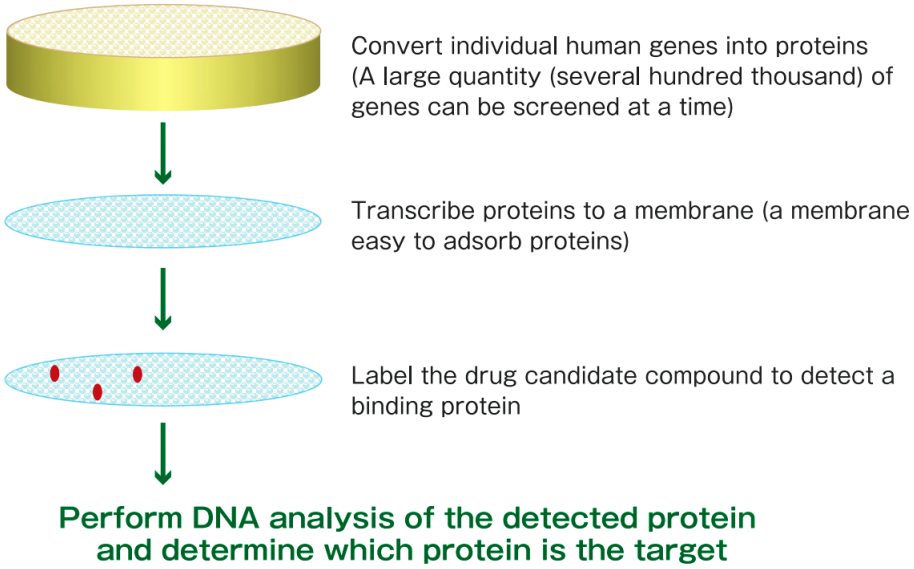


Source: excerpt from annual IR reference document "Business Plan and Growth Potential."

Drug-Western Method

- Determines the target protein of a new drug candidate compound
- Examining the protein function helps clarify safety and efficacy
- Also raises efficiency of subsequent development

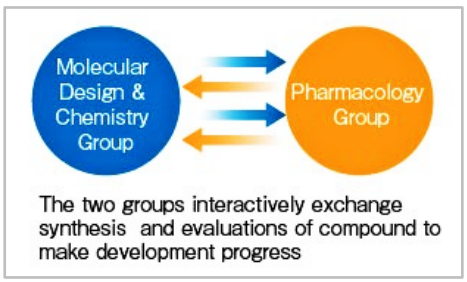
Overview of the Drug-Western Method



Source: company website

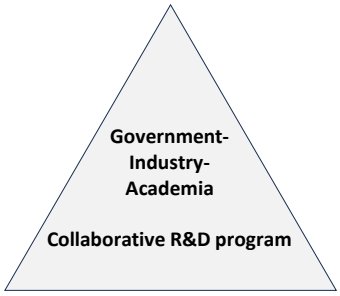
The Drug-Western Method is a method to examine to which protein an administered drug binds in the body. Under certain conditions the gene of a protein bound to the drug is isolated, and gene sequences are analyzed to identify which protein the drug bound to. By examining the function of the protein, the possibilities of the new drug to be developed can be uncovered. Identifying the molecular target of a new drug at an early stage of drug development not only clarifies the efficacy and safety of the drug but also has a great impact on the efficiency of subsequent new drug development including clinical studies.

DWTI's R&D laboratories consist of the Molecular Design & Chemistry Group and Pharmacology Group. The Molecular Design & Chemistry Group synthesizes patentable compounds on the basis of compound data from the unique compound library. The synthesized new compound is then transferred to the Pharmacology Group for evaluation testing. The Molecular Design & Chemistry Group makes improvements in the compound based on the evaluation test results to refine the compound that will demonstrate higher efficacy (beneficial effect) and safety. This process is repeated in the creation of a candidate compound for a new drug. The Pharmacology Group performs testing with compounds synthesized by the Molecular Design & Chemistry Group using animals and evaluates the efficacy and safety of the compounds. When a final candidate compound is found by repeating this process, it is also the responsibility of the Pharmacology Group to determine the target protein using the Drug Western Method and uncover the mechanism of action.

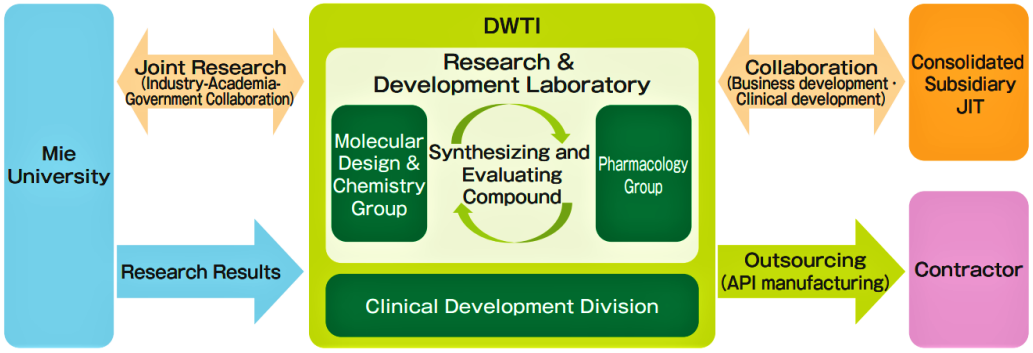


Source: company website

DWTI research and development is carried out in the government-industry-academia collaboration course, “Clinical Drug Creation Research Course,” established by the company at Mie University. The Research and Development Institute is established in the Faculty of Medicine of Mie University, having access to the knowledge and equipment available at the university to facilitate effective R&D.



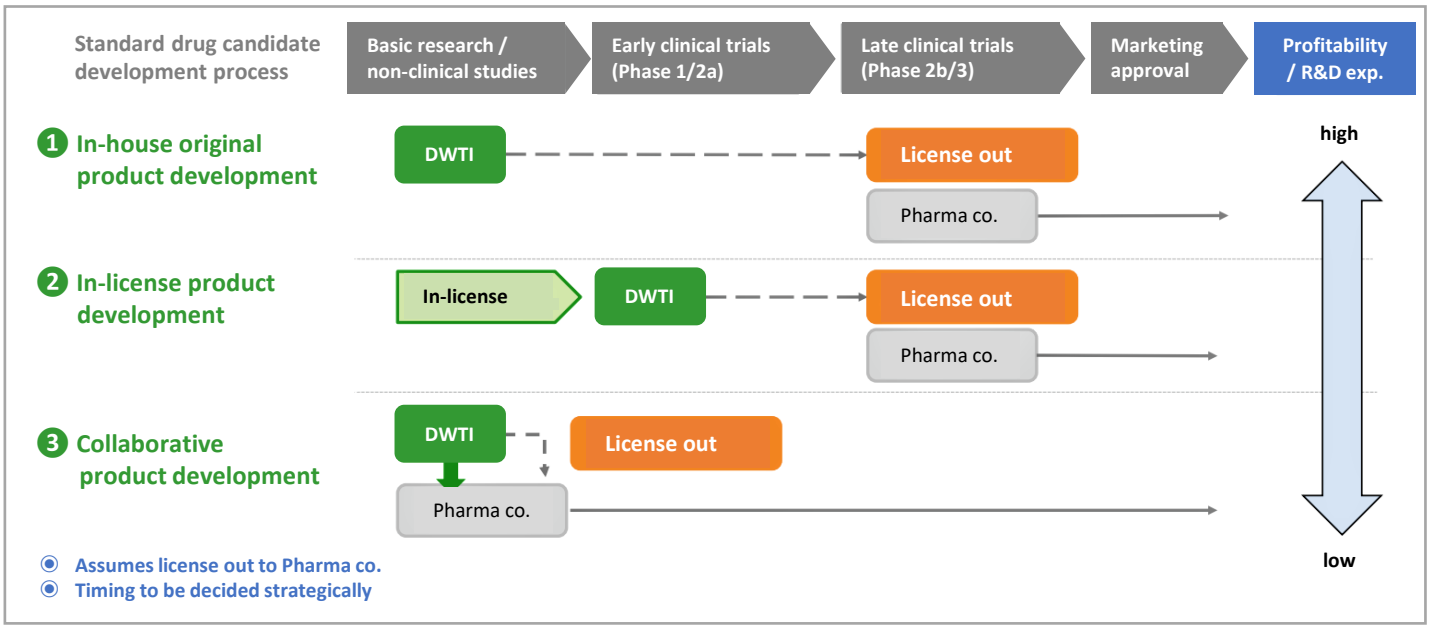
Relationships between DWTI and external organizations



Source: company website

Over time with progress in execution of the development pipeline, and as part of growth strategy to diversify revenue streams, the basic business model described on P6 has evolved to include ① from 2015, in-licensing of later stage development or repositioning products, commencing in-house clinical development, ② from 2018 collaborative drug creation applying DWTI’s technical expertise to assist in the development of products of other firms, and ③ from 2018 extending development of original in-house products beyond early out-licensing as far as proof of concept (PoC) through phase 2b. The revenue stream for collaborative research projects includes receipt of payment of R&D fees from the partner.

★DWTI initial basic business model has evolved into three business models



Source: company IR materials.

GLANATEC® ophthalmic solution 0.4%

TissueBlue™ ophthalmic surgical aid

GLA-ALPHA® combination ophthalmic solution

DWTI Corporate History – 3 products launched; pipeline expanded to 9

Date	Event / milestone
1999.02	Established D.Western Therapeutics Institute, Inc. in Nagoya, Aichi Prefecture for the purpose of conducting pharmaceutical research and development (five million yen capitalization)
2002.09	Signed a development and implementation agreement with Kowa Co., Ltd. for K-115, a drug for treating glaucoma, ocular hypertension
2004.11	Changed from a limited company to a joint-stock corporation (10 million yen capitalization)
2006.12	Entered into an industry-academia-government collaboration agreement with Mie University Faculty of Medicine for joint research, and jointly established Institute of Human Research Promotion and Drug Development at the University
2009.10	Listed on JASDAQ Securities Exchange NEO Market (now Tokyo Stock Exchange Growth market)
2014.12	GLANATEC® ophthalmic solution 0.4% (generic name: Ripasudil hydrochloride hydrate, K-115) for glaucoma launched in Japan
2015.06	Signed an in-licensing agreement to acquire exclusive Japan license for an ophthalmic drug (DW-1001)
2015.11	Made Japan Innovative Therapeutics Inc. a consolidated subsidiary
2017.04	Received transfer of business related to an ophthalmic surgical adjuvant (DW-1002)
2018.03	Initiatied Phase I/IIa clinical trials of glaucoma treatment (H-1337), DWTI's first in-house developed product, in the U.S.
2018.09	Phase I/IIa clinical trials of H-1337 glaucoma treatment completed in the U.S.
2019.08	Submitted an Investigational New Drug (IND) application for Phase II clinical trials in the U.S. of Ripasudil hydrochloride hydrate as treatment for Fuchs endothelial corneal dystrophy (K-321)
2019.12	Signed an agreement with Rohto Pharmaceutical Co., Ltd., granting exclusive Japan license for ophthalmic drug DW-1001
2020.02	Phase III clinical trials began in Japan for a fixed combination drug for treating glaucoma (Ripasudil hydrochloride hydrate and Brimonidine tartrate [K-232])
2020.04	Ophthalmic surgical adjuvant DW-1002 (TissueBlue™) launched in the U.S.
2020.08	Signed a joint development agreement with MEDRx Co., Ltd. for DW-5LBT neuropathic pain treatment
2020.08	Applied for approval of DW-5LBT neuropathic pain treatment in the U.S.
2020.09	Added new disease types (corneal and retinal disorders) for joint research with U.S.-based Glaukos, and signed a new licensing agreement
2021.10	Ophthalmic surgical adjuvant DW-1002 (TissueBlue™) launched in Canada
2021.11	Applied for approval of K-232 glaucoma and ocular hypertension in Japan
2022.03	Phase I clinical trials of DW-1001 began in Japan
2022.06	Signed a joint development agreement with ActualEyes Inc. for DWR-2206 regenerative cell therapy for bullous keratopathy
2022.08	Phase III clinical trials of K-321 for Fuchs endothelial corneal dystrophy began in U.S.
2022.12	GLA-ALPHA® combination ophthalmic solution (generic name: Ripasudil hydrochloride hydrate, brimonidine tartrate, K-232) for glaucoma and ocular hypertension launched in Japan Initiatied Phase IIb clinical trials of glaucoma treatment (H-1337)
2023.03	Commenced global Phase III clinical trials for Fuchs endothelial corneal dystrophy K-321
2023.03	Re-sumitted application for approval of DW-5LBT neuropathic pain treatment in the U.S.
2023.07	DW-1002 combination formula given orphan drug designation in the US, preparations for application DWR-2206 development plan disclosed
2023.08	H-1337 P2b dosing commenced in the US
2023.09	Receipt of Complete Response Letter for DW-5LBT from US FDA
2024.01	Re-submitted application for approval of DW-5LBT in US, FDA set target action date in Jul-2024
2024.03	Submitted clinical trial plan notification for DWR-2206, set to commence P2 trials in Japan after a 30-day investigation by the PDMA

Source: compiled by SIR from company website and recent press releases.

DWTI

❷ BACKROUND

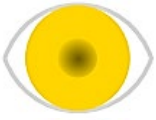
Part 2: Focus on ophthalmology: vision disorders, Glaucoma basics

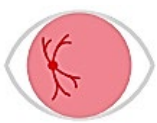
According to the World Glaucoma Association, glaucoma is a chronic, progressive, degenerative disorder of the optic nerve that leads to loss of side (peripheral) vision, blind spots, and ultimately blindness. WGA estimates roughly 80 million people have glaucoma worldwide, expected to increase to 112 million by 2040. 50% of glaucoma patients are unaware they have it because early stages are asymptomatic, and risk increases with age. Damage to the optic nerve is irreversible. The leading cause of damage to the optic nerve is buildup of intraocular pressure (IOP). The eye produces a fluid known as aqueous humor that provides nourishment to its internal structures. This fluid is then drained out through a sieve-like structure called the trabecular meshwork.

Abnormalities or obstruction to the drainage system leads to impairment of the normal outflow, and IOP increases. Although there is no cure for glaucoma, treatments include medicine (usually eye drops), laser treatment or surgery. **Some types of eye drops work by helping fluid drain from the eye, which lowers IOP (prostaglandins, rho-kinase inhibitors, nitric oxides). Other types of eyedrops work by lowering the amount of fluid the eye produces (alpha-adrenergic agonists, beta blockers, carbonic anhydrase inhibitors). We examine this market in more detail in Part ❹ covering DWTI's development pipeline**.

Common eye conditions that can cause vision impairment including blindness

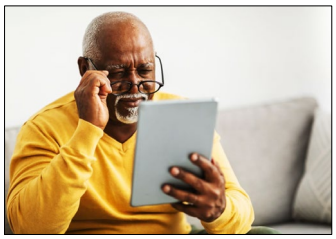
Common conditions that can cause vision impairment including blindness due to ageing	
Age-related macular degeneration	Damage to the central part of the retina responsible for detailed vision leads to dark patches, shadows or distortion of the central vision. The risk of developing macular degeneration increases with age.

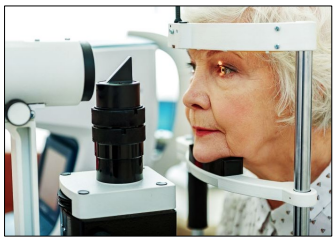




Common conditions that can cause vision impairment that are preventable or not yet treated	
Refractive error	Due to an abnormal shape or length of the eye ball; light does not focus on the retina resulting in blurred vision. There are several types of refractive error; those most commonly referred to are: • Myopia – difficulty seeing distant objects (near-sightedness). • Presbyopia – difficulty seeing objects at near distance with increasing age (i.e. after 40 years of age)
Cataract	Cloudiness in the lens of the eye, leading to increasingly blurred vision. The risk of developing cataract increases with age.
Glaucoma	**Progressive damage to the optic nerve. Initially, loss of vision occurs in the periphery and can progress to severe vision impairment (this is known as open angle glaucoma, the most common type). Damage is irreversible.**
Corneal opacity	A group of conditions causing the cornea to become scarred or cloudy. Opacity is most commonly caused by injury, infection or vitamin A deficiency in children.
Diabetic retinopathy	Damage to blood vessels in the retina which become leaky or blocked. Vision loss most commonly occurs due to swelling in the central part of the retina which can lead to vision impairment. Abnormal blood vessels can also grow from the retina, which can bleed or cause scarring of the retina and blindness.
Trachoma	Caused by a bacterial infection. After many years of repeated infections, the eyelashes can turn inwards (known as trichiasis) which can lead to corneal scarring and, in some cases, blindness

Source: compiled by SIR from "WHO World Report on Vision 2019."





Estimated Population with Vision Impairment or Blindness: over 1.2 billion

unit: million people	Condition	CY2020	CY2030
Age-related macular degeneration	Vision impairment or blindness	195.6	243.4
– of which Glaucoma	**Vision impairment or blindness**	**76.0**	**95.4**
Unaddressed refractive error	Moderate / severe distance vision impairment	123.7	—
	Near vision impairment	826.0	—
Cataract	Moderate / severe distance vision impairment	65.2	—
Glaucoma	Moderate / severe distance vision impairment	6.9	—
Corneal opacity	Moderate / severe distance vision impairment	4.2	—
Diabetic retinopathy	Moderate / severe distance vision impairment	3.0	—
Trachoma	Moderate / severe distance vision impairment	2.0	—
Total estimated population		**1,226.6**	**—**

Source: compiled by SIR from "WHO World Report on Vision 2019."

Torreya's Pharma 1000 Report: only 25 in the area of biotech ophthalmology

Torreya Partners LLC* is a global investment banking boutique focused on the pharmaceutical sector, with specialized services advising clients in biotechnology, branded pharmaceutical, generic pharmaceutical, and life sciences companies. The company publishes and maintains a list of the top 1000 pharma companies by market value (universe of over 30,000). Over half of the companies are private, so the company uses publicly traded company multiples to impute private company values.

The far-right column shows average company values, indicating that ophthalmology biotech firms tend to be smaller companies. Data above from the "WHO World Report on Vision 2019" shows that despite the small number of biotech ophthalmology firms represented in the Pharma 1000, **the estimated population with conditions causing moderate / severe vision impairment on the previous page is quite large at 1.2 billion, and the aging of developed nations will drive an increase in patients going forward**.

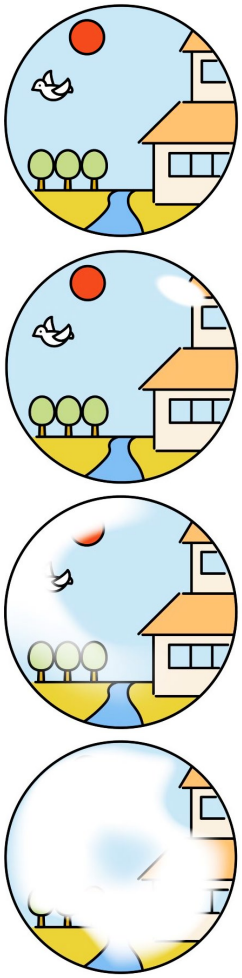
Biotech Market Value Aggregate Shares by Therapeutic Area

Therapeutic Area	2020.09.15 Cos.	2020.09.15 Share	2021.11.05 Cos.	2021.11.05 Share	CHG YOY Cos.	CHG YOY Share	AVG VAL USD mn
Oncology	140	38.2%	253	39.3%	113	1.1%	$857
Neurology	31	7.4%	62	11.6%	31	4.2%	$1,036
Rare disease	45	11.9%	60	11.6%	15	-0.2%	$1,070
Vaccines	11	3.8%	19	4.5%	8	0.7%	$1,305
Virology	9	4.1%	19	4.2%	10	0.0%	$1,206
Respiratory	11	3.3%	21	3.8%	10	0.5%	$1,008
Ophthalmology	**14**	**2.2%**	**25**	**3.1%**	**11**	**0.8%**	**$674**
Broad / platform	3	2.3%	19	2.8%	16	0.6%	$821
Immunology	9	2.2%	15	2.5%	6	0.3%	$909
Renal	5	1.1%	9	2.2%	4	1.2%	$1,366
Cardiometabolic	10	1.7%	18	1.9%	8	0.2%	$579
Gastroenterology	7	1.6%	16	1.7%	9	0.1%	$589
Endocrinology	2	2.9%	2	1.6%	0	-1.4%	$4,293
Hematology	7	2.1%	10	0.7%	3	-1.4%	$400
Bone & osteo	4	2.9%	5	0.7%	1	-2.2%	$749
Wound care	3	1.1%	4	0.6%	1	-0.5%	$862
Anti-infectives	5	5.7%	8	0.4%	3	-5.3%	$258

Source: compiled by SIR from "The Pharma 1000 Report" by Torreya.
*Torreya Partners LLC was acquired by Stifel Financial Corp. in Mar-2023.

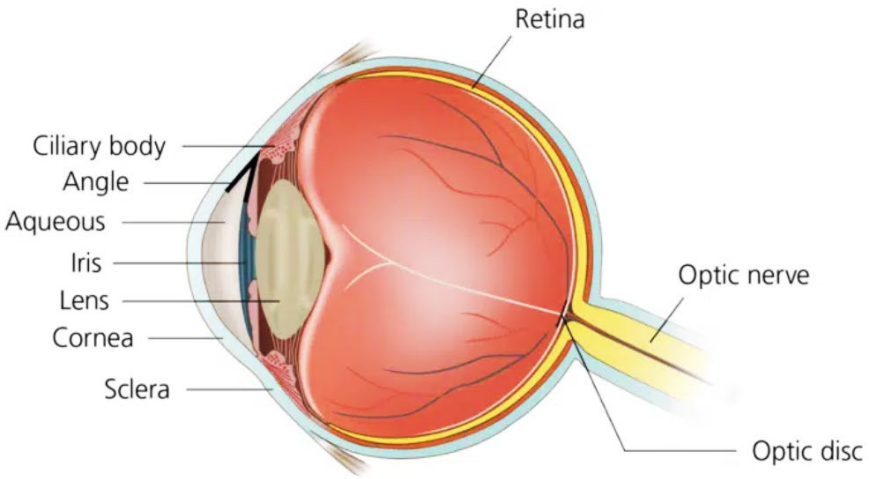
Glaucoma basics
Millions of nerve fibers that run from the retina form the optic nerve, and they meet at the optic disc. In most types of glaucoma, the eye's drainage system becomes clogged so the intraocular fluid cannot drain. As the fluid builds up, it causes increased IOP, which can result in damage and loss of these sensitive nerve fibers, and ultimately result in vision loss.

Progression of vision impairment

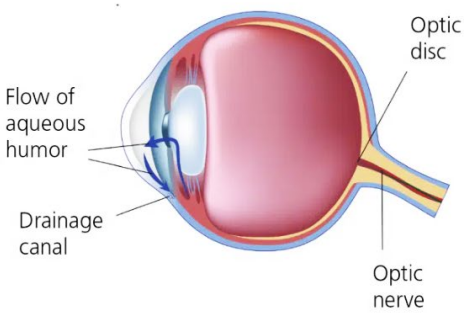


World Glaucoma Week

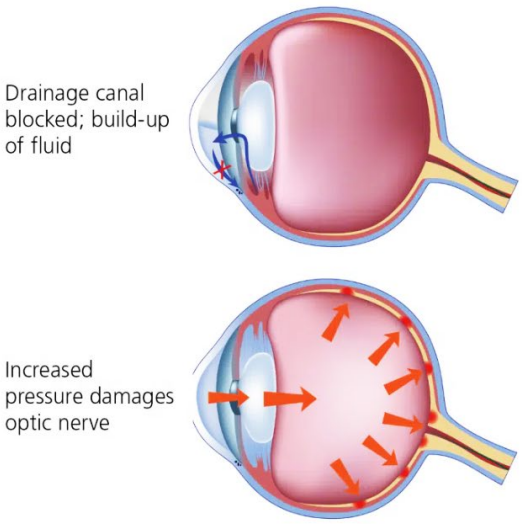
Development of Glaucoma in the Human Eye



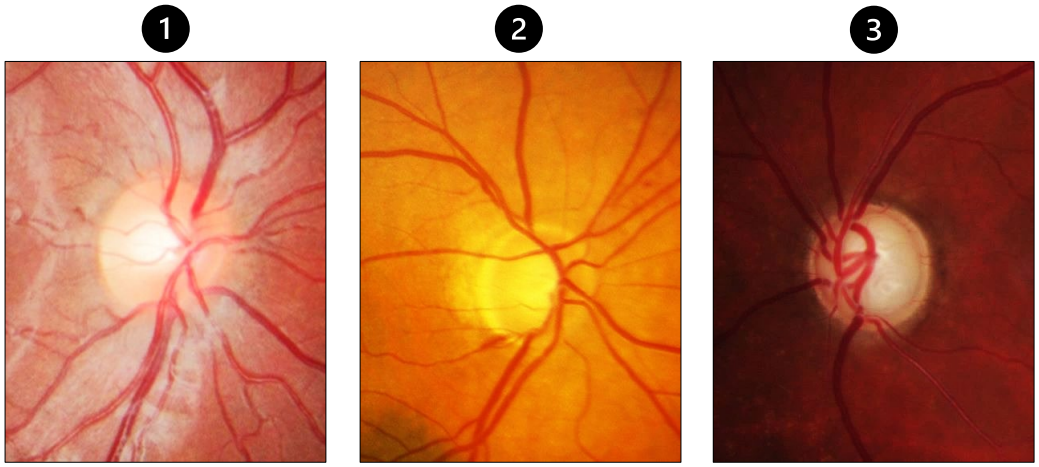
Healthy Eye



Eye with Glaucoma



Deterioration stages of the optic disc resulting in vision loss



Normal optic disc
Healthy and thick neural tissue (reddish part), associated with a small cup (whitish central part)

Glaucomatous optic disc
Loss of neural reddish tissue and increase of optic disc cupping (whitish central part)

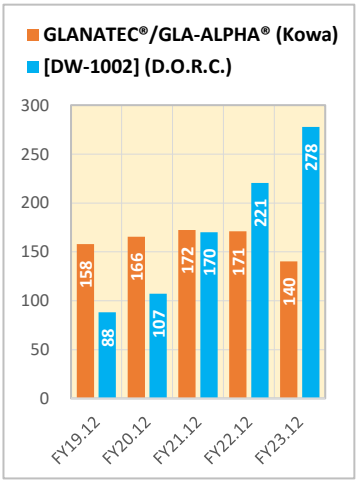
End stage optic disc
Almost no more neural tissue and eventually a total cupping of the disc can be observed

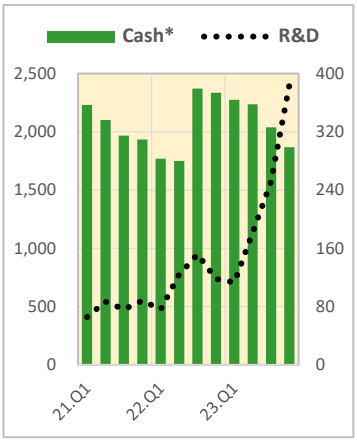
Source: compiled by SIR from websites of the GLAUCOMA Research Foundation, the US NIH National Eye Institute and World Glaucoma Association information portal GlaucomaPatients.org.

DWTI

3 EARNINGS

Royalty income from launched products





*Cash = cash and deposits on the B/S.

DW-1002 sales continue to expand globally, +26%

Top-line data for H-1337 US P2b trials expected 2H 2024

Part 3: 4Q FY23/12 Consolidated Financial Results Summary and Forecasts

❊ DWTI announced 4Q FY23/12 consolidated financial results at 15:30 on Friday 2/9. **Net sales decreased -4.4% YoY to ¥428mn**, mainly because previous FY22/12 net sales of ¥448mn included approx. ¥56mn from 1) a one-time payment from capital alliance and [DWR-2206] corneal endothelial regenerative cell therapeutic product joint development partner ActualEyes as consideration for transfer of worldwide exclusive licensing rights for commercializing the corneal endothelial therapeutic drug developed by Doshisha University held by DWTI subsidiary Japan Innovative Therapeutics in Nov-2022, and 2) a milestone payment from ROHTO Pharmaceutical upon initiation of Phase I clinical trials in Japan of [DW-1001] in Mar-2022.

❊ **Total royalty income from launched products** (see left-hand graph) from 1) eye drops for treating glaucoma by lowering intraocular pressure: GLANATEC® ophthalmic solution 0.4% and new GLA-ALPHA® combination ophthalmic solution (sold by Kowa), and 2) [DW-1002] Brilliant Blue G ophthalmic surgical aid dyes: ILM-Blue® (global sales) / TissueBlue™ (US/Canada sales) staining solution and MembraneBlue-Dual® combination staining solution (sold by D.O.R.C.), **increased by ¥26mn (+6.7%) to ¥418mn, broken down as 1) eye drops for treating glaucoma by lowering intraocular pressure (sold by Kowa): decreased by ¥31mn (-17.9%) to ¥140mn, and 2) [DW-1002] ophthalmic surgical aid dyes (sold by D.O.R.C.): increased by ¥57mn (+25.8%) to ¥278mn.** Single agent solution GLANATEC® sales declined due to the decline in the 8-year contractual royalty rate from late 2022 (launched by Kowa in Dec-14, subject patent expired, royalties to expire in Sep-24),

DWTI 4Q FY23/12 Consolidated Financial Results Summary and Forecasts

JPY mn, % [J-GAAP]	FY22/12 act 23.02.13	FY23/12 init CE 23.02.13	FY23/12 rev CE 23.12.14	CHG AMT rev	FY23/12 act 24.02.09	CHG AMT YoY	FY24/12 init CE 24.02.09	CHG AMT YoY
Net sales	**448**	**400**	**410**	**10**	**428**	**(20)**	**400**	**(28)**
YoY	*8.1*	*(10.7)*	*(8.5)*		*(4.4)*		*(6.6)*	
• Japan	**227**				**151**	**(77)**		
• Netherlands	**221**				**278**	**57**		
Cost of sales	28				37	9		
Gross profit	421				392	(29)		
SG&A expenses	726				1,190	464		
• R&D expense	**470**	**1,500**	**1,000**	**(500)**	**931**	**461**	**1,600**	**669**
as % of net sales	105%	375%	244%		217%		400%	
• Other SG&A	257				260	3	flat	
Operating profit (loss)	**(306)**	**(1,400)**	**(850)**	**550**	**(799)**	**(493)**	**(1,500)**	**(701)**
Ordinary profit (loss)	(296)	(1,410)	(850)	560	(796)	(501)	(1,510)	(714)
Profit (loss) ATOP	(430)	(1,390)	(870)	520	(812)	(383)	(1,510)	(698)
Selected B/S items	**[4Q act]**		**[3Q act]**		**[4Q act]**			
• Cash and deposits	**2,335**		**2,038**		**1,867**	**(467)**		
Total assets	2,956		2,627		2,373	(583)		
Total liabilities	1,083		974		1,094	11		
Total net assets	1,873		1,653		1,280	(594)		
Equity ratio	62.8%		62.7%		53.9%	-8.9%		

Source: compiled by SIR from Summary of Financial Results (TANSHIN) and IR results briefing materials.

continued

❊ while combination solution GLA-ALPHA® (launched in Dec-22) contributed on a full-term basis, with sales steadily expanding. The +25.8% increase in [DW-1002] ophthalmic surgical aid dyes (stronger than expected) is broken down as: sales volume +13.1% and forex effect +12.0%, with particularly strong growth for MembraneBlue-Dual® combination staining solution. **Relative to the initial forecast for ¥1,500mn, FY23/12 actual R&D expense was ¥931mn.** This was mainly due to 1) for [H-1337] multi-kinase inhibitor that inhibits various protein kinases for glaucoma and ocular hypertension, despite commencing the US P2b trial in Dec-2022, the start of actual patient dosing was pushed back to the end of Aug-2023, and 2) there was no milestone payment for [DW-5LBT].

❊ **The initial forecast for FY24/12 net sales is ¥400mn, down ¥28mn (-6.6% YoY).** For royalty income for launched products, GLANATEC® Japan sales are expected to decline with the expiration of royalty income in Sep-2024. While sales of combination solution GLA-ALPHA® are expected to continue steady growth, the total of the two products is expected to decline. Sales of [DW-1002] both single and combination solutions are expected to continue growing globally, including China approval and launch (see exhibit below). DWTI also anticipates milestone income for [DW-1002] in Japan. **The initial budget for FY24/12 R&D expense is ¥1,600mn.** This includes: 1) Increased costs for [H-1337] US P3 trials, 2) milestone payment for DW-5LBT approval, and 3) increase in research expenses (in-house drug discovery and collaborative research projects) for new drug creation.

Achievement status of 2023 events initially expected

H-1337	Publication of US P2b top-line data	Not achieved Changed to 2024
DW-5LBT	Re-application and approval	Partially achieved Re-applied in Jan-2024
DW-1001	Start of Japan P2	Not achieved
DW-1002 (single agent)	China application — market launch, Japan application	Partially achieved May-2023 China application

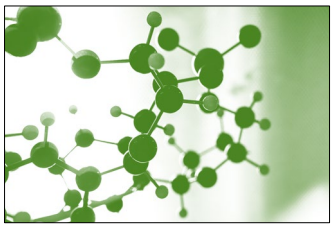
Events not originally planned

DW-1002 (combination)	Obtained US orphan drug designation, application in preparation	NEW
K-321	Start of Global P3	NEW
DWR-2206	Announced development plan	NEW

Events expected to occur in 2024

H-1337	Publication of US P2b top-line data
DW-5LBT	US re-application (achieved Jan-2024), approval — launch
DWR-2206	Start of Japan P2
DW-1002	China approval — launch, Japan application
New projects	Research progress (including new collaborations)

Source: excerpts from DWTI IR results briefing materials.



Launched Products

Active ingredient, product name, etc.			Clinical indication	Region	Licensee
Ripasudil hydrochloride hydrate		GLANATEC® ophthalmic solution 0.4%	Glaucoma and ocular hypertension	Japan, Asia (Note)	Kowa
Ripasudil hydrochloride hydrate / brimonidine tartrate		GLA-ALPHA® combination ophthalmic solution	Glaucoma and ocular hypertension	Japan	
DW-1002	Brilliant Blue G	ILM-Blue®, TissueBlue™	ILM staining	Europe, U.S., etc.	DORC
	Brilliant Blue G /trypan blue	MembraneBlue-Dual®	ILM, ERM and PVR membrane staining	Europe, etc.	

License-out partners

Note: Has been launched in Singapore, Malaysia and Thailand; approved in Korea and application submitted in Vietnam.

Development Pipeline: Status of New Drug Candidate Compound Development

Development code, etc.		Clinical indication	Development stage	Region	Licensee
K-321	Ripasudil hydrochloride hydrate	Fuchs endothelial corneal dystrophy	Phase III clinical trials	U.S., Europe, etc.	Kowa
DW-1002	Brilliant Blue G	ILM staining	Application	China	DORC
			Phase III clinical trials	Japan	Wakamoto Pharmaceutical
		ALC staining	Phase III clinical trials	Japan	
	Brilliant Blue G /trypan blue	ILM staining and ERM staining	In preparation for filing	U.S.	DORC
DW-1001		Ophthalmic treatment agent (undisclosed)	Phase I clinical trials	Japan	ROHTO Pharmaceutical
H-1337		Glaucoma and ocular hypertension	Phase IIb clinical trials	U.S.	Developed internally
DW-5LBT		Neuropathic pain after shingles	Application	U.S.	Jointly developed with MEDRx
DWR-2206		Bullous Keratopathy	Non-clinical studies	Japan	Jointly developed with ActualEyes

License-out partners

In-house, joint dev

Source: excerpts from FY23/12 Consolidated Financial Results Summary (TANSHIN financial statements).

Development Pipeline Events during FY2023/12

Development Product		Region / Country	Non-clinical	P1	P2	P3	Apply	Approval	Event TOPICS
K-321		US, etc.							23.3 Global P3 started
DW-1002	combination	US							23.7 Orphan drug designation, preparations for application
	single agent	China							23.5 Application
		Japan							
DW-1001		Japan							
H-1337		US							23.8 P2b dosing started
DW-5LBT		US							24.1 Re-submitted application
DWR-2206		Japan							23.7 Development plan disclosed

Source: compiled by SIR from 4Q FY23/12 Full-term IR Results Briefing materials.

DWTI

4 PIPELINE

—Non-ocular diseases

DW-5LBT

On September 29, 2023, DWTI and MEDRx, which are co-developing DW-5LBT in the US, received a complete response letter (CRL) from the FDA. After carefully reviewing the instructions to resubmit some non-clinical data, it was determined that re-analysis of the data without conducting additional studies would address the issues raised by the FDA, and the amended application was submitted on January 12, 2024, and accepted by the FDA on January 31, setting a target action date under the Prescription Drug User Fee Act of July 11, 2024.

Part 4: Development Pipeline Progress Status for Ocular Diseases

❊ On 8/29/23, DWTI announced that H-1337 dosing commenced in P2b clinical trials in the US. This is a multicenter, randomized, double-blind, actual drug control, dose-finding study. The efficacy and safety of H-1337 will be evaluated in patients with glaucoma and ocular hypertension by application of eye drops for 28 days. The number of patients is planned to be 200 cases in 4 groups: H-1337 0.6% (twice daily), 1.0% (twice daily), 1.0% (once daily), and Timolol (beta blocker drug for efficacy comparison, twice daily). Top-line data is expected in the 2H of 2024. DWTI will make a determination about whether to continue P3 in-house or license out.

❊ K-321 US P3 trials on 331 patients after cataract surgery were completed in Jun-2023 (updated info in December, results undisclosed). The K-321 global (US, Europe, etc.) trials from Mar-2023 through Jan-2025 will be administered to 100 patients with FECD after Descemetorhexis (surgical removal of Descemet membrane without subsequent endothelial transplant), and the global trials from Apr-2023 through Jan-2025 will be administered to 100 patients with FECD after simultaneous cataract surgery and Descemetorhexis.

❊ In Japan, Wakamoto is expected to file applications for ILM and ALC staining in 2024, receive approvals and launch in 2025. DORC filed an NDA in China in May-2023 for indication ILM peeling, targeting approval and sales launch in 2024. Under preparation, DORC is expected to file an application in the US for MembraneBlue-Dual® combination formula in 2025, targeting approval/launch in 2026.

❊ The revised DWR-2206 plan aims to submit an IND (Investigational New Drug) application and start P2 trials in Japan in 2024, start P3 trials in late 2025 though 2026, and submit an NDA (New Drug Application) on normal schedule approval in 2027.

Development Pipeline Progress Plan to Achieve Goals

Pipeline name, etc.			2023	2024	2025	2026
H-1337	Glaucoma treatment	US	P2b		P3 ※2025 onward	
DW-5LBT	Treatment for neuropathic pain after shingles	US		Re-apply / Approval	Launch	
K-321	Treatment for Fuchs endothelial corneal dystrophy (FECD)	US	P3		Apply	
DW-1001	Ophthalmic therapeutic agent (non-disclosure)	Japan			P2	
DW-1002	ILM staining	China	Apply	Approval	Launch	
	ILM staining ALC staining	Japan		Apply	Approval	Launch
	ILM staining and ERM staining	US		Preparation for application	Apply	Approval / Launch
DWR-2206	Regenerative medicine cell-product for bullous keratopathy	Japan	Non-clinical		P2	P3

※The above plans are based on the development plan assumed by the license-out company or DWTI projections and may differ from the actual development progress.

Source: excerpt from annual IR reference document “Business Plan and Growth Potential.”

US development schedule
- Phase IIb – 2023 to 2024
- Phase III – after 2025
- Secured new financing

DWTI announced on December 15, 2022 (local time) that it submitted an Investigational New Drug (IND) Application to the US FDA to commence late-stage Phase 2b clinical trials for H-1337 glaucoma and OHT, and announced August 29, 2023 commencing trial doses.

The study will be a multicenter, randomized, double-blind, active-controlled, dose-finding study investigating the efficacy and safety of H-1337 in patients with glaucoma and ocular hypertension. The study will enroll 200 patients, with top-line data expected in the 2H of 2024.

[H-1337] Glaucoma treatment

DWTI is developing a multi-kinase inhibitor that inhibits various protein kinases, chiefly leucine-rich repeat kinase 2 (LRRK2), for the treatment of glaucoma and ocular hypertension. Animal studies and other tests have confirmed that this pipeline drug has the effect of lowering intraocular pressure. DWTI believes its strong effectiveness in lowering intraocular pressure is attributed to its new mechanism of action. In 2018, DWTI carried out in-house Phase I/IIa clinical trials in the US, and safety and efficacy were confirmed (clinical PoC was obtained). For DWTI, which has typically focused on drug discovery and early out-licensing, this was the first foray into clinical development.

Strong prospects as "first choice as a second-line Glaucoma drug"

Similar to Ripasudil, H-1337 facilitates drainage of aqueous humor through the trabecular meshwork and Schlemm's canal, and it has demonstrated a "strong and long-lasting IOP pressure-lowering effect." Prostaglandin analogues (PGs) demonstrate the strongest IOP pressure-lowering effect among first-line drugs, however, PGs also have little to no effect on many patients, and more than half of drug-treated patients use multiple medications. First-line drugs have little to no effect on a surprisingly large number of patients, and single-drug treatment has shown limited efficacy. Multiple-drug treatments are standard (3–4 drugs used in some cases); however, side effects are more common when using multiple drugs.

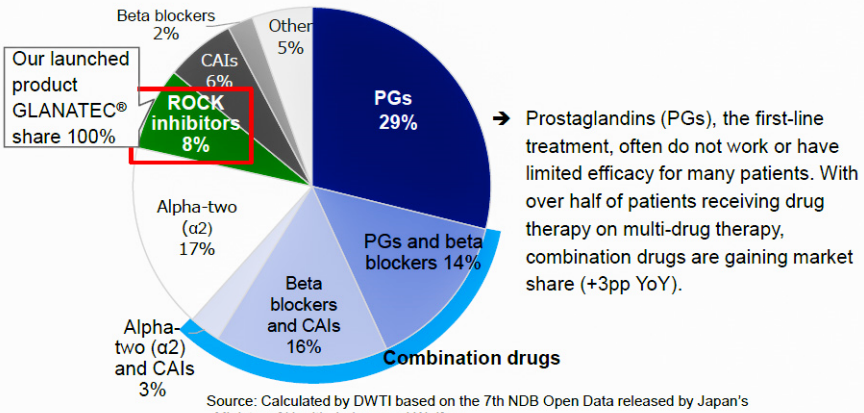
DWTI estimates the target market for 1) patients who do not respond to first-line drugs and 2) patients who receive multiple drugs and suffer side effects is up to a maximum **40% of the estimated US market of $3 billion ($1.2bn).**

Glaucoma Market

Global market: Approx. USD 6.8bn worldwide (2020)*

- The U.S. market is the largest, accounting for about USD 3bn, nearly half.*
- The prevalence of glaucoma is increasing due to the increase in the elderly population, and the number of patients is expected to increase in the future.
- Wider treatment options are now available, including surgical procedures (devices) and multi-drug therapies.

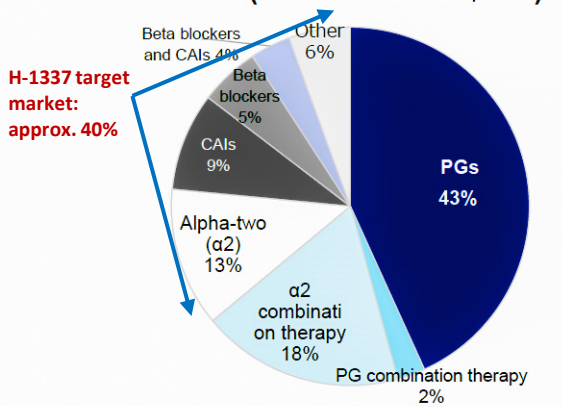
Japanese market (FY2020: about ¥89bn)



➔ Prostaglandins (PGs), the first-line treatment, often do not work or have limited efficacy for many patients. With over half of patients receiving drug therapy on multi-drug therapy, combination drugs are gaining market share (+3pp YoY).

Source: Calculated by DWTI based on the 7th NDB Open Data released by Japan's Ministry of Health, Labour and Welfare

US market (FY2020: about $3bn)*



* According to DWTI's research based on IQVIA MIDAS Dec 2020 MAT

Source: excerpt from FY2022/12 4Q IR results briefing materials. Note: the latest figure for the FY2021 Japan market is about ¥80.8bn, down due to COVID-19.

Source: MEDRx website.

Characteristics

- Confirmatory comparative (bioequivalence) clinical trial comparing DW-5LBT with innovator product Lidoderm® generated favorable results.
- Low dermal irritation
- Capable of maintaining adhesive strength during exercise

[DW-5LBT] neuropathic pain treatment (jointly developed with MEDRx)

DW-5LBT is a new type of lidocaine patch for the treatment of post-herpetic neuralgia (neuropathic pain after shingles) that uses the ILTS® (Ionic Liquid Transdermal System), an exclusive MEDRx technology incorporating the company's ionic liquid expertise. MRX-5LBT is being developed with the goal of its "Lidolyte" targeting the market for innovator product Lidoderm®, a lidocaine patch.

In April 2020, DWTI concluded a collaborative development agreement with MEDRx, and August filed the NDA application in the US. DWTI received a complete response letter (CRL) from the FDA on July 5, 2021, and the company responded appropriately to specified issues.

On March 29, 2023, DWTI announced that MEDRx re-submitted a new drug application (NDA) to the US FDA. On September 29, DWTI and MEDRx, which are co-developing DW-5LBT in the US, received a complete response letter (CRL) from the FDA. After carefully reviewing the instructions to resubmit some non-clinical data, it was determined that re-analysis of the data without conducting additional studies would address the issues raised by the FDA, and the amended application was submitted on January 12, 2024, and accepted by the FDA on January 31, setting a target action date under the Prescription Drug User Fee Act of July 11, 2024.

Based on data from MEDRx, the US market for transdermal lidocaine patches was estimated at about ¥27bn in 2020. The primary details of the development agreement with MEDRx are ① milestone payment of up to ¥200mn according to progress of commercialization in the US (expected payment delayed from 2021), and ② after launch, DWTI will receive royalties commensurate with sales.

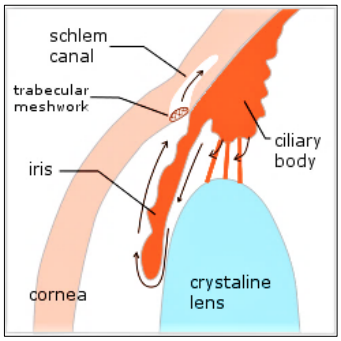
(4586 TSE Growth) MEDRx ILTS® and transdermal drug delivery

Transdermal drug delivery technology has been applied to developing local analgesics, anti-Alzheimer's drugs and antidepressants, since transdermal preparations have advantages of being able to improve patients' QOL. Developing and providing transdermal preparations represent the fulfillment of unmet medical needs.

However, skin works as the barrier for human bodies to repel foreign substances. So, it is rather difficult for drugs to penetrate the skin barrier unless the drug has some penetration capability, which is influenced by the melting point, molecular weight, solubility, lipophilicity, etc. Under the circumstances, we have applied our proprietary ILTS® technology to various drugs, including even compounds with low solubility and/or weak absorbability, such as biopharmaceuticals, etc.

Transdermal drug delivery has various advantages:
1. Overcome first pass effect.
2. Easily achieve stable blood level and high bioavailability.
3. Free of pain and fear due to needleless injection.

GLANATEC® action mechanism
High intraocular pressure due to blocked fluid drainage damages the optic nerve. GLANATEC® ophthalmic solution 0.4% promotes outflow of aqueous humor through Schlemm's canal, relieving ocular hypertension.



GLANATEC® ophthalmic solution 0.4%

GLA-ALPHA® combination ophthalmic solution

Ripasudil hydrochloride hydrate

❶ Glaucoma and ocular hypertension [GLANATEC® ophthalmic solution 0.4%]

This drug is an eye drop preparation with a novel mechanism of action, the first of its kind in the world, for treating glaucoma. The drug lowers intraocular pressure by inhibiting rho-kinase, a type of protein kinase, and promoting the outflow of aqueous humor from the main collector channel via the trabecular meshwork/Schlemm's canal. In 2002, DWTI out-licensed the rights to the drug to Kowa Co., Ltd., which then moved ahead with development and launched the drug in Japan under the brand name Ripasudil hydrochloride hydrate in December 2014. *Because all rights in Japan and worldwide relating to Ripasudil hydrochloride hydrate have been out-licensed to Kowa, the following two drugs are also being developed by Kowa. Launched (Japan, Thailand, Singapore and Malaysia); Approved (Korea); Application (Vietnam).

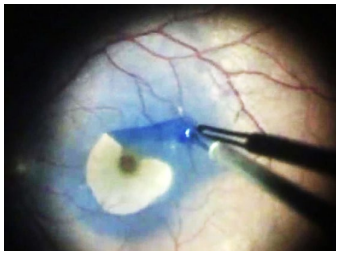
❷ Glaucoma and ocular hypertension [GLA-ALPHA® combination ophthalmic solution (Ripasudil hydrochloride hydrate and Brimonidine tartrate) K-232]

This drug is being developed as the first fixed combination eye drop containing Ripasudil hydrochloride hydrate. Since the standard treatment for glaucoma involves the use of multiple drugs, we are seeking to improve the quality of life for glaucoma patients by providing a combination drug. September 26, 2022: obtained mfg. and marketing approval for K-232, GLA-ALPHA® combination ophthalmic solution for the treatment of glaucoma and ocular hypertension (OHT), in Japan. Given an NHI Drug price listing, and Kowa launched GLA-ALPHA® on December 6, 2022.

❸ [K-321] Fuchs endothelial corneal dystrophy (development pipeline)

Since Ripasudil hydrochloride hydrate is a rho-kinase inhibitor, it has been suggested that the compound may also act on other kinases in the eye, leading to investigations of its applicability to other ophthalmic diseases. As part of these efforts, development of the compound as a treatment for Fuchs endothelial corneal dystrophy (FECD) is underway. FECD is a disease in which corneal edema and opacity occur as a result of damage to corneal endothelial cells, resulting in diminished acuity of vision. Although there are few patients suffering from FECD in Japan, it is a common disease in Europe and the U.S. There is currently no effective drug treatment for FECD, which is often treated with corneal transplant surgery.

K-321 US P3 trials on 331 patients after cataract surgery were completed in Jun-2023 (updated info in December, results undisclosed). The global (US, Europe, etc.) K-321 trials from Mar-2023 through Jan-2025 will be administered to 100 patients with FECD after Descemetorhexis (Descemetorhexis Without Endothelial Keratoplasty DWEK) which is a proposed term to describe the surgical removal of Descemet membrane (DM) without subsequent endothelial transplantation, in the treatment of Fuchs Endothelial Corneal Dystrophy, and the global study from Apr-2023 through Jan-2025 will be administered to 100 patients after simultaneous cataract surgery and Descemetorhexis.



Source: Journal of Ophthalmology

[DW-1002] ophthalmic surgical adjuvant

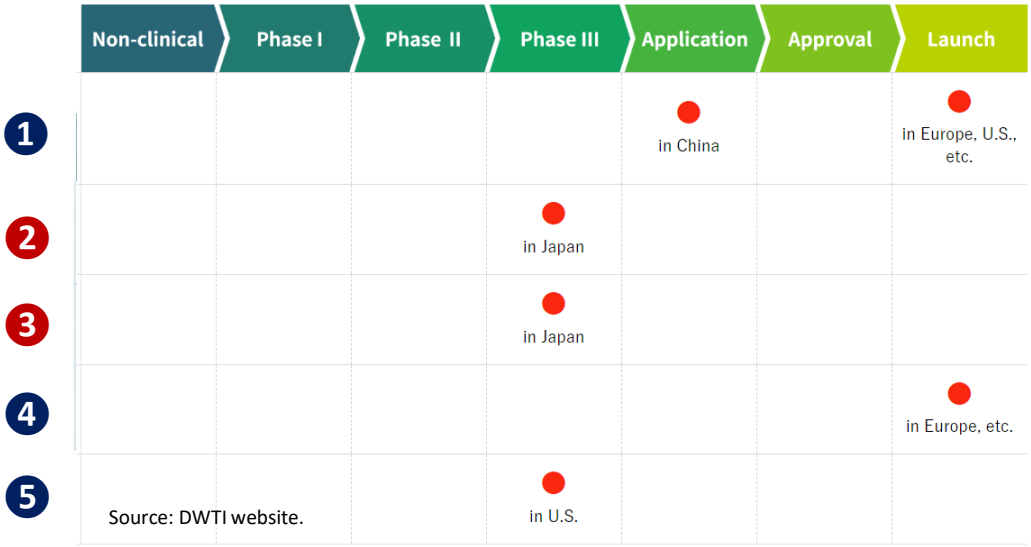
Brilliant Blue G-250 (BBG250) is an ophthalmic surgical adjuvant whose active ingredient is a dye with high staining ability. The dye temporarily and safely stains the capsule protecting the inner limiting membrane or crystalline lens in the back of the eye, making it easier to perform vitreous or cataract surgery. BBG250 was discovered by a research group at Kyushu University, and it has since been commercialized. DWTI acquired the business from Healios K.K. in 2017, and it have since been developing the dye under exclusive license from Kyushu University.

DWTI granted an exclusive sublicense for DW-1002 for all regions worldwide outside Japan to Dutch Ophthalmic Research Center (International) B.V. (DORC), which has been manufacturing and selling the product in Europe and other countries since September 2010. DW-1002 (ILM-Blue®, TissueBlue™, MembraneBlue-Dual®) is on sale in 76 countries and regions, including the US and Europe. Royalty revenue is up sharply due to higher sales in Europe, the US and Canada and the effect of yen depreciation. **DORC has obtained from the US FDA orphan-drug designation for expedited review of MembraneBlue-Dual® (DW-1002 + trypan blue) combination formula ophthalmic surgery adjuvant, and it will develop it in the US for ILM and ERM membrane staining.** Single formula TissueBlue™ has been used in over 100,000 operations since its launch in the US in 2020. MembraneBlue-Dual® combination formula has been used in over 500,000 operations since its launch in Europe in 2010.

WAKAMOTO PHARMACEUTICAL CO., LTD. has been granted an exclusive sublicense for Japan, and has been moving forward with development aiming to obtain approval. WAKAMOTO is expected to file applications for ❷ and ❸ in 2024, receive approvals and launch in 2025. DORC filed an NDA in China in May-2023 for ❶ indication ILM peeling, targeting approval and sales launch in 2024. DORC is expected to file an application in the US for ❺ MembraneBlue-Dual® combination formula in 2025, targeting approval and sales launch in 2026.

Clinical indications:
❶ ILM staining (Europe, US and Canada, China)
❷ ILM (internal limiting membrane) staining (Japan)
❸ ALC (anterior lens capsule) staining (Japan)
❹ ILM, ERM (epiretinal membrane) and PVR membrane staining (Europe, etc.)
❺ ILM staining and ERM staining (US) [NEW]

Development Stages of DW-1002



Source: DWTI website.

MembraneBlue-Dual® (DW-1002 + trypan blue) combination formula ophthalmic surgery aid

ActualEyes, Inc. (unlisted)

Business Objectives:

Doshisha University venture company established for the development and launch of two specific products: 1) eye drops for the treatment of Fuchs endothelial corneal dystrophy (FECD) and 2) a cell-therapy product for treatment of corneal endothelial decompensation.

Arctic Vision (China biotech)

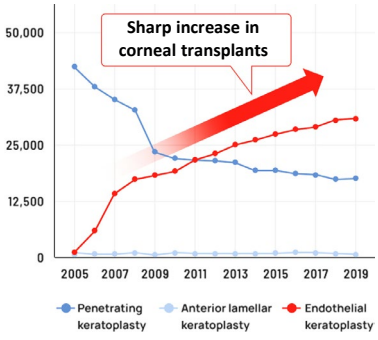
Description:

China-based ophthalmic biotech focusing on breakthrough therapies, with a leading portfolio covering pre-clinical stage to commercial stage products.

J-TEC (TSE Growth 7774)

Description:

TEIJIN Group subsidiary Japan Tissue Engineering Co., Ltd. (J-TEC, TSE 7774) has been a pioneer for regenerative medicine in the ophthalmologic field with its tissue-engineered products used in "autologous" transplants, where living cells are taken from the actual patient, cultured and then transplanted back. ActualEyes concluded a contract with J-TEC to manufacture AE101.



According to data from the Ministry of Health, Labour and Welfare, there are an estimated 7,000-10,000 patients in Japan with bullous keratopathy. According to research by DWTI, the number of corneal transplants is said to be about 3,000, with a waiting list of 10,000 to 20,000. Also, only 1 in 70 patients worldwide who need a corneal transplant can undergo the surgery (see graph above).

[DWR-2206] regenerative medicine cell-therapy treatment for corneal endothelial dystrophy (jointly developed with ActualEyes)

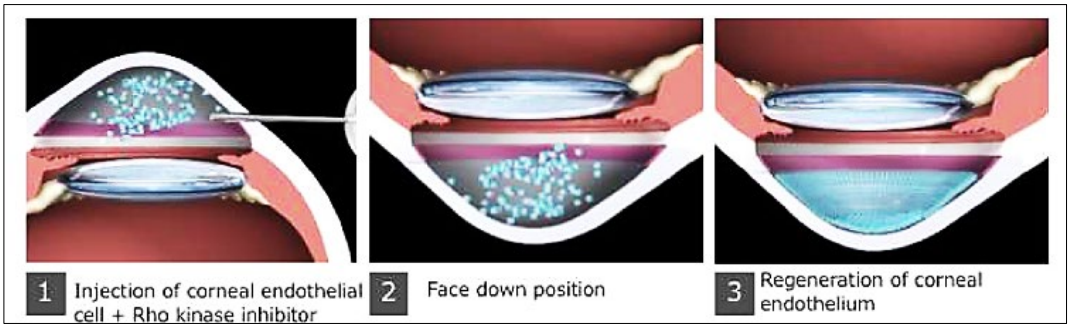
DWR-2206 (AE101) is a novel cell injection therapy developed by ActualEyes as a regenerative cell therapy for the indication of bullous keratopathy, which is an eye disorder that involves a blister-like swelling of the cornea (the clear layer in front of the iris and pupil), using cultured human corneal endothelial cells (hCECs) combined with a Rho-associated kinase (ROCK) inhibitor (see exhibit below).

All proceeds from DWR-2206 will be split between ActualEyes and DWTI (this includes milestone and royalty payments from China bio-venture Artic Vision, to which ActualEyes has already licensed out), and the two companies plan to proceed with clinical trials in Japan with the aim of obtaining manufacturing and marketing approval as soon as possible.

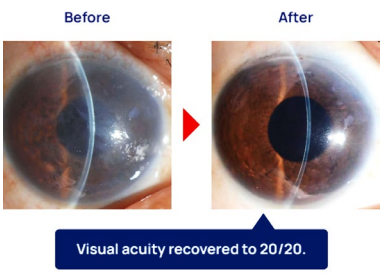
Three reasons for DWTI becoming involved with regenerative medicine cell-therapy products for corneal endothelial disorders: 1) **Ophthalmology Field:** enhances DWTI's focus on ophthalmologic diseases, 2) **Corneal Endothelial Disorders:** caused by a variety of factors, the only treatment is corneal transplant surgery, and there is no cure, and, unmet medical needs are high due to the global shortage of donors, graft failure, and difficulty of the surgical procedure, and 3) **Regenerative Medicine:** new treatment technology that can fulfill unmet medical needs, and the acquisition of new modalities can contribute to patients' optimal treatment choices.

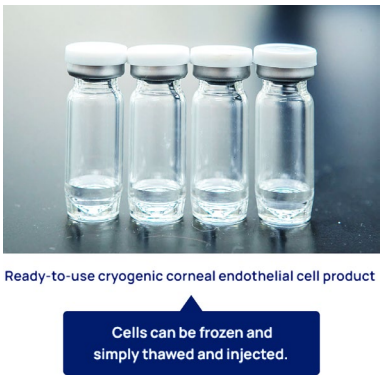
The revised DWR-2206 plan aims to submit an IND (Investigational New Drug) application and start P2 trials in Japan in 2024, start P3 trials in late 2025 though 2026, and submit an NDA (New Drug Application) on normal schedule approval in 2027. A clinical trial plan notification was submitted on March 27, and P2 trials will begin after a 30-day investigation by PDMA.

Cell-Therapy Product DWR-2206 for Treatment of Corneal Endothelial Dysfunction



Source: ActualEyes Inc. website. https://www.actualeyes.co.jp/technology/





Bullous Keratopathy Market Attributes

- Bullous keratopathy is the terminal stage of various corneal endothelial disorders, including Fuchs corneal endothelial dystrophy. It can also occur due to damage after cataract and glaucoma surgery.
- Thus, the number of potential patients is significant and on an upward trend.

Japan			US, Europe	China	Global
Number of bullous keratopathy patients estimated	Keratoplasties performed annually	Patients on waiting list	FECD* Incidence	Corneal endothelial dysfunction patients estimated	Donor corneas available
7,000–10,000	about 3,000	10,000–20,000	Approximately 4% of people over 40	1mn or greater	only one in 70 patients
*source: MHLW	* source: DWTI		*FECD：Fuchs Endothelial Corneal Dystrophy		* source: DWTI

Source: above and below are excerpts from FY2023/12 IR results briefing materials.

Competitors of DWR-2206

	DWR-2206	HCEC-1	EO2002	CLS001	EndoArt®
Cell transplantation/ device	Cultured human corneal endothelial cells	Cultured human corneal endothelial cells	Magnetic nanoparticle-loaded cultured human corneal endothelial cells	iPS cell-derived human corneal endothelial cells as an alternative to donor corneal endothelium	Artificial corneal endothelial layer (device)
Developed by	ActualEyes Inc./DWTI	Aurion (US)/CorneaGen Japan	Emmecell (US)	Cellusion	Eye-yon Medical (Israel)
Development stage	Nonclinical	Japan: Preparing to file application US: Phase I	US: Phase I	Nonclinical	CE mark Israel (AMAR)
Partners	Greater China and South Korea: Arctic Vision	--	--	Greater China: Celregen* (Subsidiary of Fosun Pharma)	--

*Hangzhou Celregen Therapeutics

Reason why new treatment is sought

Only treatment for bullous keratopathy is a corneal transplant, which has the following challenges.

- Donor shortage
- Highly skilled surgeon and sophisticated equipment required for surgery
- Risks include infection, astigmatism, rise in intraocular pressure, and adhesion failure of transplant.

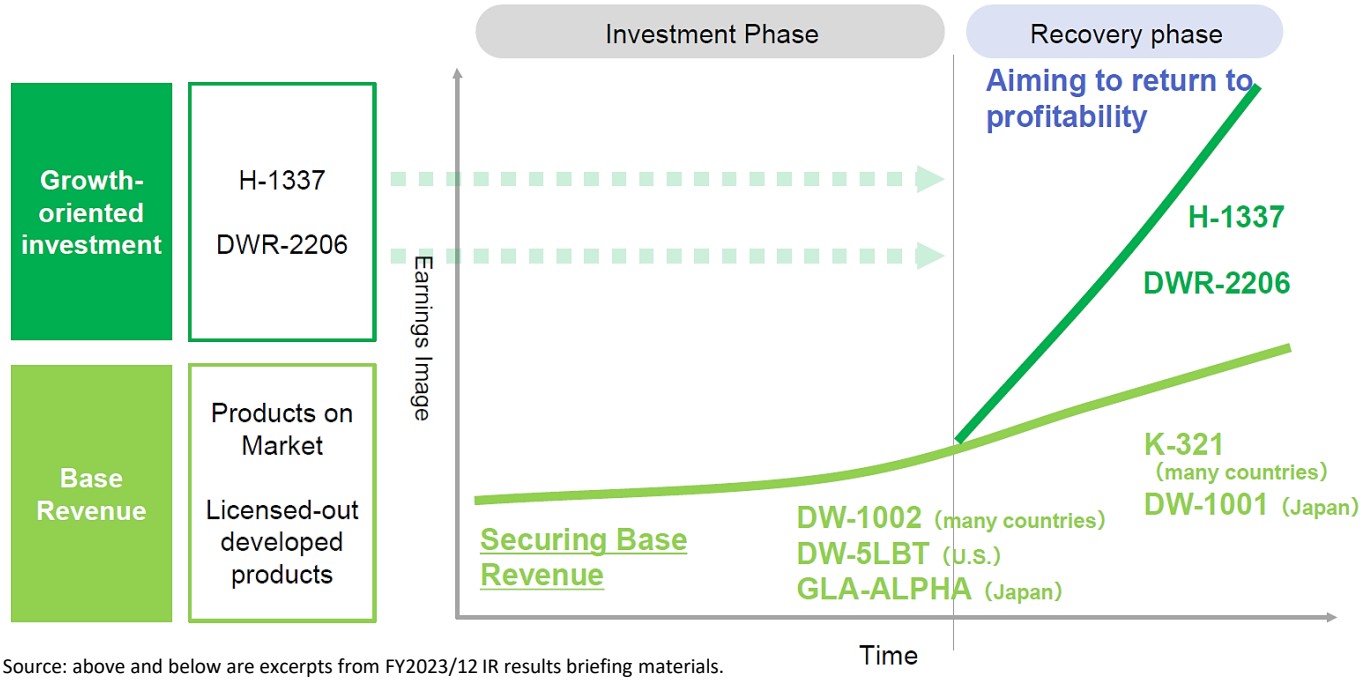
Treatment using cultured human corneal endothelial cells (which can be produced with consistent quality in large quantities) and iPS cells are being explored.

➔ The product jointly developed by DWTI aims to regenerate the corneal endothelium by injecting a suspension into the anterior chamber of the eye. It is a new, accessible treatment to replace corneal transplants.

DWTI's growth strategy: growth-oriented investment in H-1337 and DWR-2206

❇ DWTI is currently in the investment phase, securing base earnings through royalty income from DW-1002, DW-5LBT, and GLA-ALPHA. From there, the Company hopes to invest in H-1337 and DWR-2206, for which it is bearing its own development costs, in order to achieve further growth. Both DW-5LBT and DWR-2206 were financed by term loan agreements with commitment periods. In addition, the Company has raised funds through unsecured convertible bonds (CBs) and share acquisition rights (SARs). Currently, 32.7% of the CBs have been converted and 42.5% of the SARs exercised.

Investment in Growth and Securing Base Revenue



Source: above and below are excerpts from FY2023/12 IR results briefing materials.

Borrowings and Financing Status

Borrowings

Balance (as of Dec. 31, 2023)	Credit limit	Use of funds	Type
JPY100mn	JPY200mn	Funds for the milestone payment for neuropathic pain treatment DW-5LBT	Term loan contract with commitment period
JPY179mn	JPY440mn	Funds for the development of regenerative cell therapy DWR-2206	Term loan contract with commitment period

✓ Completion of repayment of DW-1002 funds

Other financing

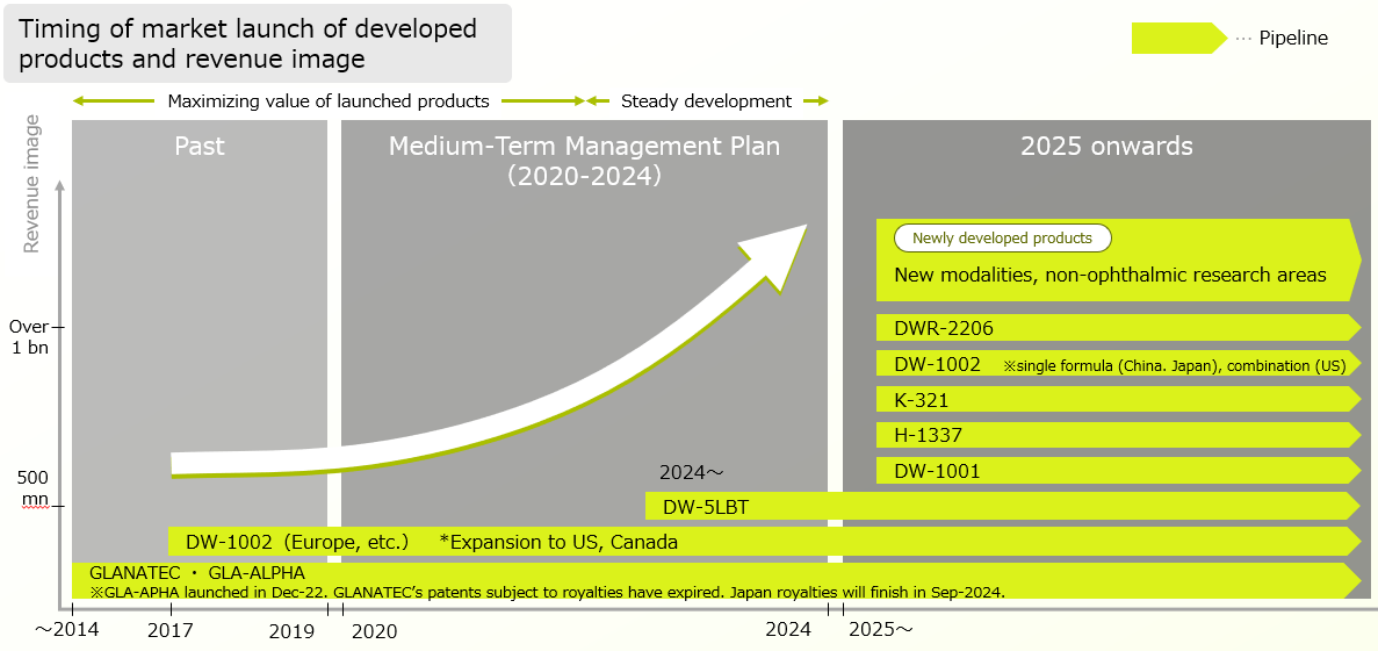
Total amount exercised (as of Dec. 31, 2023)	Conversion/ exercise ratio	Use of funds	Type
JPY293mn	32.7%	• Investment in ActualEyes Inc. • Development funds for existing pipeline products (DWR-2206, H-1337, etc.) • Drug discovery research (incl. joint research) using AI and funds to acquire and promote development of new pipeline products • Working capital	Series 1 Unsecured Convertible Bonds with Stock Acquisition Rights
JPY192mn	42.5%		Series 11 Stock Acquisition Rights

Future funding needs

✓ Funds for the next stage of development for H-1337
✓ Funds for the development of newly discovered and/or acquired pipeline products

DWTI

Development Pipeline and Estimated Timing of Revenue Contribution



Source: above and below are excerpts from annual IR reference document "Business Plan and Growth Potential."

Appropriation status of procured funds

✓ 2022/7, Series 1 unsecured CB with stock acquisition rights and Series 11 stock acquisition rights issued

- ¥900mn in convertible bonds (conversion rate at the end of FY2023: 32.7%, total converted face value: ¥293mn)
- ¥451mn in stock acquisition rights: (exercise rate at the end of FY2023: 42.5%, total amount raised: ¥192mn)

Use of proceeds	Planned expenditures (JPY mn)	Actual expenditure amt (JPY mn)	Scheduled expenditure timing
① Equity stake in ActualEyes, Inc.	130	130	Jul-2022
② Development funds for existing pipeline (DWR-2206, H-1337, etc.)	200～450	3	Jan-2023～Dec-2027
③ AI drug discovery research activities (including joint research) and acquisition of new pipeline candidates/expenses for promotion of devpt, etc.	300～600	168	Jul-2022～Dec-2027
④ Working capital	159～709	75	Jan-2023～Dec-2027

- The funds will be allocated sequentially according to the scheduled expenditure timing and procurement status.

DWTI

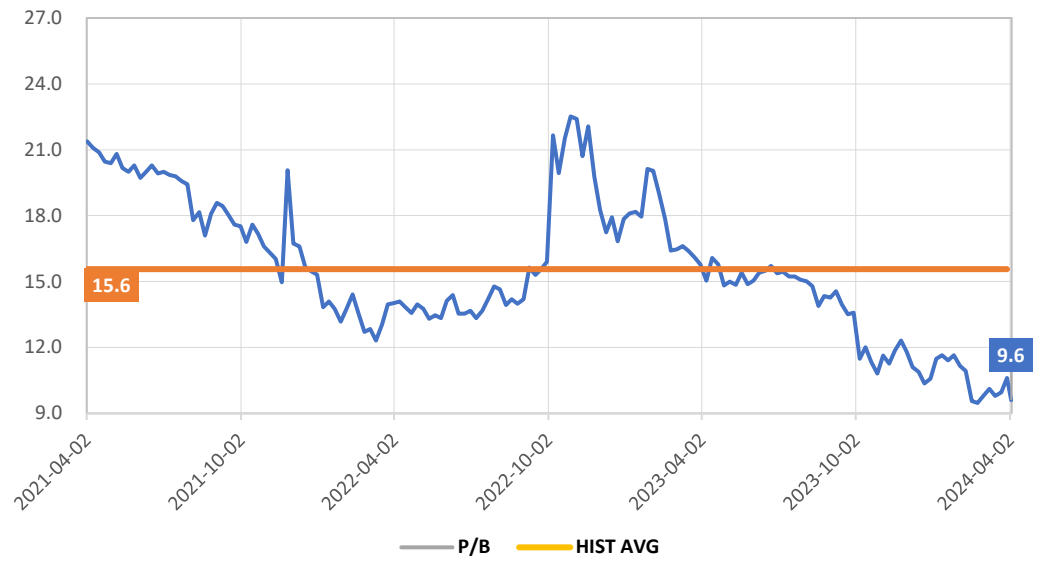
5 INSIGHTS

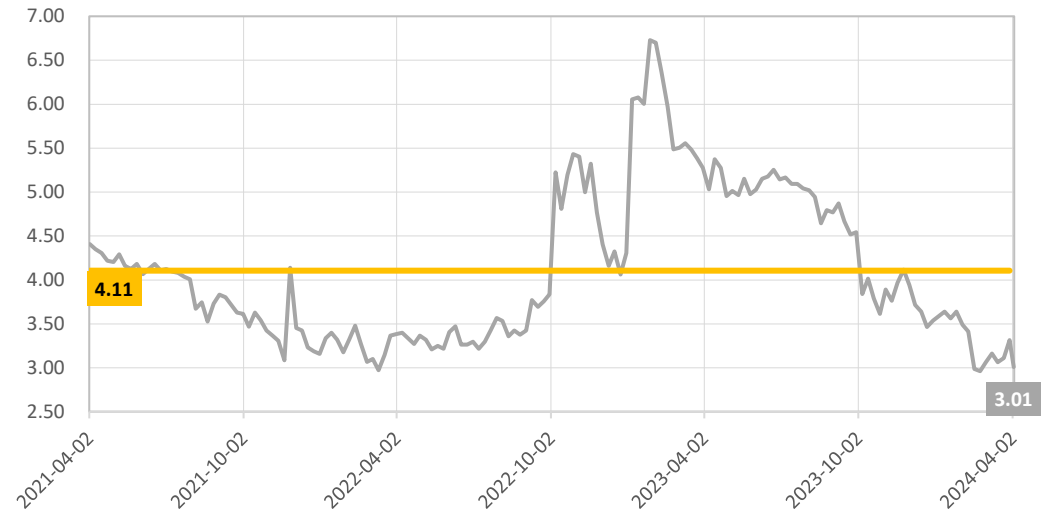
Performance and Valuations:
SESSA Smart Charts

- ✓ The price-to-sales ratio is currently trading 38% below its historical average, and the price-to-book ratio is trading 27% below its historical average, potentially reflecting some disappointment related to delays in pipeline development.
- ✓ Note that the share price reacted quite favorably to the news of Kowa obtaining domestic manufacture and marketing approval for K-232 GLA-ALPHA® in late Sep-2022. Now that DW-5LBT is back on track in the US, **progress on H-1337, DWR-2206 and DW-1002 may well renew interest in DWTI's share price against the backdrop of valuations at the bottom of the range.**

Analyst's view

3-Year Weekly Share Price, 13W/26W/52W MA and Valuations Trend





Source: compiled by SIR from SPEEDA share price and earnings database. Valuations calculated based on CE and LTM.

DWTI

DWTI Top Shareholders (as of December 31, 2023)

	Shareholder name	Shares owned	Pct owned
1	Hiroyoshi Hidaka	3,128,800	9.73%
2	Yuichi Hidaka	2,922,100	9.09%
3	Ueda Yagi Tanshi Co., Ltd.	817,700	2.54%
4	SBI Securities Co., Ltd..	749,575	2.33%
5	Meat Planning Co., Ltd.	340,000	1.05%
6	Matsui Securities Co., Ltd.	326,900	1.01%
7	Kunie Hidaka	300,000	0.93%
8	Teruo Isohata	260,200	0.80%
9	Fumishige Ehira	250,000	0.77%
10	au Kabucom Securities Co., Ltd.	238,400	0.74%
★	**Top 10 Total**	9,333,675	29.05%

Source: compiled by SIR from FY2023/12 Annual Securities Report (YUHO financial statements).
Note: percent owned calculation excludes treasury shares (200 shares) from shares outstanding.
Percent owned figures are truncated after the second decimal point.

Founder Hiroyoshi Hidaka, MD, PhD

Date	Event
1938	Born
Apr-76	Associate Professor, Kyoto University School of Medicine
Apr-78	Professor, Mie University School of Medicine
Aug-87	Professor, Nagoya University School of Medicine
Jul-98	Visiting Professor, Duke University
Feb-99	Established the Company, Representative Director
Nov-04	Director and General Manager, Development Research Institute
Mar-09	Director of Development Research Institute
Nov-09	Advisor to the President of Mie University
Jun-10	Chief Scientific Officer and Director of Development Research Institute
Mar-11	Director, Chief Scientific Officer and Director of Development Research Institute
Jun-12	Chairman and Representative Director, Chief Scientific Officer
Dec-15	Director, Japan Innovative Therapeutics, Inc.
Mar-20	Chairman and Chief Scientific Officer

CEO Yuichi Hidaka

Current President and CEO Yuichi Hidaka

Date	Event
1973	Born
Apr-96	Joined Sanwa Bank, Ltd. (currently The Bank of Tokyo-Mitsubishi UFJ, Ltd.)
Jul-06	General Manager, General Affairs and Management Department
	Director, General Manager, General Affairs and Management Department
Apr-07	Managing Director and General Manager, General Affairs and Management Dept.
Dec-08	President and Representative Director (current)
Dec-15	Director, Japan Innovative Therapeutics, Inc.
Jul-22	Outside Director, ActualEyes, Inc. (current)

Source: compiled by SIR from FY2023/12 Annual Securities Report (YUHO financial statements).

D. Western Therapeutics Institute Consolidated Financial Highlights

Selected Items from Consolidated Statements of Income

JPY mn, %	FY15.12	FY16.12	FY17.12	FY18.12	FY19.12	FY20.12	FY21.12	FY22.12	FY23.12	FY24.12
[J-GAAP]	act	act	act	act	act	act	act	act	act	init CE
Net sales	**62**	**168**	**254**	**293**	**581**	**356**	**414**	**448**	**428**	**400**
YoY	—	171.8	51.2	15.3	98.2	(38.7)	16.5	8.1	(4.4)	(6.6)
by region										
• Japan	62	168	190	158	417	184	175	227	151	
• Netherlands	—	—	64	97	88	107	170	221	278	
• US	—	—	—	38	75	59	70	—	—	
• Other (SE Asia)	—	—	—	—	—	5	—	—	—	
by major client (10%+ of net sales)										
• Kowa Company, Ltd.	62	97	120	139	158	166	172	171	140	
• WAKAMOTO PHARMACEUTICAL	0	50	50	—	209	—	—	—	—	
• Dutch Ophthalmic Research Center	—	—	64	97	88	107	170	221	278	
• Glaukos Corporation	—	—	—	38	63	59	70	—	—	
Major clients total	62	147	234	274	518	332	412	392	418	
Others	0	21	20	19	62	24	2	57	10	
Cost of sales	0	6	7	14	26	17	20	28	37	
Gross profit	62	162	247	279	555	339	394	421	392	
SG&A expenses	352	482	880	1,066	437	604	566	726	1,190	
• R&D expense	**144**	**227**	**603**	**795**	**249**	**351**	**316**	**470**	**931**	**1,600**
as % of net sales	***232.6%***	***135.1%***	***237.5%***	***271.5%***	***43.0%***	***98.6%***	***76.3%***	***104.8%***	***217.2%***	***400.0%***
• Other	209	255	277	270	188	254	250	257	260	
Depreciation	3	18	45	52	44	44	45	46	49	
Goodwill amortization	13	—	—	—	—	—	—	—	—	
EBITDA	(274)	(302)	(589)	(735)	162	(222)	(126)	(260)	(750)	
Operating profit (loss)	**(291)**	**(320)**	**(634)**	**(786)**	**117**	**(266)**	**(172)**	**(306)**	**(799)**	**(1,500)**
Ordinary profit (loss)	(295)	(304)	(669)	(797)	110	(290)	(160)	(296)	(796)	(1,510)
Impairment losses	0	0	1,040	7	0	0	0	0	6	
Profit (loss) ATOP	**(296)**	**(254)**	**(1,563)**	**(749)**	**133**	**(276)**	**(149)**	**(430)**	**812**	**(1,510)**

Selected Items from Consolidated Balance Sheets and Consolidated Statements of CF

• Cash and deposits	**1,747**	**2,292**	**2,133**	**1,584**	**1,541**	**2,308**	**1,934**	**2,335**	**1,867**
• Accounts receivable - trade	23	41	61	71	104	92	102	171	117
Total current assets	2,025	2,776	2,516	1,764	1,716	2,503	2,162	2,659	2,138
Contract-related intangible assets	—	—	329	288	247	206	165	123	82
Total non-current assets	115	136	362	309	266	234	301	297	235
Total assets	**2,140**	**2,913**	**2,877**	**2,074**	**1,981**	**2,738**	**2,463**	**2,956**	**2,373**
Current portion of LT borrowings	—	—	—	120	120	120	130	120	10
Total current liabilities	27	36	156	268	189	210	193	211	194
Unsecured CB with SAR	—	—	—	—	—	—	—	735	606
LT borrowings	—	—	600	480	360	340	210	113	269
Total non-current liabilities	—	—	625	505	384	364	234	872	900
Total liabilities	**27**	**36**	**782**	**774**	**573**	**574**	**428**	**1,083**	**1,094**
• Share capital	2,400	2,945	3,365	35	35	557	573	714	832
• Capital surplus	2,390	2,935	3,355	2,133	2,133	2,656	2,631	2,772	2,890
• Retained earnings	(2,904)	(3,157)	(4,721)	(908)	(775)	(1,051)	(1,200)	(1,630)	(2,442)
Total shareholders' equity	1,886	2,723	1,999	1,260	1,393	2,161	2,004	1,857	1,279
Share acquisition rights	30	16	2	—	—	3	3	1	1
Non-controlling interests	196	139	95	40	15	—	28	16	—
Total net assets	**2,113**	**2,877**	**2,096**	**1,300**	**1,408**	**2,164**	**2,035**	**1,873**	**1,280**
Shareholders' equity ratio	*88.1%*	*93.5%*	*69.5%*	*60.8%*	*70.3%*	*78.9%*	*81.4%*	*62.8%*	*53.9%*
Total liabilities and net assets	**2,140**	**2,913**	**2,877**	**2,074**	**1,981**	**2,738**	**2,463**	**2,956**	**2,373**

CF from operating activities	**(323)**	**(334)**	**(797)**	**(540)**	**176**	**(216)**	**(176)**	**(355)**	**(587)**
CF from investing activities	835	(231)	(763)	(8)	(100)	(13)	(111)	(140)	(15)
CF from financing activities	**98**	**1,067**	**1,407**	**—**	**(120)**	**1,004**	**(104)**	**867**	**134**
Cash and CE at beginning of period	1,167	1,767	2,292	2,133	1,584	1,541	2,308	1,934	2,335
Cash and CE at end of period	1,767	2,292	2,133	1,584	1,541	2,308	1,934	2,335	1,867
Book value per share (BPS)	83.49	109.96	76.14	47.95	53.02	73.88	68.27	60.14	39.81

Source: compiled by SIR from company TANSHIN financial statements and IR results briefing materials.

DWTI

6 SUPPLEMENT

- Key patent information
- Significant contracts – development pipeline

Key Patent Information

Devpt code, etc.	Title of Invention	Registration Status	Rights Holder/Applicant
Ripasudil hydrochloride hydrate	(S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride, dihydrate	Registered in Japan, US, Europe, etc.	DWTI Kowa Company, Ltd.
H-1337	New substituted isoquinoline derivatives	Registered in Japan, US, Europe, etc.	DWTI
DW-1001	Ophthalmic treatment agent	Registered in Japan	British Company
DW-1002	Staining compositions for ocular membrane staining	Registered in Japan, US, Europe, etc.	Kyushu University

Source: compiled by SIR from "Business Plan and Growth Potential" annual IR presentation.

Significant Contracts (1) Development Pipeline

Product devpt code	Contract party	Date signed	Contract period	Main contract details
Ripasudil hydrochloride hydrate (Glanatec, K-321, K-	Kowa Company, Ltd.	2002-09-11	From the contract signing date to the expiration date of payment of royalty	1) Grant an exclusive license with sublicensing rights to develop, manufacture, use and sell the product worldwide. 2) Receive front money, milestone payments and royalties as consideration for the license.
DW-1001	British Company	2015-06-02	From the contract signing date to 10 years after product sale or expiration of all patents, whichever is	1) To obtain an exclusive license with sublicensing rights to develop, manufacture, use and sell the product in the field of ophthalmology in Japan. 2) Pay front money, milestone payments, royalties, etc. as consideration for the license.
	ROHTO Pharmaceutical Co., Ltd.	2019-12-12	From the contract signing date to 10 years after product sale or expiration of all patents, whichever is	1) Grant an exclusive license with sublicensing rights to develop, manufacture, use and sell the product in the field of ophthalmology in Japan. 2) Receive front money, milestone payments and royalties as consideration for the license.
DW-1002	HEALIOS K.K.	2017-01-31	No fixed contract term	1) DWTI will acquire the business related to ophthalmic surgical aids containing BBG250 from HEALIOS K.K. 2) In addition to an upfront payment, milestone payments may be incurred as consideration for development and out-licensing progress from this acquisition.
	Kyushu University HEALIOS K.K.	2017-04-28	From April 30, 2017 to the expiration date of the patent	1) DWTI takes the position of Healios K.K. in the blanket license agreement between Kyushu University and Healios K.K., and Kyushu University grants an exclusive non-exclusive license with sublicensing rights to the patent rights related to BBG250 to DWTI. 2) In consideration for the license, DWTI shall pay a certain amount of license fee to Kyushu University.
	WAKAMOTO PHARMACEUTICAL CO., LTD.	2014-12-03	From the signing date to the expiration date of the term of the patent right, with automatic renewal every two years thereafter if no notice of termination is given by either party.	1) Grant an exclusive non-exclusive license to develop, use and market a pharmaceutical product containing BBG250 for the staining of the internal limiting membrane and the anterior lens capsule in Japan. 2) As consideration for the license, DWTI shall receive an upfront payment as well as certain license fees.
	Dutch Ophthalmic Research Center International B.V.	2009-09-09	From September 4, 2009 to December 6, 2025	1) Grant an exclusive license to develop, manufacture, outsource manufacture, import, use, transact, sell and distribute pharmaceutical products containing BBG250 worldwide except Japan.
DW-5LBT	MEDRx Co., Ltd	2020-04-16	From the signing date to the expiration date of the results distribution payment	1) Jointly develop DW-5LBT in the United States. 2) DWTI will make milestone payments based on commercialization progress of the product after execution of this agreement. 3) After the product is launched, MEDRx, Inc. will pay DWTI a performance distribution.
DWR-2206	ActualEyes, Inc.	2022-06-30	From the signing date to the completion date of all earnings distribution	1) Jointly develop DWR-2206 in Japan. 2) DWTI will bear the development costs in Japan. 3) Worldwide revenue to be earned in connection with this product shall be shared at a

Source: compiled by SIR from "Business Plan and Growth Potential" annual IR presentation.

Significant Contracts (2) Dev. Pipeline, Joint Research, etc.

	Contract party	Date signed	Contract period	Main contract details
Joint research	Mie University	2009-12-25	January 1, 2010 to December 31, 2026	The Industry-Academia-Government Collaboration Course shall be established for the purpose of stimulating education and research activities and supporting DWTI's R&D operations. Ownership of intellectual property rights obtained through joint research in said course shall be as follows: those invented solely by DWTI and Mie University shall be the sole property of the respective research team, and those invented jointly by both shall be shared by both research teams based on the degree of contribution agreed upon mutual

	Contract name, party	Date signed	Contract period	Main contract details
Joint investment	Shareholders Agreement ROHTO Pharmaceutical Co., Ltd.	2015-11-13	From November 13, 2015 until either party no longer owns shares of Japan Innovative Therapeutics, Inc. (JIT) or both parties agree to terminate the	1) DWTI and ROHTO Pharmaceutical Co., Ltd. will jointly invest in Japan Innovative Therapeutics, Inc. (JIT) and DWTI will underwrite 60% of the newly issued shares and ROHTO 40%. 2) ROHTO Pharmaceutical Co., Ltd. may request the Company to purchase its shares under certain conditions.
Loan	Limited Loan Agreement Mizuho Bank, Ltd.	2020-04-16	Repayment Date September 30, 2029	1) Term loan with commitment period, maximum borrowing amount: 200 million yen, unsecured and non-guaranteed 2) Compliance and forbearance of terms and conditions are stipulated in this loan.
Loan	Limited Loan Agreement Mizuho Bank, Ltd.	2022-06-30	Repayment Date June 30, 2030	1) Term Loan with Commitment Period, maximum borrowing amount: 440 million yen, unsecured and non-guaranteed 2) Compliance and forbearance of terms and conditions are stipulated in this loan.

Source: compiled by SIR from "Business Plan and Growth Potential" annual IR presentation.

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