D. Western Therapeutics Institute (DWTI) | 4576

Sponsored Research
April 13, 2023

Sessa Investment Research

Development pipeline is steadily expanding

FY23/12 initiatives: conducting H-1337 phase IIb trials in the US, DW-1002 approval/launch in China and DW-5LBT US approval

SUMMARY

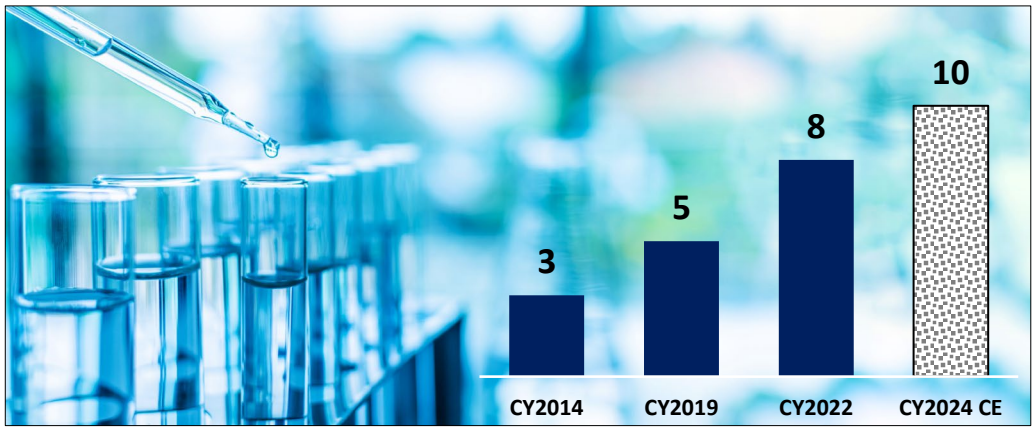
- Over time with progress in execution of the development pipeline, and as part of growth strategy to diversify revenue streams, the basic business model of drug discovery and early out-licensing has evolved to include 1) from 2015, in-licensing of later stage development products, 2) from 2018, collaborative drug creation applying DWTI's technical expertise to assist in joint R&D 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 IIb.

- Major milestones coming in the next 2-3 years: 1) high expectations for 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) high expectations for 2023 application, 2024 approval and 2025 launch of DW-1002 in Japan, as well as 2023 application/approval/launch in China, and 3) high expectations for 2023 approval and subsequent launch of DW-5LBT in the US.

- In addition to these major milestones, there is also expected to be a fairly steady and regular flow of announcements regarding enhancing the number of drugs in the development pipeline. As can be seen in the graph below, DWTI is aiming to increase the number of drug candidates in its development pipeline from 8 to 10 by the end of its 2024 Medium-Term Management Plan (MTP).

- 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.

DWTI No. of Drug Candidates in the Development Pipeline



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

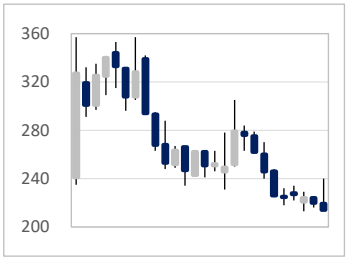
Full Report

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 (4/12)	212
YH (22/10/6)	357
YL (22/2/24)	183
10YH (14/8/19)	3,550
10YL (22/2/24)	183
Shrs out. (mn shrs)	31.323
Mkt cap (¥ bn)	6.703
Equity ratio (Dec 31)	62.8%
23.12 P/S (CE)	16.7x
22.12 P/B (act)	3.61x

6M price chart (weekly)



Source: SPEEDA price data

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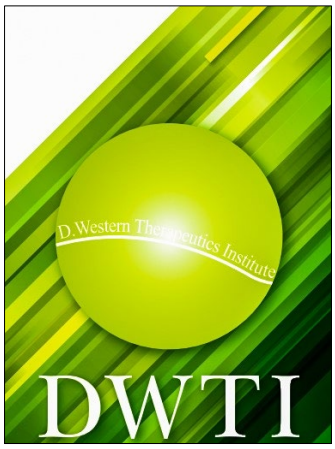
This report was prepared by Sessa Partners on behalf of D. Western Therapeutics Institute, Inc. Please refer to the legal disclaimer at the end for details.



CEO Yuichi Hidaka

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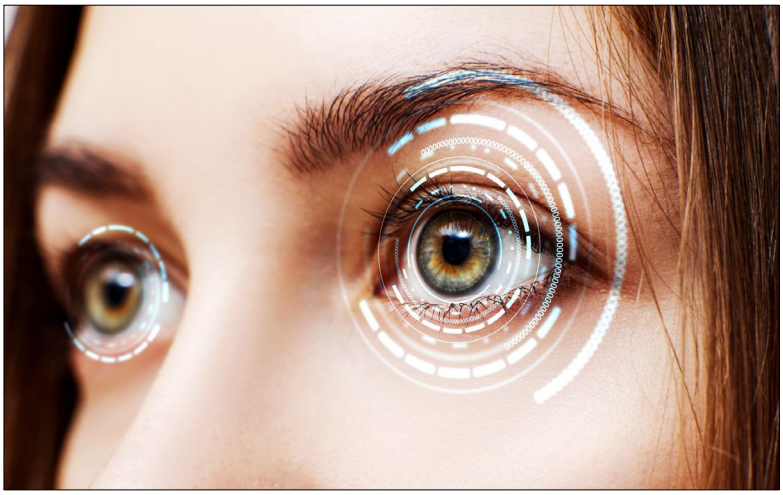
GLANATEC® ophthalmic solution 0.4% (left)
- **Launched Dec-2014**

GLA-ALPHA® combination ophthalmic solution (right)
- **Launched Dec-2022**



D. Western Therapeutics Institute Consolidated Financial Highlights

Selected Items from Consolidated Statements of Income

JPY mn, % [J-GAAP]	FY15.12 act	FY16.12 act	FY17.12 act	FY18.12 act	FY19.12 act	FY20.12 act	FY21.12 act	FY22.12 init CE	FY22.12 act	FY23.12 init CE
Net sales	**62**	**168**	**254**	**293**	**581**	**356**	**414**	**370**	**448**	**400**
YoY	—	171.8	51.2	15.3	98.2	(38.7)	16.5	(10.7)	8.1	(10.7)
by region										
• Japan	62	168	190	158	417	184	175		227	
• Europe	—	—	64	97	88	107	170		221	
• 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	
• WAKAMOTO PHARMACEUTICAL	0	50	50	—	209	—	—		—	
• Dutch Ophthalmic Research Center	—	—	64	97	88	107	170		221	
• Glaukos Corporation	—	—	—	38	63	59	70		—	
Major clients total	62	147	234	274	518	332	412		392	
Others	0	21	20	19	62	24	2		57	
Cost of sales	0	6	7	14	26	17	20		28	
Gross profit	62	162	247	279	555	339	394		421	
SG&A expenses	352	482	880	1,066	437	604	566		726	
• R&D expense	**144**	**227**	**603**	**795**	**249**	**351**	**316**	**790**	**470**	**1,500**
as % of net sales	***232.6%***	***135.1%***	***237.5%***	***271.5%***	***43.0%***	***98.6%***	***76.3%***	***213.5%***	***104.8%***	***375.0%***
• Other	209	255	277	270	188	254	250		257	
Depreciation	3	18	45	52	44	44	45		46	
Goodwill amortization	13	—	—	—	—	—	—		—	
EBITDA	(274)	(302)	(589)	(735)	162	(222)	(126)		(260)	
Operating profit (loss)	**(291)**	**(320)**	**(634)**	**(786)**	**117**	**(266)**	**(172)**	**(690)**	**(306)**	**(1,400)**
Ordinary profit (loss)	(295)	(304)	(669)	(797)	110	(290)	(160)	(700)	(296)	(1,410)
Impairment losses	0	0	1,040	7	0	0	0	0	0	
Profit (loss) ATOP	**(296)**	**(254)**	**(1,563)**	**(749)**	**133**	**(276)**	**(149)**	**(670)**	**(430)**	**(1,390)**

Selected Items from Consolidated Balance Sheets and Consolidated Statements of Cash Flows

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

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

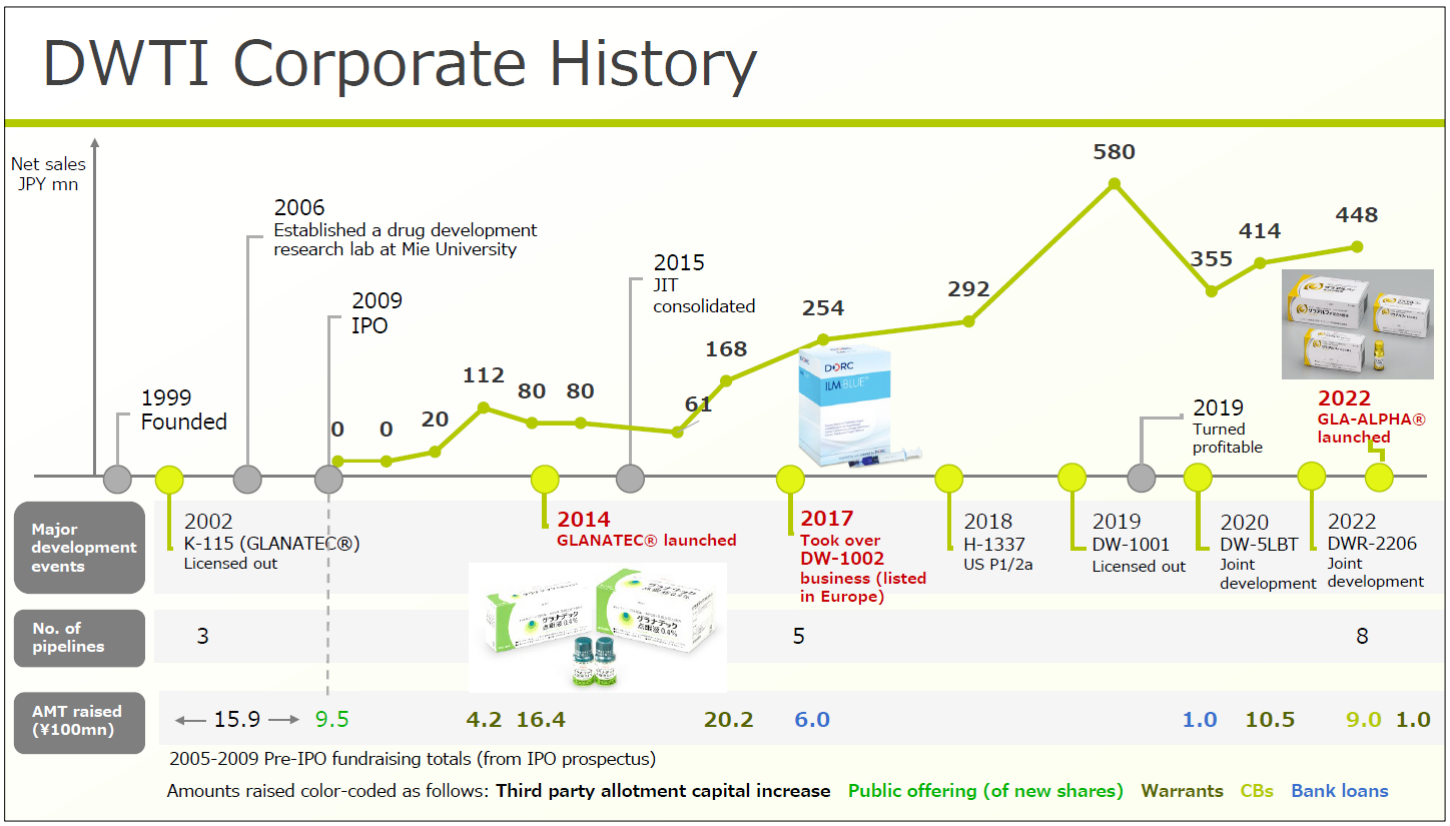
Source: compiled by SIR from company TANSHIN financial statements and IR results briefing materials.

❶ BUSINESS

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 in its corporate history.



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

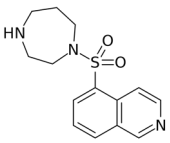
Hiroyoshi Hidaka, MD, PhD
DWTI Founder

DWTI origin story – pioneer in kinase inhibitor drug discovery

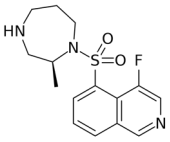
DWTI founder, Dr. Hiroyoshi Hidaka, worked as a doctor after graduating from medical school, and experienced a certain level of satisfaction as his patients recovered. But after deep deliberation, he felt that discovering new drugs might have a greater contribution to the health of many patients overall. 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.

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.

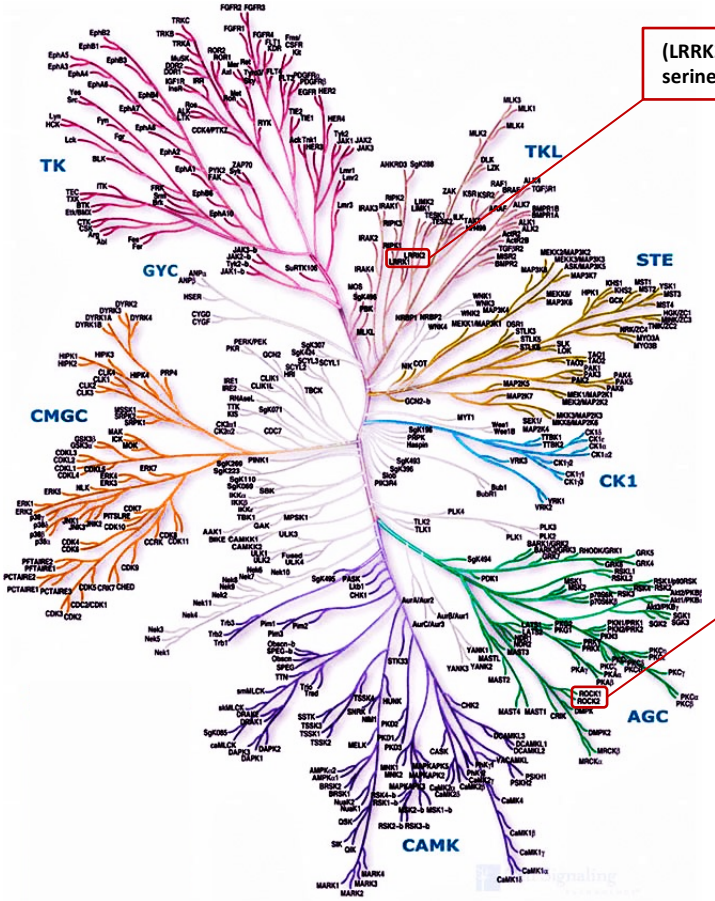
Fasudil
hydrochloride
molecule skeletal
formula



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.

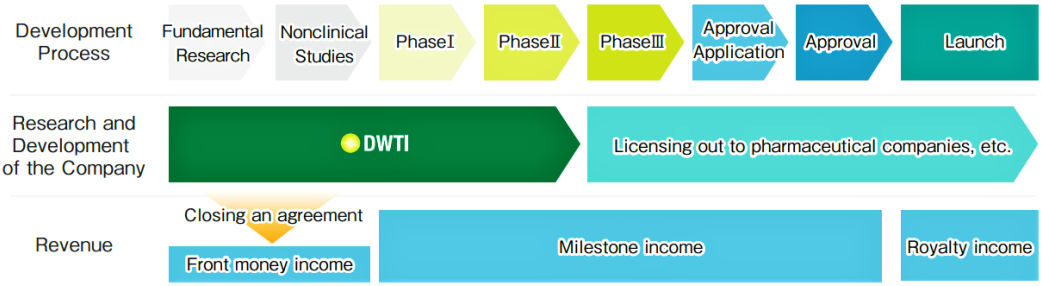
Phosphorylation regulates many biological processes, and kinase inhibitors can be used to treat diseases due to hyperactive protein kinases (including mutant or overexpressed kinases in cancer) or to modulate cell functions to overcome other disease drivers.

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



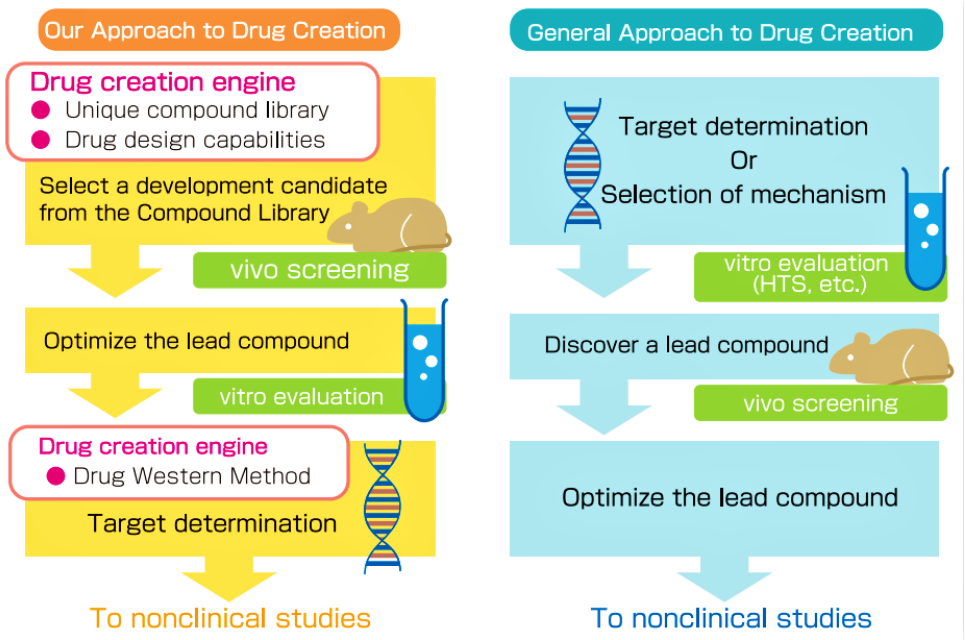
Source: company website

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).

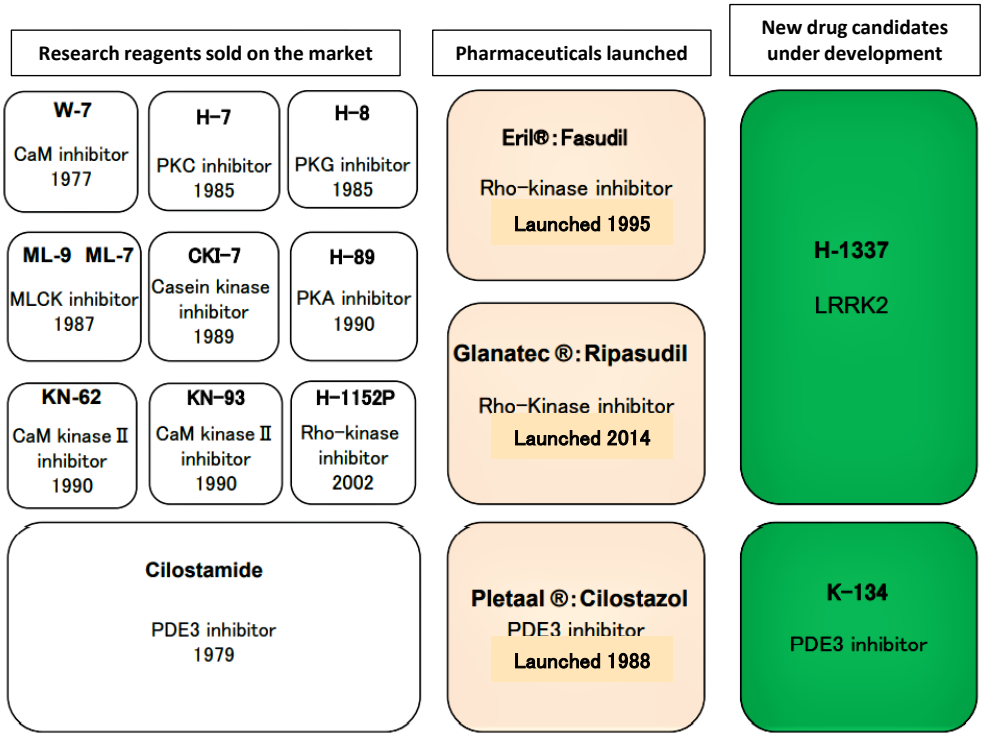
3 drug creation engines:
- Compound library
- Design capabilities
- Drug-Western Method

DWTI approach to drug creation based on 3 drug creation engines



Source: company website

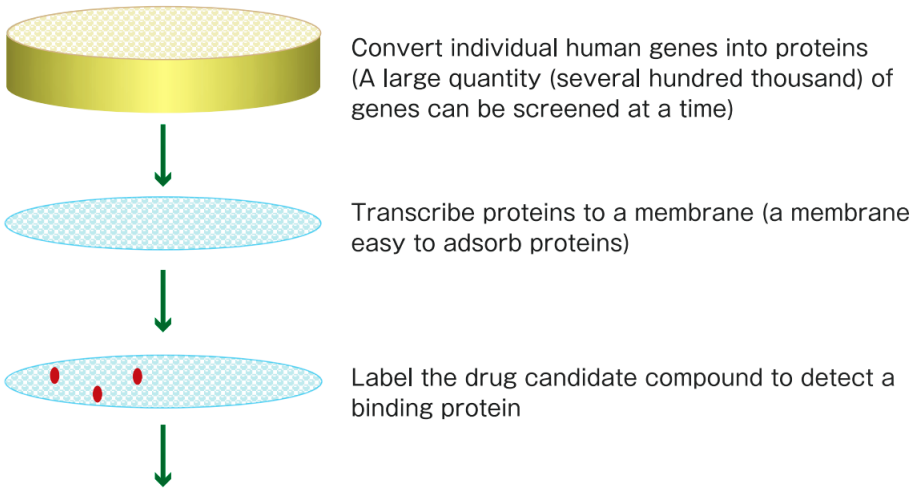
Highlights from DWTI's extensive compound library accumulated over decades



Source: company IR materials. Note: K-134 is under review by the out-license partner for the target disease.

- 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

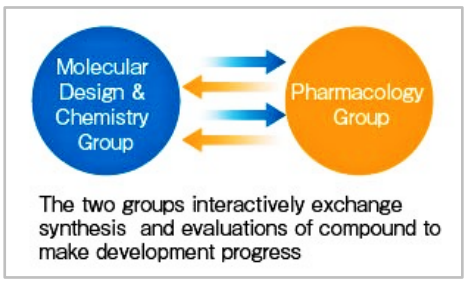
Overview of the Drug-Western Method



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.

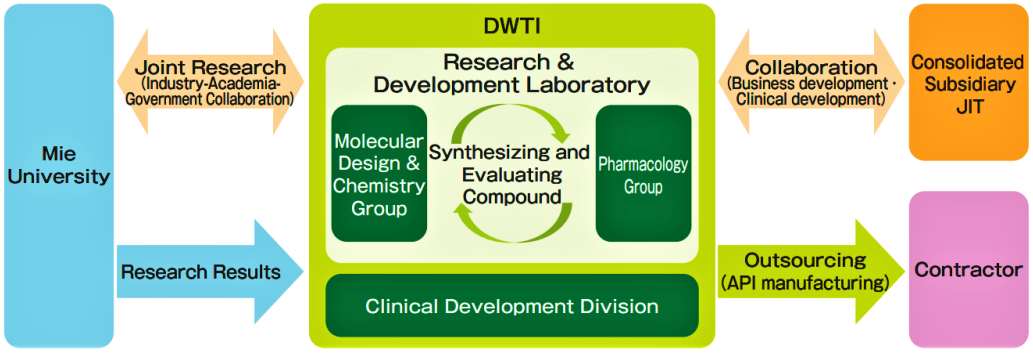


Source: company website

Government-industry-academia Collaborative R&D program

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.

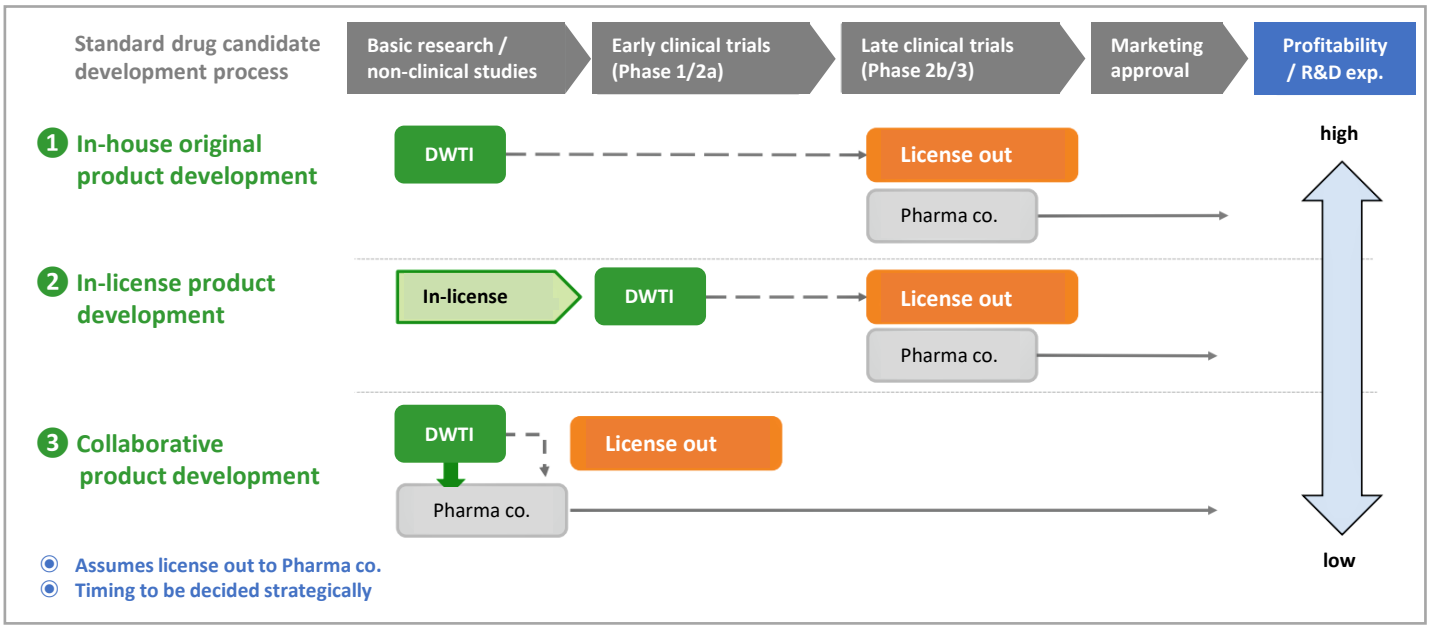
Relationships between DWTI and external organizations



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

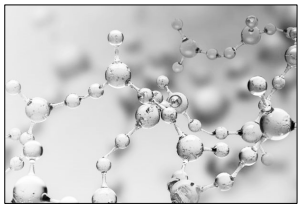
GLA-ALPHA® combination ophthalmic solution

DWTI Corporate History – 3 products launched; pipeline expanded to 8

Date	Event
1999.02	Established D.Western Therapeutics Institute, Inc. in Nagoya, Aichi Prefecture for the purpose of conducting pharmaceutical research and development (5 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-submitted application for approval of DW-5LBT neuropathic pain treatment in the U.S.

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

DWTI Group Head Office and R&D Labs



Japan Innovative Therapeutics

Rohto Research Village Kyoto

DWTI

D.WESTERN THERAPEUTICS INSTITUTE

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	714 million yen (as of December 31, 2022)
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: 17, JIT: 3 (as of December 31, 2022), total 33 including executive officers
Group Subsidiary	Japan Innovative Therapeutics, Inc. (consolidated subsidiary)

Source: company website.

❷ BACKROUND

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.

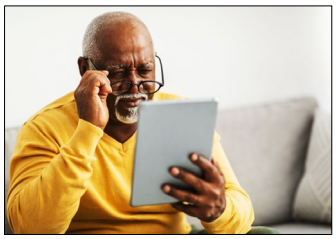
Abnormalities or obstruction to the drainage system leads to impairment of the normal outflow, and IOP increases. Although there is no cure for glaucoma, treatments include medicine (usually eye drops), laser treatment or surgery. **Some types of eye drops work by helping fluid drain from the eye, which 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 ❸ covering DWTI's development pipeline**.

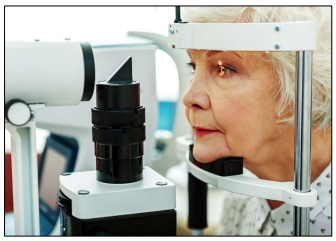
Common eye conditions that can cause vision impairment including blindness

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."





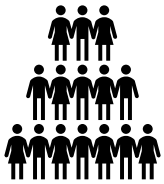
Estimated Population with Vision Impairment or Blindness: over 1.2 billion

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 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**.

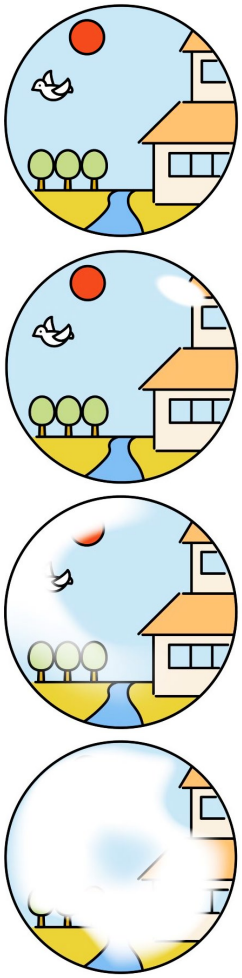
Biotech Market Value Aggregate Shares by Therapeutic Area

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.

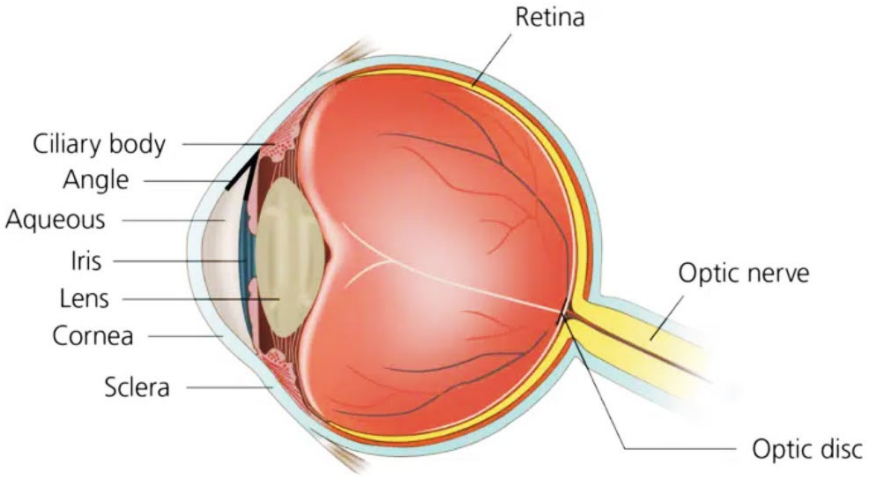
Glaucoma basics
Millions of nerve fibers that run from the retina form the optic nerve, and they meet at the optic disc. In most types of glaucoma, the eye's drainage system becomes clogged so the intraocular fluid cannot drain. As the fluid builds up, it causes increased IOP, which can result in damage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

Progression of vision impairment

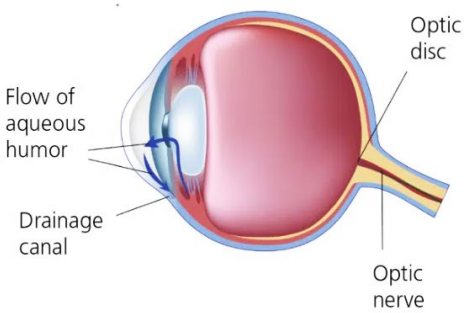


World Glaucoma Week

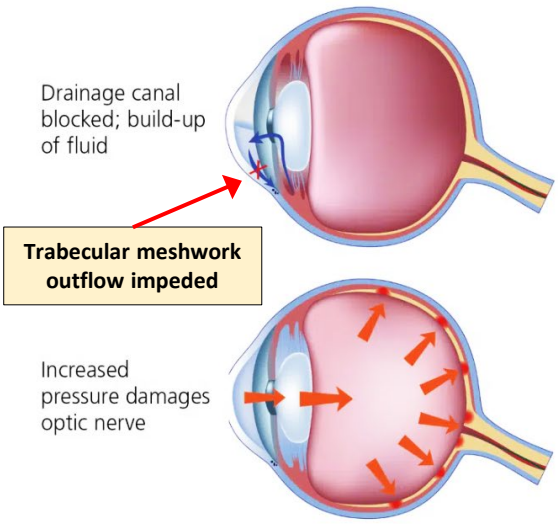
Development of Glaucoma in the Human Eye



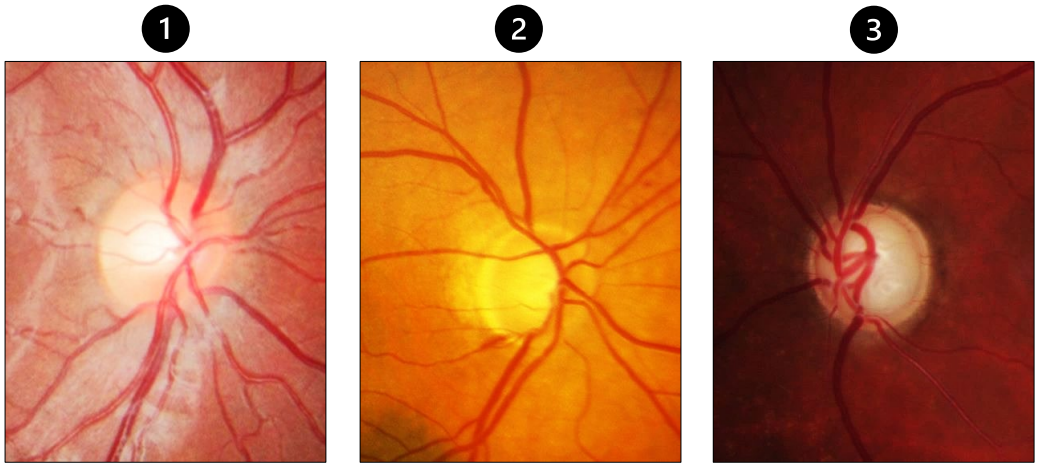
Healthy Eye



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

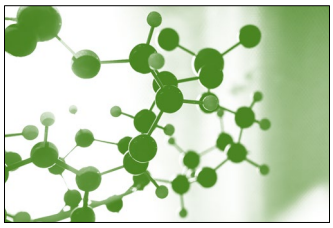
Source: compiled by SIR from websites of the GLAUCOMA Research Foundation, the US NIH National Eye Institute and World Glaucoma Association information portal GlaucomaPatients.org.

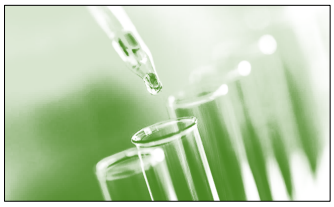
❸ PIPELINE

Steadily expanding and diversifying development pipeline

Since the Group's business in drug candidate development involves a long period of time from basic research to market launch and is an up-front investment type business model, management believes that setting general management indicators such as financial statement targets is not a suitable benchmark. Therefore, the Group sets the number of development pipeline candidates and their progress as management indicators. DWTI will continue to invest management resources in R&D activities with the aim of expanding these development pipelines by working to discover and promote in-licensing and clinical development of highly profitable new drug candidates.

The exhibit below is an excellent summary of DWTI's business explained in **Part ❶**, and is a useful framework for **out-licensed products** versus **internal clinical development**.





3
- Three products available on the market
- Three products in late stages of development (Phase III study or later)

1,500
- About 1,500 kinase inhibitors included in DWTI's compound library
- A pioneer in the field of kinase inhibitors

7
- Out-licensed seven products
- Internally developing Four additional products (including joint development)

Our Businesses

Drug Discovery	Internal drug discovery	✓ Create promising kinase inhibitors from our original compound library with efficiency ✓ Create new drug seeds by collaborating with other companies
Drug Development	Clinical development	✓ Internal clinical development (including the evaluation of safety and efficacy in humans)
	Business development	✓ Out-licensing activities for original products and in-licensed products ✓ Consider in-licensing of products in late development stages and repurposed drugs

Development Pipeline

	Products		Clinical indication	Region	Non-clinical	P-I	P-II	P-III	Application	Approval	Launch	Licensee
1	Ripasudil hydrochloride hydrate	GLANATEC®	Glaucoma and ocular hypertension	Japan, Asia*								Kowa
		K-321	Fuchs endothelial corneal dystrophy	US								
	Ripasudil hydrochloride hydrate/ Brimonidine tartrate	GLA-ALPHA® (K-232)	Glaucoma and ocular hypertension	Japan								
	DW-1002		ILM staining	Europe, US, Canada								DORC
			ILM staining	Japan								Wakamoto Pharmaceutical (WP-1108)
			ALC staining	Japan								
	DW-1001		Ophthalmic treatment agent (undisclosed)	Japan								ROHTO Pharmaceutical
2	H-1337		Glaucoma and ocular hypertension	US								Developed internally
	DW-5LBT		Neuropathic pain after shingles	US								Jointly developed with MEDRx (MRX-5LBT)
	DWR-2206		Bullous keratopathy	Japan								Joint development with ActualEyes (AE101)
	Treatment for retinopathy of prematurity		Retinopathy of prematurity	Japan								Developed by subsidiary JIT

*Thailand, Singapore, and Malaysia

・・・ophthalmology pipeline

❶ Out-licensed products (4)

❷ Internal clinical development (4)

Source: excerpts from FY2022/12 4Q IR results briefing materials.

FY2022 review of significant events related to the development pipeline

FY2022 was an eventful and remarkable year for DWTI's development pipeline, both in making progress on existing development pipeline candidates, as well as expanding and diversifying the portfolio with new candidates and collaborative research projects, culminating the year with the successful launch of its 3rd drug product. In February, out-license partner Kowa Company launched GLANATEC® ophthalmic solution 0.4% in Singapore.

In March, out-license partner ROHTO Pharmaceutical commenced a Phase I domestic clinical study on DW-1001. DWTI in-licensed this ophthalmic drug compound from a British company in 2015, with the aim of expanding the indications of compounds already on the market to other disease types. The expected benefits of this so-called repositioning approach are relatively low development costs and risks. DWTI received a milestone payment from ROHTO based on the contract.

In June, DWTI concluded a joint development agreement with ActualEyes for DWR-2206 regenerative cell therapy treatment for corneal endothelial dysfunction. This novel cell injection therapy developed by ActualEyes is a regenerative cell therapy for the indication of bullous keratopathy. 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.

In August, out-license partner Kowa Company commenced a Phase III clinical study in the US investigating K-321, an ophthalmic solution containing as active ingredient the Rho-kinase inhibitor ripasudil hydrochloride hydrate originated by DWTI, for the indication of Fuchs endothelial corneal dystrophy (FECD).

In September, out-license partner Kowa Company obtained manufacture and marketing approval in Japan for K-232 GLA-ALPHA® combination ophthalmic solution, the world's first fixed combination eye drop containing ripasudil hydrochloride hydrate, the active pharmaceutical ingredient in Rho-kinase inhibitor GLANATEC®ophthalmic solution 0.4%, and α2-adrenergic agonist brimonidine tartrate. Since the drug has a different pharmacological point of action than existing combination eye drops, it can be used in combination with various other treatments for glaucoma and ocular hypertension. It was given an NHI Drug price listing in November, and Kowa Company launched GLA-ALPHA® on December 6, 2022.

In October, joint development partner MEDRx notified DWTI that an agreement was reached with the US FDA on the details of an additional study to be conducted on DW-5LBT. On January 17, it was announced that preliminary results of the additional study were favorable. On March 29, DWTI and MEDRx re-submitted a new drug application (NDA) to the US FDA. The review process is expected to take approx. 6 months, expecting approval after that (no impact on FY23/12 results).

In November, a decision was announced to transfer an exclusive license for an endothelial corneal dystrophy treatment granted to consolidated subsidiary Japan Innovative Therapeutics (JIT) by Doshisha University to joint development partner ActualEyes. JIT was granted an exclusive worldwide license for the endothelial corneal dystrophy treatment with a right to sublicense by Doshisha University.

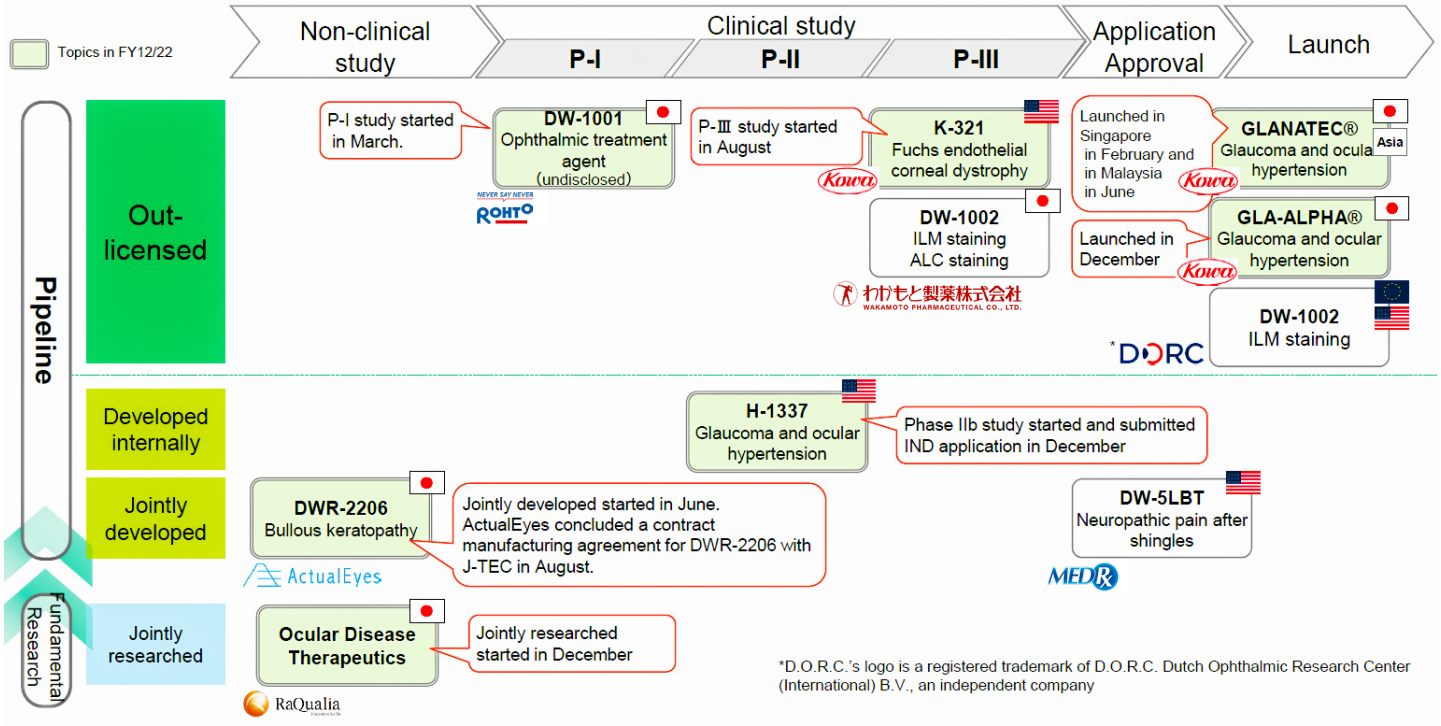
DWTI decided that commercializing the treatment at ActualEyes, whose business is based on the research findings of Professors Noriko Koizumi and Naoki Okumura of Doshisha University, and has a capital alliance with DWTI, was most consistent with the Group's strategy and optimization of its overall development pipeline portfolio. JIT received a payment for the transfer.

In December, DWTI announced that it concluded a joint research agreement with RaQualia Pharma for the discovery of a new drug for the treatment of ocular diseases. DWTI will focus on evaluation in the ophthalmology field, and RaQualia will focus on synthesis of a group of compounds targeting ion channels.

Achievement of 2022 event calendar

H-1337	Start of Phase IIb study in US	Achieved Submitted IND application in December
K-232	Approval in Japan	Achieved Launched in December
K-321	End of Phase II study in US	Achieved Started Phase III in August
DW-1001	Start of Phase I study in Japan	Achieved Started Phase I in March
DW-1002	Approval filing in China	
New projects	Research progress (including new collaborations)	Achieved Joint development with ActualEyes in June Joint research with RaQualia in December

Topics in FY12/22



Source: excerpts from FY2022/12 4Q IR results briefing materials.

Then on December 15 local time in the US, to close out a banner year for the company, DWTI announced that it submitted an Investigational New Drug (IND) Application to the US FDA to commence late-stage Phase IIb clinical trials for H-1337 glaucoma and ocular hypertension treatment. 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 2023. H-1337 has strong prospects as "first choice as a second-line Glaucoma drug," for patients who do not respond to first-line drugs such as prostaglandins, and patients who receive multiple drugs and suffer side effects. 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, this was the first foray into clinical development. Proceeds of fundraising during FY2022 are summarized below.

Use of Procured Funds

Specific use of funds	Amount (JPYmn)	Anticipated timing of expenditure					
		2022	2023	2024	2025	2026	2027
① **Investment in Actual Eyes**	130	Invested in July ●					
② **Development funds for existing pipelines (DWR-2206, H-1337, etc.)**	200～450		■	■	■	■	■
③ **Expenses for AI-based drug discovery research activities (including joint research) and acquisition and development of new pipelines, etc.**	300～600		■	■	■	■	■
④ **Working capital**	159～709		■	■	■	■	■

Note: The above amount excludes issuance costs of JPY12mn

FY2022 Fundraising Overview

- Concluded a loan agreement in June 2022. Also issued Series 1 Unsecured Convertible Bonds with Stock Acquisition Rights and Series 11 Stock Acquisition Rights in July 2022 to procure funds for future development and growth-oriented investment.
- Plan to raise up to a maximum JPY1.8bn from financing activities undertaken in FY2022

(JPYmn)

Borrowings 440 (maximum)	Development funds for DWR-2206
Convertible bonds 900	Investment in ActualEyes + Growth-oriented investment
Stock Acquisition rights 451	(Funds for development of existing pipeline and funds for acquisition of new pipeline and progressing development)

Loan (term loan contract with commitment period)	
Borrowing limit	JPY440mn
Commitment period	June 30, 2022–June 30, 2026

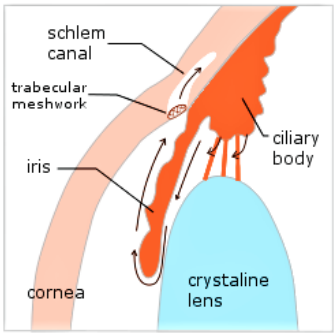
Series 1 Unsecured Convertible Bonds with Stock Acquisition Rights	
Funds to be raised	JPY900mn
Redemption date	December 27, 2027
Number of dilutive shares, shares already converted*	4,864,864; 893,538 (percentage of bonds converted: 18.4%)

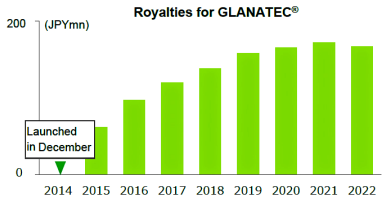
Series 11 Stock Acquisition Rights	
Number of stock acquisition rights issued	24,324
Funds to be raised	JPY451mn (JPY1.2mn from the issue of stock acquisition rights, and JPY450mn from the exercise of the rights)
Exercise price, exercise period	JPY185, July 19, 2022–December 24, 2027
Dilutive shares, shares issued by the exercise of the rights*	2,432,400; 544,800 (22.4% of stock acquisition rights exercised)
Total sum procured in FY12/22	JPY102mn

* As of December 31, 2022

Source: excerpts from FY2022/12 4Q IR results briefing materials.

GLANATEC® point of action
High 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).

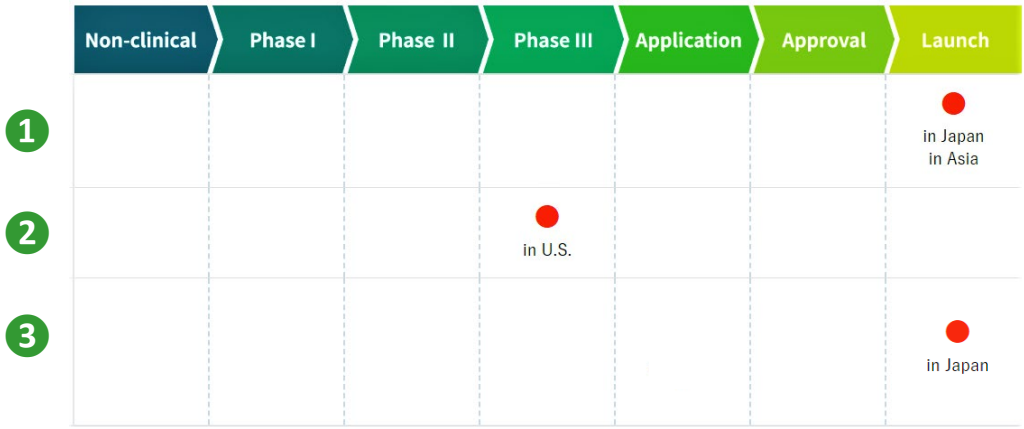
❷ Fuchs endothelial corneal dystrophy [K-321]

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. DWTI hopes that the compound will become a new drug for treating FECD. Phase III clinical study started in the US on August 26, 2022.

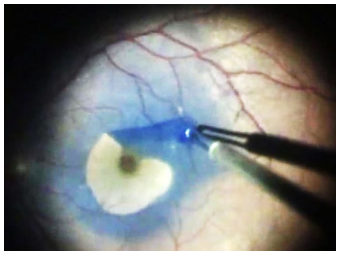
❸ Glaucoma and ocular hypertension [GLA-ALPHA® combination ophthalmic solution (Ripasudil hydrochloride hydrate and Brimonidine tartrate) K-232]

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.

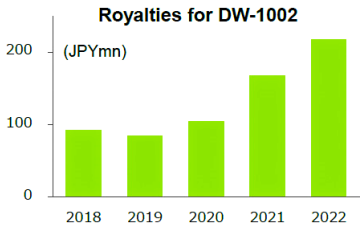
Development Stages of Ripasudil hydrochloride hydrate



Source: DWTI website.



Source: Journal of Ophthalmology



TissueBlue™ ophthalmic surgical aid

[DW-1002]

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. Approved in the US in 2019, and launched in April 2020. Approved in Canada in 2021, and launched in October 2021. 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 (+30% YoY) due to higher sales in Europe, the US and Canada (+22% YoY) and the effect of yen depreciation.

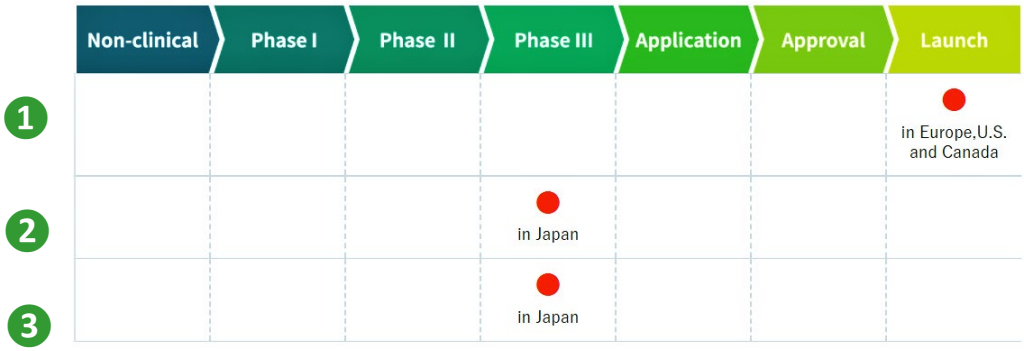
WAKAMOTO PHARMACEUTICAL CO., LTD. has been granted an exclusive sublicense for Japan, and has been moving forward with development aiming to obtain approval. WAKAMOTO is expected to file applications for ❷ and ❸ in 2023, receive approvals in 2024 and launch in 2025.

Clinical indications:
❶ ILM staining (Europe, US and Canada)
❷ ILM (internal limiting membrane) staining (Japan)
❸ ALC (anterior lens capsule) staining (Japan)

Development stages:
❶ Launched (Europe, US and Canada)
❷ Phase III clinical trials (Japan) completed
❸ Phase III clinical trials (Japan) completed

*New: DORC is filing an NDA in China in 2023 for indication ILM peeling, targeting approval and sales launch in 2023.

Development Stages of DW-1002



Source: DWTI website.

[H-1337]
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 ocular hypertension treatment.

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 2023.

[H-1337]

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 basic research, 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.

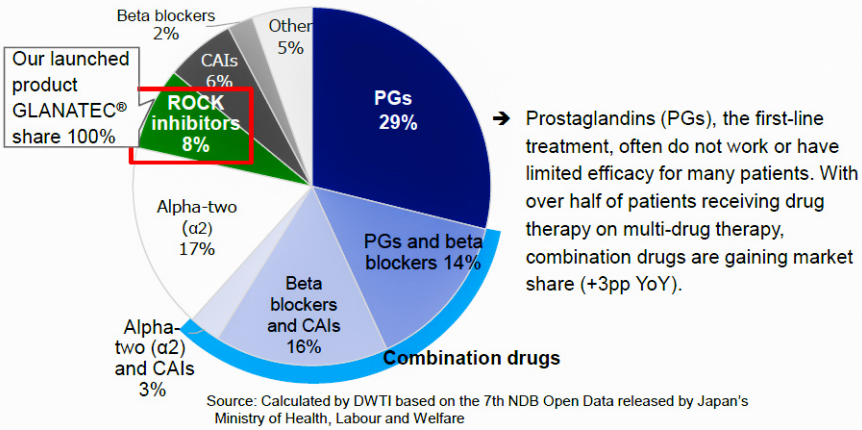
DWTI estimates the target market for 1) patients who do not respond to first-line drugs and 2) patients who receive multiple drugs and suffer side effects is up to a maximum 40% of the estimated US market of $3 billion.

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.

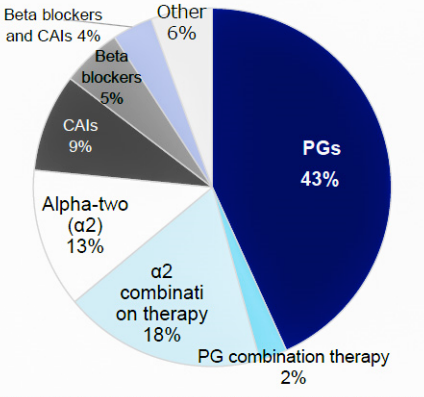
Japanese market (FY2020: about ¥89bn)



➔ 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.

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（MRX-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 October 4, 2022, an agreement was reached with the US FDA on the details of an additional study to be conducted on DW-5LBT. On January 17, DWTI announced that preliminary results of the additional study were favorable. On March 29, DWTI announced that MEDRx re-submitted a new drug application (NDA) to the US FDA. The review process is expected to take approx. 6 months, expecting approval after that (no impact on FY23/12 results).

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.

Development Stage of DW-5LBT

Source: DWTI website.

(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.

ActualEyes

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

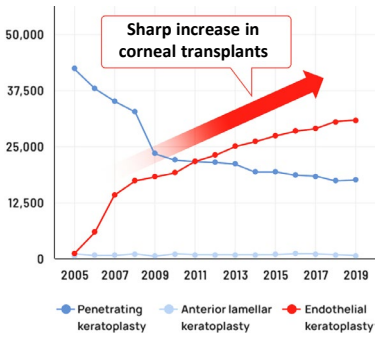
Description:

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

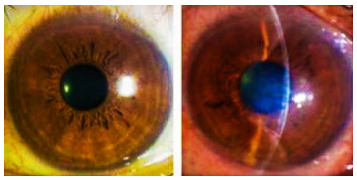
J-TEC

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.



Normal cornea (left), FECD (right)



Source: ActualEyes website.

[DWR-2206] regenerative medicine cell-therapy treatment for corneal endothelial dysfunction (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: i) **Ophthalmology Field:** enhances DWTI's focus on ophthalmologic diseases, ii) **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 iii) **Regenerative Medicine:** new treatment technology that can fulfill unmet medical needs, and the acquisition of new modalities can contribute to patients' optimal treatment choices.

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 left-hand graph from ActualEyes).

Development Stage of DWR-2206

Source: DWTI website.

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

Number of bullous keratopathy patients estimated	Keratoplasties performed annually	Patients on waiting list
7,000–10,000	about 3,000	10,000–20,000
*source: MHLW	* source: DWTI	

US, Europe	China	Global
FECD* Incidence	Corneal endothelial dysfunction patients estimated	Donor corneas available
Approximately 4% of people over 40	1mn or greater	only one in 70 patients
*FECD：Fuchs Endothelial Corneal Dystrophy		* source: DWTI

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.

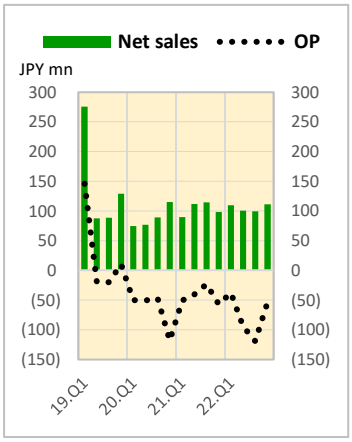
- Donor shortage
- Highly skilled surgeon and sophisticated equipment required for surgery
- Risks include infection, astigmatism, rise in intraocular pressure, and adhesion failure of transplant.

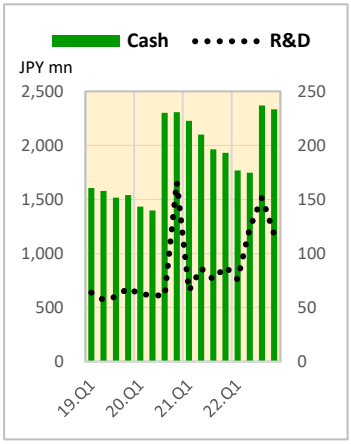
Treatment using cultured human corneal endothelial cells (which can be produced with consistent quality in large quantities) and iPS cells are being explored.

➔ 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.

Source: excerpts from FY2022/12 4Q IR results briefing materials.

4 EARNINGS REVIEW





Source: compiled by SIR from TANSHIN financial statements. Cash = cash and deposits on the B/S.

Deployment of R&D expense going into full swing as late-stage US clinical trials for H-1337 get underway

RESULTS SUMMARY

❇ DWTI announced FY22/12 4Q consolidated financial results at 15:30 on Monday 2/13, and it held a results briefing via ZOOM at 13:30 on Friday 2/17. After successful completion of the roughly ¥1.8bn financing last summer, the key takeaway is the Company is budgeting ¥1.5bn R&D expense for FY23/12 as multiple pipeline development projects go into full swing. According to the results briefing materials, main uses of R&D expense in FY23/12 include: 1) late stage Phase 2b clinical trials for H-1337 in the US, 2) development cost In Japan for DWR-2006 regenerative medicine cell-therapy treatment for bullous keratopathy (jointly developed with ActualEyes) and 3) a milestone payment on approval of DW-5LBT.

❇ On October 4, 2022, DWTI reached an agreement with the US FDA on the details for an additional study to be conducted on DW-5LBT, a new type of lidocaine patch for treatment of neuropathic pain (jointly developed with MEDRx). On January 17, DWTI announced that preliminary results of the additional study were favorable. On March 29, 2023, DWTI announced that MEDRx re-submitted a new drug application (NDA) to the US FDA. The review process is expected to take approx. 6 months, expecting approval after that (no impact on FY2023/12 results).

❇ On December 16, DWTI announced that it has submitted an Investigational New Drug (IND) amendment to the US FDA to commence late-stage Phase 2b clinical trials for H-1337 glaucoma and ocular hypertension treatment. H-1337 has strong prospects as "first choice as a second-line Glaucoma drug" for patients who do not respond to PGs, and those who suffer side effects from multiple drug regimens. DWTI estimates the target market up to a maximum 40% of the estimated US market of $3 billion.

DWTI FY12/22 Consolidated Financial Results Summary and FY23/12 Initial Forecasts

JPY mn, % [J-GAAP]	FY18/12 act	FY19/12 act	FY20/12 act	FY21/12 act	FY22/12 init CE	FY22/12 rev CE	FY22/12 act	FY23/12 init CE
Net sales	**293**	**581**	**356**	**414**	**370**	**440**	**448**	**400**
YoY	***15.3***	***98.2***	***(38.7)***	***16.5***	***(10.7)***	***6.2***	***8.1***	***(10.7)***
Cost of sales	14	26	17	20			28	
Gross profit	279	555	339	394			421	
SG&A expenses	1,066	437	604	566			726	
• R&D expense	**795**	**249**	**351**	**316**	**790**	**NA**	**470**	**1,500**
as % of net sales	*271.5%*	*43.0%*	*98.6%*	*76.3%*	*213.5%*		*104.8%*	*375.0%*
• Other	270	188	254	250			257	
Operating profit (loss)	**(786)**	**117**	**(266)**	**(172)**	**(690)**	**(400)**	**(306)**	**(1,400)**
Ordinary profit (loss)	(797)	110	(290)	(160)	(700)	(390)	(296)	(1,410)
Profit (loss) ATOP	(749)	133	(276)	(149)	(670)	(380)	(430)	(1,390)
Selected B/S items	**FY18/12**	**F19/12**	**FY20/12**	**FY21/12**			**FY22/12**	
• Cash and deposits	**1,584**	**1,541**	**2,308**	**1,934**			**2,335**	
Total assets	2,074	1,981	2,738	2,463			2,956	
Total liabilities	774	573	574	428			1,083	
Total net assets	1,300	1,408	2,164	2,035			1,873	
Equity ratio	*60.8%*	*70.3%*	*78.9%*	*81.4%*			*62.8%*	

Source: compiled by SIR from TANSHIN financial statements and IR results briefing. Initial CE 22.2.10, revised CE 22.11.18.

FY23/12 initial outlook and MTP initiatives in FY2023

FY22/12 net sales increased +8.1% YoY, in large part due to higher-than-expected royalty income from DW-1002 (+30% YoY, +22% in LC terms, with an 8% boost from the weak yen), as well as milestone revenue accompanying the start of domestic Phase I study of DW-1001 and a one-time payment for the transfer of exclusive enforcement rights to subsidiary JIT's corneal endothelium therapeutic agents. As can be seen from the earnings table on P3, initial guidance for FY23/12 net sales is for ¥400mn, -10.7% YoY. In addition to the disappearance of the one-time rights transfer payment, GLANATEC sales have peaked and are expected to decline. However, DWTI expects a solid contribution from DW-1002, GLA-ALPHA sales ramping up, and a milestone payment for DW-1002 in Japan. R&D expenses are set to more than triple to ¥1.5bn, mainly due to expenses for commencing the Phase IIb trial of H-1337 in the US, development expenses for DWR-2006, and a milestone payment to MEDRx after obtaining approval for DW-5LBT in the US. MTP initiatives in FY2023 are summarized on the following page.

2023 Event Calendar

H-1337	Publish top-line data of Phase IIb study in US
DW-5LBT	Re-application and approval in US
DW-1001	Start of Phase II study in Japan
DW-1002	Application, approval and Launch in China, Application in Japan
New projects	Research progress (including new collaborations)

Development Pipeline Plan

Products and Clinical indication		Region	2022	2023	2024	2025
H-1337	Glaucoma and ocular hypertension	US	Preparing for P2b	P2b		P3 *2025 or later
K-321	Fuchs endothelial corneal dystrophy	US	P2 P3	*Phase III study started in August 2022. Future plan undecided.		
DW-5LBT	Neuropathic pain after shingles	US		Re-application Approval	Launch	
DW-1001	Ophthalmic treatment agent	Japan	P1		P2	P3
DW-1002	ILM staining	China		Application Approval	Launch	
	ILM staining ALC staining	Japan		Application	Approval	Launch

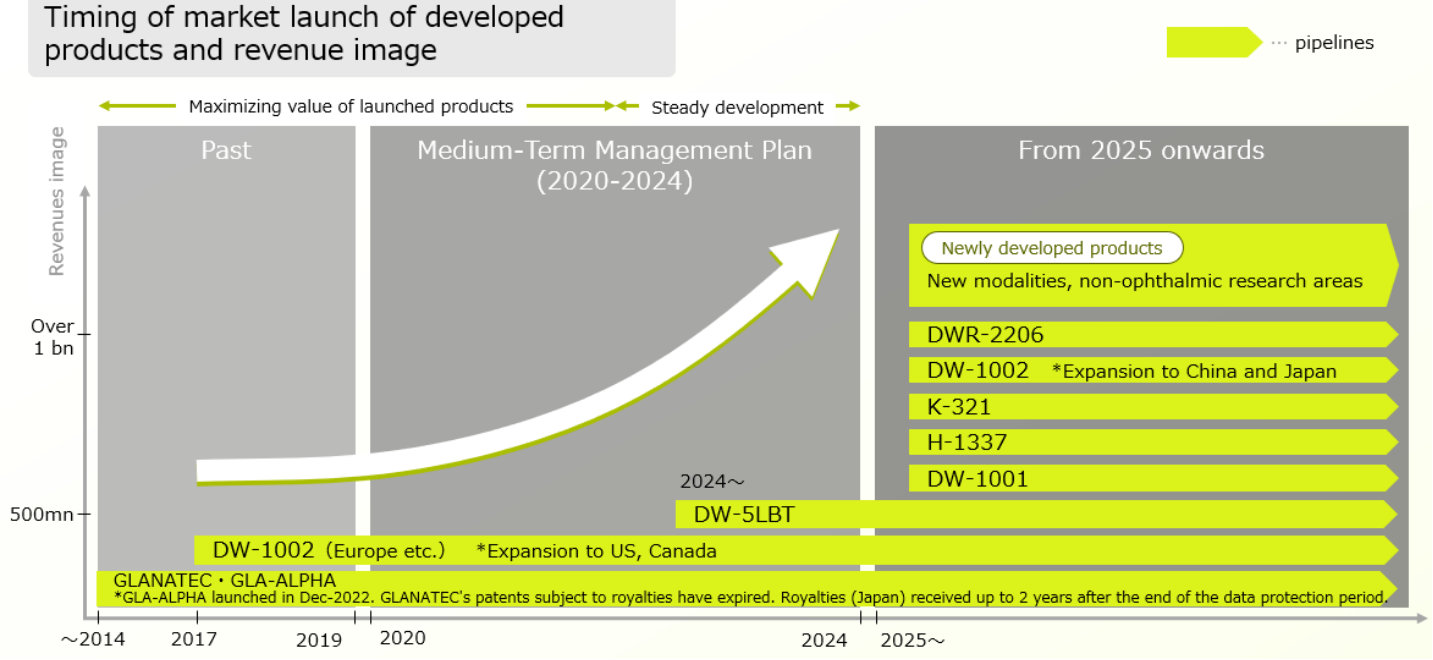
Note: Development plans for out-licensed products are based on development plans of the licensees and the company's expectations. Hence, actual development progress may differ from the plan.

★ **Development plan for regenerative cell therapy DWR-2206 will be released once finalized.**

Source: excerpt from FY2022/12 4Q IR results briefing materials.

Development Pipeline and Estimated Timing of Revenue Contribution

Timing of market launch of developed products and revenue image

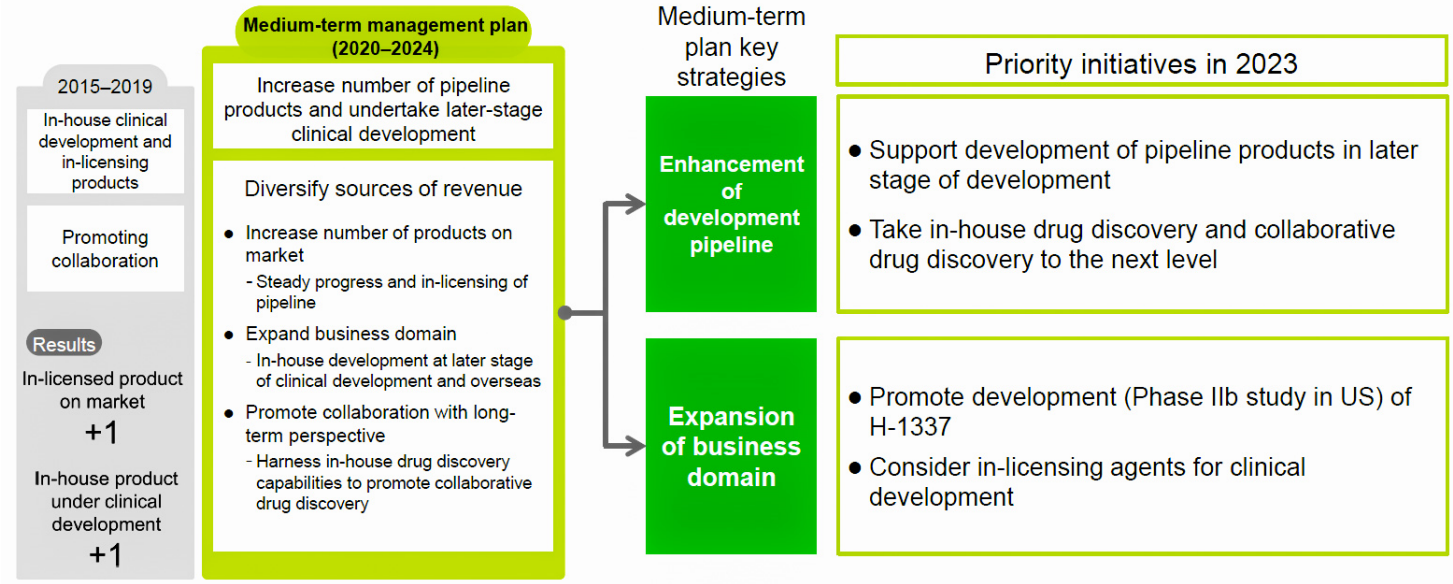


Source: excerpt from "Business Plan and Growth Potential" annual IR presentation.

Management Themes of Medium-Term Management Plan and Initiatives in 2023

Management themes

Enhancement of development pipeline and Expansion of business domain (2015-2024)



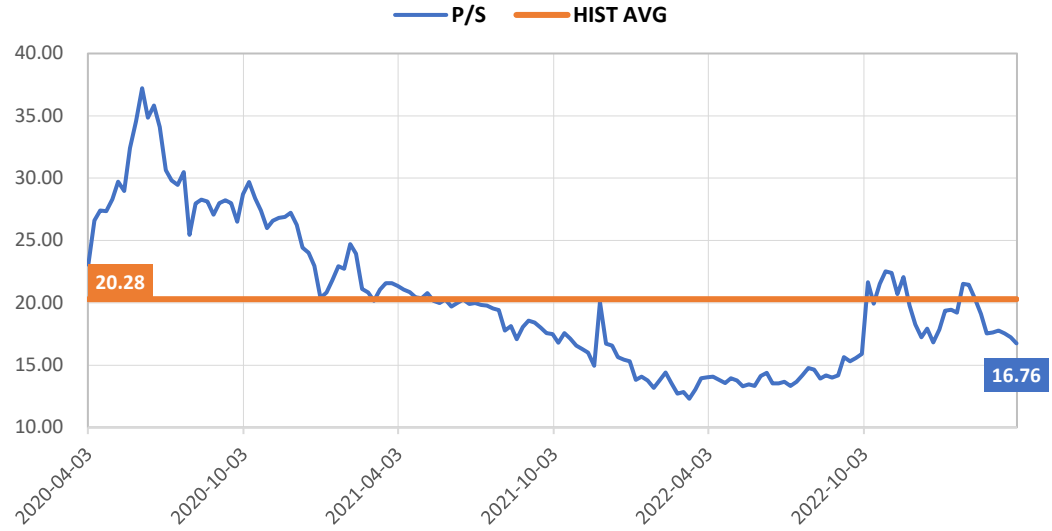
Source: excerpt from FY2022/12 4Q IR results briefing materials.

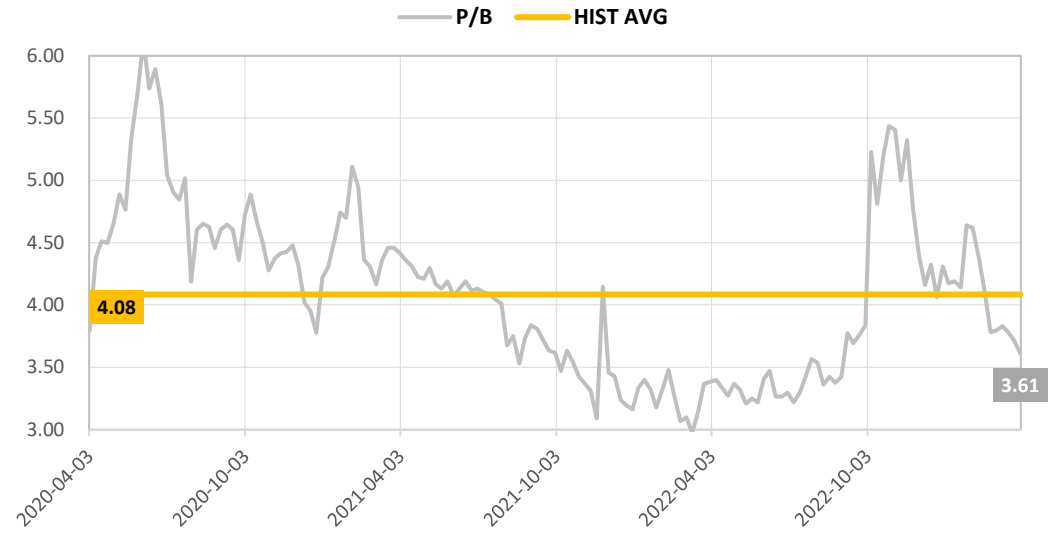
5 FOR INVESTORS

Performance and Valuations:
SESSA Smart Charts

- ✓ The price-to-sales ratio is currently trading 17.4% below its historical average, and the price-to-book ratio is trading 11.6% below its historical average, likely reflecting the reality oh higher losses in FY2023 as R&D expense ramps up.
- ✓ 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 September, followed by progress on DW-5LBT in the US in October. In any event, progress on H-1337 in the US is a positive development after some delays.

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



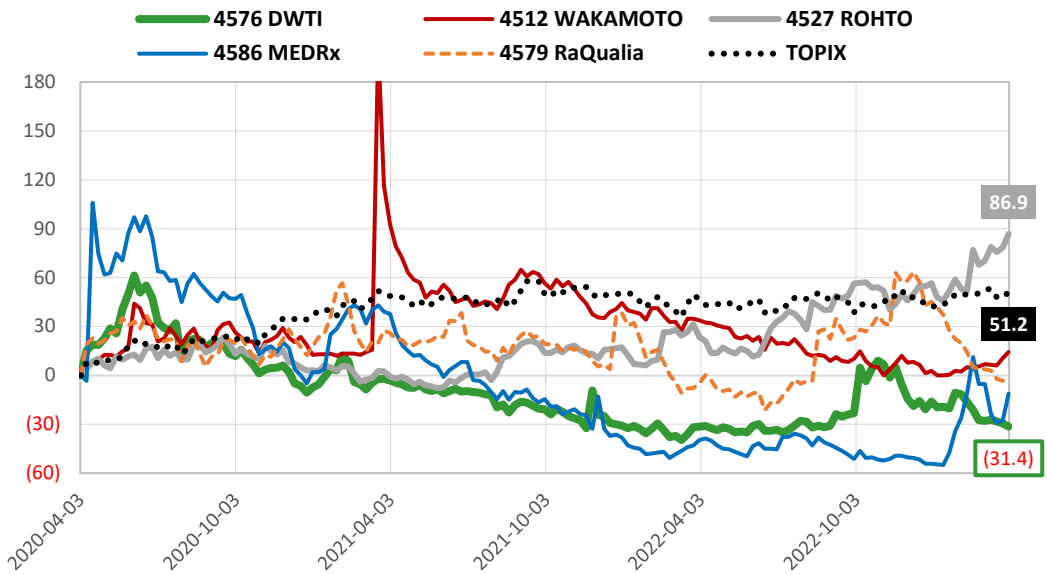


Source: compiled by SIR from SPEEDA share price and earnings database. Valuations calculated based on CE.

Analyst's view

- ✓ Over the last three years, DWTI has significantly under-performed. Ultimately bio-ventures are relatively high-risk business due to 1) high R&D costs, 2) low probability of success and 3) steady red ink in the early growth stage with limited revenue.
- ✓ However, risk appears weighted on the upside here given current low valuations and good potential for positive news flow in 2023.

3-Year Weekly Relative Performance



Source: compiled by SIR from SPEEDA share price database.

Valuation comparison with listed development partners

JPY mn, times, %	4576 TSE G	4512 TSE S	4527 TSE P	4586 TSE G	4579 TSE G
[J-GAAP]	DWTI	WAKAMOTO	ROHTO	MEDRx	RaQualia
FY-end	FY2023/12	FY2023/03 NC	FY2023/03	FY2023/12	FY2023/12
Net sales (CE)	400	8,500	236,000	127	2,799
Net assets (act)	1,873	11,768	213,452	1,213	5,497
Adj. (SAR, min interest, etc.)	17	0	5,674	64	8
Shareholders' equity (act)	1,857	11,768	207,778	1,149	5,489
Shareholders' equity ratio	62.8%	77.7%	66.5%	82.2%	87.7%
Market cap (treas. shrs adj.)	6,703	8,573	631,946	5,648	18,103
Profit ATOP (CE)	(1,390)	150	24,000	(786)	183
P/S ratio (x)	16.76	1.01	2.68	44.47	6.47
P/B ratio (x)	3.61	0.73	3.04	4.92	3.30
P/E ratio (x)	—	57.2	26.3	—	98.9
Dividend yield (%)	—	1.21%	0.79%	—	—

Source: compiled by SIR from SPEEDA share price and earnings database, and respective TANSHIN financial statements. Valuations calculated based on March 31, 2023 closing prices. NC = non-consolidated.

DWTI

Delivering innovative new drugs from Japan to patients worldwide

DWTI Top Shareholders (as of December 31, 2022)

	Shareholder name	Shares owned	Pct owned
1	Hiroyoshi Hidaka	3,128,800	10.13%
2	Yuichi Hidaka	2,863,600	9.27%
3	SBI SECURITIES Co., Ltd.	932,064	3.01%
4	Rakuten Securities, Inc.	704,300	2.28%
5	au Kabucom Securities Co., Ltd.	596,100	1.93%
6	Matsui Securities Co., Ltd.	437,000	1.41%
7	Kunie Hidaka	300,000	0.97%
8	Teruo Isohata	260,200	0.84%
9	Shigejiru Kimura	166,700	0.54%
10	Toru Watanabe	161,700	0.52%
★	**Top 10 Total**	9,550,464	30.93%

Source: compiled by SIR from company YUHO financial statements.

Note: percent owned calculation excludes treasury shares (100 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

Curent 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 company YUHO financial statements.

Key Patent Information

Devpt code, etc.	Title of Invention	Registration Status	Rights Holder/Applicant
Ripasudil hydrochloride hydrate	Isoquinoline derivatives and pharmaceuticals	Registered in Japan	DWTI Kowa Company, Ltd.
	(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
Retinopathy of prematurity therapeutic treatment	Agents for the treatment or prevention of retinopathy of prematurity, methods for testing for retinopathy of prematurity, and screening methods for substances for the treatment or prevention of retinopathy of prematurity	Registered in Japan, US, Europe, etc.	Japan Innovative Therapeutics, Inc. (DWTI consolidated subsidiary) Tokyo University of Agriculture and Technology

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

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

Product devpt code	Contract party	Date signed	Contract period	Main contract details
Retinopathy of Prematurity Treatment and Diagnostic Agent	Tokyo University of Agriculture and Technology	2015-04-27	From April 27, 2015 until the patent expiration date	1) Transfer of half of the equity interest in the patent application of TUAT for "a drug for treatment or prevention of retinopathy of prematurity, a method for testing for retinopathy of prematurity, and a method for screening substances for treatment or prevention of retinopathy of prematurity" to Japan Innovative Therapeutics, Inc. (JIT). 2) JIT will obtain an exclusive license with sublicensing rights to the patents in question. 3) JIT shall pay royalty income, etc. as consideration for the license.

	Contract party	Date signed	Contract period	Main contract details
Joint research	Mie University	2009-12-25	January 1, 2010 to December 31, 2023	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	Loan Agreement Certificate Mizuho Bank, Ltd.	2017-02-16	Repayment Date December 31, 2023	1) Loan amount: 600 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.	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.

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