D. Western Therapeutics Institute (DWTI) | 4576

Sponsored Research
September 22, 2023

Sessa Investment Research

Flurry of pipeline activity continuing in the 3Q

Expedited development plans for DWR-2206, dual formula DW-1002 in the US, and commenced dosing of H-1337 in US Phase IIb trials

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) 2023 application, 2024 approval and 2025 launch of DW-1002 in Japan, 2023 application/approval/launch in China, as well as expedited development of combination formula MembraneBlue-Dual® (DW-1002 + trypan blue) in the US **[NEW]**, 3) 2023 approval and subsequent 2024 launch of DW-5LBT lidocaine patch for treatment of neuropathic pain in the US, and 4) clinical trials in 2024 in Japan and application for approval in 2025 of regenerative cell medicine DWR-2206 **[NEW]**.

- Coming into the 3Q, DWTI announced 2 updates not included in its "Business Plan and Growth Potential." On 7/13, DWTI announced the **development plan for regenerative cell medicine DWR-2206, aiming to submit a notification of clinical trial at the end of 2023, start clinical trials in 2024, and submit application for approval (NDA) in 2025 (using the expedited conditional and term-limited approval system for regenerative therapeutics)**. On 7/24, DWTI announced that licensee **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 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.

- On 8/29, **DWTI announced that H-1337 dosing has commenced in PIIb 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).

Decision to develop combination formula DW-1002 + trypan blue in the US

Source: images from D.O.R.C. (Dutch Ophthalmic Research Center) global website and US TissueBlue™ product website.

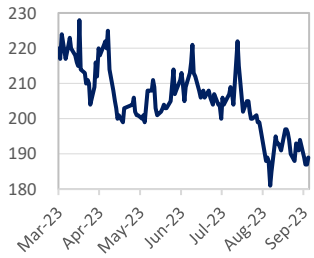
2Q Follow-up

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 (9/21)	174
YH (23/1/25)	305
YL (23/9/21)	174
10YH (14/8/19)	3,550
10YL (23/8/14)	181
Shrs out. (mn shrs)	32.128
Mkt cap (¥ bn)	6.072
Equity ratio (6/30)	64.2%
23.12 P/S (CE)	15.2x
23.06 P/B (act)	3.35x

6M price chart (weekly)

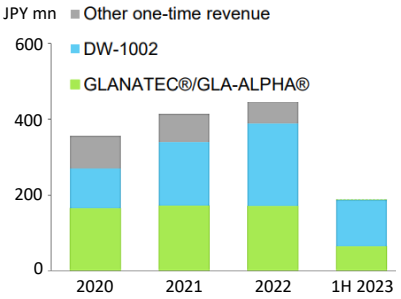


Source: SPEEDA price data

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

EARNINGS REVIEW

Trend of Royalties and Other One-time Revenue



Source: excerpt from IR results briefing.

GLA-ALPHA® combination ophthalmic solution

DWTI

String of 1H advances in pipeline development have continued unabated coming into the 3Q

1H FY23/12 RESULTS SUMMARY

❊ DWTI announced 1H FY23/12 consolidated financial results at 15:30 on Thursday 8/10, and it held a results briefing hosted by CEO Yuichi Hidaka via webinar from 13:30 on Friday 8/18. Net sales declined -10.6% YoY to ¥188mn, due to the absence of the one-time milestone payment from ROHTO which initiated a Phase I trial in Japan for DW-1001 last year. Overall, royalties were up slightly YoY. Ophthalmic surgical aid DW-1002 sales continue to expand globally, and royalties increased sharply by +25.2% YoY. While the contractual royalty fee rate for GLANATEC® declined from late 2022, and sales are peaking out as the drug patent has expired (royalties to end in Sep-2024), GLA-ALPHA® combination ophthalmic solution sales are ramping up and beginning to make a full-year contribution.

❊ R&D expense increased +47.5% YoY to ¥295mn, due to increased spending on development of H-1337 (Phase IIb study in the US) and DWR-2206. Note that the progress ratio is only 19.7% relative to the full-year budget, however, as described on the cover page, dosing of H-1337 has commenced as of 8/29, and the development plan for DWR-2206 has been officially announced, so deployment of R&D expense is set to ramp up from the 2H.

❊ DWTI made steady progress during the 1H in advancing pipeline development. On 3/29, DWTI resubmitted the NDA filing for DW-5LBT, lidocaine patch for treatment of neuropathic pain, being jointly developed in the US with MEDRx, which was accepted by the US FDA on 5/12, with a target action review date of 9/28. Following the 2022/8/26 announcement that licensee Kowa had initiated PIII clinical trials in the US of K-321 for the indication of Fuchs endothelial corneal dystrophy (FECD), DWTI announced on 3/22 and 4/6 that Kowa had initiated new global PIII clinical trials for

DWTI 1H FY23/12 Consolidated Financial Results Summary

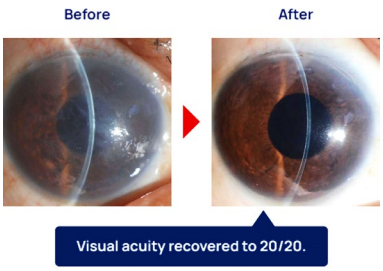
JPY mn, % [J-GAAP]	FY20/12 1H act	FY21/12 1H act	FY22/12 1H act	FY23/12 1H act	AMT CHG	progress ratio*	FY23/12 init CE
Net sales	**151**	**202**	**210**	**188**	**(22)**	**46.9%**	**400**
YoY	**(58.3)**	**33.1**	**4.2**	**(10.6)**			
Cost of sales	6	9	13	15	2		—
Gross profit	146	192	197	173	(24)		—
SG&A expenses	247	284	329	431	102		—
• R&D expense	**124**	**152**	**200**	**295**	**95**	**19.7%**	**1,500**
as % of net sales	81.7%	75.4%	95.1%	157.0%			*375.0%*
• Other	123	132	130	137	7		—
Operating profit (loss)	**(101)**	**(91)**	**(132)**	**(258)**	**(126)**		**(1,400)**
Ordinary profit (loss)	(111)	(82)	(118)	(255)	(136)		(1,410)
Profit (loss) ATOP	(97)	(83)	(110)	(248)	(138)		(1,390)
Selected B/S items	**2020/6**	**2021/6**	**2022/6**	**2023/6**	**vs '22 4Q**		**2022/12**
• Cash and deposits	1,398	2,100	1,749	2,235	(100)	←	**2,335**
Total assets	1,795	2,604	2,287	2,821	(136)	←	2,956
Total liabilities	485	491	358	1,000	(83)	←	1,083
Total net assets	1,310	2,113	1,929	1,821	(53)	←	1,873
Equity ratio	*73.0%*	*81.0%*	*83.5%*	*64.2%*		←	*62.8%*

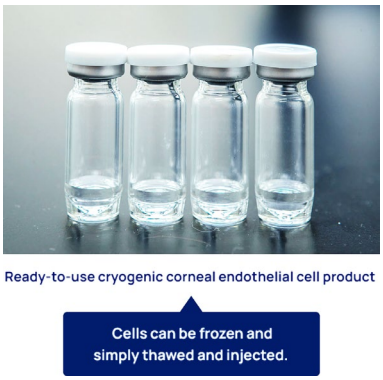
Source: compiled by SIR from TANSHIN financial statements. *Note: progress ratio to initial full-term guidance.

PIPELINE PROGRESS

[DWR-2206]
Expedited development plan

Non-clinical – 2022 to 2023
PI / PII – 2024 to 2025
NDA – late 2025





Source: ActualEyes website.

…continued from P2

- K-321, the US PIII study from Aug-2022 through Jun-2023 was administered to 331 patients after cataract surgery.

- The global (US, Europe, etc.) K-321 study from Mar-2023 through Jan-2025 will be administered to 100 patients with FECD after Descemetorhexis (Descemetorhexis Without Endothelial Keratoplasty (DWEK) 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.

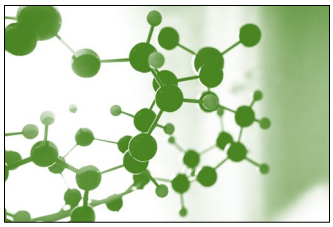
- And on 5/30, DORC filed a marketing application for single formula DW-1002 to China's NMPA (National Medical Products Administration) as a medical device for clinical indication ILM staining, aiming for approval and launch before the end of 2023. In Japan, licensee Wakamoto Pharmaceutical is in ongoing consultation with PDMA (Pharmaceuticals and Medical Devices Agency) toward submitting an NDA application in 2023 for marketing approval for the clinical indications of ILM and ALC staining, aiming for approval in 2024 and launch in 2025.

- Coming into the 3Q, on 7/13 DWTI and ActualEyes announced formulation of the development plan for regenerative cell medicine DWR-2206 for the clinical indication of bullous keratopathy (a disease in which corneal endothelial cells are damaged, causing corneal edema (swelling), which results in a cloudy cornea and significant vision loss. It is caused by a decrease in corneal endothelial cells due to Fuchs endothelial corneal dystrophy, or eye surgeries for cataracts or glaucoma. Treatment involves corneal transplant surgery, where there is a long waiting list due to shortage of donors, where only 1 in 70 patients receives a transplant).

- The DWR-2206 plan aims to submit an IND (Investigational New Drug) application at the end of 2023, start clinical trials in 2024, and submit an NDA (New Drug Application) in 2025 using Japan's conditional and term-limited approval system for regenerative therapeutics (approval system designed to facilitate the early commercialization of regenerative medicines. The system was introduced as a mechanism to allow special expedited approval of non-homogeneous regenerative medical products with conditions and a time limit, if their efficacy is presumed and safety is confirmed. After approval, the efficacy and safety of the product are to be verified again).

- On 7/24, DWTI announced that licensee DORC has decided to develop combination formula ophthalmic surgery adjuvant MembraneBlue-Dual® (DW-1002 + trypan blue) in the US for indications ILM and ERM membrane staining, and it has obtained from the US FDA orphan-drug designation for expedited review for approval. Higher marketability is expected in response to the current strong sales of TissueBlue™ in the US, and in addition to expedited review under ophan-drug status, DORC may be entitled to an extended exclusive marketing period after the launch of the product. **Both the determination of the expedited development plan for DWR-2206 and DORC's decision to develop combination formula ophthalmic surgery adjuvant MembraneBlue-Dual® in the US are new updates to "Business Plan and Growth Potential."**

PIPELINE PROGRESS



- On 8/29, DWTI announced that H-1337 dosing has commenced in PIIb 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."

- 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 second half of 2024. 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).

- Approval of the resubmitted NDA filing for DW-5LBT from the US FDA is expected at the end of Sep-2023 (target action review date of 9/28), aiming for launch in the US in 2024. CONCLUSION: the flurry of advances in pipeline development during the 2Q and 3Q point to a ramping up of deployment of R&D expense, however that is already included in initial guidance shown on the right-hand side of the table on P2. **In SIR's view, there is potential for this progress to refocus investor interest in and the trajectory of DWTI's share price, which has likely been languishing due to perceived delays in progress of development. At any rate, development is now progressing on multiple fronts, and funding is in place to implement development.**

Development Pipeline Plan

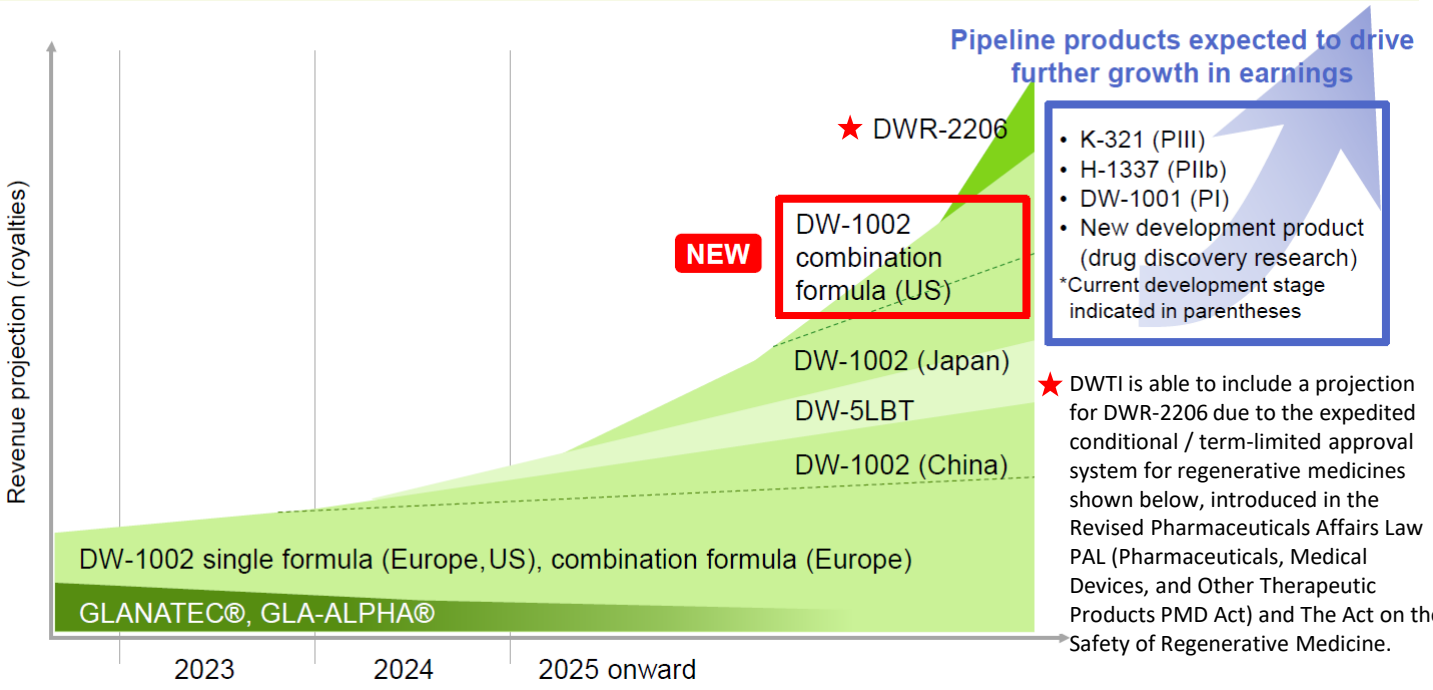
Products and Clinical indication		Region	2022	2023	2024	2025
H-1337	Glaucoma and ocular hypertension	U.S.	Preparing for P2b	P2b		P3 *2025 or later
K-321	Fuchs endothelial corneal dystrophy	U.S.	P2 P3	*Phase III study (New Global) started in March 2023. Future plan undecided.		
DW-5LBT	Neuropathic pain after shingles	U.S.		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
	ILM staining and ERM staining ★NEW	U.S.			Application preparation	Application
DWR-2206	Bullous Keratopathy ★NEW	Japan		Nonclinical	P1/P2	Application

*Use of conditional and time-limited approval systems

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

Source: excerpt from FY23/12 1H IR results briefing materials.

Timing of Pipeline Product Launch and Revenue Projections



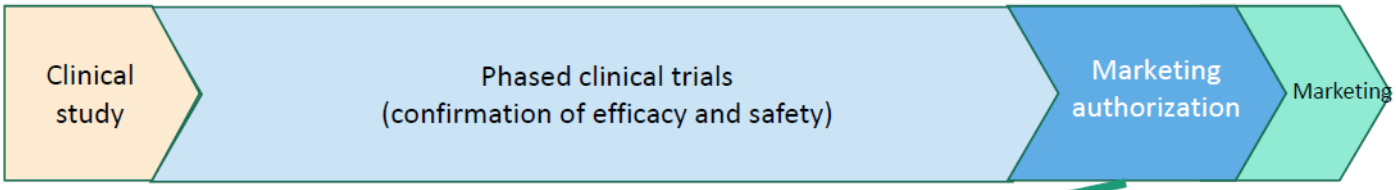
★ DWTI is able to include a projection for DWR-2206 due to the expedited conditional / term-limited approval system for regenerative medicines shown below, introduced in the Revised Pharmaceuticals Affairs Law PAL (Pharmaceuticals, Medical Devices, and Other Therapeutic Products PMD Act) and The Act on the Safety of Regenerative Medicine.

Source: excerpt from FY23/12 1H IR results briefing materials.

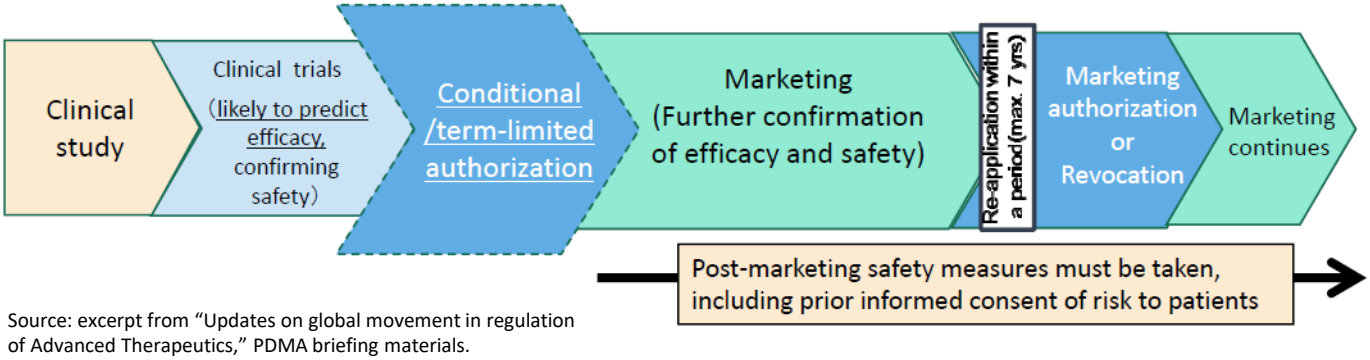
Expedited approval system under PMD Act

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]

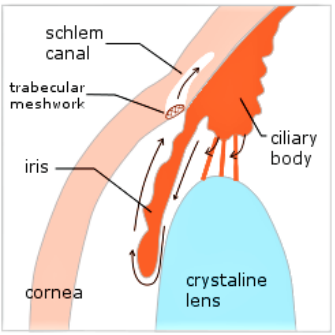


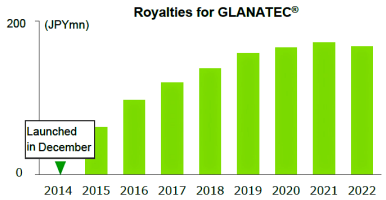
[New scheme for regenerative medical products]



Source: excerpt from "Updates on global movement in regulation of Advanced Therapeutics," PDMA 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).

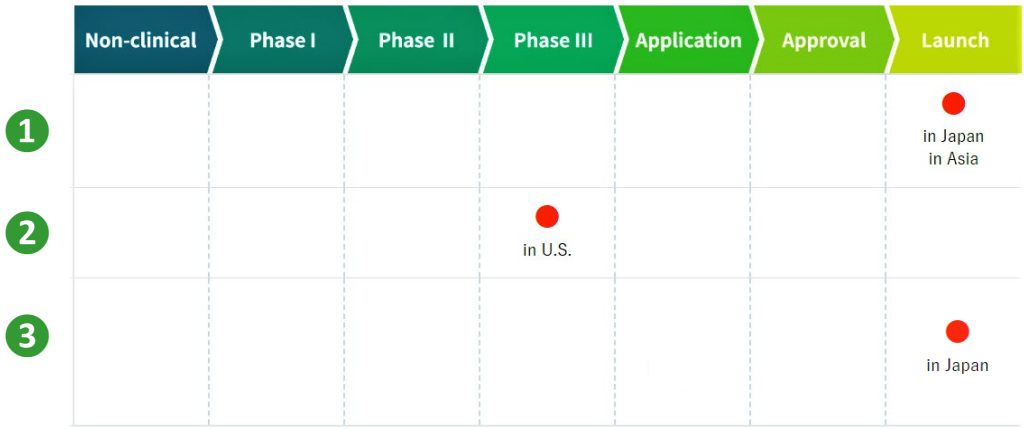
❷ Fuchs endothelial corneal dystrophy [K-321]

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 trial started in the US on August 26, 2022, and new global Phase III trials commenced from March/April 2023.

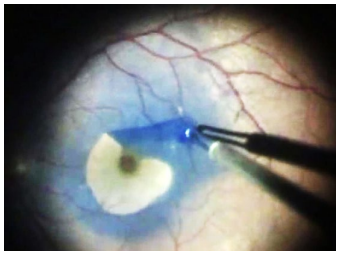
❸ Glaucoma and ocular hypertension [GLA-ALPHA® combination ophthalmic solution (Ripasudil hydrochloride hydrate and Brimonidine tartrate) K-232]

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.

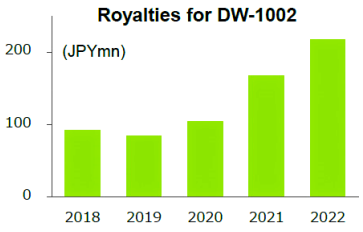
Development Stages of Ripasudil hydrochloride hydrate



Source: DWTI website.



Source: Journal of Ophthalmology



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

[DW-1002]

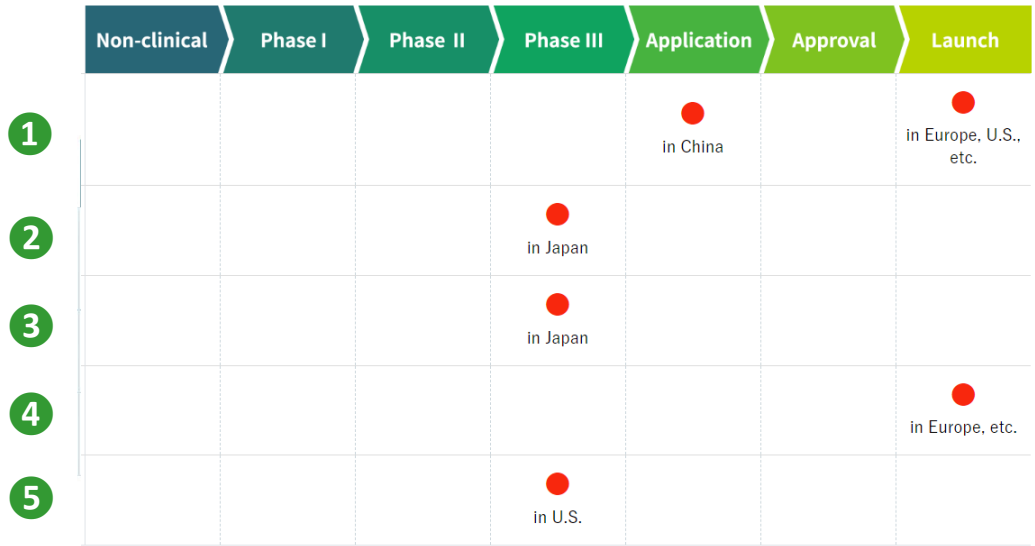
Brilliant Blue G-250 (BBG250) is an ophthalmic surgical adjuvant whose active ingredient is a dye with high staining ability. The dye temporarily and safely stains the capsule protecting the inner limiting membrane or crystalline lens in the back of the eye, making it easier to perform vitreous or cataract 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. 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 2023, receive approvals in 2024 and launch in 2025. DORC filed an NDA in China in May-2023 for indication ILM staining, targeting approval and sales launch in 2023.

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.

[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 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]

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.

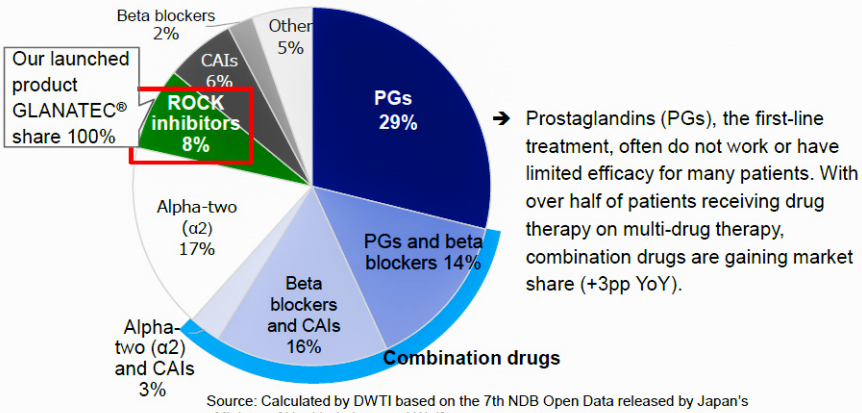
DWTI estimates the target market for 1) patients who do not respond to first-line drugs and 2) patients who receive multiple drugs and suffer side effects is up to a maximum 40% of the estimated US market of $3 billion ($1.2bn).

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.

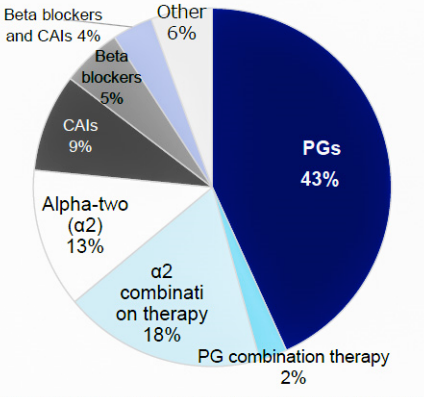
Japanese market (FY2020: about ¥89bn)



➔ 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.

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 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 at the end of Sep-2023 (target action review date of 9/28), aiming for launch in the US in 2024.

Based on data from MEDRx, the US market for transdermal lidocaine patches was estimated at about ¥34bn in 2022. 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

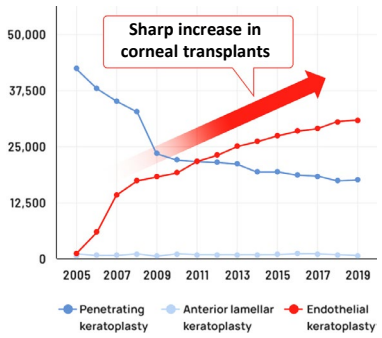
Description:

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.



Source: ActualEyes website.

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

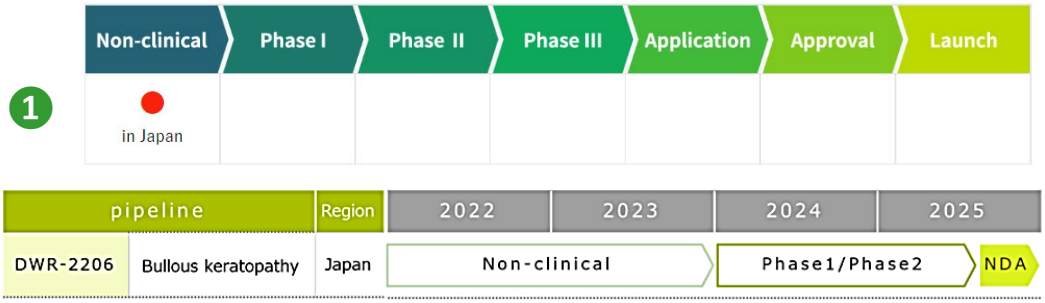
DWR-2206 (AE101) is a novel cell injection therapy developed by ActualEyes as a regenerative cell therapy for the indication of bullous keratopathy, which is an eye disorder that involves a blister-like swelling of the cornea (the clear layer in front of the iris and pupil), using cultured human corneal 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.

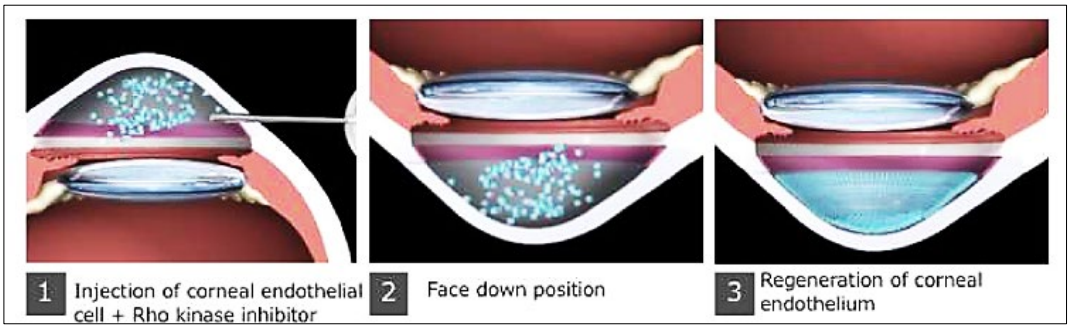
Three reasons for DWTI becoming involved with regenerative medicine cell-therapy products for corneal endothelial disorders: i) **Ophthalmology Field:** enhances DWTI's focus on ophthalmologic diseases, ii) **Corneal Endothelial Disorders:** caused by a variety of factors, the only treatment is corneal 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



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.

Borrowings and Financing Status

Borrowings

Balance (as of June 30, 2023)	Credit limit	Use of funds	Type
JPY60mn	JPY600mn	Fund for the acquisition of the ophthalmic surgical adjuvant DW-1002 business	Loans on deeds
JPY100mn	JPY200mn	Funds for the milestone payment for neuropathic pain treatment DW-5LBT	Term loan contract with commitment period
JPY44mn	JPY440mn	Funds for the development of regenerative cell therapy DWR-2206	Term loan contract with commitment period

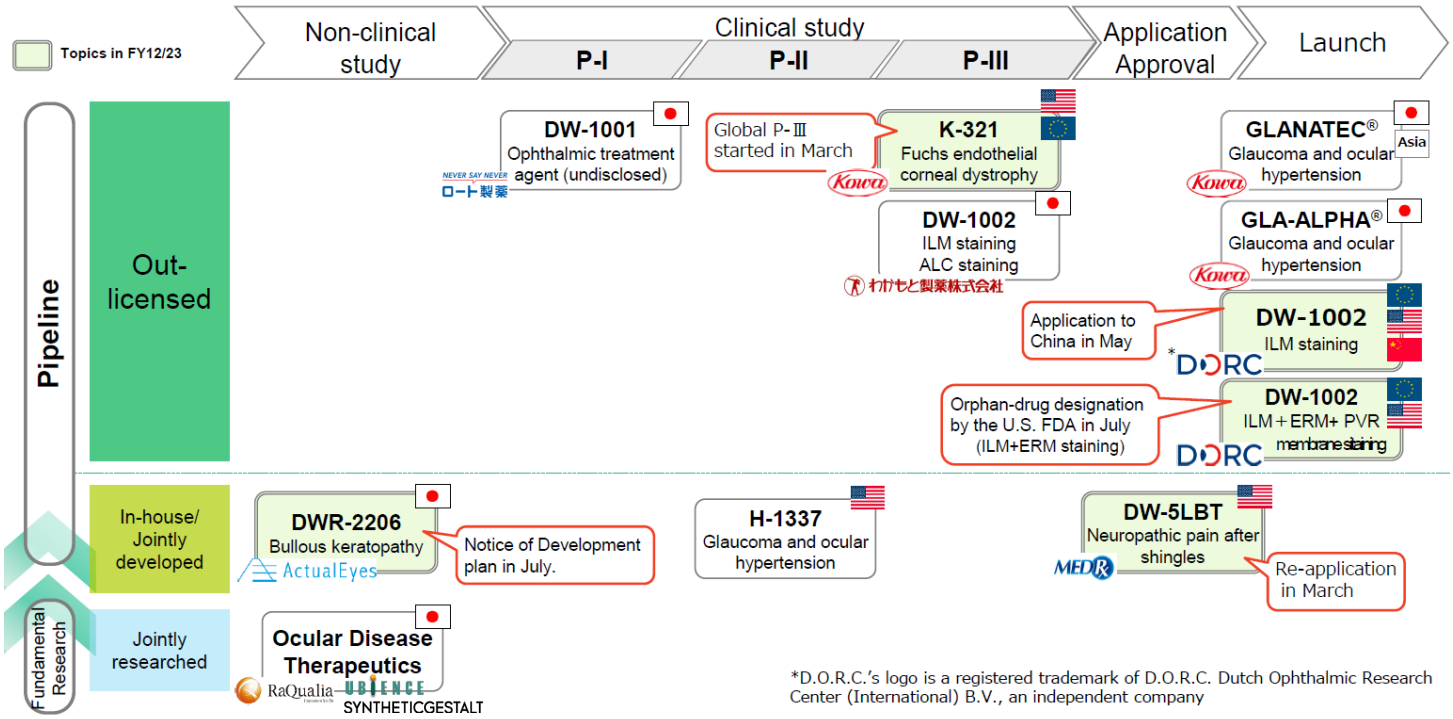
Other financing

Total amount exercised (as of June 30, 2023)	Conversion/ exercise ratio	Use of funds	Type
JPY275mn	30.6%	• 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
JPY178mn	39.5%		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

Topics in FY12/23



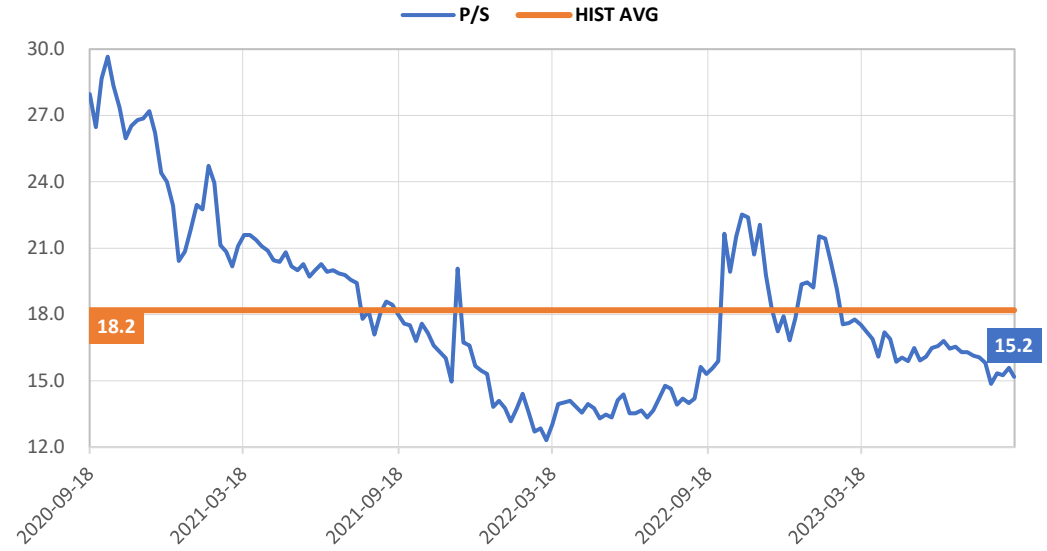
Source: excerpts from FY2023/12 1H IR results briefing materials.

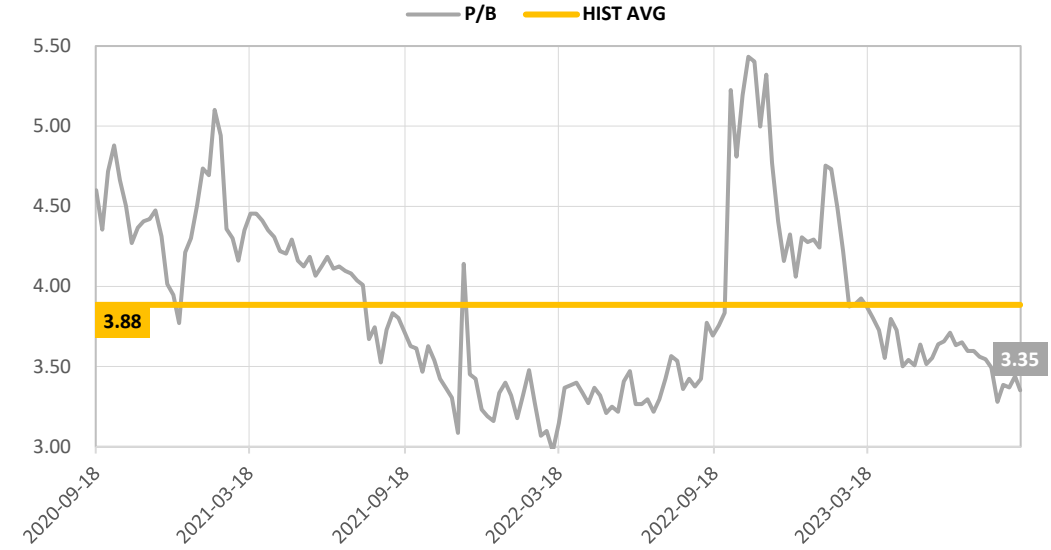
SHARE PRICE

Performance and Valuations:
SESSA Smart Charts

- ✓ The price-to-sales ratio is currently trading 16.6% below its historical average, and the price-to-book ratio is trading 13.7% below its historical average, likely reflecting concerns over perceived delays in R&D deployment.
- ✓ 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. **Progress on H-1337 in the US and DWR-2206 is likely to renew interest in DWTI's share price.**

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.

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.

LEGAL DISCLAIMER

This report is intended to provide information about the subject company, and it is not intended to solicit or recommend investment. Although the data and information contained in this report have been determined to be reliable, we do not guarantee their authenticity or accuracy.

This report has been prepared by Sessa Partners on behalf of the concerned company for which it has received compensation. Officers and employees of Sessa Partners may be engaged in transactions such as trading in securities issued by the company, or they may have the possibility of doing so in the future. For this reason, the forecasts and information contained in this report may lack objectivity. Sessa Partners assumes no liability for any commercial loss based on use of this report.

Sessa Partners Inc.

#5a i-o Azabu, 2-8-14
Azabujyuban, Minato-ku, Tokyo
info@sessapartners.co.jp