D. Western Therapeutics Institute | 4576

Sponsored Research
November 30, 2022

Sessa Investment Research

Earnings revision and transfer of JIT license

GLA-ALPHA® combination ophthalmic solution launching on December 6

SUMMARY

❇ DWTI announced FY22/12 3Q consolidated financial results at 15:30 on Thursday 11/10 (see summary on P2). Then at 15:30 on Friday 11/18, DWTI announced a revision of earnings forecasts (see table below), as well as notice of transfer of licensing rights for a corneal endothelial treatment drug by consolidated subsidiary Japan Innovative Therapeutics, Inc. (JIT) to DWTI capital tie-up and joint development partner ActualEyes Inc. Net sales were revised up mainly due to strong royalty income from DW-1002, an ophthalmic surgical aid, in Europe, the US and other regions (an increase of approx. 20% over initial plan due to strong demand and forex impact), as well as the receipt of a lump-sum payment as consideration for the transfer of the exclusive worldwide license with sublicensing rights granted to JIT by Doshisha University for a corneal endothelial treatment drug to ActualEyes (consideration approx. 6.8% of revised net sales forecast). Profit (loss) forecasts were also revised up due to lower deployment of R&D expense for H-1337 glaucoma treatment clinical trials in the US (going into full swing from now on).

❇ DWTI announced on 9/26 that out-license partner Kowa had obtained mfg. and marketing approval for K-232, GLA-ALPHA® combination ophthalmic solution for the treatment of glaucoma and ocular hypertension (OHT), in Japan. The active ingredients GLANATEC® ophthalmic solution 0.4% (rho-kinase inhibitor ripasudil hydrochloride hydrate) and an Alpha-2 adrenergic receptor agonist (brimonidine tartrate) have a pharmacological point of action that differs from that of existing fixed combination eye drops, allowing the product to be used in combination with a variety of glaucoma and OHT treatments (the use of multiple drug combinations is becoming the standard of care for the treatment of glaucoma). DWTI announced on 11/16 that Kowa received notice from MHLW that GLA-ALPHA® combination ophthalmic solution was given an NHI Drug price listing, and that Kowa is on schedule to launch on December 6.

DWTI Q3 FY12/22 Consolidated Financial Results Summary and Revised Forecast

[J-GAAP] JPY mn, %	FY18/12 act	FY19/12 act	FY20/12 act	FY21/12 act	FY22/12 init CE	FY22/12 rev CE	21.Q3 9M act	22.Q3 9M act
Net sales	**293**	**581**	**356**	**414**	**370**	**440**	**316**	**309**
YoY	***15.3***	***98.2***	***(38.7)***	***16.5***	***(10.7)***	***6.2***	***31.3***	***(2.1)***
Cost of sales	14	26	17	20			14	19
Gross profit	279	555	339	394			301	290
SG&A expenses	1,066	437	604	566			416	542
• R&D expense	**795**	**249**	**351**	**316**	**790**		**228**	**351**
as % of net sales	*271.5%*	*43.0%*	*98.6%*	*76.3%*	*213.5%*		*72.2%*	*113.7%*
• Other	270	188	254	250			188	190
Operating profit (loss)	**(786)**	**117**	**(266)**	**(172)**	**(690)**	**(400)**	**(114)**	**(252)**
Ordinary profit (loss)	(797)	110	(290)	(160)	(700)	(390)	(106)	(239)
Profit (loss) ATOP	(749)	133	(276)	(149)	(670)	(380)	(102)	(226)
Selected B/S items	**FY12/18**	**FY12/19**	**FY12/20**	**FY12/21**			**21.Q3**	**22.Q3**
• Cash and deposits	**1,584**	**1,541**	**2,308**	**1,934**			**1,966**	**2,370**
Total assets	2,074	1,981	2,738	2,463			2,559	3,056
Total liabilities	774	573	574	428			470	1,203
Total net assets	1,300	1,408	2,164	2,035			2,089	1,853
Equity ratio	*60.8%*	*70.3%*	*78.9%*	*81.4%*			*80.2%*	*60.1%*

Source: compiled by SIR from TANSHIN financial statements and 11/18 revision press release.

3Q Follow-up

DWTI
D.WESTERN THERAPEUTICS INSTITUTE

Focus Points:

Drug discovery bio-venture with strengths in the kinase inhibitor mechanism and treatments for ophthalmic diseases such as glaucoma and ocular hypertension.

Key Indicators	
Share price (11/30)	278
YH (22/10/6)	357
YL (22/2/24)	183
10YH (13/5/8)	3,755
10YL (13/1/4)	131
Shrs out. (mn shrs)	30.129
Mkt cap (¥ bn)	8.255
Shr equity ratio (9/30)	60.2%
22.12 P/S (CE)	22.1x
22.12 P/E (CE)	—
22.09 P/B (act)	5.29x
21.12 ROE (act)	—
22.12 DY (CE)	—

6M price chart (weekly)

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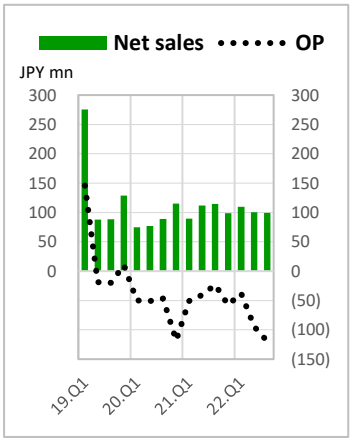
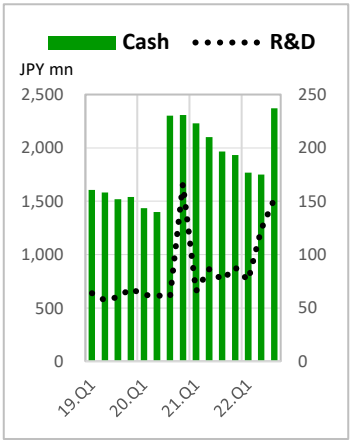




Source: compiled by SIR from TANSHIN final statements. Cash = cash and deposits on the B/S. Unit: JPY mn.

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

RESULTS SUMMARY

❊ DWTI announced FY22/12 3Q consolidated financial results at 15:30 on Thursday 11/10. Headline numbers were net sales ¥309mn (-2.1% YoY), maintaining steady royalty income from launched products, and the operating loss expanded from ¥114mn → ¥251mn. As can be seen in the table on P1, **R&D expense increased +54.1% YoY to ¥351mn as clinical trial preparation expenses for H-1337 go into full swing ahead of late-stage Phase IIb trials getting underway in the US**. 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.

❊ Looking at changes in selected B/S items shown at the bottom of the table on P1, liabilities increased from the end of the previous fiscal year mainly due to **non-current liabilities increasing by ¥782mn to ¥1,017mn, mainly reflecting an increase of ¥863mn from the issuance of convertible bond-type bonds with stock acquisition rights**.

❊ On August 26, DWTI announced that licensee Kowa commenced Phase III trials in the US for K-321 for the indication of Fuchs endothelial corneal dystrophy (FECD). On September 26, DWTI announced that **Kowa obtained domestic manufacturing and marketing approval for GLA-ALPHA® eye drops that can be used in combination with other glaucoma and ocular hypertension treatments, sales to commence before the end of 2022**. On October 4, an agreement was reached with the US FDA on the details of an additional study to be conducted on DW-5LBT, a new type of lidocaine patch for treatment of neuropathic pain (jointly developed with MEDRx). DWTI expects the additional study to be completed and file for approval in the first half of 2023, and to receive approval in the second half of 2023.

Pipeline expansion and successful financing

Flurry of pipeline activity and series of in-house development progress

PIPELINE EXPANSION

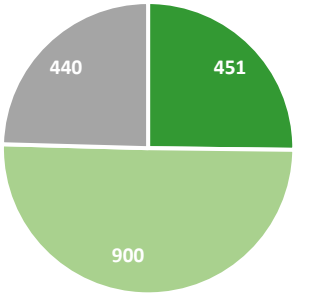
PIPELINE EXPANSION SUMMARY

❊ DWTI announced on June 30 that it concluded a capital tie-up and joint development agreement with ActualEyes Inc. for joint development in Japan of regenerative medicine cell-therapy product candidate AE101 (DWR-2206) for treatment of corneal endothelial dysfunction.

❊ This novel cell injection therapy for the indication of bullous keratopathy (blister-like swelling of the cornea) uses cultured human corneal endothelial cells combined with a Rho-kinase inhibitor, and aims to fulfill large unmet needs as a less invasive, alternate procedure to keratoplasty (transplant of corneal tissue from a donor), where it is estimated that only 1 in 70 patients globally actually receive transplants due to the lack of donors. (pipeline expansion continued on PP 3-6)

PIPELINE EXPANSION

¥1,791 million Fund-Raising Summary



SUMMARY (continued from P2)

❊ In a separate announcement on June 30, DWTI announced details of its new fund-raising through issuance of Series 1 unsecured convertible bonds with stock acquisition rights and Series 11 stock acquisition rights by third-party allotment. DWTI's Board of Directors resolved to borrow funds for the development of DWR-2206 through the conclusion of a line of credit agreement with Mizuho Bank, Ltd. (borrowing limit up to ¥440 million). Funds for investment in ActualEyes (DWTI as one of two investors will underwrite ¥130 million of the ¥330 million third-party allotment of shares issued by ActualEyes, for an ownership ratio of 7% of total shares outstanding) as well as ongoing in-house pipeline development etc., will be financed through the aforementioned CB and stock acquisition rights (see left).

❊ DWTI announced the results of its financing transaction on July 19 as follows: payment was completed for convertible bonds with stock acquisition rights (¥900mn) and the total issue price of the stock acquisition rights (¥1.2mn; up to ¥450mn if all SAR are exercised by December 24, 2027, exercise price ¥185).

❊ DWTI announced on August 8 that ActualEyes concluded a partial product development contract with TEIJIN Group subsidiary Japan Tissue Engineering Co., Ltd. (J-TEC, TSE 7774) to support early commercialization. J-TEC 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.

❊ DWTI announced on August 26 that licensee Kowa completed Phase II clinical trials in the US for K-321, an ophthalmic solution containing as active ingredient the rho-kinase inhibitor ripasudil hydrochloride hydrate originated by DWTI, for the…

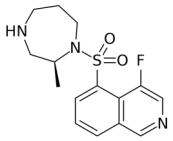
DWTI Development Pipeline adds DWR-2206, K-321 starts P-III in US

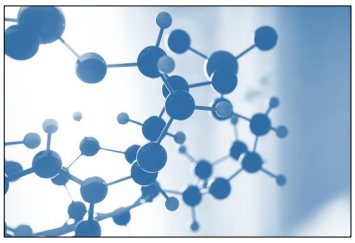
Products		Clinical indication	Region	Non-clinical	P-I	P-II	P-III	Application	Approval	Launch	Licensee
Ripasudil hydrochloride hydrate	GLANATEC®	Glaucoma and ocular hypertension	Japan, Asia*								Kowa
	K-321	Fuchs endothelial corneal dystrophy	US				*New				
K-232 (Ripasudil hydrochloride hydrate/ Brimonidine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

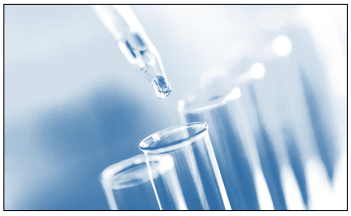
*Launched in Thailand, Singapore, and Malaysia

Source: excerpt from Q2 FY22/12 IR results briefing materials, updated after Q3 results.

Ripasudil hydrochloride hydrate molecule skeletal formula







SUMMARY (continued from P3)

…indication of Fuchs endothelial corneal dystrophy (FECD), and Kowa has commenced Phase III clinical trials.

❇ Phase II trials investigated the efficacy and safety of ripasudil hydrochloride hydrate eye drops applied in 12-week treatments in patients with FECD after DWEK (Descemetorhexis Without Endothelial Keratoplasty) / DSO (Descemet Stripping Only), in other words surgical removal of the Descemet membrane (DM) without subsequent endothelial transplantation, compared with a placebo, and all subject visits were completed by June 2022. Phase III trials are scheduled to run through June 2023. The start of Phase III was not included in DWTI's initial plan for 2022.

❇ Preparations are underway for late-stage Phase IIb clinical trials in the US for glaucoma treatment H-1337. The results of Phase I/IIa clinical trials in the US for twice-daily administration of H-1337 (in three dosage levels) versus a placebo in patients with glaucoma: **Efficacy** demonstrated significant reduction of intraocular pressure (IOP) in all three groups versus the placebo, and **Safety** was sufficiently well tolerated, with low occurrence of localized adverse effects. Discussions on Phase IIb study design have progressed with the FDA, targeting once-daily doses.

❇ US development of H-1337 to Phase IIb trials is DWTI's first foray into late-stage clinical development. H-1337 is a multi-kinase inhibitor that inhibits various protein kinases, chiefly leucine-rich repeat kinase 2 (LRRK2), for the treatment of glaucoma and ocular hypertension. Its strong effectiveness in lowering intraocular pressure is attributed to its new mechanism of action. It has strong prospects as "first choice as a second-line Glaucoma drug" for patients who do not respond to prostaglandins (PGs), and those who suffer side effects from multiple drug regimens. DWTI estimates potential up to 40% of the estimated US market of $3 billion.

In-house late-stage development of Glaucoma Treatment H-1337

● Preparing to start PIIb study in US in FY2022

Summary of Phase I/IIa study results

Evaluating twice-daily administration of H-1337 (three dosage levels) versus placebo in patients with glaucoma and ocular hypertension

- Efficacy: Significant reduction in IOP versus placebo ($p<0.0001$)
- Safety: Sufficiently well tolerated

⇒ **Deemed appropriate to advance to Phase IIb study**

Toward PIIb study

✓ **Considering favorable safety profile, looking at raising dosage and administering once daily**

⇒ **Aiming to enhance efficacy, prolong duration of action**

✓ **In discussions with FDA on Phase IIb study design, dosage, endpoints, etc.**

Efficacy

- IOP-lowering effect demonstrated in all three groups (0.06%, 0.2%, and 0.6%) compared to placebo

	Median diurnal IOP change (8 hours) on Day 28
0.6% dosage group (n=21)	-5.1mmHg
Placebo group (n=22)	-0.4mmHg
Difference	-4.7mmHg

Safety

- 100% of patients completed study, with no treatment interruption or discontinuation
- Sufficiently well tolerated, with low occurrence of localized adverse effects

Rate of occurrence	5% or above*	0.1~5%
Eyes	Discomfort	Conjunctival hyperemia

*: Common to all three groups

Conference presentation

- Planning to present Phase I/IIa results at Annual Meeting of American Academy of Ophthalmology (AAO) in September

Source: excerpt from Q2 FY22/12 IR results briefing materials.

DWTI 2022 Event Calendar Update

H-1337	Start of Phase IIb study in US
K-232	Approval in Japan ✓ Achieved *New
K-321	End of Phase II study in US ✓ Achieved
DW-1001	Start of Phase I study in Japan ✓ Achieved
DW-1002	Approval filing in China
New projects	Research progress (including new collaborations) ✓ Achieved

Source: excerpt from Q2 FY22/12 IR results briefing materials, updated after Q3 results.

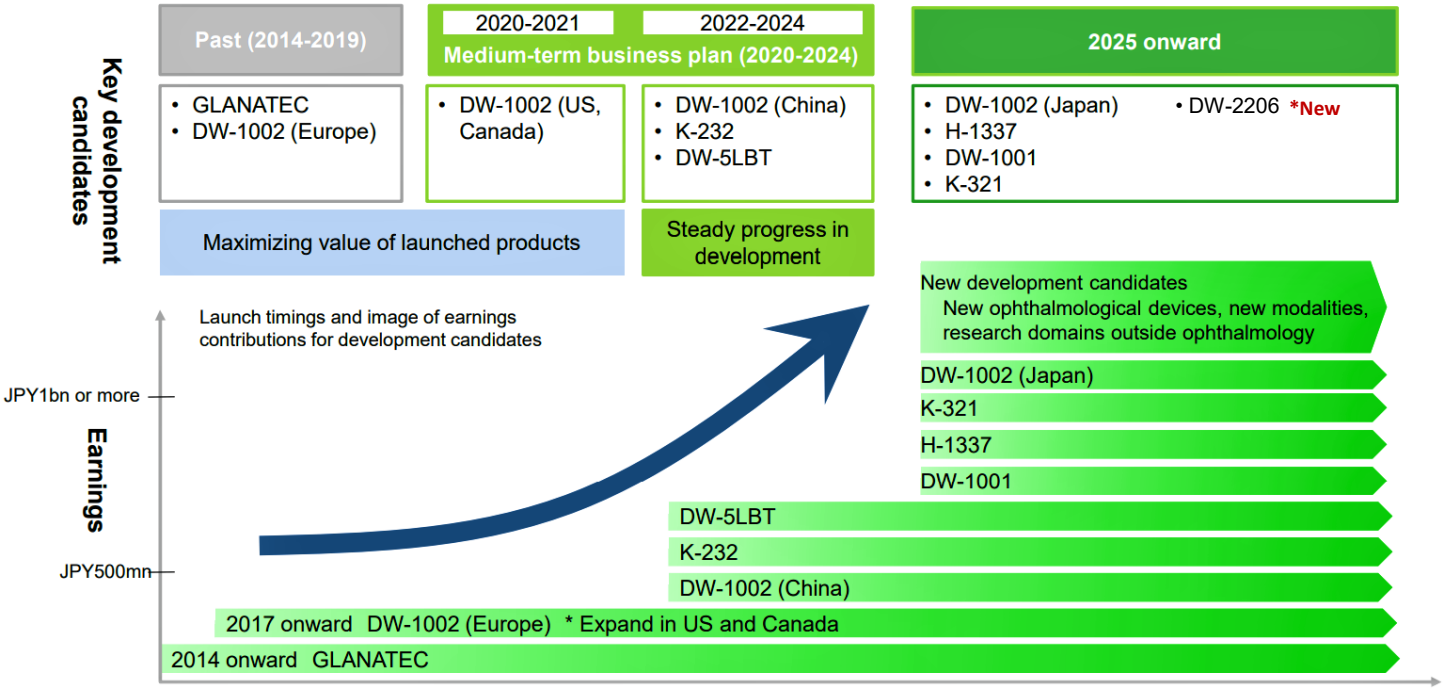
DWTI Development Pipeline Plan Update

Products and Clinical indication		Region	2021	2022	2023	2024
H-1337	Glaucoma and ocular hypertension	US	Preparing for P2b	**P2b**		P3 *2024 or later
DW-5LBT	Neuropathic pain after shingles	US	Received CRL	Additional study	Approval/Launch *Approval expected in 2023	
K-232	Glaucoma and ocular hypertension (combination eye drop)	Japan	Application	Approval	Launch 22.12.06	Launch
K-321	Fuchs endothelial corneal dystrophy	US		**P2**	*New Phase III underway in US thru 23/6.	
DW-1001	Ophthalmic treatment agent	Japan	Non-clinical	**P1**	**P2**	
DW-1002	ILM peeling	China		Application	Approval	Launch
	ILM staining Cataract surgery	Japan			Application	Approval

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 DWR-2206 will be released once finalized.

Source: excerpt from Q2 FY22/12 IR results briefing materials. K-321 plan updated per 8/26 press release.

Estimated Timing of Development Pipeline Earnings Contribution



Source: excerpt from Q2 FY22/12 IR results briefing materials.

Series 1 Unsecured CB with Stock Acquisition Rights and Series 11 Stock Acquisition Rights

Use of funds

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

Note: The above amount excludes issuance costs of JPY12mn

(Ref.) Series 10 Stock Acquisition Rights

Remainder acquired and canceled by May 11, 2022. Total funds raised: JPY1,050mn

Specific use of funds	Amount (JPYmn)	Appropriation status (JPYmn)	Anticipated timing of expenditure
① H-1337 development funds	600	29	Through December 2023
② Funds for drug discovery research activities (including joint research)	266	138	Through December 2023
③ Working capital	183	29	Through December 2023

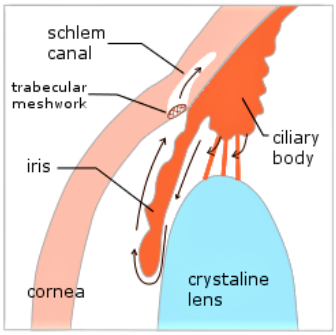
Source: excerpt from Q2 FY22/12 IR results briefing materials.

PIPELINE

Original and Licensed-in

GLANATEC® ophthalmic solution 0.4% (K-115) sold by Kowa in Japan

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.



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.

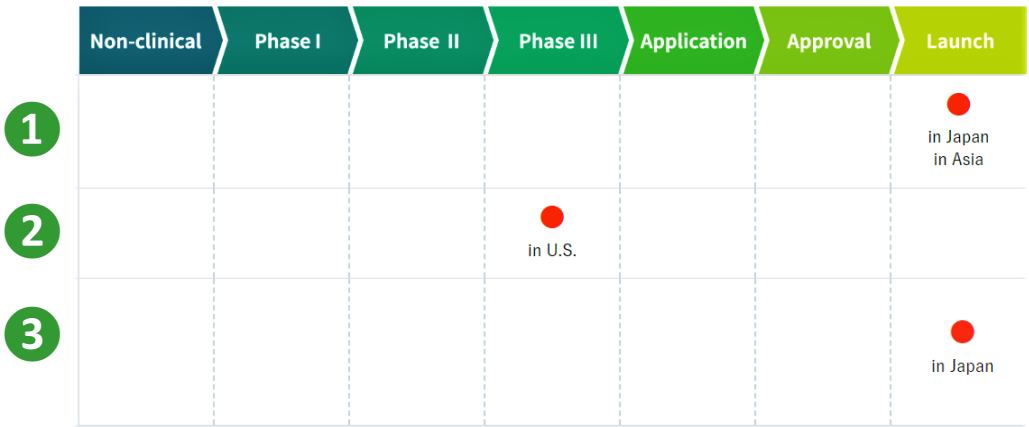
In 2002, DWTI out-licensed the rights to the drug to Kowa Co., Ltd., which then moved ahead with development and launched the drug in Japan under the brand name Ripasudil hydrochloride hydrate in December 2014. *Because all rights in Japan and worldwide relating to Ripasudil hydrochloride hydrate have been out-licensed to Kowa, the following two drugs are also being developed by Kowa. The company announced on February 25, 2022 that GLANATEC® has been launched by Kowa in Singapore.

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. We hope that our compound will become a new drug for treating FECD.

❸ Glaucoma and ocular hypertension [Fixed-dose combination eye drop (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 is on schedule to launch on December 6.

Development Stages of Ripasudil hydrochloride hydrate

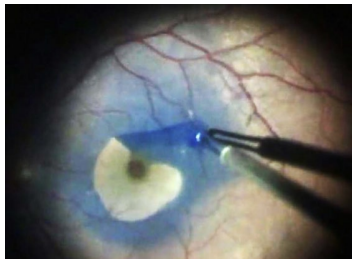


Source: DWTI website.

PIPELINE

Original and Licensed-in

ILM BLUE® (DW-1002) sold by DORC in Europe



Source: Journal of Ophthalmology

[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 we have since been developing the dye under exclusive license from Kyushu University.

We have 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.

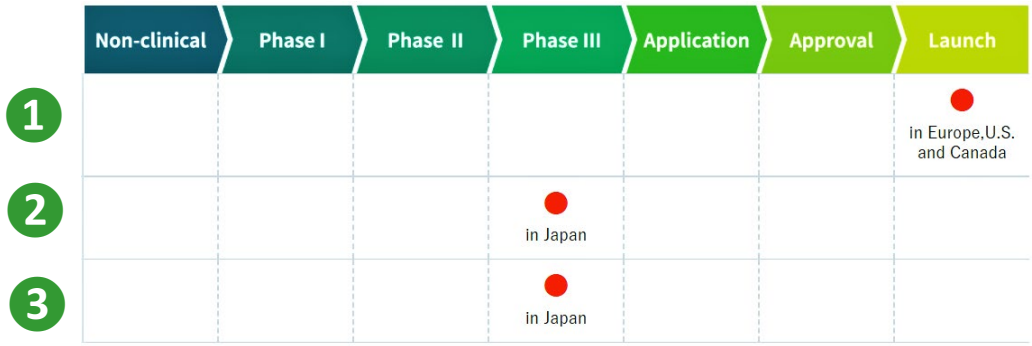
Wakamoto Pharmaceutical Co., Ltd. has been granted an exclusive sublicense for Japan, and is moving forward with development aiming to obtain approval. Wakamoto is expected to file applications for ❷ and ❸ in 2023, and receive approvals in 2024.

Clinical indications:
❶ ILM peeling (Europe, US and Canada)
❷ ILM staining (Japan)
❸ Cataract surgery (Japan)

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

*Newly added: DORC is filing an NDA in China in 2022 for indication ILM peeling, targeting approval in 2023 and sales launch in 2024.

Development Stages of DW-1002



Source: DWTI website.

PIPELINE

Original and Licensed-in

[H-1337]
US development schedule

- Phase IIb – 2022 to 2023
- Phase III – 2024 or later
- Secured necessary funding through previous and new financing

[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. We believe 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. DWTI is currently preparing for late-stage Phase IIb clinical trials to commence in 2022. In addition, in efforts to expand indications for the drug, DWTI confirmed its effects on pulmonary hypertension in animal studies, etc.

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

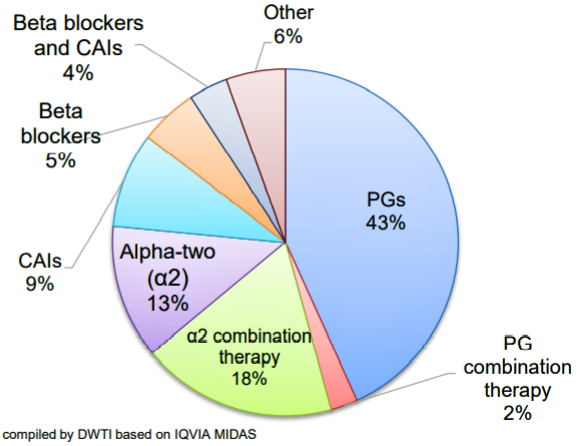
Similar to Ripasudil, H-1337 facilitates drainage of aqueous humor through the trabecular meshwork and Schlemm's canal, and it has demonstrated a "strong and long-lasting IOP pressure-lowering effect." The sole reliable evidence-based method of treatment for glaucoma (including normal-tension glaucoma) is the reduction of intraocular (IOP) pressure.

Prostaglandin analogues (PGs) demonstrate the strongest IOP pressure-lowering effect among first-line drugs; generic drugs are available and are most frequently used (see pie chart below). 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 treatment market

US market (FY2020: about $3bn)



Source: Classified and compiled by DWTI based on IQVIA MIDAS Dec 2020 MAT
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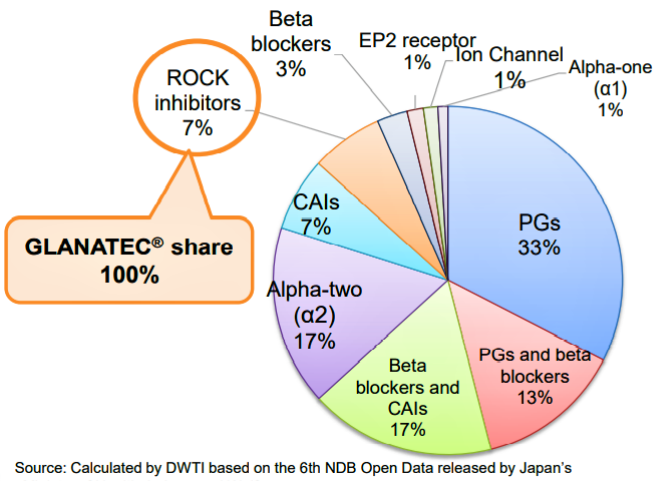
Japanese market (FY2019: about ¥94bn)



Source: Calculated by DWTI based on the 6th NDB Open Data released by Japan's Ministry of Health, Labour and Welfare

Source: excerpt from Q2 FY22/12 IR results briefing materials.

PIPELINE

Original and Licensed-in

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

Source: MEDRx website.

[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 is currently responding appropriately to specified issues. Following consultation with the FDA, DWTI plans to apply for approval again after conducting additional studies. The company expects to obtain approval in 2023.

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.

On October 4, an agreement was reached with the US FDA on the details of an additional study to be conducted on DW-5LBT. DWTI expects the additional study to be completed and file for approval in the first half of 2023, and to receive approval in the second half of 2023.

(4586 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.

PIPELINE

Original and Licensed-in

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:

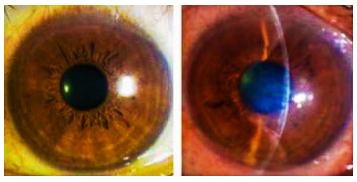
China-based ophthalmic biotech focusing on breakthrough therapies, with a leading portfolio covering pre-clinical stage to commercial stage products.

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), Fuchs' corneal endothelial dystrophy (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. In Europe and the US, the estimated number of patients with Fuchs' corneal endothelial dystrophy (FCED) has an incidence rate of approx. 4% in the Caucasian population over 40 years old.

Development Stage of DWR-2206

	Non-clinical	Phase I	Phase II	Phase III	Application	Approval	Launch
1	in Japan						

Source: DWTI website.

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

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

CHART ROOM

Share Price, Valuations

Performance and Valuations:
SESSA Smart Charts

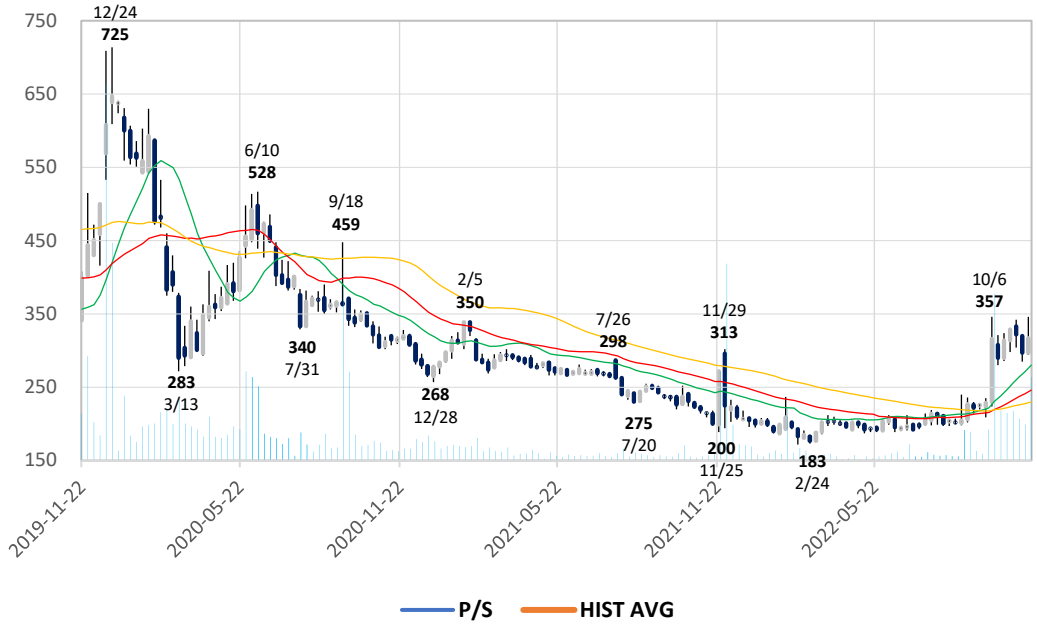
On 8/26, Kowa began Phase III trials in the US for K-321 for FECD, on 9/26, Kowa obtained approval in Japan for GLA-ALPHA® eye drops, to launch on 12/6, and on 10/4 an agreement was reached with the US FDA on details of the additional study for DW-5LBT, the study to be completed and file for approval in the 1H of 2023, and to receive approval in the 2H of 2023. **On 10/6, the share price closed limit up at 357 (+80, +28.9%).**

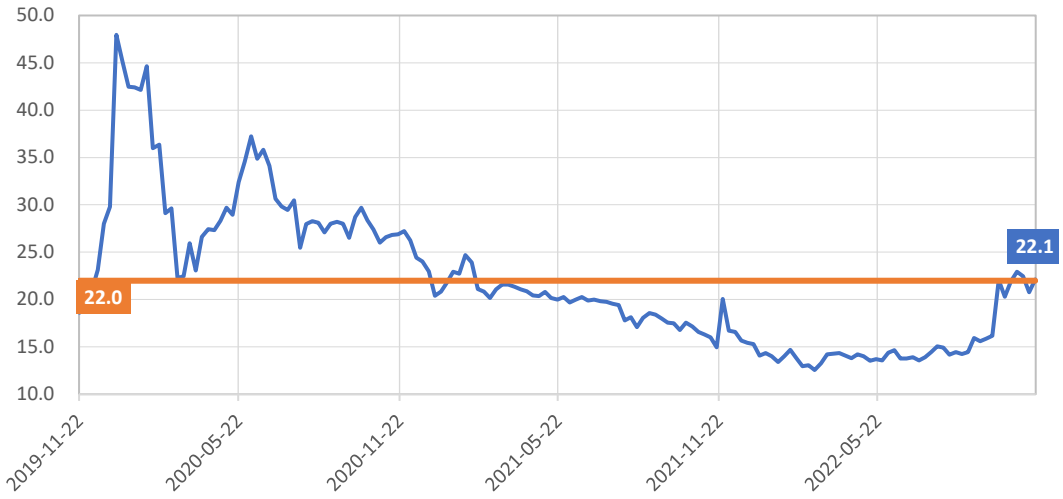
5-Year historical valuations

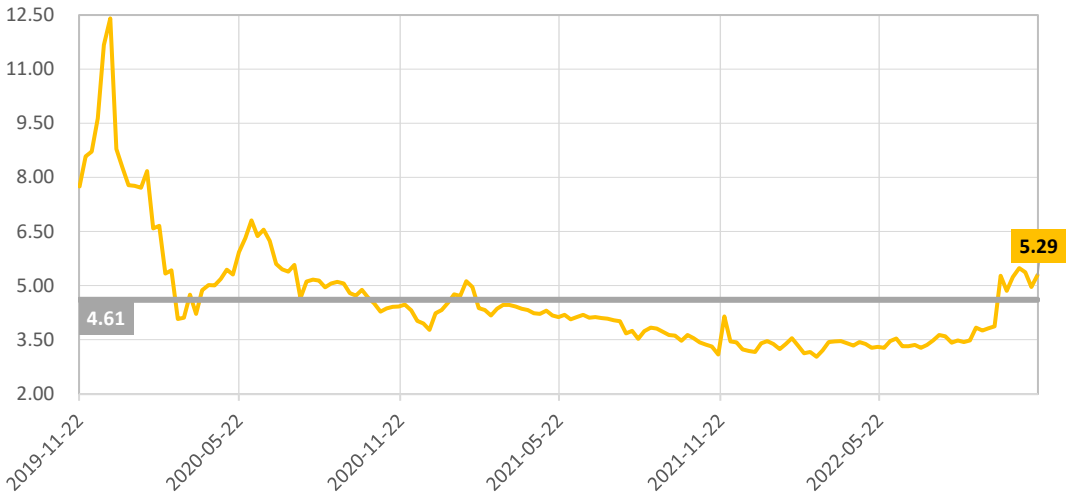
FY (times)	Price-to-sales DWTI	Price-to-sales AERI	Price-to-book DWTI	Price-to-book AERI
18.12	51.5	67.9	12.0	7.2
19.12	29.4	16.0	12.2	6.7
20.12	23.8	7.6	3.9	26.4
21.12	15.3	1.7	3.2	neg eq
current	22.1	5.5	5.3	neg eq

Source: SPEEDA.

Sessa Smart Charts: 3-Year Weekly Share Price and Valuations Trend







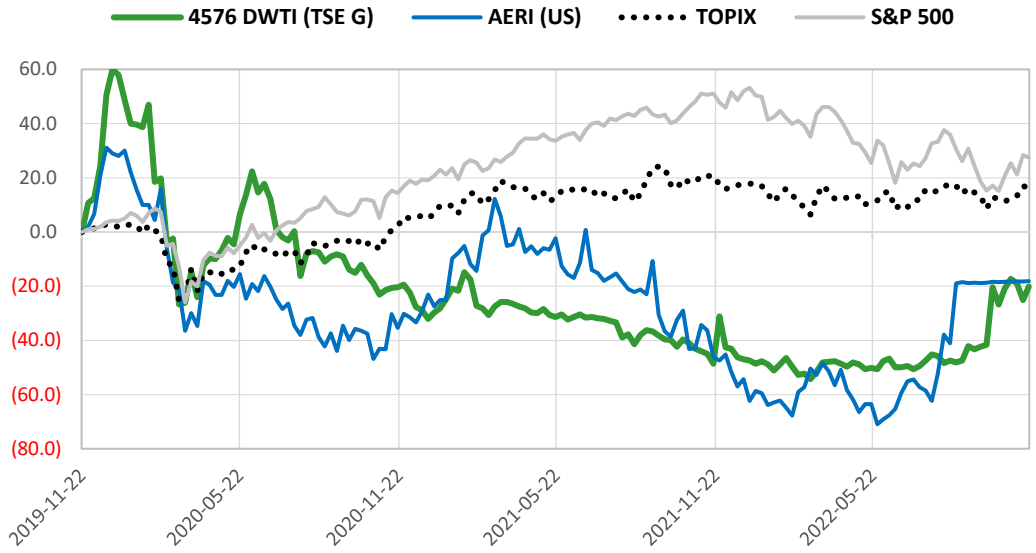
Source: compiled by Sessa Partners from SPEEDA historical earnings and price data. Valuations calculated based on CE.

Analyst's view

On August 22, DWTI's peer in the US, **Aerie Pharmaceuticals entered into a merger agreement with Alcon Research to be acquired by Alcon**, subject to approval, explaining the flat share price trend after the initial pop.

One market research firm estimates the **global ophthalmology drugs market to grow from $24.4bn in 2021 to $32.6bn in 2025 (+7.5% CAGR)**, driven by drugs to treat glaucoma diseases, anti-inflammatory and tear stimulating drugs for dry eye, and other drugs to treat retinal disorders, anti-infectives/allergy, etc. In 2020, North America accounted for 41%, followed by Asia-Pacific at 28%. **R&D is recovering from the impact of COVID-19 restrictions.**

3-Year Weekly Relative Performance (local currency basis)

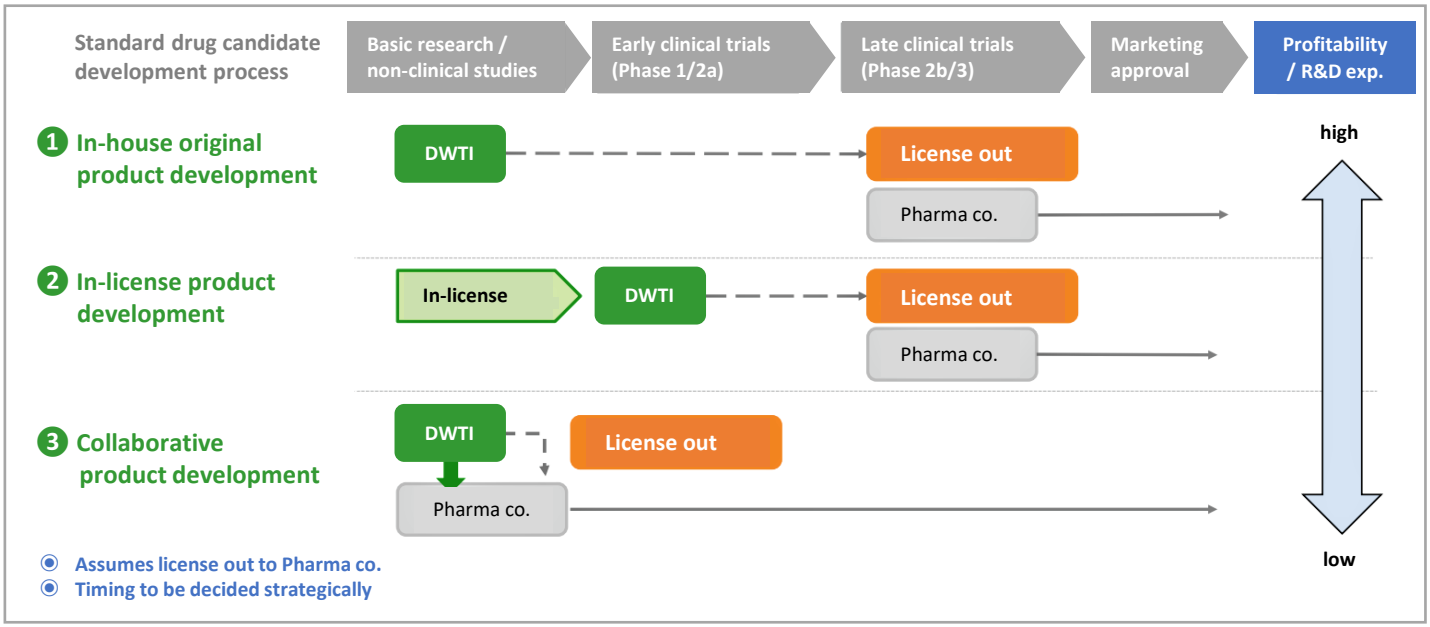


Source: compiled by SIR from SPEEDA price data. Note: not adjusted for foreign exchange rate effects.

Growth strategy has expanded business models along with enhancing the pipeline

Over time with progress in execution of the development pipeline, and as part of growth strategy to diversify revenue streams, the basic drug discovery business model 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 IIb. The revenue stream for collaborative research projects includes receipt of payment of R&D fees from the partner.

★DWTI's initial drug discovery basic business model has evolved into three business models



Source: company IR materials.

D. Western Therapeutics Institute Consolidated Financial Highlights

Selected Items from Consolidated Statements of Income

[J-GAAP] JPY mn, %	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 rev CE	FY12/21 MTP	FY12/22 MTP	FY12/23 MTP
Net sales	62	168	254	293	581	356	414	370	440	340	390 ~ 690	480 ~ 820
YoY	—	171.8	51.2	15.3	98.2	(38.7)	16.5	(10.7)	6.2			
by region												
• Japan	62	168	190	158	417	184	175					
• Europe	—	—	64	97	88	107	170					
• 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					
• WAKAMOTO PHARMACEUTICAL	0	50	50	—	209	—	—					
• Dutch Ophthalmic Research Center	—	—	64	97	88	107	170					
• Glaukos Corporation	—	—	—	38	63	59	70					
Major clients total	62	147	234	274	518	332	412					
Others	0	21	20	19	62	24	2					
Cost of sales	0	6	7	14	26	17	20					
Gross profit	62	162	247	279	555	339	394					
SG&A expenses	352	482	880	1,066	437	604	566					
• R&D expense	144	227	603	795	249	351	316	790		610	450	810
as % of net sales	*232.6%*	*135.1%*	*237.5%*	*271.5%*	*43.0%*	*98.6%*	*76.3%*	*213.5%*				
• Other	209	255	277	270	188	254	250					
Depreciation	3	18	45	52	44	44	45					
Goodwill amortization	13	—	—	—	—	—	—					
EBITDA	(274)	(302)	(589)	(735)	162	(222)	(126)					
Operating profit (loss)	(291)	(320)	(634)	(786)	117	(266)	(172)	(690)	(400)	(580)	(370) ~ (70)	(660) ~ (320)
Ordinary profit (loss)	(295)	(304)	(669)	(797)	110	(290)	(160)	(700)	(390)	(580)	(380) ~ (80)	(660) ~ (320)
Impairment losses	0	0	1,040	7	0	0	0	0				
Profit (loss) ATOP	(296)	(254)	(1,563)	(749)	133	(276)	(149)	(670)	(380)	(530)	(320) ~ (30)	(630) ~ (290)

Selected Items from Consolidated Balance Sheets and Consolidated Statements of CF

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

CF from operating activities	(323)	(334)	(797)	(540)	176	(216)	(176)
CF from investing activities	835	(231)	(763)	(8)	(100)	(13)	(111)
CF from financing activities	98	1,067	1,407	—	(120)	1,004	(104)
Cash and CE at beginning of period	1,167	1,767	2,292	2,133	1,584	1,541	2,308
Cash and CE at end of period	1,767	2,292	2,133	1,584	1,541	2,308	1,934

Book value per share (BPS)	83.49	109.96	76.14	47.95	53.02	73.88	68.27

Source: compiled by Sessa Partners from company TANSHIN financial statements and company IR materials and 11/18 revision press release.

DWTI Group Head Office and R&D Labs

Source: compiled by Sessa Partners from company IR materials.

President and CEO
Yuichi Hidaka

DWTI Corporate Profile

	Details
Company Name	D. Western Therapeutics Institute, Inc.
Business Field	Discovery and development of new drugs
Established	February 26, 1999
Share Capital	573 million yen (as of December 31, 2021)
Head Office	1-18-11, Nishiki, Naka-ku, Nagoya-shi, Aichi 460-0003, Japan
Main Switchboard	052-218-8785
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 shi, Mie, Japan 514-8507
Employees	DWTI: 16, JIT: 3 (as of December 31, 2021), total 32 including executive officers
Group Subsidiary	Japan Innovative Therapeutics, Inc. (consolidated subsidiary)

Source: company website.

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