

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

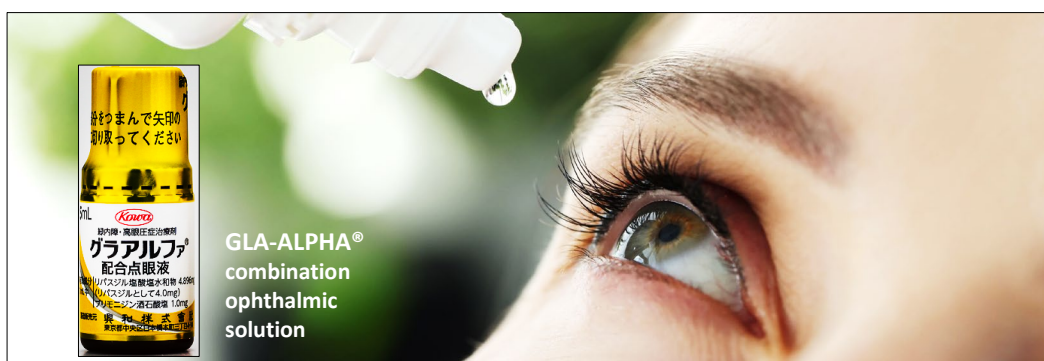
✳ According to “Ophthalmology Drugs Global Market Report 2021: COVID 19 Impact and Recovery to 2030” issued by the Business Research Company in Feb-2021, the global ophthalmology drugs market is expected to grow from \$22.03 billion in 2020 to \$32.64 billion in 2025 (+8.2% CAGR). M&A in this segment has become active in recent years, with global eye care leader Alcon (SIX/NYSE:ALC) acquiring DWTI’s closest rival in the US, Aerie Pharmaceuticals, Inc. in Nov-2022, adding Rhopressa® (similar to DWTI’s GLANATEC®) among others, and Aerie’s development pipeline.

✳ Over time with progress in execution of the development pipeline, and as part of growth strategy to diversify revenue streams, DWTI’s 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 2024 launch of DW-5LBT in the US.

✳ 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.

Multiple drug combinations are becoming standard treatment for Glaucoma



GLA-ALPHA®
combination
ophthalmic
solution

World’s first fixed combination eye drops containing the active ingredients GLANATEC® ophthalmic solution 0.4% (rho-kinase inhibitor ripasudil hydrochloride hydrate) and an Alpha-2 adrenergic receptor agonist (brimonidine tartrate). Launched in Japan on December 6, 2022 by Nagoya-based our-licensor partner Kowa Company, Ltd.

1Q Follow-up



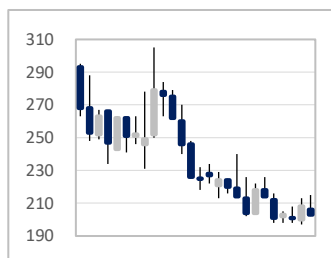
Focus Points:

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 (5/30)	203
YH (23/1/25)	305
YL (23/5/15)	197
10YH (14/8/19)	3,550
10YL (22/2/24)	183
Shrs out. (mn shrs)	31.692
Mkt cap (¥ bn)	6.433
Equity ratio (Mar 31)	66.1%
23.12 P/S (CE)	16.1x
23.03 P/B (act)	3.41x

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.

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)
<i>by region</i>										
• 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	—		—	
<i>by major client (10%+ of net sales)</i>										
• 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

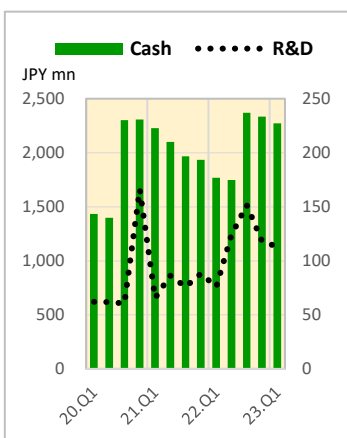
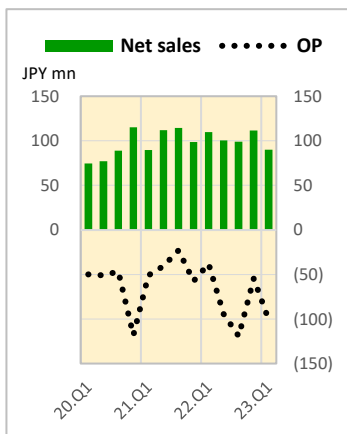
• Cash and deposits	1,747	2,292	2,133	1,584	1,541	2,308	1,934		2,335	
• Accounts receivable - trade	23	41	61	71	104	92	102		171	
Total current assets	2,025	2,776	2,516	1,764	1,716	2,503	2,162		2,659	
Contract-related intangible assets	—	—	329	288	247	206	165		123	
Total non-current assets	115	136	362	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.



EARNINGS



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

DWTI



US FDA confirmed acceptance of NDA resubmission for DW-5LBT post-herpetic neuralgia treatment

1Q RESULTS SUMMARY

✳ DWTI announced 1Q FY23/12 consolidated financial results at 15:30 on Friday 5/12. Net sales declined -18.0% YoY to ¥90mn, comprised of royalty income from GLANATEC® ophthalmic solution 0.4%, GLA-ALPHA® combination ophthalmic solution (both sold by Kowa) and DW-1002 (TissueBlue™ ophthalmic surgical aid sold by D.O.R.C.). The breakdown from the Quarterly Securities Report (YUHO) by geographic segment (HQ of the out-license partner) is Japan ¥62mn → ¥29mn (-53%) and the Netherlands ¥48mn → ¥61mn (+27%). Last year DWTI received a milestone payment from ROHTO which initiated a Phase I trial in Japan for DW-1001, while the contractual royalty fee rate for GLANATEC® declined from late 2022. DW-1002 sales continue to expand globally.

✳ On October 4, 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 results of the additional study were favorable, and that it plans to resubmit the application for approval in the 1H of 2023, and to receive approval in the 2H of 2023 after a 6-month review period. DWTI announced May 12 that the US FDA confirmed acceptance of the resubmission of the NDA filed March 29.

✳ 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 1Q FY23/12 Consolidated Financial Results Summary

JPY mn, %	FY19/12	FY20/12	FY21/12	FY22/12	FY23/12	FY22/12	FY23/12
[J-GAAP]	act	act	act	act	init CE	1Q act	1Q act
Net sales	581	356	414	448	400	110	90
YoY	98.2	(38.7)	16.5	8.1	(10.7)	22.3	(18.0)
Cost of sales	26	17	20	28	—	7	7
Gross profit	555	339	394	421	—	103	83
SG&A expenses	437	604	566	726	—	141	184
• R&D expense	249	351	316	470	1,500	76	113
as % of net sales	43.0%	98.6%	76.3%	104.8%	375.0%	69.2%	125.8%
• Other	188	254	250	257	—	65	71
Operating profit (loss)	117	(266)	(172)	(306)	(1,400)	(38)	(101)
Ordinary profit (loss)	110	(290)	(160)	(296)	(1,410)	(26)	(101)
Profit (loss) ATOP	133	(276)	(149)	(430)	(1,390)	(22)	(98)
Selected B/S items	FY12/19	FY12/20	FY12/21	FY22/12	FY22/12 23/12 1Q		
• Cash and deposits	1,541	2,308	1,934	2,335	→	2,335	2,274
Total assets	1,981	2,738	2,463	2,956	→	2,956	2,852
Total liabilities	573	574	428	1,083	→	1,083	953
Total net assets	1,408	2,164	2,035	1,873	→	1,873	1,899
Equity ratio	70.3%	78.9%	81.4%	62.8%	→	62.8%	66.1%

Source: compiled by SIR from TANSHIN financial statements

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 P2, 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)

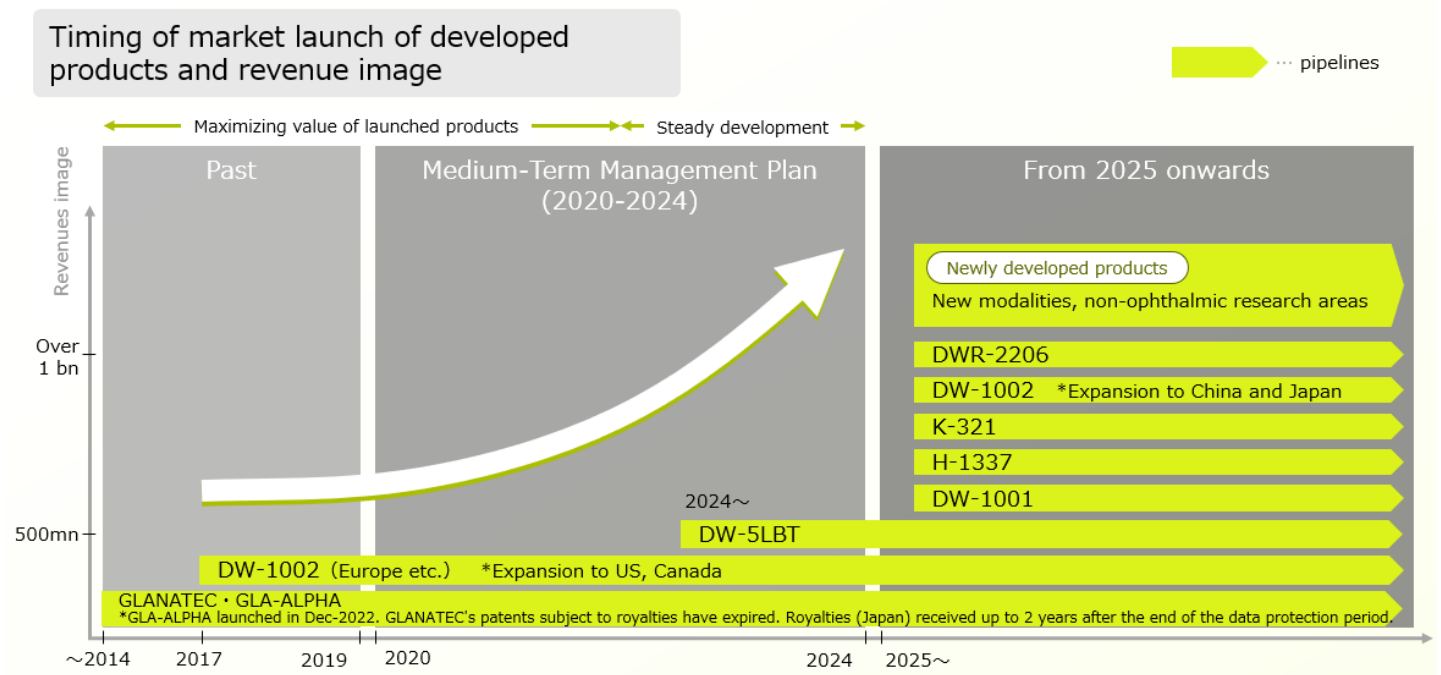
Development Pipeline Plan

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

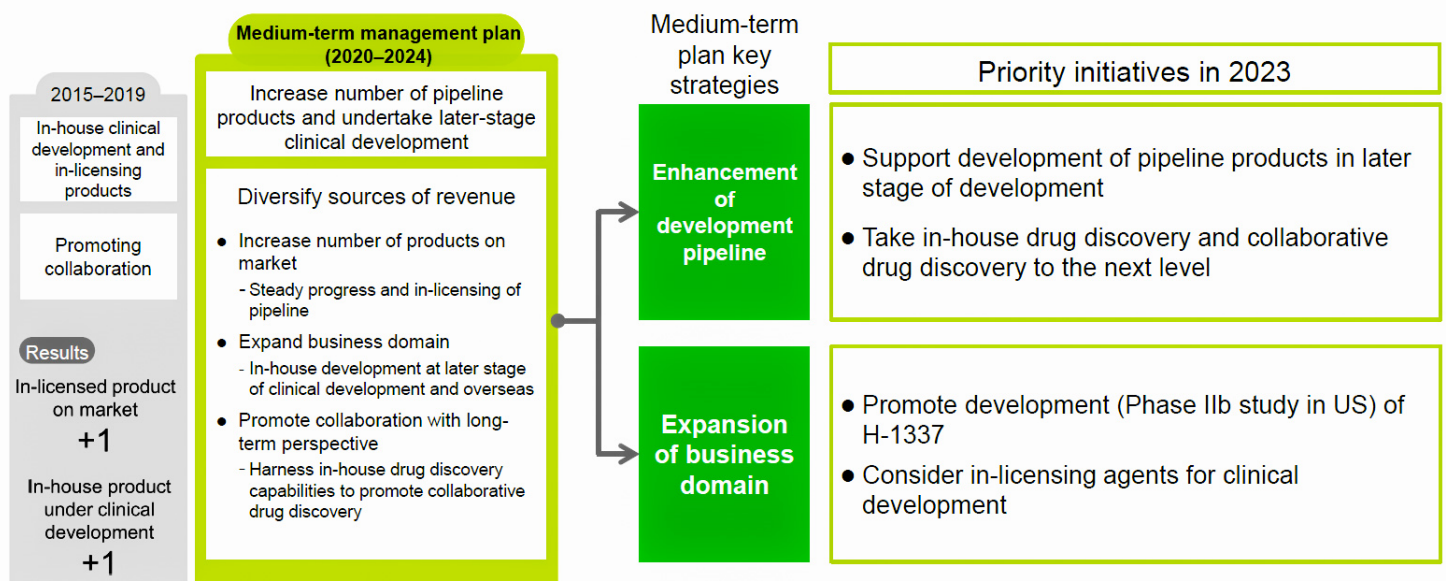


Source: excerpt from "Business Plan and Growth Potential" annual IR presentation.

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.

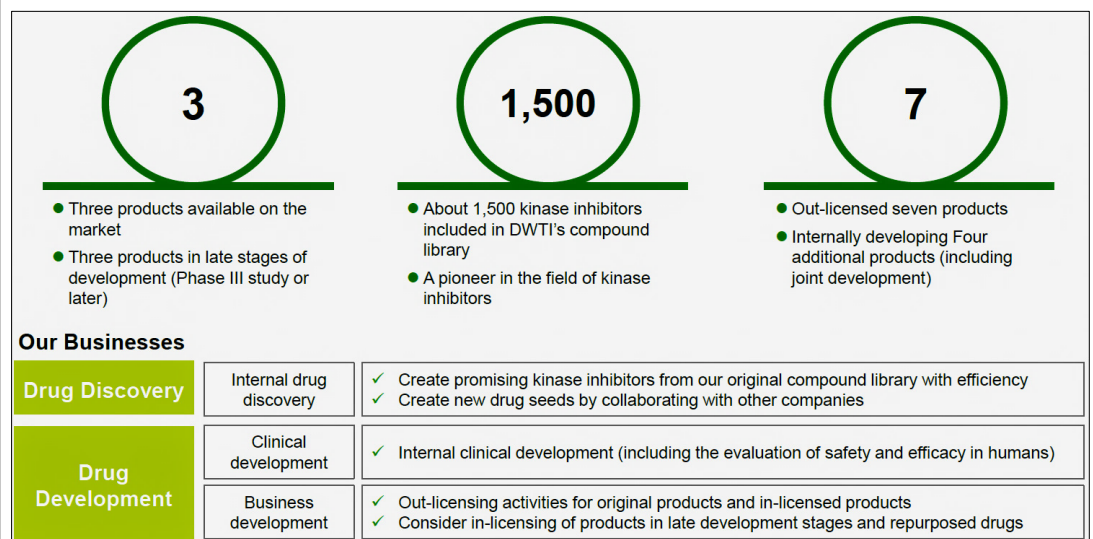
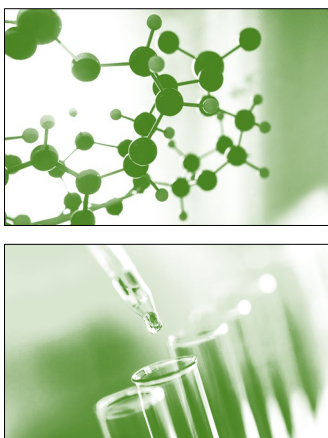


PIPELINE

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 and is a useful framework for **out-licensed products** versus **internal clinical development**.



Development Pipeline

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*	[Progress bar]							Kowa
	K-321	Fuchs endothelial corneal dystrophy	US	[Progress bar]							
Ripasudil hydrochloride hydrate/ Brimonidine tartrate	GLA-ALPHA® (K-232)	Glaucoma and ocular hypertension	Japan	[Progress bar]							DORC
DW-1002	ILM staining	Europe, US, Canada	[Progress bar]								
	ILM staining	Japan	[Progress bar]								
	ALC staining	Japan	[Progress bar]								
DW-1001	Ophthalmic treatment agent (undisclosed)	Japan	[Progress bar]							ROHTO Pharmaceutical	
H-1337	Glaucoma and ocular hypertension	US	[Progress bar]							Developed internally	
DW-5LBT	Neuropathic pain after shingles	US	[Progress bar]							Jointly developed with MEDRx (MRX-5LBT)	
DWR-2206	Bullous keratopathy	Japan	[Progress bar]							Joint development with ActualEyes (AE101)	
Treatment for retinopathy of prematurity	Retinopathy of prematurity	Japan	[Progress bar]							Developed by subsidiary JIT	

*Thailand, Singapore, and Malaysia

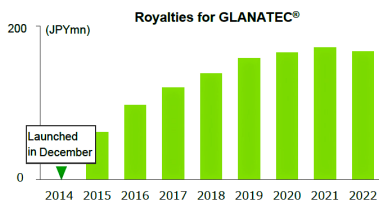
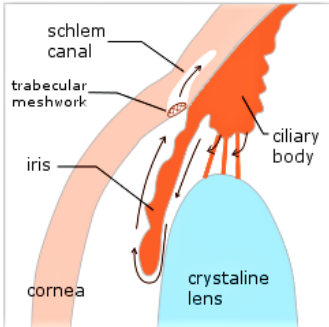
[Green box] ··· ophthalmology pipeline

1 Out-licensed products (4)

2 Internal clinical development (4)

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

① 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).

② 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.**

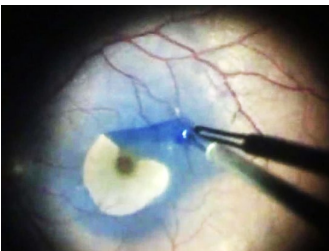
③ Glaucoma and ocular hypertension [GLA-ALPHA® combination ophthalmic solution (Ripasudil hydrochloride hydrate and Brimonidine tartrate) K-232]

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.**

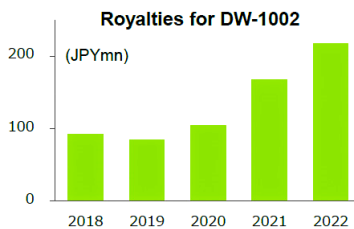
Development Stages of Ripasudil hydrochloride hydrate

	Non-clinical	Phase I	Phase II	Phase III	Application	Approval	Launch
①							● in Japan ● in Asia
②				● in U.S.			
③							● in Japan

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 has 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 ② and ③ in 2023, receive approvals in 2024 and launch in 2025.**

Clinical indications:

- ① ILM staining (Europe, US and Canada)
- ② ILM (internal limiting membrane) staining (Japan)
- ③ ALC (anterior lens capsule) staining (Japan)

Development stages:

- ① Launched (Europe, US and Canada)
- ② Phase III clinical trials (Japan) completed
- ③ 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

	Non-clinical	Phase I	Phase II	Phase III	Application	Approval	Launch
①							● in Europe, U.S. and Canada
②				● in Japan			
③				● in Japan			

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.

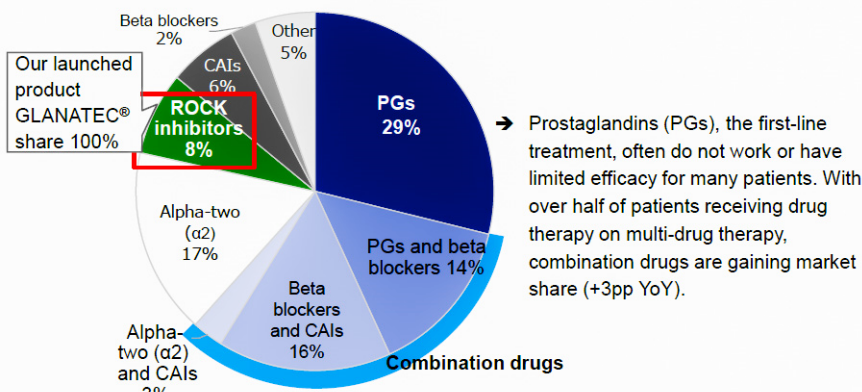
DWTI estimates the target market for 1) patients who do not respond to first-line drugs and 2) patients who receive multiple drugs and suffer side effects is up to a maximum 40% of the estimated US market of \$3 billion.

Glaucoma Market

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

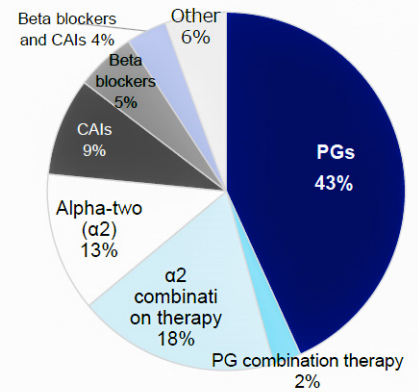
- The U.S. market is the largest, accounting for about USD 3bn, nearly half.*
- The prevalence of glaucoma is increasing due to the increase in the elderly population, and the number of patients is expected to increase in the future.
- Wider treatment options are now available, including surgical procedures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

Japanese market (FY2020: about ¥89bn)



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.



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.



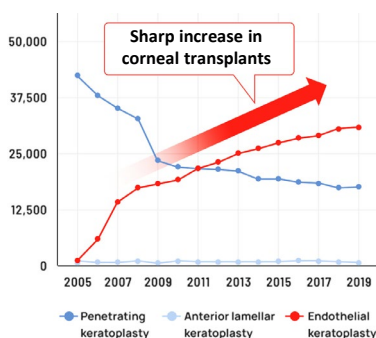
Description:

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

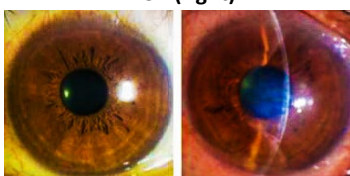


Description:

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.

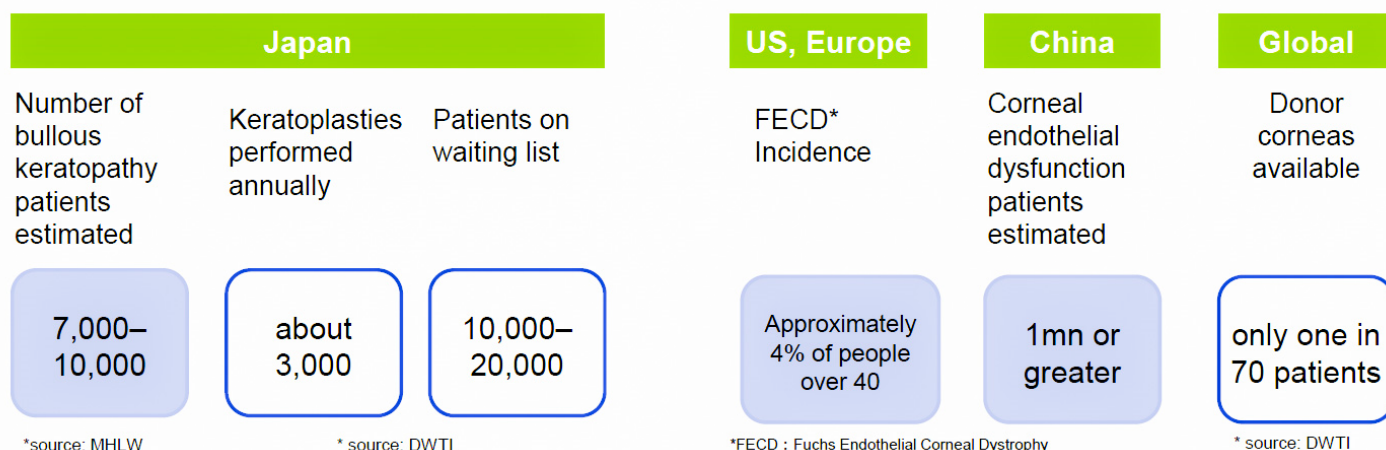
Cell-Therapy Product DWR-2206 for Treatment of Corneal Endothelial Dysfunction



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.



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.

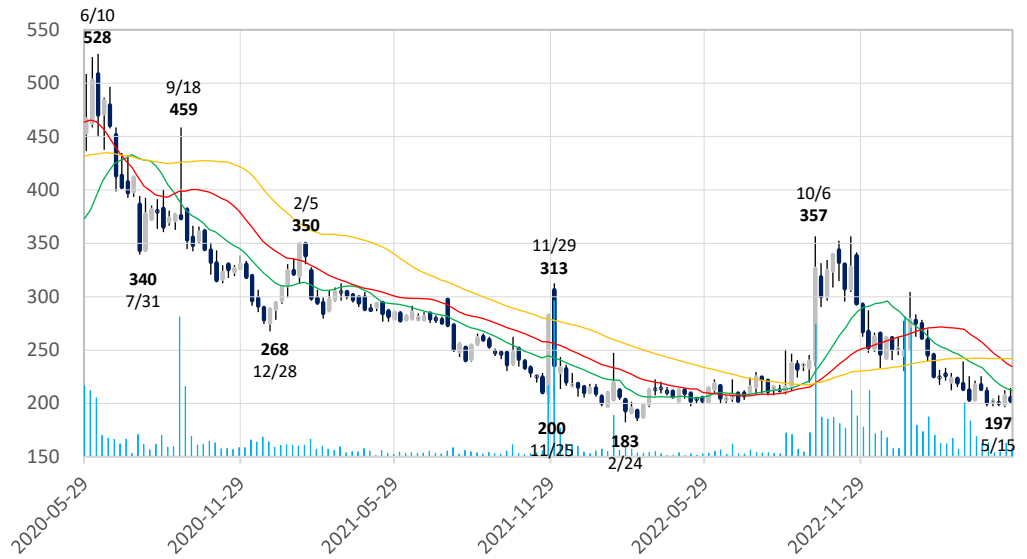
Source: excerpts from FY2022/12 4Q IR results briefing materials.



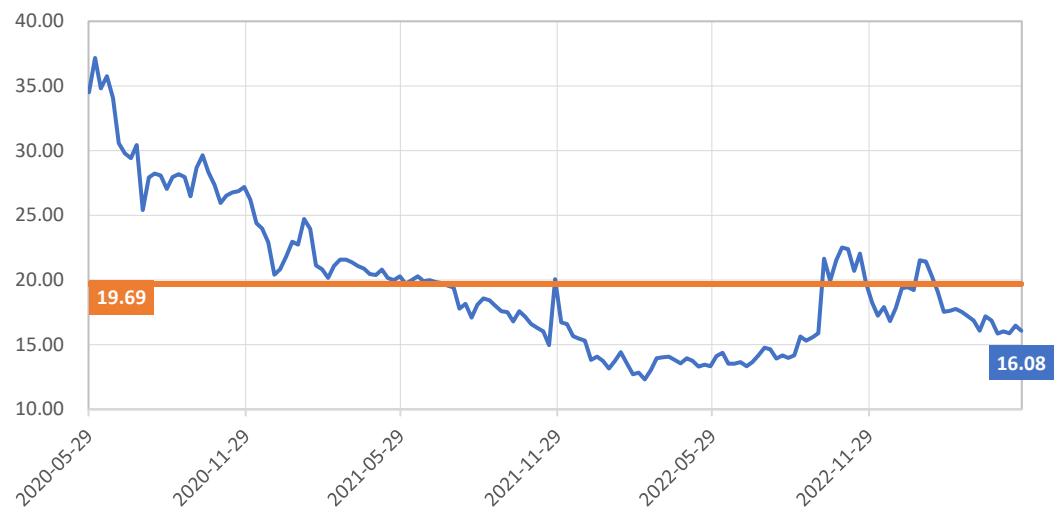
SHARE PRICE



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



P/S HIST AVG



P/B HIST AVG



Performance and Valuations:
SESSA Smart Charts

- ✓ The price-to-sales ratio is currently trading 18.3% below its historical average, and the price-to-book ratio is trading 15.1% below its historical average, likely reflecting the reality of 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.

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

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