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RaQualia Pharma

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Executive summary

Business overview

RaQualia Pharma Inc. is an R&D-focused drug discovery company. It primarily uses exploratory research into small molecule compounds to discover the “seeds” of new drugs and out-licenses development and marketing rights to pharmaceutical companies and others. The company covers the drug discovery stage from exploratory research through early clinical development (Phase II clinical trials). It develops new drugs targeting various fields, including pain, gastrointestinal disorders, cancer, and immunological disorders. The company receives operating revenue from companies that in-license its products in the form of upfront payments, milestone payments, post-launch royalties, and joint development cooperation payments. Licensees have already launched four products, providing the company with stable long-term royalty revenue, its main source of earnings. In FY12/22, operating revenue was JPY2.9bn, comprising royalty revenue (over 50%) and upfront and milestone payments (over 40%).

The company started as an independent entity when US-based Pfizer Inc. (NYSE: PFE) decided to close its central research laboratory in Japan as part of a global research restructuring in 2007. The research lab spun off from Pfizer through an employee buyout, and RaQualia was established in July 2008, after Pfizer transferred its intellectual property rights covering a number of projects in the exploratory or development stages in June 2008. When RaQualia out-licenses rights for some compounds transferred from Pfizer, it pays royalties to Pfizer and records them under operating expenses.

RaQualia has four products already commercialized by licensees (tegoprazan [launched as K-CAB® in South Korea], GALLIPRANT®, ENTyce®, and ELURA®), ten pipelines already out-licensed, and six at the pre-out-licensing stage. Human drug tegoprazan is a potassium-competitive acid blocker (P-CAB)^{*2}, with the main indication of gastroesophageal reflux disease (GERD)^{**}. In September 2010, the company reached an out-licensing agreement for marketing in South Korea, China (including Hong Kong), and Taiwan with South Korea's CJ CheilJedang Corporation (currently HK inno.N Corporation [KOSDAQ]). Since 2019, it has gradually expanded the territories covered and has granted global rights to HK inno.N (excluding Japan). HK inno.N has launched tegoprazan under the brand name K-CAB® in South Korea and aims to roll out the drug to 100 countries around the world by 2028. In 2022, a sublicensee of HK inno.N launched tegoprazan in China, the Philippines, and Mongolia. The drug has also been approved for sale in Indonesia, Mexico, and Singapore. Licensees have applied or are preparing to file for approval in another 26 countries.

* P-CAB: Potassium-competitive acid blockers act differently than the proton pump inhibitors (PPIs) used in existing therapies. While PPIs inhibit gastric acid secretion after being activated by acid in the body, P-CABs do not require acid activation. Instead they inhibit the binding of potassium ions necessary for gastric acid secretion, with a rapid and beneficial impact.

^{*2} Gastroesophageal reflux disease (GERD): A disease whereby stomach contents, in particular stomach acid, flow back into the esophagus (food pipe), causing characteristic symptoms such as heartburn. Non-erosive reflux disease (NERD) is a condition in which damage to the esophageal mucosa cannot be confirmed by endoscopy, despite symptoms such as heartburn and acid reflux caused by reflux of stomach acid and stomach contents.

GALLIPRANT®, ENTyce®, and ELURA® are drugs for pets. In December 2010, the company out-licensed worldwide rights to the three drugs to US-based Elanco Animal Health, Inc. (NYSE: ELAN) a former subsidiary of US-based Eli Lilly and Co. (NYSE: LLY). GALLIPRANT® revenue reached USD100mn (roughly JPY12.5bn) in FY12/21, becoming Elanco's tenth blockbuster drug.

RaQualia plans to conduct in-house development of two programs, tegoprazan (in Japan) and a ghrelin receptor agonist, to increase the probability of successfully commercializing new drugs and add value. It retains Japanese rights to tegoprazan after out-licensing it to HK inno.N in all territories excluding Japan by FY12/21. Initially, the company planned to complete clinical pharmacological studies (equivalent to Phase I), in FY12/23, hoping to out-license tegoprazan in FY12/24. However, in order to launch the drug at the earliest possible date, the company decided to out-license the drug in FY12/23 without conducting clinical pharmacological studies. The company is also developing a ghrelin receptor agonist for the main indications of anorexia/cachexia syndrome associated with cancer and constipation associated with spinal cord injury. It plans to complete preclinical studies by end-2023.

The company adopted a new management structure in March 2021 and expanded its disease coverage from pain and gastrointestinal diseases to include neurological diseases. As of FY12/22, it plans to focus on areas with significant unmet medical needs* including neurodegenerative, genetic, and rare diseases, with the aim of consistently discovering new

drugs. The previous management team focused on out-licensing drug candidates at the preclinical preparation stage. However, out-licensing at an early development stage, when the probability of commercialization is relatively low, not only makes it difficult to find a licensing partner, but also results in lower upfront payments, milestone payments, and royalties. The company therefore changed its policy to out-licensing after developing drug candidates in-house until it can demonstrate proof of concept (POC)*².

* Unmet medical needs: Medical needs involving diseases for which effective remedies are not yet available. This includes serious illnesses such as cancer, dementia, and multiple sclerosis as well as those that are not life-threatening but require innovative drugs to improve quality of life, such as insomnia and migraines.

*² Proof of concept (POC): The hypothesis (concept) that a new drug candidate substance under development can be a potential therapeutic agent for a disease (in terms of its usefulness and efficacy) is tested and validated through administration to humans. In the drug discovery process, Phase II of a three-stage clinical trial is used to demonstrate whether or not the candidate substance demonstrates a therapeutic effect during administration to a small number of patients, as measured using appropriate benchmarks.

The company has successfully out-licensed five drug discovery research programs targeting ion channels. Ion channels are membrane proteins that allow ions to pass into and out of cells. They are expressed in a variety of cells, and the type of ions that can pass through depend on the type of channels. Ion channels are vital to maintaining cell functions, and are deeply involved in a variety of physiological phenomena. Controlling the ion channels could help treat a wide range of diseases, but they are widely expressed in vital organs such as the heart and brain, and there is a tendency for life-threatening side effects such as cardiotoxicity and neurotoxicity. Few companies have entered the market due to the difficulty of drug discovery targeting ion channels, and such drugs account for just 5% of all drugs. RaQualia says it is the only company in the world to have out-licensed five drugs in the area.

Earnings trends

In FY12/22, operating revenue was JPY2.9bn (+5.1% YoY), operating profit JPY866mn (+22.4% YoY), recurring profit JPY904mn (+4.7% YoY), and net income attributable to owners of the parent JPY723mn (-4.3% YoY). Expanding global earnings of GERD treatment tegoprazan (out-licensed to HK inno.N and sold under the brand name K-CAB®) drove results, and sales of pet drugs by Elanco (GALLIPRANT®, ENTyce®, and ELURA®) were solid. In addition to rising royalty revenue from the above four commercialized drugs, the company received a milestone payment accompanying the launch of a Phase II clinical trial on a P2X7 receptor antagonist and upfront payment from a new pet drug license agreement, aided by yen weakness, booking its second consecutive operating profit.

The company forecast for FY12/23 calls for operating revenue of JPY2.8bn (-4.1% YoY), operating profit of JPY260mn (-70.0% YoY), recurring profit of JPY242mn (-73.2% YoY), and net income attributable to owners of the parent of JPY183mn (-74.7% YoY). It expects to receive steady royalty revenue from the four commercialized drugs mentioned previously, upfront payments from new licensing agreements, and milestone revenue based on development progress. The company expects profit to decline on a 23.7% YoY increase in operating expenditures due to changes in its development schedule. The company's exchange rate assumption is JPY125.00/USD. The company maintained its full-year forecast at the time of announcing Q1 results.

Along with the announcement of its full-year FY12/22 earnings results, the company also unveiled a three-year medium-term business plan covering FY12/23 to FY12/25. The plan targets FY12/25 operating revenue of JPY4.2bn (three-year CAGR of 12.8%), operating profit of JPY1.3bn (15.2%), recurring profit of JPY1.3bn (13.7%), and net income attributable to owners of the parent JPY1.2bn (17.2%). The company forecasts increased capex and development spending with a view to longer term growth, but expects operating profit in three consecutive years due to steady operating revenue. It assumes a forex rate of JPY125.00/USD.

Strengths and weaknesses

Shared Research thinks the company has the following three strengths.

- 1) Focus on ion channel drug discovery based on research processes and operating procedures on par with pharmaceutical companies
- 2) Several hundred patents held

3) Ability to efficiently identify candidate compounds from its massive compound library using SCARA robotic system

We think it has the following three weaknesses.

1) Drug discovery modality* (methodology) relies on small molecule compounds

* Drug discovery modality refers to the method of drug discovery, i.e., what kind of drug to make from what sources and by what method. Traditionally, most drugs have been small molecule drugs synthesized from chemical substances with molecular weights of under 500 Daltons. Currently there is a range of modalities including proteins (hormones, biological materials), antibody drugs, nucleic acid drugs, middle molecule drugs, and regenerative medicine.

2) Lack of control over amount or timing of revenue, because milestone and royalty payments depend on development progress and earnings at licensees

3) Difficulty in recruiting and training researchers due to high degree of specialization

Key financial data

Income statement (JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Est.
Operating revenue	228	154	146	705	1,419	745	1,703	1,107	2,776	2,918	2,799
YoY	687.0%	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.7%	-35.0%	150.7%	5.1%	-4.1%
Operating expenses	2,366	2,276	2,010	1,465	1,570	1,820	1,719	1,593	2,068	2,052	
YoY	-11.2%	-3.8%	-11.7%	-27.1%	7.1%	15.9%	-5.5%	-7.3%	29.8%	-0.8%	
Operating profit	-2,138	-2,123	-1,865	-760	-150	-1,075	-16	-486	708	866	260
YoY	-	-	-	-	-	-	-	-	-	22.4%	-70.0%
Operating profit margin	-	-	-	-	-	-	-	-	25.5%	29.7%	9.3%
Recurring profit	-1,820	-1,942	-1,795	-721	-81	-1,065	22	-528	864	904	242
YoY	-	-	-	-	-	-	-	-	-	4.7%	-73.2%
Recurring profit margin	-	-	-	-	-	-	1.3%	-	31.1%	31.0%	8.6%
Net income	-1,108	-465	-1,854	-728	-58	-1,105	5	-607	756	723	183
YoY	-	-	-	-	-	-	-	-	-	-4.3%	-74.7%
Net margin	-	-	-	-	-	-	0.3%	-	27.2%	24.8%	6.5%
Per-share data (split-adjusted; JPY)											
Shares issued (year-end; '000)	13,557	14,857	18,767	18,767	20,295	20,388	20,950	20,952	20,955	20,977	
EPS (JPY)	-82.7	-45.7	-116.5	-38.8	-3.0	-54.2	0.3	-29.0	36.1	34.5	8.7
EPS (fully diluted; JPY)	-	-	-	-	-	-	0.3	-	36.0	34.5	
Dividend per share (JPY)	-	-	-	-	-	-	-	-	-	-	-
Book value per share (JPY)	424	315	240	201	240	189	220	191	228	262	
Balance sheet (JPYmn)											
Cash and cash equivalents	4,035	1,891	1,840	1,428	2,268	1,671	2,174	1,394	2,345	3,675	
Total current assets	4,364	3,261	2,708	1,806	3,322	1,962	3,067	2,834	4,004	4,822	
Tangible fixed assets	7	85	261	249	216	318	249	333	299	391	
Investments and other assets	2,266	1,844	1,769	1,951	1,516	1,738	1,488	1,051	897	1,020	
Intangible assets	12	12	14	13	10	34	32	33	34	24	
Total assets	6,648	5,202	4,752	4,019	5,064	4,052	4,837	4,251	5,234	6,258	
Short-term debt	-	-	-	-	-	1	1	18	22	46	
Total current liabilities	233	262	200	190	149	164	183	187	401	494	
Long-term debt	-	-	-	-	-	2	2	27	18	177	
Total fixed liabilities	669	109	38	41	27	31	33	53	46	267	
Total liabilities	902	371	238	231	176	195	216	240	446	761	
Shareholders' equity	5,713	4,821	4,503	3,773	4,871	3,845	4,608	3,999	4,777	5,489	
Total net assets	5,746	4,831	4,514	3,788	4,888	3,857	4,621	4,011	4,788	5,497	
Total interest-bearing debt	-	-	-	-	-	3	2	46	39	222	
Cash flow statement (JPYmn)											
Cash flows from operating activities	-2,179	-2,081	-2,117	-681	-307	-404	-531	-289	366	1,480	
Cash flows from investing activities	952	-796	666	-441	534	-368	216	225	-279	-48	
Cash flows from financing activities	309	762	1,702	-	1,007	99	696	-7	-16	-30	
Financial ratios											
ROA (RP-based)	-30.0%	-32.8%	-36.1%	-16.4%	-1.8%	-23.4%	0.5%	-11.6%	18.2%	15.7%	
ROE	-20.1%	-8.8%	-39.8%	-17.6%	-1.3%	-25.3%	0.1%	-14.1%	17.2%	14.1%	
Equity ratio	85.9%	92.7%	94.8%	93.9%	96.2%	94.9%	95.3%	94.1%	91.3%	87.7%	

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Note: Operating expenses include cost of operating revenue, R&D expenses, and other SG&A expenses.

Recent updates

Termination of the joint research agreement with ASKA Pharmaceutical regarding drug discovery targeting a specific ion channel

2023-06-09

RaQualia Pharma Inc. announced the termination of its joint research agreement with ASKA Pharmaceutical Co., Ltd. regarding drug discovery targeting a specific ion channel.

The two companies started working together in July 2019 to develop a new drug targeting a specific ion channel. However, they recently decided to terminate their agreement after discussing the possibility of further joint research using the results obtained so far. RaQualia will take ownership of the results of their joint research. In the future, RaQualia plans to continue the R&D activities for this project independently.

According to RaQualia, this termination will have no impact on the consolidated financial results for FY12/23.

Ion channels are membrane proteins that allow ions to pass through cell membranes. They are expressed in a number of cells, and each has a specific ion that can pass through it. As ion channels are deeply involved in various physiological phenomena such as nerve signal transmission, muscle contraction and hormone secretion, there is potential to treat a wide range of diseases by controlling ion channels.

Collaboration with leadXpro AG for drug discovery project targeting membrane proteins

2023-04-25

RaQualia Pharma Inc. announced a collaboration with leadXpro AG for a drug discovery project targeting membrane proteins.

The company announced that it has partnered with leadXpro AG (unlisted), a Swiss company with expertise in membrane protein biochemistry, to accelerate drug discovery research targeting membrane proteins, a challenging area for drug development. RaQualia has a strong track record in ion channel drug discovery targeting membrane proteins and aims to accelerate drug discovery projects in this area through collaboration with leadXpro.

leadXpro is a biotech company specializing in membrane protein structure-based drug discovery with expertise in structural biology, ligand design^{*1}, and biophysical characterization of membrane proteins. By using structural biology techniques such as cryogenic electron microscopy^{*2} to observe how ligands bind to proteins at the atomic level, the company believes it is possible to logically design drug candidates and accelerate drug discovery research.

*1 A ligand is a substance that binds specifically to a particular receptor, such as an amino acid, protein, or small molecule. Drug development involves identifying receptors that are targets for specific diseases and developing drugs that exert therapeutic effects through interactions with ligands or selective actions of ligand-based drugs.

*2 Cryogenic electron microscopy is a device used to observe and analyze the three-dimensional structure of biomolecules such as proteins by irradiating them with an electron beam while cooled with liquid nitrogen to -196°C.

Agreement with French company Vetbiolix SAS to develop treatments for intestinal motility disorders in pets

2023-04-06

RaQualia Pharma Inc. announced that it has entered into an agreement with the French company Vetbiolix SAS to develop treatments for intestinal motility disorders in pets.

The company announced that it has entered into an option and license agreement with Vetbiolix for RQ-00000010 (RQ-10), a 5-HT₄ agonist discovered by RaQualia, for the development of pet drugs. Under the terms of the agreement, Vetbiolix is granted an exclusive option for an exclusive, worldwide, sublicensable license to develop, manufacture and commercialize pet drugs containing RQ-10. The exclusive option will be valid for up to 24 months, during which time Vetbiolix will conduct research activities related to proof-of-concept studies with RQ-10 for the development of pet drugs targeting intestinal motility disorders in cats and dogs.

RQ-10 is a potent, highly selective, and orally bioavailable small molecule developed by RaQualia. In non-clinical studies in dogs, RQ-10 promoted gastric and colonic motility at doses as low as 1 µg/kg. The drug also demonstrated a favorable pharmacokinetic and safety profile in several non-clinical studies and a Phase I clinical trial.

Upon exercise of the exclusive option, Vetbiolix will pay option fees to RaQualia, which is also eligible to receive development milestone payments and royalties on sales. According to RaQualia, this development will have a minimal impact on its FY12/23 earnings and the company has made no changes to its FY12/23 earnings forecast issued on February 14, 2023.

Trends and outlook

Quarterly trends and results

Earnings (cumulative) (JPYmn)	FY12/21				FY12/22				FY12/23	FY12/23	
	Q1	Q1-Q2	Q1-Q3	Q1-Q4	Q1	Q1-Q2	Q1-Q3	Q1-Q4	Q1	% of Est.	FY Est.
Operating revenue	656	1,321	1,623	2,776	339	1,447	1,904	2,918	370	13.2%	2,799
YoY	430.7%	254.3%	183.0%	150.7%	-48.3%	9.6%	17.3%	5.1%	9.2%		-4.1%
Operating expenses	507	1,006	1,516	2,068	459	896	1,403	2,052	420	16.5%	2,538
YoY	27.6%	29.6%	29.1%	29.8%	-9.4%	-10.9%	-7.4%	-0.8%	-8.5%		23.7%
Operating expense ratio	77.3%	76.2%	93.4%	74.5%	135.3%	61.9%	73.7%	70.3%	113.3%		90.7%
R&D expenses	256	497	781	1,127	264	528	840	1,249	268	16.0%	1,674
YoY	14.4%	10.2%	15.6%	20.9%	3.0%	6.4%	7.6%	10.8%	1.7%		34.1%
R&D expense ratio	39.0%	37.6%	48.1%	40.6%	77.7%	36.5%	44.1%	42.8%	72.4%		59.8%
Operating profit	149	315	107	708	-120	551	501	866	-109		260
YoY	-	-	-	-	-	75.1%	367.6%	22.4%	-		-70.0%
Operating profit margin	22.7%	23.8%	6.6%	25.5%	-	38.1%	26.3%	29.7%	-		9.3%
Recurring profit	268	433	238	864	-70	681	676	904	-110		242
YoY	-	-	-	-	-	57.4%	183.8%	4.7%	-		-73.2%
Recurring profit margin	40.9%	32.8%	14.7%	31.1%	-	47.1%	35.5%	31.0%	-		8.6%
Net income	189	303	169	756	-121	469	467	723	-148		183
YoY	-	-	-	-	-	55.0%	175.9%	-4.3%	-		-74.7%
Net margin	28.8%	22.9%	10.4%	27.2%	-	32.4%	24.5%	24.8%	-		6.5%
Earnings (quarterly) (JPYmn)	FY12/21				FY12/22				FY12/23		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1		
Operating revenue	656	665	302	1,153	339	1,108	457	1,014	370		
YoY	430.7%	166.9%	50.6%	116.0%	-48.3%	66.6%	51.1%	-12.1%	9.2%		
Operating expenses	507	499	510	552	459	437	507	649	420		
YoY	27.6%	31.6%	28.2%	31.8%	-9.4%	-12.5%	-0.6%	17.4%	-8.5%		
Operating expense ratio	77.3%	75.0%	168.7%	47.9%	135.3%	39.4%	111.0%	64.0%	113.3%		
R&D expenses	256	241	284	347	264	265	312	409	268		
YoY	14.4%	6.0%	26.6%	34.7%	3.0%	10.0%	9.8%	17.8%	1.7%		
R&D expense ratio	39.0%	36.2%	93.9%	30.1%	77.7%	23.9%	68.2%	40.3%	72.4%		
Operating profit	149	166	-208	601	-120	671	-50	365	-109		
YoY	-	-	-	423.7%	-	304.5%	-	-39.2%	-		
Operating profit margin	22.7%	25.0%	-	52.1%	-	60.6%	-	36.0%	-		
Recurring profit	268	165	-195	626	-70	751	-5	228	-110		
YoY	-	-	-	614.1%	-	356.5%	-	-63.6%	-		
Recurring profit margin	40.9%	24.8%	-	54.3%	-	67.8%	-	22.5%	-		
Net income	189	114	-133	586	-121	590	-2	256	-148		
YoY	-	-	-	539.8%	-	416.8%	-	-56.3%	-		
Net margin	28.8%	17.2%	-	50.9%	-	53.3%	-	25.3%	-		

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Q1 12/23 results (out May 15, 2023)

Earnings summary

Q1 FY12/23 (January–March 2023) results

- Revenue: JPY370mn (+9.2% YoY)
- Operating loss: JPY109mn (JPY120mn loss in Q1 FY12/22)
- Recurring loss: JPY110mn (JPY70mn loss in Q1 FY12/22)
- Net loss attributable to owners of the parent: JPY148mn (JPY121mn loss in Q1 FY12/22)
- R&D expenses: JPY268mn (+1.7% YoY)

Progress versus the company's full-year FY12/23 forecast was 13.2% for revenue and 16.0% for R&D expenses..

Factors behind higher revenue and losses

In Q1, royalty revenue from tegoprazan and pet drugs amounted to JPY350mn (+90.2% YoY), while other revenue totaled JPY20mn (-87.1% YoY). Revenue was up 9.2% YoY, but the company noted that a simple comparison with the previous year is not possible due to several factors (i.e., until the previous year, the company received royalty payments from HK inno.N twice a year, and also in Q1 FY12/22, RaQualia received a one-time payment of JPY115mn for the filing of ELURA® in Europe).

In pet drugs, sales were firm for GALLIPRANT® and ENTyce®/ELURA®, and royalty revenue increased.

In human drugs, sales in South Korea remained strong for tegoprazan (K-CAB®), buoyed by the launch of an orally disintegrating tablet formulation and approval for a fifth indication (maintenance therapy for healed erosive

esophagitis). Cumulative tegoprazan sales in South Korea (based on prescription records) reached KRW35.7bn (approx. JPY3.6bn), up 15.2% YoY.

Licensees of HK inno.N are also moving ahead with the development, manufacture, and sales of the compound in their respective countries and regions. At end-Q1 FY12/23, tegoprazan had been out-licensed in 36 countries and regions, with products already on the market in four countries (South Korea, China, the Philippines, and Mongolia). The company received a one-time payment based on an agreement with HK inno.N after sub-licensees obtained marketing approval for tegoprazan from the regulatory authorities in Singapore and Mexico.

Operating expenses totaled JPY479mn (+4.4% YoY), of which R&D expenses were JPY268mn (+JPY5mn, or 1.7%, YoY) and other SG&A expenses were JPY152mn (+6.6% YoY). R&D spending is primarily focused on exploratory research, as well as the preparation of preclinical studies and API manufacturing for a ghrelin receptor agonist candidate.

Pipeline

Brisk royalties from four commercialized products

Pet drugs

Sales of GALLIPRANT® (generic name: grapiprant), a treatment for osteoarthritis in dogs, ENTyce® (capromorelin), a treatment for anorexia in dogs, and ELURA® (capromorelin), a treatment for weight loss in cats with CKD, continued to be solid as in FY12/22. All three products are out-licensed to Elanco. The company filed for approval of ELURA® in Europe (currently marketed in the US) in February 2022 and the regulatory review is ongoing.

Development of tegoprazan in countries around the world

Sales of GERD treatment K-CAB® in South Korea by licensee HK inno.N continued to be robust, with sales from prescriptions outside hospitals amounting to KRW35.7bn (+15.2% YoY; roughly JPY3.5bn at JPY0.1/KRW) in Q1 FY12/23. HK inno.N began sales of a new formulation K-CAB® tablets 25mg (with the quantity of tegoprazan halved compared with existing products) as a maintenance therapy for healed erosive esophagitis. As a result, K-CAB® is the only potassium-competitive acid blocker (P-CAB) sold in South Korea that can be used to treat all stages of erosive esophagitis from onset through to maintenance therapy. Orally disintegrating (OD) tablets (accounting for 14% of sales) continue to gain market share. According to the company, K-CAB® is the market leader for P-CAB, with a market share of 12%.

HK inno.N aims to roll out the drug to 100 countries around the world, and licensees are gaining approval and launching sales in succession. In China, Shandong Luoxin Pharmaceutical Group Stock Co., Ltd. (SHE: 002793) began sales of tegoprazan in April 2022 under the brand name Tai Xin Zan®, which was covered by China's public health insurance from March 2023. Previously, patients had to pay for the product themselves as it was not covered by health insurance. The company expects sales to expand now that the product is covered by public health insurance.

Global development of tegoprazan

Country/region	Licensee	Sales and development status	Progress	Market size (JPYmn)
South Korea	HK inno.N	On market (2019-)	Sales growing	100,000
China	Luoxin	Oral: On market(May 2022-) Injection: Under development	Launched	410,000
Philippines	MPPI	On market (Nov 2022-)	Launched	8,000
Mongolia	Monos	On market (Oct 2022-)	Launched	-
Indonesia	Kelbe	In preparation for launch	Approved	20,000
Singapore	UITC	In preparation for launch	Approved	1,600
Thailand, Vietnam, Malaysia	Pond's, Lyhn farma, Pharmaniaga	Application under review		27,000
17 Latin American countries including Mexico	Carnot	Approved in Mexico (Feb 2023) Under review for approval in 16 other countries	Approved	57,000
7 countries including India	Dr. Reddy	In preparation for filing / In preparation for development	Contract signed	130,000
US	Braintree	Phase III trials in progress (2022-)	Late stage clinical trial	370,000
Brazil	Eurofarma	In preparation for filing / In preparation for development	Contract signed	80,000

Source: Shared Research based on company data

Note: Licensees include sublicensees of HK inno.N. The market size is as of end-2021..

Out-licensed and pre-out-licensing programs

Out-licensed programs

Out-licensed programs are in the preclinical development stage or later at licensees.

In Q1 FY12/23, Oxford Cannabinoid Technologies Ltd. (LSE: OCTP) applied to the UK authorities and Research Ethics Committee to conduct Phase I clinical trials of a cannabinoid CB2 receptor agonist (RQ-00202730/AAT-730/OCT46120), which was out-licensed to Oxford Cannabinoid Technologies by AskAt Inc. (unlisted), a licensee of RaQualia.

Pre-outlicensing programs

In pre-out-licensing programs, preclinical trials are continuing from FY12/22 on a ghrelin receptor agonist being developed in-house. With tegoprazan, aiming for rapid approval in Japan, the company decided to abandon in-house clinical trials and focus on out-licensing instead, and is in talks with potential licensing partners. The company also engaged in business development activities for other pre-out-licensing programs, flexibly combining in-person and online meetings to seek potential licensing partners.

Exploratory research phase

In the exploratory research phase, continuing from FY12/22, RaQualia steadily advanced collaborative and in-house research, working on in-house discovery of development candidates and strengthening its drug discovery research base. In addition, the company established a new research facility at Shonan Health Innovation Park (Shonan HIP) in Fujisawa, Kanagawa Prefecture, to further strengthen its drug discovery value chain and portfolio. At the Shonan HIP facility, RaQualia is exploring opportunities to collaborate with companies that have the latest knowledge and technologies related to new modalities, exploratory research on molecular targeted drugs, and the AI application in drug discovery.

Status at subsidiary TMRC

In addition, Phase III clinical trials for the treatment of myelodysplastic syndrome (MDS) and Phase II trials for acute myeloid leukemia (AML) are under way in the US by Syros Pharmaceuticals Inc. (NASDAQ: SYRS) for a retinoic acid receptor alpha agonist (tamibarotene), which was discovered by consolidated subsidiary TMRC Co., Ltd. and licensed to Syros. In January 2023, tamibarotene received fast-track designation from the US Food and Drug Administration (FDA) for higher-risk myelodysplastic syndrome (HR-MDS). Companies whose drug candidates obtain fast-track designation can hold more frequent meetings to discuss development plans with the FDA, and may be eligible for priority and fast-track review if the plan can be supported by clinical data.

In addition, investigator-initiated clinical trials (Phase I/II) for unresectable pancreatic cancer are ongoing at the Department of Gastroenterology and Hepatology, Nagoya University and the Department of Gastroenterology, University of Tokyo. The company has also initiated exploratory research for new development candidates.

Development Status of tamibarotene at Syros

Indications	Development stage	Orphan drug designation	Progress and outlook
Acute myeloid leukemia (AML)	Phase II (US)	US: Designated, Europe: Designated	Announcement of results of randomized trial part in Q4 2023
Myelodysplastic syndrome (MDS)	Phase III (US)	US: Designated, Europe: Positive opinion	Announcement of results in Q3 2024 and filing for approval in 2024

Source: Shared Research based on company data

Series 16 share subscription rights issued

In the medium-term management plan, RaQualia has outlined the total R&D investment of JPY2.4bn by the end of 2024 (JPY1.2bn for explorative research and JPY1.2bn for non-clinical and clinical studies, not including personnel expenses). In addition, the company plans to invest approximately JPY2.8bn over the next five years to enhance its R&D activities further and accelerate progress. It will use this fund to explore new modalities, promote AI-driven drug discovery, and revamp laboratory facilities. Because these funding needs cannot be covered by cash on hand (about JPY4.0bn) or expected income, the company determined that it needed to secure new funds to invest in development and decided to issue new shares and share subscription rights via third-party allotment. The payment process was completed on January 5, 2023.

FY12/23 company forecast

(JPYmn)	FY12/21			FY12/22			FY12/23		
	1H Act.	2H Act.	FY Act.	1H Act.	2H Act.	FY Act.	1H Est.	2H Est.	FY Est.
Operating revenue	1,321	1,456	2,776	1,447	1,471	2,918	795	2,004	2,799
YoY	254.3%	98.2%	150.7%	9.6%	1.1%	5.1%	-45.1%	36.2%	-4.1%
Operating expenses	1,006	1,063	2,068	896	1,156	2,052	1,119	1,419	2,538
YoY	29.6%	30.0%	29.8%	-10.9%	8.8%	-0.8%	24.9%	22.7%	23.7%
Cost of revenue	175	146	321	105	127	232	117	116	233
YoY	201.8%	82.1%	132.4%	-40.2%	-12.9%	-27.8%	11.8%	-8.6%	0.6%
R&D expenses	497	631	1,127	528	720	1,249	698	976	1,674
YoY	10.2%	30.9%	20.9%	6.4%	14.2%	10.8%	32.1%	35.5%	34.1%
R&D expense ratio	37.6%	43.3%	40.6%	36.5%	49.0%	42.8%	87.8%	48.7%	59.8%
SG&A expenses	334	286	620	263	309	572	304	327	631
YoY	24.9%	12.0%	18.8%	-21.4%	8.0%	-7.9%	15.7%	5.9%	10.4%
SG&A ratio	25.3%	19.6%	22.3%	18.2%	21.0%	19.6%	38.2%	16.3%	22.5%
Operating profit	315	393	708	551	315	866	-324	584	260
YoY	-	-	-	75.1%	-19.9%	22.4%	-158.8%	85.5%	-70.0%
Operating profit margin	23.8%	27.0%	25.5%	38.1%	21.4%	29.7%	-40.8%	29.1%	9.3%
Recurring profit	433	431	864	681	223	904			242
YoY	-	-	-	57.4%	-	4.7%			-73.2%
Recurring profit margin	32.8%	29.6%	31.1%	47.1%	15.2%	31.0%			8.6%
Net income	303	453	756	469	254	723			183
YoY	-	-	-	55.0%	-	-4.3%			-74.7%
Net margin	22.9%	31.1%	27.2%	32.4%	17.3%	24.8%			6.5%

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Note: The 1H FY12/22 forecast is for internal management purposes, and is not disclosed as the company's 1H forecast.

FY12/23 (January–December 2023) company forecast (announced February 14, 2023)

- Operating revenue: JPY2.8bn (-4.1% YoY)
- Operating profit: JPY260mn (-70.0% YoY)
- Recurring profit: JPY242mn (-73.2% YoY)
- Net income attributable to owners of the parent: JPY183mn (-74.7%)
- Assumed exchange rate (USD/JPY): JPY125.0 (JPY134.25 in FY12/23)

For FY12/23, the company forecasts operating expenses of JPY2.5bn (+23.7% YoY) due to increased capex and R&D spending, but looks for the third consecutive year of operating profit due to steady operating revenue. The company maintained its full-year forecast at the time of announcing Q1 results.

Earnings (cumulative) (JPYmn)	FY12/23				FY12/23	
	Q1	Q1–Q2 forecast	Q1–Q3 forecast	Q1–Q4 forecast	% of Est.	Est.
Operating revenue	370	795	1,356	2,799	13.2%	2,799
YoY	9.2%	-45.0%	-28.8%	-4.1%		0.8%
Royalties	350					
YoY	90.2%					
% of total	94.5%					
Other (Upfront and milestone payments)	20					
YoY	-87.1%					
% of total	5.4%					
R&D expenses	268	698	1,095	1,674	16.0%	1,674
YoY	1.7%	32.1%	30.3%	34.1%		34.1%
Research	219	575	878	1,362	16.1%	1,362
YoY	-14.1%	19.3%	15.4%	33.0%		33.0%
% of total	81.6%	82.4%	80.2%	81.4%		
Development	49	123	217	312	15.7%	312
YoY	512.5%	167.4%	174.7%	38.7%		38.7%
% of total	18.3%	17.6%	19.8%	18.6%		

Source: Shared Research based on company data

Assumptions underlying forecast

For FY12/23, the company expects operating revenue to be underpinned by solid sales of tegoprazan (GERD treatment), GALLIPRANT® (for osteoarthritis in dogs), and ENTyce® (for anorexia in dogs). In addition to royalty revenue from the four launched products, expects to receive upfront payments from new licensing agreements and milestone payments as development progresses. Regarding the development of tegoprazan in Japan, the company has decided to pursue early out-licensing without conducting pharmacological clinical trials and is in talks with one or two pharmaceutical companies regarding collaboration. As RaQualia is still discussing and reviewing the clinical trial design and other details, it conservatively estimates the timing of the contract signing and expects to receive an upfront payment in Q4 FY12/23.

The main factor behind the expected YoY decline in revenue is a USD4mn (JPY500mn based on JPY125/USD) milestone payment for the P2X7 receptor antagonist brought forward and booked in FY12/22. The company had previously factored in operating revenue of JPY250mn each in FY12/22 and FY12/23, in view of the probability of achieving the development milestone. However, with the start of Phase II clinical trials in November 2022, the company achieved the milestone and

recorded the full amount in FY12/22. In Eli Lilly's pipeline, three Phase II clinical trials for P2X7 are underway and are expected to be completed between June and October 2023.

In April 2022, Luoxin started selling tegoprazan under the brand name Tai Xin Zan® in China. FY12/23 operating revenue forecasts include some royalty revenue from China sales of tegoprazan. In Mongolia, HK inno.N's licensee Monos Pharma LLC (unlisted) received approval for tegoprazan, and the company has started supply in preparation for commercialization. In May 2022, HK inno.N's Philippines licensee, Metro Pharma Philippines, Inc. (unlisted), acquired approval in the Philippines and is also preparing to market the drug. It was also approved for non-erosive reflux disease in Indonesia in October and launched in Mexico in May 2023.

HK Inno.N plans to grow further by expanding into Europe and other regions. Sublicensees of HK Inno.N will conduct sales in these countries, so there will be a time lag before RaQualia receives royalties on sales. Shared Research understands that these additional royalty revenues will contribute to earnings from FY12/24 onwards.

In Q1, OCT, one of the sublicensees, applied for clinical trials for a CB2 agonist and in Q2 (May 2023) received approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) in the UK. These trials, primarily targeting chemotherapy-induced peripheral neuropathy (CIPN), will be the first in humans for CB2 agonists, and the first dosing of subjects is expected to take place soon. OCT expects to complete the Phase I clinical trial in Q3 2023. According to OCT, the global market for CIPN will be approx. USD1.6bn (JPY201bn, calculated at JPY125/USD) in 2020 and is expected to reach USD2.4bn (JPY296bn) by 2027.

Rising R&D expenses drag on profit

The company expects a decrease in profits as it plans to increase R&D expenses to JPY1.7bn (+34.1% YoY). This includes investments of JPY312mn for preclinical and clinical trial preparations for the ghrelin receptor agonist, as well as JPY1.4bn for the discovery of development compounds and the exploration of new areas and technologies. The company aims to acquire drug discovery technology as a growth driver and has been collaborating with startups and venture companies since 2022, planning strategic investments including acquisitions.

New license agreement signed

In April 2023, the company entered into an option and license agreement with Vetbiolix SAS, an unlisted company based in France, for the development of a pet drug based on the company's 5-HT4 agonist compound (code: RQ-00000010, hereinafter RQ-10). Under the agreement, the company grants Vetbiolix an exclusive, worldwide license option (with sublicense rights) to develop, manufacture, and commercialize a pet drug containing RQ-10. This exclusive option will be for a period of up to 24 months, during which time Vetbiolix will conduct research activities to demonstrate the concept of a pet drug targeting gastrointestinal motility disorders in dogs and cats using RQ-10.

Upon exercise of the exclusive option by Vetbiolix, the company will receive option fees and be eligible to receive milestones and royalties on sales based on the progress of development. The company expects this agreement to have a minimal impact on its full-year results for FY12/23.

Difference between initial company forecasts and results

Results vs. Initial Est. (JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Operating revenue (Initial Est.)	1,014	300	600	950	1,100	1,388	2,022	2,129	2,738	2,605
Operating revenue (Results)	228	154	146	705	1,419	745	1,703	1,107	2,776	2,918
Results vs. Initial Est.	-77.5%	-48.7%	-75.8%	-25.8%	29.0%	-46.4%	-15.8%	-48.0%	1.4%	12.0%
Operating profit (Initial Est.)	-1,082	-1,684	-1,395	-819	-760	-698	187	70	420	420
Operating profit (Results)	-2,138	-2,123	-1,865	-760	-150	-1,075	-16	-486	708	866
Results vs. Initial Est.	-	-	-	-	-	-	-	-	68.5%	106.2%
Recurring profit (Initial Est.)	-1,071	-1,685	-1,415	-819	-761	-680	195	85	427	420
Recurring profit (Results)	-1,820	-1,942	-1,795	-721	-81	-1,065	22	-528	864	904
Results vs. Initial Est.	-	-	-	-	-	-	-88.9%	-	102.3%	115.3%
Net income (Initial Est.)	-1,075	-282	-1,661	-825	-767	-686	153	13	343	342
Net income (Results)	-1,108	-465	-1,854	-728	-58	-1,105	5	-607	756	723
Results vs. Initial Est.	-	-	-	-	-	-	-96.5%	-	120.3%	111.5%

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Up to FY12/20, earnings had substantially undershot initial forecasts, so new management plans to issue conservative guidance to avoid further downward revisions to forecasts.

In FY12/21, the company booked an operating profit for the first time since its founding in 2008. Brisk sales of the four products on the market (tegoprazan [K-CAB®], GALLIPRANT®, ENTyce®, and ELURA®) generated strong royalty

revenue. Milestone payments for out-licensed programs and upfront payments for new license agreements also contributed to profitability. The significant difference between the initial recurring profit and net income forecasts and actual results is due to JPY146mn in forex gains stemming from yen depreciation.

In FY12/22, in addition to rising royalty revenue from the above four commercialized drugs, the company received a milestone payment accompanying the launch of a Phase II clinical trial on a P2X7 receptor antagonist and upfront payment from a new pet drug license agreement, aided by yen weakness, booking its second consecutive operating profit.

Medium-term business plan (FY12/23 to FY12/25)

	FY12/21	FY12/22	FY12/23	FY12/24	FY12/23	FY12/24	FY12/25	3-year
(JPYmn)	Cons.	Cons.	Prev. plan	Prev. plan	Est.	Targets	Targets	CAGR
Operating revenue	2,776	2,918	2,957	3,752	2,799	2,966	4,185	
YoY	150.7%	5.1%	-3.6%	26.9%	-4.1%	6.0%	41.1%	12.8%
Operating expenses	2,068	2,052	2,691	2,504	2,538	2,657	2,860	
YoY	29.8%	-0.8%	0.6%	-6.9%	23.7%	4.7%	7.6%	11.7%
Operating expense ratio	74.5%	70.3%	91.0%	66.7%	90.7%	89.6%	68.3%	
Operating profit	708	866	266	1,248	260	309	1,325	
YoY	-	22.4%	-32.3%	369.2%	-70.0%	18.8%	328.8%	15.2%
Operating profit margin	25.5%	29.7%	9.0%	33.3%	9.3%	10.4%	31.7%	
Recurring profit	864	904	256	1,238	242	317	1,330	
YoY	-	4.7%	-36.5%	383.6%	-73.2%	31.0%	319.6%	13.7%
Recurring profit margin	31.1%	31.0%	8.7%	33.0%	8.6%	10.7%	31.8%	
Net income	756	723	204	990	183	248	1,166	
YoY	-	-4.3%	-37.6%	385.3%	-74.7%	35.5%	370.2%	17.2%
Net margin	27.2%	24.8%	6.9%	26.4%	6.5%	8.4%	27.9%	
EBITDA	849	1,013			464	584	1,582	
YoY	-	19.3%			-54.2%	25.9%	170.9%	16.0%
Assumed exchange rate (USD/JPY)	110.00	134.24	135.00	135.00	125.00	125.00	125.00	

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods. The previous forecast was as of November 17, 2022.

Aims at three straight years of operating profit

Along with the announcement of its full-year FY12/23 earnings results, the company also unveiled a three-year medium-term business plan covering FY12/23 to FY12/25. The plan targets FY12/25 operating revenue of JPY4.2bn (three-year CAGR of 12.8%), operating profit of JPY1.3bn (15.2%), recurring profit of JPY1.3bn (13.7%), and net income attributable to owners of the parent JPY1.2bn (17.2%). The company forecasts increased capex and development spending with a view to longer term growth, but expects operating profit in three consecutive years due to steady operating revenue. It assumes a forex rate of JPY125/USD.

Performance vs. previous plan and latest forecast

	Three-year targets vs. FY12/22	Progress as of end-FY12/22	Forecast
Earnings	Operating profit in 3 consecutive years to FY12/24 Cumulative operating revenue: JPY8.9bn	FY12/22 operating revenue JPY2.9bn, operating profit JPY866mn	Ongoing
Research	Discover one candidate compound by FY12/24	Currently underway	Ongoing
Development	Complete preclinical trials for ghrelin receptor agonist in FY12/23	Currently underway	Policy change
	Complete clinical trials for tegoprazan in Japan in FY12/23	Talks with PMDA and out-licensing activities	Policy change
Out-licensing	License one drug annually from pre-out-licensing program	Incomplete (no licensing contracts)	Ongoing

Source: Shared Research based on company data

Key points of new business plan

- Increase in royalty revenue: The company expects global growth of tegoprazan to drive earnings, with pet drugs also solid.
- Tegoprazan in Japan: Change in plans to out-licensing after in-house development. Currently collaborating with pharma companies, starting late stage clinical trials aiming at rapid commercialization.
- Ghrelin receptor agonist: Conduct Phase I clinical trials in-house to boost program value and increase future earnings.
- Growth investments: Company views accelerated R&D essential for future growth, and plans to invest in strengthening drug discovery research capabilities and pipeline using funds raised while maintaining operating profit over three years.

Outlook for operating revenue: Three-year total of JPY9.9bn

- ▶ FY12/23: The company looks for growing sales royalties on solid sales of tegoprazan and pet drugs. It expects upfront payments from the launch of tegoprazan in Japan and milestone revenue, for a total of JPY2.8bn.
- ▶ FY12/24: The company expects increased sales of tegoprazan in China and solid sales of pet drugs. It looks for a total of JPY3.0bn in revenue, including royalty revenue and milestone and upfront payments for out-licensed programs.
- ▶ FY12/25: The company expects growth in global sales of tegoprazan and solid sales of pet drugs. It forecasts a total of JPY4.2bn in revenue including royalty revenue and upfront and milestone payments.

Three-year R&D budget overview

- ▶ FY12/23: The company plans to invest JPY1.4bn (+33.0% YoY) in research on development compound discovery and strengthening its drug discovery research infrastructure. On the development side, it plans to spend JPY312mn (+38.7% YoY) on pre-clinical trials of its ghrelin receptor agonist and preparations for clinical trials.
- ▶ FY12/24: The company plans to invest a similar amount to FY12/23, JPY1.4bn (+4.3% YoY) in research on development compound discovery and strengthening its drug discovery research infrastructure. On the development side, it plans to spend JPY298mn (-4.5% YoY), including clinical trials of its ghrelin receptor agonist.
- ▶ FY12/25: The company plans to invest JPY1.5bn (+2.5% YoY) in research on technological infrastructure for new modalities and development compound discovery. On the development side, it plans to spend JPY518mn (+73.8% YoY), including its ghrelin receptor agonist and in-house development of new development compounds.

Alters development plans for ghrelin receptor agonist and tegoprazan

The company has changed its approach to in-house development of tegoprazan. It now aims to collaborate with drug companies to launch late stage clinical trials with a view to rapid commercialization. For its ghrelin receptor agonist, the company plans to launch Phase I clinical trials to boost its value. It plans to complete the preclinical studies for the ghrelin receptor agonist in FY 12/23, and launch clinical trials in FY12/24.

The company is developing ghrelin receptor agonist RQ-00433412 in-house in a bid to increase the probability of successfully commercializing new drugs and increasing expected earnings, and intends to focus on out-licensing activities for the following four programs, including tegoprazan.

In-house development programs

- ▶ Ghrelin receptor agonist (RQ-00433412): Complete preclinical studies by end-2023, launch Phase I clinical trials by end-2024

Programs RaQualia plans to out-license at current development stage

- ▶ Tegoprazan: Negotiating with one or two drug companies re collaboration
- ▶ 5-HT4 partial agonist (RQ-00000010, RQ-10): Complete Phase I clinical trials
- ▶ 5-HT2B antagonist (RQ-00310941, RQ-941): Complete Phase I clinical trials
- ▶ Motilin receptor agonist (RQ-00201894, RQ-894): Complete preclinical studies

Out-licensing: Aims to sign one new out-licensing agreement each year

The company was successful in signing two out-licensing agreements in 2H FY12/21. In FY12/22, it conducted negotiations on six potential out-licensing programs, but did not conclude any agreements. It aims to out-license at least one compound yearly from FY12/23 onward.

Business

Business overview

Predecessor was Pfizer's central research laboratory in Japan

RaQualia Pharma Inc. is an R&D focused drug discovery company. It primarily uses exploratory research into small molecule compounds ("seeds") for new drugs, and out-licenses development and marketing rights to pharmaceutical and other companies. The company got its start when US-based Pfizer Inc. (NYSE: PFE) decided to close its central research laboratory in Japan as part of global research restructuring in 2007. The research lab spun off from Pfizer through an employee buyout, and RaQualia Pharma was established in July 2008. Pfizer held 19% of the company's shares at its inception, but sold them after the company's initial public offering (IPO), and as of end-December 2022 it held about 3.5%.

In addition to six exploratory programs and six development programs, Pfizer transferred to the company Japanese rights* to three products already approved and marketed in the US (GEODON® [ziprasidone], Dalvance® [dalbavancin], and ERAXIS® [anidulafungin]). Under development at that time were tegoprazan and GALLIPRANT® (grapiprant), which the company continued developing and has already launched. Some compounds transferred from Pfizer are among the pre-out-licensing and out-licensed programs in the development pipeline.

* Programs transferred from Pfizer that are currently in RaQualia's development pipeline include a potassium-competitive acid blocker (tegoprazan), EP4 receptor antagonist (grapiprant), ghrelin receptor agonist (capromorelin), 5-HT₄, CB2, and 5-HT_{2B}, as well as those at a stage of research where the compound candidate has not yet been determined. Convinced of its value, the company was committed to developing tegoprazan, which it took over after Pfizer decided to withdraw from gastrointestinal diseases in 2007. Tegoprazan has been a key driver of the company's growth.

Business territory

Drug discovery from exploratory research to early clinical development

RaQualia Pharma is an R&D focused drug discovery company that uses leading-edge technology with the aim of developing drugs for diseases with high unmet medical needs. The stages of drug discovery it focuses on are from exploratory research of target molecules to early clinical development. Basically, the company's development processes are aimed at lessening R&D expenses and risk by conducting activities up to the early clinical trial (Phase II) stage, where efficacy and safety can be broadly evaluated. Under new management from March 2021, the company broadened its targets from pain and gastrointestinal diseases to include neurological diseases. The company plans to focus on areas with significant unmet medical needs including neurodegenerative, genetic, and rare diseases, with the aim of consistently creating new drugs.

Neurological diseases: Newly added to the company's disease coverage, these involve damage to the brain, spinal cord, and nerves. A wide range of conditions comes under this category due to the number of bodily functions controlled by the nerves. Typical examples include cerebrovascular disease, Alzheimer's, epilepsy, and Parkinson's disease, as well as migraine and tension headaches.

Drug development process

Generally, R&D into drugs goes through several stages. Basic research looks for new compounds ("seeds") that drugs will be based on; nonclinical studies confirm the efficacy and safety of the compounds discovered through experiments on animals; clinical trials confirm efficacy and safety of administration to humans (healthy individuals and patients). First stage (Phase I) clinical trials check for safety and side effects in a small number of healthy individuals. Phase II clinical trials identify effective dosages and dosing regimens using a small number of patients. Phase III clinical trials compare efficacy and safety with existing drugs using large numbers of patients.

Time required and success rates

Before a new drug is launched, applications are filed with regulatory authorities in individual countries based on huge volumes of trial data regarding its quality, efficacy, and safety. The drug is marketed following reviews and approval by experts. The process involves a long R&D period of roughly 10 to 15 years, and expenditure of tens of billions to hundreds of billions of yen. Few development pipelines succeed, as development may be halted during the long R&D period due to risks such as changes in the business environment and failure to obtain sought-after data. The difficulty of drug development continues to increase and likelihood of success has declined over time. The Japan Pharmaceutical Manufacturers Association puts the probability of success at 1 in 23,000 currently, versus 1 in 13,000 20 years ago.

Typical drug discovery processes and company's business territory

Research	Process	Duration	Details	RaQualia's business territory
	Exploratory (basic) research	3–5 years	Development of therapeutic concepts, compound synthesis and evaluation	✓
	Preclinical (nonclinical) studies	2–3 years	Evaluation of efficacy and safety mainly in animals	✓
Development	Clinical trials Phase I	3–7 years	Evaluation of efficacy and safety in humans	✓
	Phase II			
	Phase III			
	Approval filing	approx. 1 year	Application and regulatory review	
	Time until launch	Total 9-16 years		

Source: Shared Research based on company data

Success rates in new drug development

	2000–2004	2005–2009	2010–2014	2015–2019
Preclinical trial launch	1 : 2,158	1 : 3,213	1 : 3,748	1 : 3,740
Clinical trial launch	1 : 3,653	1 : 8,698	1 : 9,622	1 : 10,301
Regulatory approval (own company)	1 : 12,888	1 : 31,064	1 : 24,553	1 : 22,749
Number of approvals (own company)		36	21	29

Source: Shared Research based on MHLW, Pharmaceutical Industry Vision 2021

RaQualia's drug discovery modality (methodology)

Small molecule drug development

The company is primarily engaged in R&D into small molecule compounds, and as of FY12/22, they comprise its entire development pipeline. The company got its start through an employee buyout of the central research laboratory in Japan of US-based Pfizer. When it was established in 2008, RaQualia took over research equipment and some research programs from Pfizer. As a result, it succeeded in out-licensing tegoprazan, its potassium-competitive acid blocker, less than two years after its founding.

Using expertise from Pfizer which had focused on compound synthesis and design, the company conducts experiments with the 100–150 compounds it synthesizes every week. It assigns an eight-digit compound code starting with 00000001 for all the compounds that it researches, develops, and evaluates. The number of digits in the codes attests to the company's ongoing exploratory research to find the seeds of new drugs using its vast stores of data. The compound database which it uses on a daily basis numbers approximately 800,000, including a library of about 300,000 compounds used for screening.

World's shortest research cycle: two weeks

The company uses a robotics system called SCARA (Selective Compliance Assembly Robot Arm) which allows it to evaluate 10,000 compounds a day from its vast compound library. New compounds that will become the seeds of new drugs are synthesized by analyzing multidimensional data, with designs based on empirical rules and computational methods according to an efficient synthesis plan based on accumulated expertise. Synthetic samples (including impurities) synthesized by company chemists are delivered promptly to pharmacologists in solution form with purity guaranteed through the company's CAP (Centralized Analysis & Purification) system that automates the purification, weighing, dissolution, and dispensing processes. The company says that using CAP increases the SCARA robotic system's efficiency by roughly 10 times, enabling it to supply 200 compounds per week.

All information concerning compounds is managed using two-dimensional barcodes in a database and used for the structure-activity relationship (SAR)* research. Barcode-controlled 384-hole plates conduct rapid, accurate pharmacological, safety, metabolic, and other studies. Results are promptly recorded in a database and reported to design and synthesis staff. This research cycle takes two weeks, which the company says is the fastest in the world.

* Structure-activity relationship: Refers to the statistical relationship between the structure of a chemical substance and its biological (pharmacological or toxicological) activity. In the drug discovery process, researchers conduct studies aimed at making predictions about the efficacy of structurally similar compounds.

Patent expiry management

Aims to extend life of its hundreds of patents

RaQualia applies for basic patents (substance patents) and obtains rights in major countries around the world on an ongoing basis. While the regions and expiry dates differ, the company has several hundred patents, with some effective until around 2040. After filing for a basic patent, the company aims to extend the effective life of patents by seeking extensions and applying for peripheral patents. Compound patents are effective for 20 years, which may be extended by as much as five years, and filing for peripheral patents (such as use patents and manufacturing process patents) can extend exclusivity for a further 20 years. The company has extended the life of patents that Pfizer originally applied for until the mid-2030s via extensions and peripheral patent applications. The aim is to ensure revenue over the long term by delaying the launch of lower-priced generic drugs with the same ingredients and efficacy after the basic patent for a new drug has expired.

Examples of patent types

Patent	Coverage	Example
Substance patent	Substance structure only	Compound as indicated in chemical formula X
Process patent	Substance manufacturing method	Method of producing substance C through reaction of substance A and substance B
Use patent	Uses and target diseases	Agents for treating specific diseases containing substance A
Dosage and administration patent	Dosage and administration method	Administering xx mg per dose x times daily
Formulation patent	Formulation technology	Compressed solid preparation containing substance A, disintegrant B, and binder C
Compound in combination patent	Multiple active ingredients	Pharmaceutical composition containing substance A and substance B
Crystal patent	Substance crystal structure	Crystal of substance A (definition of diffraction angle)

Source: Shared Research based on company data

Management renewal and fresh initiatives

At the ordinary general meeting of shareholders held in March 2021, a shareholder resolution for a management renewal put forth by current board member Yuichi Kakinuma (the largest shareholder with an 11% stake), was adopted with the approval of an overwhelming majority (about 85%) of individual shareholders. Mr. Kakinuma had three concerns: that the company's initial forecast was lowered for three consecutive years starting in FY12/19, that the existing pipeline development program was halted, and that the company was unable to out-license its new pipeline. In addition, in 2017, former president Naoki Tani had pledged that the company would have a market capitalization of JPY100bn in 2020, but as of end-2020 it was significantly below this figure, at about JPY20bn.

Below are the main initiatives in research, development, and out-licensing under new management since March 2021 (details not disclosed).

Research

- ▶ Next-generation growth: Investigating new modality concepts
- ▶ Streamlining compound creation: Building next-generation drug discovery value chain
- ▶ Expanding territories: Using AI to search for drug targets and diseases

Development

- ▶ Expanding territories: Recruitment of clinical development director
- ▶ Enhancing value of existing programs: Looking into added value, notably in-house development of tegoprazan and ghrelin receptor agonist

Outlicensing

- ▶ TRPM8 blocker: Out-licensed to Xgene Pharmaceutical (September 2021)
- ▶ Sodium channel blocker: Out-licensed to Hisamitsu Pharmaceutical (December 2021)

Higher funding demands due to strategy change under new management

The company has traditionally aimed at out-licensing at the preclinical preparation stage, and many of the out-licensing deals to date have been in the early development stages. However, due to the low likelihood of market launch for pipeline drugs in the early development stage, upfront, milestone, and royalty payment rates tend to be lower. For this reason, the new management team has decided to carry on development of new drug candidate compounds until the proof of concept (POC) stage (which confirms the usefulness and efficacy of a new drug candidate compound under development through administration to humans) in a bid to enhance the value of its future pipelines. POC demonstration entails carrying on clinical trials until the Phase II stage, and require more R&D spending than previously. Because the company intends to develop two projects in-house in FY12/23, it expects an increase of roughly 20% in operating expenses, and said it plans to raise funds through a combination of equity financing and commitment lines.

Trying new modality

Drugs can be broadly classified into two categories: chemically synthesized small molecule drugs and biopharmaceuticals (also called biopharmaceuticals) made from biological materials. Small molecule drugs are generally less expensive to produce because they have smaller molecules, a fixed chemical structural formula, and are easy to mass produce. Biopharmaceuticals have active ingredients derived from proteins, such as growth hormones, insulin, or antibodies, and are manufactured from cells, yeast, or bacteria. The molecules of biopharmaceuticals are large and complex, and their properties and characteristics depend on the manufacturing process, boosting costs. Biopharmaceuticals launched as new drugs tend to be more expensive, and the market is also larger.

When the Ministry of Health, Labour and Welfare puts a new prescription drug on the national health insurance (NHI) price list, the price of the newly developed drug is based on a comparison with drugs already in use with similar efficacy (comparable drug method). If the new drug is more effective or novel, a premium is added, boosting the price. If there is no comparable drug with similar efficacy, the price is based on costs such as raw materials and manufacturing (cost accounting method). This can lead to a price difference of 1.5 to 3.5 times between original and generic drugs with the same ingredients. There are more existing drugs in the company's main therapeutic areas of pain and gastrointestinal diseases than neurodegenerative diseases, genetic diseases, and rare diseases, which have significant unmet medical needs. This means that the price at time of launch for the former tends to be low, as does royalty revenue.

In its medium-term plan up to December 2024, the company is testing new modality concepts. Its strength lies in small molecule drug discovery. It plans to try out new modalities involving collaborations with university start-ups and others for drugs that are challenging to develop with the technology and expertise it has accumulated thus far. It is also looking into AI and cloud collaboration initiatives for a structural biological approach to ion channels.

Collaboration with drug discovery start-ups and others

Using AI to look for treatments for intractable and rare diseases

In May 2022, the company and Socium Inc. (unlisted) signed a joint research agreement to look for indications for RaQualia's compounds to treat intractable and rare diseases. Socium's intractable and rare disease program has a database of gene expression patterns for all intractable and rare diseases registered at the Intractable Disease Information Center. Socium can estimate compounds' possible indications based on their gene expression pattern. Estimating indications based on gene expression patterns can identify novel indications in a few months that could not be predicted from the conventional pharmacological mode of action of the compound. The company thinks this will help maximize the value of the compound.

Using new modality (intracellular antibodies) to control ion channels

In August 2022, RaQualia entered into an agreement with STAND Therapeutics (unlisted) to explore the possibility of applying STAND's technologies to drug discovery, and began collaborating with STAND with the aim of discovering treatments for intractable and rare diseases. Many target molecules of drugs and other medical therapies exist within cells; however, because antibodies cannot function within cells as they become unstable and aggregate in the cytosol, antibody drugs until now have focused on targets in the extracellular space. By utilizing STAND's technology to generate intracellular

antibodies that can function within cells, the company believes it can stabilize antibody drugs by attaching stabilizing peptide tags to them and have them approach target molecules in the intracellular space without aggregating.

Aims at mRNA-targeted small-molecule anti-cancer drug discovery

In December 2022, the company announced a joint research agreement with Veritas In Silico Inc. (unlisted) to discover breakthrough small-molecule drugs targeting messenger RNAs (mRNA). Veritas In Silico has proprietary platform technologies specialized in mRNA-targeted drug discovery. Through joint research over multiple years, the company and Veritas In Silico will target a number of genes associated with cancer specified by the company and identify target structures on corresponding mRNA; identify hit compounds by high-throughput screening; identify lead compounds by synthesizing analogues (hit expansion); and determine development candidate compounds through lead optimization.

Looking for compounds targeting ion channels to treat eye diseases

In December 2022, the company announced a joint research agreement with D. Western Therapeutics Institute, Inc. (TSE Growth: 4576, DWTI). The partners will use their respective technologies, resources, and expertise in pharmaceutical R&D in joint research aimed at discovering and developing therapeutic agents for specific optic nerve disorders. The company will draw on its ion channel drug discovery technology to synthesize a group of compounds that target specific ion channels. DWTI will verify the compounds' potential as therapeutic agents for eye diseases through pharmacological tests and other methods using its evaluation technology in the field of ophthalmology. Technological achievements and intellectual property obtained from the joint research will be jointly owned by the company and DWTI, and after the research program finishes, the partners plan to hold discussions on the next stage of collaboration.

Structural biology analysis of ion channels

The company announced that it has partnered with leadXpro AG (unlisted), a Swiss company with expertise in membrane protein biochemistry, to accelerate drug discovery research targeting membrane proteins, a challenging area for drug development. RaQualia has a strong track record in ion channel drug discovery targeting membrane proteins and aims to accelerate drug discovery projects in this area through collaboration with leadXpro. leadXpro is a biotech company specializing in membrane protein structure-based drug discovery with expertise in structural biology, ligand design*1, and biophysical characterization of membrane proteins. By using structural biology techniques such as cryogenic electron microscopy*2 to observe how ligands bind to proteins at the atomic level, the company believes it is possible to logically design drug candidates (i.e., improve drug activity and selectivity) and accelerate drug discovery research.

*1 A ligand is a substance that binds specifically to a particular receptor, such as an amino acid, protein, or small molecule. Drug development involves identifying receptors that are targets for specific diseases and developing drugs that exert therapeutic effects through interactions with ligands or selective actions of ligand-based drugs.

*2 Cryogenic electron microscopy is a device used to observe and analyze the three-dimensional structure of biomolecules such as proteins by irradiating them with an electron beam while cooled with liquid nitrogen to -196°C.

Technologies owned by startups and drug discovery companies

	Proprietary technologies
Socium	Proprietary database of intractable and rare diseases and AI drug discovery platform
STAND	Proprietary technology (STAND technology) to generate antibodies in cells and approach target molecules
Veritas In Silico	Informatics technology to find target substructures on mRNA
DWTI	Expertise in ophthalmic drug discovery (glaucoma drug: Glanatec®)
LeadXpro	Technology for structural analysis of membrane proteins using cryo-electron microscopy

Source: Shared Research based on company materials

Earnings structure

RaQualia is an R&D focused drug discovery company. It primarily conducts exploratory research into development compounds ("seeds") for new drugs, and out-licenses development and marketing rights pharmaceutical companies and others to generate revenue. In general, revenue can be broken down based on drug development stage into: 1) upfront payments received when a contract is signed; 2) milestone payments that depend on pipeline progress such as launching clinical trials; 3) research cooperation payments when conducting joint research) and 4) royalty revenue received once the drug under development is launched on the market.

Types of company revenue

Upfront payment	Revenue received upon signing out-licensing or R&D cooperation contract. Compensation for value and potential of new drug candidate the company has developed.
Milestone payment	Revenue earned in line with R&D progress of out-licensee. Received when key barriers are crossed in process of transforming new drug candidate into a new drug such as moving to the next phase of clinical trials.
Royalty revenue	Revenue based on sales of out-licensee. Rate increases progressively with sales, depending on contract terms.
Research cooperation payment	Payment from partner for joint research to discover new drug candidate in early-stage alliance. Compensation for the company's drug discovery technology.

Source: Shared Research based on company data

Revenue by region

	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Total	228	154	146	705	1,419	745	1,703	1,107	2,776	2,918
YoY	687.0%	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.6%	-35.0%	150.7%	5.1%
US	88	-	-	646	818	278	761	549	1,004	1,142
YoY	3,726.4%	-	-	-	26.5%	-66.0%	173.8%	-27.8%	82.7%	13.8%
% of total	38.8%	-	-	91.6%	57.6%	37.3%	44.7%	49.6%	36.2%	39.1%
Japan	70	131	106	50	471	349	196	28	1,187	742
YoY	162.5%	86.9%	-19.4%	-52.6%	841.1%	-25.8%	-43.7%	-85.9%	4,175.6%	-37.5%
% of total	30.7%	85.0%	72.5%	7.1%	33.2%	46.8%	11.5%	2.5%	42.8%	25.4%
Asia	-	20	40	9	131	121	746	530	585	1,034
YoY	-	-	100.0%	-77.5%	1,355.0%	-7.8%	517.9%	-28.9%	10.3%	76.8%
% of total	-	13.0%	27.5%	1.3%	9.2%	16.2%	43.8%	47.9%	21.1%	35.4%
Europe	50	-	-	-	-	-	-	-	-	-
YoY	-	-	-	-	-	-	-	-	-	-
% of total	21.8%	-	-	-	-	-	-	-	-	-
Other	20	3	-	-	-	-	-	-	-	-
YoY	-	-84.7%	-	-	-	-	-	-	-	-
% of total	8.8%	2.0%	-	-	-	-	-	-	-	-

Source: Shared Research based on company data

Note: Revenue is based on customer location, and classified by country or region

Licensees have already launched four products, providing the company with stable long-term royalty revenue, its main source of earnings. In FY12/22, operating revenue was JPY2.9bn, comprising royalty revenue (over 50%) and upfront and milestone payments (over 40%).

Pipeline overview

Ample pipeline based on pharmaceutical company standard research processes and operating procedures

The company took over the expertise and methodology in drug discovery R&D from its predecessor, the Pfizer central research laboratory, and has continued with the research projects it inherited. Accordingly, it has a large number of "seeds," and has been able to create a series of candidate compounds. It has advanced technological capabilities based on its standard operating procedures (SOP) equivalent to those of pharmaceutical companies, and is engaged in difficult drug discovery targeting ion channels, and has out-licensed five projects at an early stage. The company has four products already commercialized (tegoprazan, GALLIPRANT®, ENTyce®, and ELURA®), and an ample pipeline: 10 already out-licensed, including ion channel projects, and six at the pre-out-licensing stage.

It also had nine programs in its exploratory research pipeline as of February 2022, and in addition to in-house research, it is conducting joint research with ASKA Pharmaceutical Co., Ltd. (unlisted; subsidiary of ASKA Pharmaceutical Holdings Co., Ltd. [TSE Prime: 4886]), Interprotein, Nagasaki University, and Gifu Pharmaceutical University. In March 2018, the company signed an agreement with Nagoya University to establish the RaQualia Pharma Industry-Academia Collaborative Research Center (RARC) within the university which houses the Department of Pharmacology and Department of Pharmaceutical Sciences. It conducts research aimed at discovering drug candidate compounds and aims to accelerate drug discovery with industry-academia collaboration.

Out-licensed pipeline (human)

Out-licensed programs (human)

Program name	Generic name/compound code	Key indication	Rollout area	Development stage
Tegoprazan (potassium-competitive acid blocker [P-CAB]; K-CAB®)	RQ-00000004 (tegoprazan)	GERD	South Korea	On market (Mar 2019)
			China	On market (May 2022)
			Philippines	On market (Nov 2022)
			Mongolia	Approved, Preparing launch
			Indonesia	Approved, Preparing launch
			Singapore	Approved, Preparing launch
			Thailand, Vietnam, Malaysia	Application under review
			Mexico	Approved (Feb 2023)
			16 countries in Latin America	Preparing for approval filing
			US, Canada	Phase III underway in US (2022-)
Retinoic acid receptor alpha agonist	Tamibarotene TM-411/SY-1425	Myelodysplastic syndrome (MDS)	US	Phase III underway
		Acute myeloid leukemia (AML)	US	Phase II underway
EP4 receptor antagonist	RQ-00000007 (grapiprant)	Pain	US	Early Phase II completed
		Cancer	China	Phase I complete
			US	Phase I underway
5-HT4 partial agonist	RQ-00000009	Alzheimer's disease	China	Phase I underway
COX-2 inhibitor	RQ-00317076	Pain	US	Phase I complete
			China	Phase I underway
CB2 agonist	Not disclosed	Pain associated with IBS	-	Preclinical trials underway
Selective sodium channel blocker	Not disclosed	Analgesic and antipruritic	-	Not disclosed
P2X7 receptor antagonist	Not disclosed	Neuropathic pain	-	Phase II underway
Specific ion channel target	Not disclosed	Gastroenterology	-	Not disclosed
TRPM8 blocker	RQ-00434739	Chronic pain	-	Preparing for preclinical trials
Sodium channel blocker	RQ-00350215	Chronic pain	-	Preparing for preclinical trials

Source: Shared Research based on company data (as of end-May 2022)

Potassium-competitive acid blocker: P-CAB (generic name: tegoprazan)

Out-licensed worldwide (excluding Japan) to HK inno.N

Tegoprazan is primarily used to treat gastrointestinal reflux disease (GERD)*, and is an alternative to the existing mainstream therapy of proton pump inhibitors (PPIs). RaQualia inherited the development compound from Pfizer, and many of the employees who had been involved with development of tegoprazan were transferred to the company, so preclinical studies were launched soon after its establishment. In June 2010, after Phase I trials in the US were completed, the company entered a strategic alliance with South Korea-based HK inno.N in gastrointestinal diseases, and reached an out-licensing agreement covering South Korea, China including Hong Kong, and Taiwan for the commercialization of tegoprazan in September 2010. The geographic regions covered gradually increased from 2019, and currently HK inno.N has been granted rights to cover the entire world except Japan.

*Gastroesophageal reflux disease (GERD): A disease whereby stomach contents, in particular stomach acid, flow back into the esophagus (food pipe), causing characteristic symptoms such as heartburn. Non-erosive reflux disease (NERD) is a condition in which damage to the esophageal mucosa cannot be confirmed by endoscopy, despite symptoms such as heartburn and acid reflux.

Frontrunner was Takeda Pharmaceutical's TAKECAB®

Vonoprazan (brand name, TAKECAB®) is a potassium-competitive acid blocker (P-CAB) launched by Takeda Pharmaceutical Company Limited (TSE Prime 4502) in February 2015, and has a different action than the current mainstream treatment, proton pump inhibitors (PPIs). PPIs are activated by acid in the body, and inhibit gastric acid secretion. Vonoprazan does not require activation by acid, and is fast acting and effective at preventing gastric acid secretion by inhibiting the binding of potassium ions needed for secretion (source: Takeda). P-CABs have progressively replaced PPIs and H2RAs (H2 blockers: histamine H2 receptor antagonists) and while the NHI price of TAKECAB® was cut by 4.1% in 2021, its revenue on an NHI price basis was still JPY111.1bn (+13.5% YoY), the third highest among domestic drugs.

No. 1 market share in South Korea

HK inno.N gained marketing approval for the company's out-licensed drug tegoprazan for South Korea in July 2018, and launched it in March 2019 as K-CAB®. Revenue of K-CAB® in South Korea in 2022 (non-hospital prescriptions) came to KRW125.2bn (+14.2% YoY, roughly JPY12.5bn converted at KRW/JPY0.1) for a strong CAGR of 61.4% from 2019, and the No. 1 market share in South Korea for gastrointestinal disease treatments.

K-CAB® for sale in South Korea



Source: HK inno.N homepage

In February 2022, HK inno.N gained manufacturing and marketing approval for orally disintegrating K-CAB® tablets, and launched sales in May 2022. These can be taken by elderly who have trouble swallowing tablets, those with restricted fluid intake, or those unable to drink water because they are away from home. The company expects that improved dosing convenience and expanded patient population will boost HK inno.N's earnings and be reflected in royalty revenue.

In July 2022, HK inno.N obtained approval for K-CAB® as maintenance therapy for healed erosive esophagitis. This makes K-CAB® the most widely indicated P-CAB marketed in South Korea. The five indications for which tegoprazan received marketing approval in South Korea are erosive esophagitis, non-erosive reflux disease (NERD), gastric ulcer, adjuvant therapy for *Helicobacter pylori* eradication, and maintenance therapy for healed erosive esophagitis. Following its approval for health insurance coverage in January 2023, a new formulation used in maintenance therapy for GERD was launched. The new formulation contains half of the tegoprazan volume of existing medicines, and maintains the condition of the patient once healed. This means that tegoprazan is the only P-CAB marketed in South Korea able to be used in all stages from the onset of GERD to the post-treatment stage.

Characteristics of tegoprazan

Gastroesophageal reflux disease (GERD) is characterized by the reflux of stomach contents, especially stomach acid, into the esophagus with characteristic symptoms such as heartburn. The main symptoms are heartburn and acid regurgitation*, especially heartburn on an empty the stomach or during the night. The main differences between tegoprazan and existing drugs is the inhibition of acid secretion and speed of onset. Tegoprazan has the ability to inhibit acid secretion similar to vonoprazan (brand name TAKECAB®) and superior to PPIs. Like PPIs, tegoprazan is also indicated for non-erosive reflux disease (NERD), but vonoprazan is not. The pH value in the stomach is used as an indicator for onset of effect. PPIs require stomach acid for activation, so tend not to take effect on the first day (raising the intragastric pH level above 4) and vonoprazan takes about four hours, compared to about one hour for tegoprazan. Furthermore gastrin*² levels tend to rise with vonoprazan, but less so with tegoprazan, which is similar to PPIs.

* Acid regurgitation is a symptom of the backward flow of stomach acid into the esophagus, followed by downward flow that causes a sour or bitter sensation in the mouth and throat.

*² Gastrin is a hormone secreted mainly from cells in the pyloric antrum of the stomach. Under normal conditions, it temporarily rises after meals and promotes gastric acid secretion. When abnormally secreted, causing extreme hyperacidity, if the serum gastrin level is maintained at an elevated level over an extended period, this increases the risk of developing peptic ulcers and neuroendocrine tumor development and should be carefully monitored. Medication is sometimes discontinued due to high gastrin levels.

Revenue increasing as tegoprazan sales territory expanded

Licensee HK inno.N's sales expansion plans

In September 2010, the company reached an out-licensing agreement with South-based HK inno.N Corporation for marketing tegoprazan in South Korea, China including Hong Kong, and Taiwan. It has gradually been expanding the territories covered, and since 2019, HK inno.N has global rights excluding Japan. Since its establishment in 2008, RaQualia Pharma carried on with and invested in R&D into tegoprazan, one of Pfizer's development programs. HK inno.N has started acquiring marketing approval in countries around the world under its global sales strategy, so the company thinks it is on the cusp of a long-term period where it can recoup its investment from FY12/22 onward.

In April 2022, HK inno.N completed Phase I clinical trials for tegoprazan in the US, and sub-licensee Braintree Laboratories launched Phase II in November 2022, with a view to gaining approval in the US and Canada. Also in April 2022, Luoxin Pharmaceutical, a sublicensee of HK inno.N, gained marketing approval from the Chinese authorities and launched the drug just 15 days later. In February 2022, HK inno.N reached a manufacturing supply agreement for Malaysia with the country's largest drug company, Pharmaniaga Logistics Sdn Bhd (PHARMA 7081), and in May 2022 it signed a licensing agreement covering India and six other countries with Dr. Reddy's Laboratories.

Royalty revenue expected to increase due to expansion of sales territories

In May 2022, HK inno.N's sublicensee Metro received marketing approval for four indications in the Philippines, including erosive esophagitis, and launched sales in November 2022. The peptic ulcer medicine market in the country is over USD60mn (about JPY7.5bn), making it the fourth largest market in Southeast Asia. Metro has successfully marketed proton pump inhibitors (PPIs) in the Philippines and has sales infrastructure and marketing expertise in the field of peptic ulcers, so the company hopes it will be able to make quick inroads in the market with tegoprazan. As of March 2023, in addition to being on sale in South Korea, China, and the Philippines, tegoprazan has been rolled out to 36 countries, where it is in the development, awaiting approval, or preparing to launch stage. It has received approval in Mongolia, and product supply has begun, with plans to put the drug on sale during FY12/23.

The company says that the global peptic ulcer market is potentially worth JPY2tn, and HK inno.N aims to roll out tegoprazan to 100 countries around the world by 2028. The largest market is North America at JPY400bn, followed by China at JPY310bn. As mentioned, the sublicensee is preparing for the next stage of clinical trials in the US and Canada, sales have begun in China and the Philippines, preparations for launch are underway in Mongolia, and approval has been obtained for Singapore and Mexico, with sales projected to start in 2023. Assuming a global market share of 10% for tegoprazan and a royalty rate of 5%, the company could potentially receive annual royalty payments of JPY10bn.

Estimate of company royalties

$$\begin{array}{l} \text{Potential global market size} \\ \text{JPY2bn} \end{array} \times \begin{array}{l} \text{Share captured} \\ 11\% \text{ in South Korea} \end{array} \times \begin{array}{l} \text{Royalty rate} \\ \text{Generally 1-10\%} \end{array} = \begin{array}{l} \text{Maximum royalties} \\ \text{company can receive} \end{array}$$

Source: Shared Research based on company data

Development status and market size for HK inno.N by key country/region

Country/region	Licensee*	Development stage	Launch year (est.)	Market size*
South Korea	HK inno.N	On sale	2019	JPY90bn
China	Luoxin	Oral on sale (IV under development)	May 2022	JPY410bn
Philippines	MPPi	On sale	November 2022	JPY8bn
Mongolia	Monos	Approved, preparing to launch	2023	Not disclosed
Indonesia	Kalbe	Approved, preparing to launch	2023	JPY20bn
Singapore	UITC	Approved, preparing to launch	2023	
Thailand, Vietnam, Malaysia	Pond's, Lyhn farma, Pharmaniaga	Application under review	-	JPY28bn
17 Latin American countries incl. Mexico	Carnot	Approved (Mexico), other 16 countries under review	-	JPY210bn
India and six others	Dr. Reddy	Preparing to file/develop	-	JPY130bn
US	Braintree	Phase III underway (from 2022)	-	JPY370bn
Brazil	Eurofarma	Preparing to file	-	JPY80bn

Source: Shared Research based on company data

Note: Licensees include HK inno.N sublicensees

Note: Market sizes from HK inno.N data (September 2022). Calculated at JPY0.1/KRW

Growth potential for peptic ulcer drug market in China

According to Scientific Reports, in 2020 there were 58mn GERD patients in China (4.2% of the population), with an estimated market size of JPY350bn. The mainstream treatments are conventional PPIs and H2RAs (H2 blockers), with treatment costs per patient of JPY6,000. With the entry of P-CAB, prescription costs per patient in Japan and South Korea have risen to JPY14,000 and JPY20,000 respectively, and the company thinks that prescription costs per patient in China will also increase as PPIs and H2RAs are replaced. Furthermore, due to the adoption of Western dietary habits and the aging of the population, the number of GERD patients is also in an uptrend and it is likely that the market will also expand due to a growing share of patients in the population.

GERD patient numbers and peptic ulcer drug market size

Country/region	No. of patients (% of population)	Market size (JPYmn)	Treatment costs per patient	Mainstream treatment
China	58mn (4.2%)	350,000	JPY6,000	PPI, H2RA
US	67mn (21.0%)	450,000	JPY6,700	PPI, H2RA
South Korea	3mn (5.8%)	60,000	JPY20,000	PPI, H2RA, P-CAB
Japan	17mn (14.0%)	250,000	JPY14,000	PPI, H2RA, P-CAB

Source: Shared Research based on company data

Note: Calculated at JPY0.1/KRW, JPY19.6/CNY, JPY125/USD

Sales plans in China

Luoxin Pharmaceutical is selling tegoprazan under the brand name Tai Xin Zan® in China. After receiving Category 1 approval in China, designating it an innovative drug, on April 13, 2022, it launched the drug just 15 days later, on April 28. In addition to selling it at major hospitals and retail drugstores in China, it is also selling it over the internet via online medical services, and is targeting sales of CNY1.0bn (roughly JPY19.6bn converted at JPY19.6/CNY) in 2023, and CNY3.0bn in the longer term (roughly JPY58.8bn). In Q2 FY12/22, the company received a milestone payment of JPY300mn, and is set to receive further royalty payments reflecting sales. Because Luoxin is a sublicensee, royalty revenue will come through HK inno.N, so the company expects a time lag of about six months.

EP4 receptor antagonist (RQ-00000007, grapiprant)

Grapiprant is an EP4 receptor antagonist that was under development by Pfizer. It is the same compound as GALLIPRANT®, which is already marketed as a pet drug. In January 2013, the company transferred the intellectual property rights for grapiprant to AskAt (a wholly-owned subsidiary at the time) in return for a set percentage of royalty income AskAt receives. AskAt has been developing grapiprant since the IP transfer, mainly for the indications of cancer and pain. In December 2017, AskAt concluded a licensing agreement with Arrys Therapeutics (unlisted, a subsidiary of Ikena) for global rights to grapiprant, excluding China and Taiwan. Subsequently, Ikena took over rights from Arrys and has been conducting clinical trials.

Ikena started a US expansion phase I clinical trial (Phase Ib) in October 2018, targeting patients with unresectable or advanced microsatellite stable colorectal cancer. However, in November 2022, Ikena announced it had suspended in-house development and was considering alternative strategic plans. As of March 2023, Ikena had not returned its license to AskAt, nor had it announced an alternative plan, so the company thinks Ikena suspended the program so it could concentrate its resources on other programs. Results of a study evaluating concurrent treatment with grapiprant and Keytruda® (pembrolizumab) are scheduled for presentation at the European Society for Medical Oncology (ESMO) annual meeting. An investigator-initiated clinical trial is being conducted at the University of Texas MD Anderson Cancer Center to evaluate concurrent treatment with grapiprant and Halaven® (eribulin) for metastatic inflammatory breast cancer.

In addition, Chinese licensee 3D Medicines Co., Ltd. (unlisted) concluded Phase I trials of grapiprant for pain management. Another licensee in China, Ningbo NewBay Medical Technology Development Co., Ltd. (unlisted), is conducting Phase I clinical trials for oncological applications.

CB2 agonist (RQ-00202730)

The CB2 agonist is a compound the company originated after inheriting the theme from Pfizer. AskAt's UK-based licensee Oxford Cannabinoid Technologies Ltd. (LSE: OCTP), a business partner since November 2015, is conducting preclinical studies in the UK. In January 2023, OCTP submitted an application for a Phase I clinical trial to the UK Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC). The Phase I clinical trial for the CB2 agonist OCTP plans to run mainly targets chemotherapy induced peripheral neuropathy (CIPN).

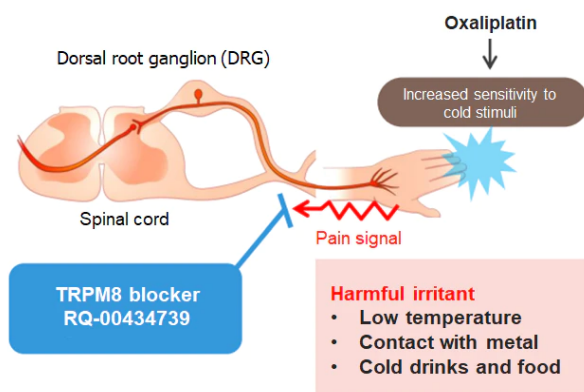
P2X7 receptor antagonist (RQ-00466479)

The company created a P2X7 receptor antagonist through joint research with Asahi Kasei Pharma (a license agreement signed in March 2018). Phase I clinical trials targeting peripheral neuropathic pain have been completed. Eli Lilly, with whom Asahi Kasei Pharma has a license agreement, will take over global development from Phase II. Based on the licensing agreement with Asahi Kasei Pharma, the company will receive royalty payments based on a certain percentage of Asahi Kasei Pharma's earnings. With the start of Phase II by Eli Lilly in November 2022, RaQualia achieved the development milestone and received an upfront payment of USD4mn (JPY500mn based on JPY125/USD translation).

TRPM8 blocker (RQ-00434739)

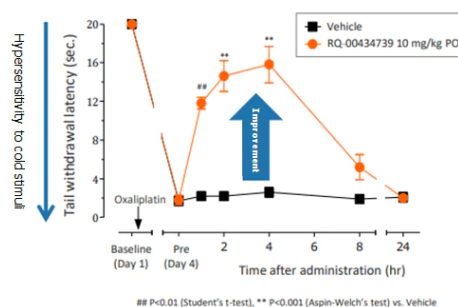
The TRPM8 blocker is a program RaQualia created. TRPM8 is a temperature-sensitive ion channel activated by cold stimuli under 28°C or by menthol (mint) and its involvement has been suggested in a variety of chronic disorders, including chronic pain. In-house discovered selective TRPM8 blocker (azaspiro derivative) demonstrated a different mechanism of action in animal models of chronic pain from existing drugs, and the company hopes it will be a breakthrough drug. For example, about 90% of patients who receive cancer treatment using oxaliplatin are susceptible to cold pain. The company's TRPM8 blocker blocks TRPM8 (the cold receptor) directly, suppressing the transmission of pain signals.

Effect of TRPM8 blocker



Source: Company data

Effects of RQ-00434739 in monkey model with oxaliplatin-induced neuropathic pain



In September 2021, RaQualia entered a licensing agreement with Hong Kong-based Xgene Pharmaceutical Co. Ltd. (unlisted), granting it exclusive global rights (excluding Japan) to develop, manufacture, and sell the TRPM8 blocker. Xgene has moved to the preclinical study phase in its quest to develop a pain therapy, and the company is set to receive milestone payments as research moves through development stages and royalties based on sales if the product is launched (specific target conditions and amounts have not been disclosed).

Sodium channel blocker (RQ-00350215)

Sodium channels, along with other ion channels such as potassium channels, control the generation and transmission of nerve action potentials, and are deeply involved in neurotransmission. The company hopes that the sodium channel blocker it developed will become a breakthrough new drug for chronic pain (that existing drugs do not provide sufficient analgesic effect for) by selectively blocking the function of specific sodium channels involved in pain signal transmission.

In December 2021, RaQualia entered a licensing agreement with Hisamitsu Pharmaceutical Co., Inc., (TSE Prime: 4530) granting it exclusive worldwide development, manufacturing, and marketing rights. Although the out-licensing occurred in the early development stage, the company received JPY600mn as an upfront payment and may receive up to JPY3.0bn in milestone payments as development progresses from FY12/22 onward. Further, if drugs containing the sodium channel blocker the company developed are approved and launched, it has the right to receive sales royalties with a royalty rate in the range of 5–10%, and milestone payments in line with sales to a maximum of over JPY10bn. Hisamitsu Pharmaceutical plans to develop transdermal medication (one of its strengths) for pain containing the sodium channel blocker RaQualia developed, starting with the preclinical trial phase.

The company has two other projects underway in addition to the above, although the development stages are undisclosed. These are a selective sodium channel blocker for analgesic and anti-pruritic indications out-licensed to Maruho and a compound for a specific ion channel target for gastrointestinal indications out-licensed to EA Pharma.

Cyclooxygenase-2 (COX-2) inhibitor (RQ-00317076)

The company discovered a cyclooxygenase-2 (COX-2) inhibitor from a compound with a different type of chemical structure from existing COX-2 inhibitors.

In January 2013, the company signed an agreement to transfer all intellectual property rights, related data, and the drug substance for RQ-00317076 to AskAt in return for a percentage of the revenue AskAt earns from RQ-00317076 as royalties. AskAt has positioned RQ-00317076 as a third-generation COX-2 inhibitor. In early-stage Phase II clinical trials conducted in the US targeting postoperative pain, RQ-00317076 was shown to have superior efficacy, more rapid response, and longer-lasting effect, as well as higher safety and tolerability compared to ibuprofen, the standard treatment. As of FY12/22, AskAt's China-based licensee 3D Medicines Co., Ltd. (unlisted) was conducting a Phase I clinical trial of the drug for human use.

In July 2022, AskAt entered into a license agreement with US-based Velo-1 for global rights to RQ-00317076 as a drug for animals, as well as a two-year development support agreement with Velo-1. Signing of these agreements meant that RQ-00317076 was being developed not only for human use, but also for animals. RQ-00317076 has lower risk of adverse effects when used in dogs compared with existing NSAIDs and COX-2 inhibitors, and AskAt believes it is a promising compound for treating acute pain, e.g., postoperative pain, and chronic pain associated with osteoarthritis.

Pipeline of TMRC (consolidated subsidiary)

Tamibarotene (TM-411) (retinoic acid receptor alpha agonist: anticancer agent)

The company's consolidated subsidiary TMRC Co., Ltd. is a drug discovery company specializing in the field of cancer.

TMRC was established in January 2002 as a contract research organization (CRO) specializing in cancer. In February 2004, it obtained exclusive manufacturing and marketing rights in Japan and overseas for tamibarotene (TM-411) as an antineoplastic (anticancer) drug. In March 2009 it spun off the CRO business and established it as a subsidiary, and transferred 100% of the shares to Sugi Medical Co., Ltd. (unlisted, subsidiary of Sugi Holdings Co., Ltd. [TSE Prime: 7649]). In February 2017, TMRC became a wholly-owned subsidiary of RaQualia.

Tamibarotene is TMRC's main pipeline. In February 2004, TMRC obtained exclusive development and marketing rights in Japan and overseas for tamibarotene as an anticancer drug. In April 2005, licensee Toko Pharmaceutical Industries Co., Ltd. (unlisted) received manufacturing and marketing approval in Japan and launched the drug as an orphan drug* (for rare diseases) for acute promyelocytic leukemia (APL). The drug is sold by Nippon Shinyaku Co., Ltd. (TSE Prime: 4516) as Amnolake® tablets.

* Orphan drugs are drugs used to treat rare diseases, and they are called so because they are often not actively developed, i.e., ignored or rarely adopted by pharmaceutical companies, due to their limited market and accompanying difficulty in recouping development costs.

In September 2015, TMRC granted development and marketing rights in Europe and North America for tamibarotene as a cancer therapy to US-based Syros Pharmaceuticals Inc. (NASDAQ: SYRS) in exchange for rights to receive milestone payments in accordance with development progress and sales royalties after launch. Syros aims to file a new drug application for tamibarotene as a precision medicine* for RAR alpha gene (RARA)-positive patients. RARA is expressed as a biomarker in 25% of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Syros is currently conducting Phase III clinical trials for MDS and Phase II clinical trials for AML in the US.

It plans to announce topline data from the Phase III clinical trial of tamibarotene administered in combination with azacitidine, the standard therapy for higher-risk MDS, in patients with newly diagnosed higher-risk MDS in Q4 FY12/23 or Q1 FY12/24, and file an NDA in 2024. It released data from the safety lead-in part of the Phase II clinical trial of tamibarotene + venetoclax + azacitidine three-drug combination therapy in elderly and other patients not suitable for standard chemotherapy in December 2022. Based on the promising data, Syros announced that it would advance the study to the randomized part, which it launched in Q1 FY12/23, with data expected in 2023 or 2024. In January 2023, tamibarotene received fast-track designation from the US Food and Drug Administration for higher-risk myelodysplastic syndrome (HR-MDS). The company hopes it will be eligible for or priority expedited review.

* Precision medicine: This is a kind of tailor-made, personalized medicine that entails analyzing cancer cell genes using a next-generation sequencer (a device for high-speed, large-scale decoding of the base sequences that represent the order in which the bases that make up DNA are bound together) to find the cancer-causing genetic mutation. It uses a molecular targeted drug designed to be effective against that particular gene mutation.

RaQualia is entitled to receive milestone payments from Syros in line with the development stages and royalties once tamibarotene is launched on the market. Tamibarotene has received orphan drug designation* for MDS and AML in the US and for AML in Europe. In addition, in July 2022 the company obtained a use patent (jointly filed with the National Institute of Advanced Industrial Science and Technology [AIST]) for tamibarotene as a growth inhibitor for cancer stem cells*² in Europe. In August the same year, Syros announced that the European Medical Agency (EMA) indicated it was in favor of granting orphan drug designation to tamibarotene for MDS.

* Orphan drug designation: A system designed to support development of drugs for life-threatening, rare diseases that affect only a small number of people (diseases that affect less than 200,000 [inclusive] patients in the US; less than five [exclusive] patients out of 10,000 persons in Europe; and less than 50,000 [exclusive] patients in Japan). Drugs that have obtained orphan drug designation enjoy various benefits, including preferential treatment in approval review, development funding, and guaranteed time-limited first mover advantage (market exclusivity) from the start of sales.

*² Cancer stem cells are cancer cells that have the characteristics of stem cells (i.e., self-renewal ability to divide and produce identical cells and multilineage differentiation ability to differentiate into various types of cells). They are malignant cells that self-renew and serve as the source of cancer cells. Cancer stem cells are either 1) normal stem cells that have become cancerous or 2) cells that have differentiated to some degree and become cancer stem cells through long-term inflammation. The former is often seen in childhood cancers such as osteosarcoma and hematologic cancers, and is thought to be the cause of disease recurrence and metastasis, as its slow cell division makes it difficult to respond to radiotherapy and anticancer drugs.

In Japan, RaQualia is conducting investigator-initiated Phase I/II clinical trials for tamibarotene as a pancreatic cancer treatment at Nagoya University. RaQualia has rights for Asia, and aims to out-license rights for treatment of MDS in Japan and China and pancreatic cancer in Japan as development in the US progresses.

Generic name	Tamibarotene
Mechanism of action	TM-411 has a high affinity for RAR alpha, and inhibits leukemia cell differentiation and cancer cell proliferation by regulating gene expression. The inhibitory effect includes suppression of IL-6 production and IL-6R expression, enhancement of IGFBP-3 expression, and suppression of VEGF-dependent angiogenesis, and may be applicable to a range of cancer tumors. Meanwhile, it acts on hematopoietic stem cells (CDK-activating kinase (CAK)-RAR alpha) in the bone marrow to promote differentiation into neutrophils via progenitor cells, induces granule formation and reactive oxygen species (ROS), and displays antibacterial activity. It is expected to be more effective when used in combination with the G-CSF preparations used to treat neutropenia.
Indications	Myelodysplastic syndrome, acute myelogenous leukemia, breast cancer, childhood cancers, acute promyelocytic leukemia, neuroblastoma, and neutropenia.
Administration	Oral (tablets, capsules)
Licensors	Toko Pharmaceutical Industry, Chemfizz

Source: Shared Research based on company data

Out-licensed pipeline (pet drugs)

Three products on the market

Two of the pet drugs the company has already launched, EP4 receptor antagonist grapiprant and ghrelin receptor agonist capromorelin, are compounds inherited from Pfizer. In December 2010, it granted US-based Aratana Therapeutics Inc. (acquired by Elanco in 2019) an exclusive global license with sublicensing rights to develop, market, and manufacture veterinary drugs.

Out-licensed programs (veterinary)

Program name	Generic name/compound code	Licensee	Key indication	Rollout area	Development stage
EP4 antagonist GALLIPRANT®	RQ-0000007 (grapiprant)	Elanco Animal Health Inc. (US)	Osteoarthritis in dogs	US	On market
				Europe	On market
				Japan	On market
Ghrelin receptor agonist ENTYCE®	RQ-0000005 (capromorelin)		Anorexia in dogs	US	On market
Ghrelin receptor agonist ELURA®				Weight loss in cats with CKD	US
COX-2 inhibitor	RQ-00317076	AskAt	Pain	—	Preparing for pilot test

Source: Shared Research based on company data (as of end-May 2022)

GALLIPRANT® (EP4 receptor antagonist, generic name: grapiprant)

This compound was launched in the US in January 2017 as GALLIPRANT® for osteoarthritis in dogs by US-based Elanco and is now being sold in over 20 countries around the world by Elanco (US). The nonsteroidal anti-inflammatory analgesic and first-in-class (breakthrough)* drug was launched in Japan in October 2020, and sales are growing steadily. Sales reached USD100mn (roughly JPY12.5bn) in FY12/21, becoming Elanco's tenth blockbuster drug.

* A first-in-class (breakthrough) drug is one that is highly novel and useful, and groundbreaking in that it significantly changes existing treatments. It often has a new chemical structure or therapeutic concept. Best-in-class (improved) drugs compensate for shortcomings of first-in-class drugs and have a clear advantage over existing drugs.

ENTYCE®, ELURA® (ghrelin receptor agonist, generic name: capromorelin)

Elanco sells ENTYCE® in the US as a treatment for anorexia in dogs. It is also sold under the brand name ELURA® in the US as a drug for the management of weight loss in cats with chronic kidney disease (CKD). Elanco filed for approval in Europe in March 2022. The company received an associated milestone payment of JPY115mn in Q1 FY12/22. The company receives milestone payments as set out in its contract and royalties in line with sales when there is progress such as expanding sales territories. The company said that sales of ENTYCE® and ELURA® were tracking well due to the absence of similar products.

Potential for ELURA®

According to the company, over 30% of cats aged 10 and over and over 9% overall (roughly 648,000 cats) in Japan have CKD. Cats with CKD may show ongoing weight loss and reduced life expectancy due to loss of appetite and repeated vomiting as the disease progresses. Over 80% of the cats with CKD that were administered ELURA® for 56 days gained weight. There are 74.1mn pet cats in the US and 56.6mn in Europe, so the company thinks the potential market is significant.

Cyclooxygenase-2 (COX-2) inhibitor (RQ-00317076)

RaQualia's in-house discovered cyclooxygenase-2 (COX-2) inhibitor has a different type of chemical structure than those of existing COX-2 inhibitors. In January 2013, the company signed an agreement to transfer all intellectual property rights, related data, and the drug substance for RQ-00317076 to AskAt, in return for a percentage of the revenue that AskAt earns from RQ-00317076 as royalties. AskAt had been developing RQ-00317076 as a human drug, but in July 2022, signed a license agreement with US-based Velo-1 for global rights to the drug for use in animals, as well as a two-year development support agreement with Velo-1. Signing of these agreements signaled the start of RQ-00317076 development as an animal drug. RQ-00317076 has lower risk of adverse effects when used in dogs compared with existing NSAIDs and COX-2 inhibitors, and AskAt believes it is a promising compound for treating acute pain, e.g., postoperative pain, and chronic pain associated with osteoarthritis.

Royalty revenue stable for pet drugs, as not affected by drug price revisions

In Japan, the Ministry of Health, Labour and Welfare (MHLW) sets uniform nationwide prices (NHI prices) for human prescription drugs. However, in the distribution chain, pharmaceutical wholesalers sell drugs to medical institutions and insurance pharmacies at wholesale prices that are different from the NHI prices. In order to reduce the burden on the insurance scheme, the MHLW surveys sales prices and volumes for each individual drug, and revises (lowers) prices based on its findings every year (every second year until April 2018). On the five occasions leading up to the April 2021 round of price revisions, the dispensing price was reduced by 5.69% on average. Expensive drugs are covered by public insurance and are thought to have a significant impact on the insurance budget, leading to this arrangement for stepwise reductions. This means it is difficult for pharmaceutical companies to generate expected profits for drugs that they launch following prolonged periods of development and massive investments.

The market for veterinary drugs for which the company receives royalty revenue is smaller than that for human drugs, but there is no similar NHI drug price system either in Japan or overseas. This enables prices to be maintained or lifted, and Shared Research thinks royalty revenue, which is a percentage of sales, tends to be stable and resilient to downward pressure as a result.

Pet drugs versus human drugs

	Pet drugs	Human drugs
Curtailling medical expenses/price revisions	Basically deregulated treatment with no price-setting system. Manufacturers have the right to set prices.	In countries with national drug price systems, the government (insurers in countries without such systems) influences price setting.
Generic drugs	A small number of companies enter market with slightly lower prices once patent expires. Japanese government provides little administrative guidance to promote generics.	Many companies enter market with lower prices once patent expires. Japanese government promotes use of generics.
Consumer behavior	Pet owners (consumers) have strong focus on brand/quality, and tend to keep using the same product after patent expiry.	Price is an important consideration, and consumers tend to shift to low-priced generic products after patent expiry.

Source: Shared Research based on company data

Pre-out-licensing programs

The company has six pre-out-licensing programs (i.e., pipelines in preparation for out-licensing). This includes some that have been out-licensed outside Japan such as tegoprazan and a TRPM8 blocker.

Pre-out-licensing programs

Program name	Generic name/compound code	Key indication	Target market	Development stage
Potassium-competitive acid blocker (P-CAB)	tegoprazan RQ-00000004	GERD	Japan	Preparing for Phase I
5-HT4 partial agonist	RQ-00000010	Gastroparesis, functional dyspepsia, chronic constipation	Worldwide	Phase I complete
5-HT2B agonist	RQ-00310941	Irritable bowel syndrome with diarrhea (IBS-D)	Worldwide	Phase I complete
Motilin receptor agonist	RQ-00201894	Gastroparesis, functional dyspepsia, post-operative ileus	Worldwide	Preclinical trials completed
Ghrelin receptor agonist	RQ-00433412	Cancer-related anorexia/cachexia syndrome, constipation from spinal cord injury	Worldwide	Preclinical trials underway
TRPM8 blocker	RQ-00434739	Pain	Japan	Preclinical trials under consideration

Source: Shared Research based on company data (as of end-May 2022)

Potassium ion-competitive acid blocker: P-CAB (generic name: tegoprazan)

Tegoprazan is primarily used to treat gastrointestinal reflux disease (GERD), and is an alternative to the existing mainstream therapy of proton pump inhibitors (PPIs). It was out-licensed to HK inno.N in September 2010, but the company retains the rights for Japan. It is preparing to start pharmacological studies as part of Phase I clinical trials. It plans to complete the pharmacological studies by the end of FY12/23, and is looking for an out-licensee in Japan. It expects tegoprazan to drive domestic out-licensing revenue after it reaches a deal in FY12/24.

Preparing to file for domestic approval using South Korean data

The company is working to maximize the value of tegoprazan. It is aiming at rapid and efficient development and approval in Japan using South Korean data and is getting ready to launch clinical pharmacological studies. RaQualia is investigating the study protocol based on advice from medical experts and is in discussions with the Pharmaceuticals and Medical Devices Agency (PMDA) concerning the trial. Tegoprazan has already been approved in South Korea for GERD, non-erosive reflux disease (NERD), gastric ulcers, and adjuvant therapy for *Helicobacter pylori* eradication. The company thinks it needs to evaluate ethnic differences between Japanese and Korean people in order to use South Korean data when filing for approval in Japan. It anticipates completing the clinical pharmacological studies in 2023 at a cost of JPY500mn.

Could become best in class

RaQualia's tegoprazan is the only P-CAB indicated for NERD. TAKECAB® is the frontrunner in Japan, China, and the US, but has not received approval for NERD. In Japan, NERD accounts for 60% of GERD cases (source: Osaka City Medical Association, "Pathophysiology and treatment of gastroesophageal reflux disease and related disorders" [2016]). Another advantage of tegoprazan is that gastrin values tend to rise less than with vonoprazan (TAKECAB®). Shared Research thinks that if tegoprazan is approved in Japan, there is a high probability that it will replace TAKECAB®. The company says that there are some 17mn GERD patients in Japan as of 2020 (14% of the population) with a market size of JPY250bn.

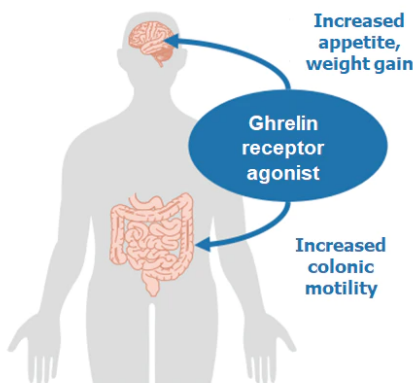
5-HT4 partial agonist (RQ-0000010)

This compound is under development for target indications of gastrointestinal dysmotility including gastroparesis, functional dyspepsia, and chronic constipation. In January 2013, the company entered a business alliance with AskAt. Phase I clinical trials in the UK of healthy individuals and patients have been completed. In addition to moving forward with out-licensing activities, the company is looking into the next stage of development, Phase II clinical trials.

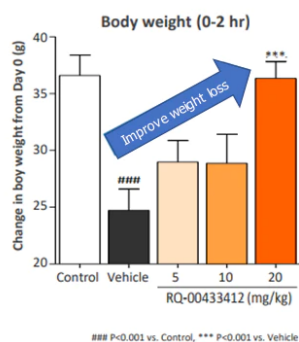
Ghrelin receptor agonist (RQ-00433412)

The compound is under development for the target indication of cancer-related anorexia and cachexia syndrome and constipation resulting from spinal cord injury. The company originated the compound after its establishment. The manufacturing of APIs for preclinical study has been completed, and an outsourced preclinical study began in Q4 FY12/21. The company plans to out-license worldwide rights in 2024 after completing preclinical studies by the end of FY12/23, and is looking for a licensee.

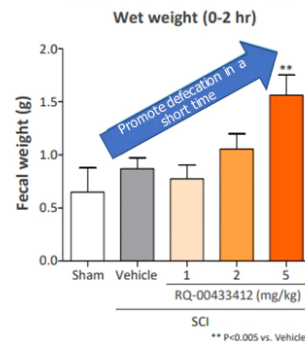
Cancer cachexia is a complication seen in about 50% of patients with advanced cancer at the time of initial diagnosis and 80% at the terminal stage. The main symptoms are weight loss, skeletal muscle loss, and anorexia. It calls for aggressive treatment because it can weaken the effect of chemotherapy, exacerbate side-effects, interrupt treatment, and ultimately impact survival rates. The ghrelin receptor agonist works on the hypothalamus to increase appetite, stimulate the release of growth hormone from the pituitary gland, and increase muscle mass and body weight. Many spinal cord injury patients live with defecation disorders due to autonomic neuropathy. Conventional laxatives may cause diarrhea, so the healthcare community is calling for easier-to-use drugs to promote defecation. The ghrelin receptor acts directly on the sacral spinal defecation center to promote colonic motility and voluntary defecation.



Effects of RQ-00433412 in rat model with cancer cachexia



Effects of RQ-00433412 in rat model with spinal cord injury



TRPM8 (RQ-00434739)

TRPM8 is a temperature-sensitive ion channel activated by cold stimuli under 28°C or menthol (mint) and its involvement has been suggested in a variety of chronic disorders, including chronic pain. The company discovered a selective TRPM8 blocker (azaspiro derivative) that demonstrated a different mechanism of action in animal models of chronic pain and cystitis than existing drugs, and hopes it will be a breakthrough new drug in the pain and urological disease fields. RaQualia entered an agreement with Hong Kong-based Xgene, granting it exclusive global (excluding Japan) development, manufacturing, and marketing rights for its TRPM8 blocker in September 2021 (see TRPM8 blocker in the out-licensed pipeline (human) section).

Motilin receptor agonist (RQ-00201894)

The compound is under development for the target indication of gastrointestinal dysmotility including gastroparesis, functional dyspepsia, and post-operative ileus, and the preclinical studies required for Phase I clinical trials have been completed. In addition to moving forward with licensing activities, the company is considering conducting Phase I clinical trials, the next development phase.

Exploratory and discovery phase pipeline

As of March 2023, the company had eight programs in exploratory and discovery research, six of which were joint research with companies or academia.

	Collaboration partner	Target diseases	Target molecule	Beginning of 2022	Beginning of 2023	
Company	ASKA Pharmaceutical	Not disclosed	Ion channel	✓	✓	
	Socium	Intractable and rare diseases	Not disclosed	AI drug discovery	—	✓
	STAND	Intractable and rare diseases	Ion channel	New modality	—	✓
	DWTI	Ocular diseases	Ion channel		—	✓
	VIS	Cancers	Not disclosed	New modality	—	✓
	Interprotein	Pain	Not disclosed		✓	Ended
Academia	Gifu Pharmaceutical University	Ocular diseases	Not disclosed	✓	✓	
	Nagasaki University	COVID-19	Not disclosed	Academic research	✓	Ended
	—	Not disclosed	Ion channel	✓	✓	
In-house (independent)	—	Not disclosed	Ion channel	✓	✓	
	—	Not disclosed	Ion channel	✓	Ended	
	—	Heart failure	GPCR (CRHR2)	✓	Ended	
	—	Not disclosed	Other	✓	Ended	
	—	Not disclosed	Other	✓	Ended	

Source: Shared Research based on company data

Drug discovery research targeting specific ion channel

The company has been conducting joint research with ASKA Pharmaceutical since July 2019, with the goal of developing new drugs targeting specific ion channels (main indication undisclosed). After extensive discussions on the future development based on the results achieved to date, the two companies have agreed to terminate the joint research agreement in June 2023. Upon termination of the agreement, the research results of the joint research will belong to RaQualia and the company will continue to develop new drugs independently.

RaQualia is also conducting joint research with Gifu Pharmaceutical University for the main indication of retinal vein occlusion (details not disclosed). By constantly conducting seven to ten programs in exploratory and discovery phases, the company thinks it will be able to continue to create groundbreaking development compounds.

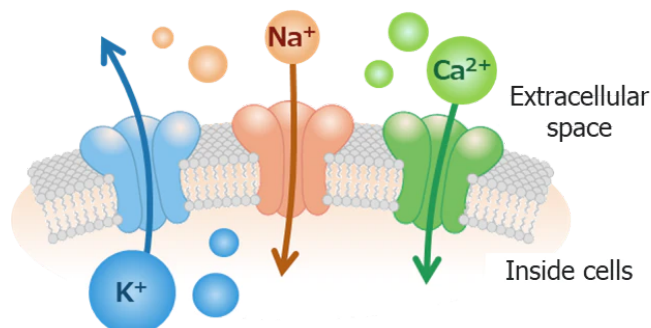
Ion channel drug discovery

The company has already out-licensed five drug discovery programs targeting ion channels. Ion channels are membrane proteins which allow the passage of ions across cell membranes. Expressed in a range of cells, each has a specific ion that can pass through it; examples include the sodium channel, calcium channel, potassium channel, and chloride ion channel.

Ion channels are vital for the maintenance of cell functions, and are deeply involved in a variety of physiological phenomena. There are over 100 types. Controlling ion channels could help treat a wide range of diseases, but selective blocking is required to avoid strong side effects, as blocking one ion channel affects the entire body by simultaneously blocking another in a different location. Ion channels are widely expressed in vital organs such as the heart and brain, so there is a tendency for life-threatening side effects such as cardiotoxicity and neurotoxicity to emerge. Compound design expertise and systems enabling constant high throughput screening* to evaluate compounds are necessary, so this is a niche territory where few companies operate. Consequently, drugs that target ion channels account for only 5% of all drugs, and RaQualia is the only company in the world to have out-licensed five drugs in the area.

* High throughput screening (HTS) is a technology used to select useful drug candidates from a vast number of compounds rapidly and efficiently. Fast, efficient screening requires a systematic approach covering all processes, including compound storage, structural diversity, solution preparation, plate preparation, assay technology, robotic assays, measurement methodologies, data processing, and database building.

Ion channel mechanism



Source: Company data

Key physiological phenomena involving ion channels

Nerve signaling	→	Cognition, memory, five senses	→	Psychiatric and neurological disorders
Myocardial contraction	→	Arrhythmia	→	Cardiovascular disease
Skeletal muscle contraction	→	Quadriplegia, muscle atrophy	→	Muscular disorders
Hormone secretion	→	Blood sugar, diuresis	→	Metabolic and urological diseases

Source: Shared Research based on company data

Researchers originally involved when the company was under the Pfizer umbrella are conducting a large number of drug discovery research programs targeting ion channels based on advanced technology and abundant experience. In order to improve screening efficiency, the company teamed up with Hamamatsu Photonics K.K. (TSE Prime: 6965) to develop a voltage-gated ion channel assay system (EFS-FRET Assay System). The system acquires about 1,000 data points per day, enabling highly accurate, low-cost ion channel assays. It enables the company to conduct electrophysiological* research in-house, allowing it to distinguish its assays.

* Electrophysiology refers to both a branch of physiology and an experimental technique that elucidates the electrical properties of nerves, the brain, muscles, and other tissues or cells, and their effects on the body. The interior of cell membranes in living cells maintains an electrically charged state against the outside, and stimuli and information received by sensory cells and nerve cells from outside the cells change the membrane's potential. Neurophysiology in particular focuses on electrophysiological research, and conducts molecular-level research on ion channels and receptors.

The company has a track record of collaborative research in ion channel drug discovery with companies in Japan and overseas, which has resulted in some out-licensed programs.

- Eli Lilly & Company (US): 2010–2014
- Ajinomoto Pharmaceuticals Co., Ltd. (currently EA Pharma Co., Ltd., Japan): 2012–2017
- Asahi Kasei Pharma Corporation (Japan): 2013–2018
- XuanZhu Pharma Co., Ltd. (China): 2015–2018
- ASKA Pharmaceutical Co., Ltd. (Japan): Since 2019–2023

Development candidate compounds created by the company and licensees

Program	Compound code	Main indications	Licensee	Development stage
P2X7 receptor antagonist	RQ-00466479/AK1780	—	Asahi Kasei Pharma	Joint research in 2013 Eli Lilly running Phase II trials
Selective sodium channel blocker	Not disclosed	Analgesic and antipruritic	Maruho	Out-licensed in 2017 Not disclosed
Specific ion channel target	Not disclosed	Specific gastrointestinal disorders	EA Pharma	Joint research in 2012 Not disclosed
TRPM8 blocker	RQ-00434739	Chronic pain	Xgene	Out-licensed in 2021 Preparing for preclinical trials
Sodium channel blocker	RQ-00350215	Chronic pain	Hisamitsu	Out-licensed in 2021 Preparing for preclinical trials

Source: Shared Research based on company data

The TRPM8 blocker and sodium channel blocker programs were out-licensed in FY12/21, and are drug discovery programs targeting ion channels.

Expanding coverage to neurological diseases

The company has decided to shift the direction of in-house development from a line-up focused mainly on pain and gastrointestinal diseases to include neurological diseases. From FY12/22 onward, RaQualia plans to focus on areas with significant unmet medical needs including neurodegenerative, genetic, and rare diseases, and continue to discover new drugs by searching for target molecules and collaborating with academia in its disease models. The company has been working on pain, which is a nervous system related disorder, for many years, and with growing needs related to nervous system diseases among rare diseases, it decided that its technology and facilities were suitable.

Market and value chain

Global drug market

According to US-based IQVIA Holding Inc. (NYSE: IQV), global prescription drug sales in 2021 totaled USD1.4tn (JPY187.1tn, converted at JPY130.0/USD). It forecasts growth to a global market of USD1.9tn (JPY247.0tn) in 2027.

Global drug sales

(USDbn)	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	CAGR
US	331	326	343	389	431	455	465	493	521	545	586	5.2%
Japan	112	109	91	85	79	89	85	85	88	88	87	-0.5%
China	67	85	97	111	121	123	128	137	151	148	170	6.8%
Europe	263	246	258	266	239	245	259	279	284	301	338	6.7%
Latin America	67	71	73	65	75	87	98	69	70	63	73	-3.5%
Other	124	128	132	138	161	143	146	156	163	164	186	5.4%
Worldwide	963	964	994	1,056	1,104	1,141	1,179	1,218	1,277	1,309	1,440	4.8%

Source: Shared Research based on Japan Pharmaceutical Manufacturers Association (JPMA) DATA BOOK 2023 (data sourced from IQVIA)

Note: 5-year CAGR s are five years to 2021

Potential market for main target diseases

Disease	Number of patients	Market size	Region	Existing therapies	RaQualia's development pipeline
GERD	58mn (US)	JPY2tn	Worldwide	H2RA,	Tegoprazan
	17mn (Japan)	JPY450bn	US	PPI,	
		JPY250bn	Japan	vonoprazan	
Pain	50mn (US)	JPY2tn	Worldwide	Pregabalin,	EP4 receptor antagonist , COX-2 inhibitor,
	23mn (Japan)	JPY300bn	Japan	duloxetine,	TRPM8 blocker, P2X7 receptor antagonist,
				celecoxib, etc.	Sodium channel blocker
Cancer immunity	Approx. 12% of cancer patients respond to cancer immunotherapy	JPY10tn	Worldwide	Nivolumab, pembrolizumab, etc.	EP4 receptor antagonist
Chronic constipation	42mn (US)	JPY660bn JPY60bn	Worldwide Japan	Linacotide, lubiprostone, etc.	5-HT4 partial agonist
Gastroparesis	80,000–400,000	JPY200bn	Worldwide	Metoclopramide, etc.	5-HT4 partial agonist Motilin receptor agonist
Irritable bowel syndrome	5–20% of Japanese/Western adults	JPY100bn	Worldwide	Rifaximin, ramosetron, etc.	5-HT2B agonist
Cancer cachexia	Over 20% of cancer patients develop cachexia	JPY200bn	Worldwide	Anamorelin	Ghrelin receptor agonist
Constipation associated with spinal cord injury	300mn	Over JPY20bn	Worldwide	Laxatives	Ghrelin receptor agonist
Myelodysplastic syndrome	60,000–170,000 (US)	JPY100bn	Worldwide	Azacitidine, etc.	Tamibarotene
Acute myeloid leukemia	160,000 (worldwide), 7,000 (Japan) 7,000 (Japan)	JPY100bn	Worldwide	Azacitidine, venetoclax, etc.	Tamibarotene

Source: Shared Research based on company data

Peptic ulcer drug market

Global Industry Analysts, Inc. forecasts that the market for peptic ulcer drugs will grow at a CAGR of 2.6% from USD4.9bn (JPY0.6tn converted at JPY120.0/USD) in 2020 to USD5.9bn (JPY0.7tn) in 2027. It projects the market for proton pump inhibitors (PPIs) that suppress gastric acid secretions to reach USD4.2bn (JPY0.5tn, CAGR of 2.5%) in 2027.

Japanese drug market

According to IQVIA, prescription drug sales in Japan in 2022 reached JPY10.9tn (+3.2% YoY), the eighth consecutive year above JPY10tn. Sales of antacids, flatulence agents, and ulcer agents came to JPY331.7bn (-5.7% YoY) with sales of Takeda's antiulcer drug TAKECAB® at JPY111.9bn (+0.7% YoY), the fourth highest among domestic drugs.

Prescription drug sales in Japan

JPYmn	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Prescription drug sales in Japan	6,455,972	6,698,087	6,775,152	7,056,186	7,203,310	7,745,509	7,696,972	8,047,859	8,254,290	8,851,647	8,873,623
YoY	0.0%	3.8%	1.2%	4.1%	2.1%	7.5%	-0.6%	4.6%	2.6%	7.2%	0.2%
Antacids, flatulence/ulcer agents	391,242	400,632	383,713	392,301	395,660	418,112	408,593	422,148	427,027	446,651	429,890
YoY	-1.0%	2.4%	-4.2%	2.2%	0.9%	5.7%	-2.3%	3.3%	1.2%	4.6%	-3.8%
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Prescription drug sales in Japan	9,481,578	9,547,314	9,846,641	9,983,426	10,597,934	10,623,980	10,514,878	10,337,471	10,625,631	10,371,733	10,599,031
YoY	6.9%	0.7%	3.1%	1.4%	6.2%	0.2%	-1.0%	-1.7%	2.8%	-2.4%	2.2%
Antacids, flatulence/ulcer agents	434,997	408,604	418,289	397,394	389,788	376,365	377,550	349,783	351,329	347,142	351,640
YoY	1.2%	-6.1%	2.4%	-5.0%	-1.9%	-3.4%	0.3%	-7.4%	0.4%	-1.2%	1.3%
	2022										
Prescription drug sales in Japan	10,939,481										
YoY	3.2%										
Antacids, flatulence/ulcer agents	331,675										
YoY	-5.7%										

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Impact of Japan's NHI drug price revisions

The Ministry of Health, Labour and Welfare (MHLW) sets uniform nationwide prices (NHI prices) for human drugs. The price of a newly developed drug is based on a comparison with drugs already in use with similar efficacy (comparable drug method). If the new drug is more effective or novel, a premium is added, boosting the price. If there is no comparable drug with similar efficacy, the price is based on costs such as raw materials and manufacturing (cost accounting method). This can lead to a price difference of 1.5 to 3.5 times between original and generic drugs with the same ingredients.

However, the distribution process involves free price competition. Medical institutions and insurance pharmacies charge drug costs based on NHI prices, but the prices of drugs sold from drug companies to wholesalers and wholesalers to medical institutions and insurance pharmacies are freely set wholesale prices, resulting in differences from the NHI price (i.e., drug-price margins). In order to reduce the insurance benefit burden, the MHLW surveys sales prices and volumes for each individual drug, and revises (lowers) prices based on its findings every year (every second year until April 2018). Expensive drugs are covered by public insurance and are thought to have a significant impact on the insurance budget, leading to this arrangement for stepwise reductions. On the five occasions leading up to the April 2021 price revisions, the dispensing price was reduced by 5.69% on average.

Japan's arrangements to set NHI drug prices make it difficult for pharmaceutical companies to generate expected profits after launching drugs following extended periods of development and massive investments. The April 2022 drug price revisions featured a cut of 1.44% on a medical fee basis and a cut of 6.69% on a drug fee basis. This acted to shrink the domestic drug market by over JPY600bn in FY2022.

According to an August 2022 survey by MHLW, there were shortages, suspended shipments, or limited shipments for 28.2% of drugs overall and 41.0% of generic drugs due to a sharp rise in demand during the pandemic and steep cost increases due to the Russia-Ukraine war and yen weakness. As a consequence, in the off-year price revisions for FY2023, the ministry took limited extraordinary measures to reassess unprofitable products, resulting in price hikes to 1,100 relevant items. In the FY2023 revisions, prices were cut for 48% of all listed drugs (9,300) items, maintained for 46% (9,000), and raised for 6% (1,100).

NHI price revisions and average deviation

	1994	1996	1998	2000	2002	2004	2006	2008	2010
NHI price revisions (drug fee basis)	-6.6%	-4.4%	-9.7%	-7.0%	-6.3%	-4.2%	-6.7%	-5.2%	-5.75%
NHI price revisions (medical fee basis)	-2.0%	-1.3%	-2.7%	-1.6%	-1.3%	-0.9%	-1.6%	-1.1%	-1.23%
Average deviation	17.8%	13.1%	9.5%	7.1%	6.3%	8.0%	6.9%	8.4%	8.4%
	2012	2014	2016	2018	2020	2021	2022	2023	
NHI price revisions (drug fee basis)	-6.00%	-5.64%	-5.57%	-7.48%	-4.35%	-4.38%	-6.69%	-	
NHI price revisions (medical fee basis)	-1.26%	-1.22%	-1.22%	-1.65%	-0.93%	-0.99%	-1.44%	-	
Average deviation	8.2%	8.8%	9.1%	7.2%	8.0%	8.0%	7.6%	7.0%	

Source: Shared Research based on MHLW "NHI drug price revisions"

Global pet drug market

Global Market Insights Research Inc. (unlisted) estimates the value of the global pet drug market at about USD13.1bn (JPY1.7tn converted at JPY130.0/USD) in 2022, and projects a CAGR of about 6.8% through 2032. The market continues to expand as the number of pets is increasing due to growth in emerging economies and a burgeoning middle class.

Number of pet dogs and cats ('000)

Number of pet dogs			Number of pet cats	
US	69,929	1	US	74,059
China	27,400	2	China	53,100
Russia	12,520	3	Russia	17,800
Japan	12,000	4	Brazil	12,466
Philippines	11,600	5	France	11,480
India	10,200	6	Germany	8,200
Argentina	9,200	7	UK	8,000
UK	9,000	8	Italy	7,400
France	7,570	9	Ukraine	7,350
South Africa	7,400	10	Japan	7,300

Source: Shared Research based on The Hollard Insurance Company Pty Ltd., A Guide to Worldwide Pet Ownership

Changes to drug discovery modalities





Traditionally, small molecule compounds accounted for the bulk of drug discovery in the pharmaceutical industry, but starting in the 1990s, biopharmaceuticals (made from antibodies, enzymes, hormones, and other substances) produced using biotechnology started being approved. Currently modalities span a diverse range including middle molecule drugs, antibody drugs, nucleic acid drugs, gene therapies, and regenerative medicine.

Difference between small molecule drugs and biopharmaceuticals

Small molecule drugs have a molecular weight of under 500 Daltons, stable chemical structures, and are produced by chemical synthesis. Manufacturing and development costs are comparatively low, and there is a wide variety of dosage forms, not just tablets. Biopharmaceuticals have large molecular weights ranging from several thousand to 150,000 Daltons, complex structures, and are nonuniform. They are made from cells and microorganisms, and manufacturing and development costs are much higher than small molecule drugs. Because they are proteins that are broken down by digestive enzymes if taken orally, they are mainly administered by injection.

Biopharmaceuticals are made within cells using genetic recombination technology. The manufacturing process is extremely complicated, and slight variations in temperature, oxygen concentration, agitation speed, and cell density can affect the quality. Establishing manufacturing methods requires advanced technology and significant costs. While chemically synthesized small molecule drugs entail about 50 in-process tests, biopharmaceuticals require about 250. In some cases, culture methods have not been established for biopharmaceuticals, and in other cases, overseas companies may hold the patents even if the culture method has been established, and Japan has a lack of specialists. Regulators demand compliance with exacting quality control standards (good manufacturing practice or GMP) and stipulated standards, to constantly maintain the safety and efficacy of products during mass production.

Characteristics of small molecule drugs, medium molecule drugs, and biopharmaceuticals

Type of drug	Small molecule drugs	Medium molecule drugs, biopharmaceuticals		
		Peptide	Nucleic acid	Antibody
Shape (image)				
Molecular weight	100-500	100-10,000	Up to 10,000	About 100,000 or more
Manufacturing method	Chemical synthesis	Chemical synthesis/culture	Chemical synthesis/culture	Culture
Target molecule	Protein	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Nucleic acid (DNA/RNA)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Target molecule location	Intracellular	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Extracellular	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Administration route	Oral	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Other	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Source: Shared Research based on company data

Number of approvals by FDA (US)

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
New Molecular Entities (NMEs)	23	19	28	47	34	25	33	25	19	11	15	31	18	18	16
% of total	92.0%	90.5%	96.6%	88.7%	87.2%	83.3%	94.3%	92.6%	79.2%	64.7%	71.4%	86.1%	90.0%	81.8%	88.9%
Biologics License Applications (BLAs)	2	2	1	6	5	5	2	2	5	6	6	5	2	4	2
% of total	8.0%	9.5%	3.4%	11.3%	12.8%	16.7%	5.7%	7.4%	20.8%	35.3%	28.6%	13.9%	10.0%	18.2%	11.1%
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
New Molecular Entities (NMEs)	21	20	15	24	33	25	30	33	15	34	42	38	40	36	22
% of total	87.5%	76.9%	71.4%	80.0%	84.6%	92.6%	73.2%	73.3%	68.2%	73.9%	71.2%	79.2%	75.5%	72.0%	59.5%
Biologics License Applications (BLAs)	3	6	6	6	6	2	11	12	7	12	17	10	13	14	15
% of total	12.5%	23.1%	28.6%	20.0%	15.4%	7.4%	26.8%	26.7%	31.8%	26.1%	28.8%	20.8%	24.5%	28.0%	40.5%

Source: Shared Research based on company data

Note: New Molecular Entities (NMEs) are drugs containing new active ingredients and refer to small molecule drugs. Biologics License Applications (BLAs) are for new biopharmaceuticals

The advantage of biopharmaceuticals is that they enable an approach to targets that are difficult for small molecule drugs, but the disadvantage is that they cannot be administered orally. The share of small molecule drugs in FDA approvals declined in 2022 from 2021, but remained the most common at 59.5% of the total.

Competition

The Ministry of Economy Trade and Industry (METI) categorizes biotech start-ups into three broad groups. RaQualia can be classified as a "pipeline-type" as it is involved in the exploratory research, preclinical study, and early clinical trial stages. It looks for seed compounds in the fields of pain and gastrointestinal diseases and its development pipeline is based on its core ion channel drug discovery technology.

Types of biotech start-up business model

Business model		Japanese company example
Drug discovery platform technology-type (platform-type)	Has technology to create drug discovery seeds, which it out-licenses	PeptiDream, Carna Biosciences
Drug discovery pipeline-type (pipeline-type)	Integrated from seed exploration through in-house development and sales	NanoCarrier, RaQualia
Pipeline acquisition-type (In-licensing-type)	Acquires promising pipeline drugs through corporate acquisitions or in-licensing	Sosei Group, Solasia Pharma

Source: Shared Research based on Ministry of Economy, Trade and Industry, 2017, "Business models and financing activities of biotech startups" and company data

Note: The drug discovery pipeline model employs a variety of strategies, such as partial out-licensing for particular indications and selling territories, and development and sales through alliances.

Latest full-year results from biotech start-ups

Stock code	Company	Latest full-year results			Key characteristics
		Revenue (JPYmn)	Operating profit margin (%)	ROE (%)	
4579	RaQualia	2,918	29.7%	14.1%	Predecessor was Pfizer's central research laboratory in Japan. Business focuses on revenue from out-licensing new development compounds. Expanding from pain and gastrointestinal diseases to include neurological diseases.
2160	GNI Group	17,419	7.9%	7.9%	Vertically integrated company based in China, involved in drug discovery, clinical development, and manufacturing through sales. Has a leading share in idiopathic pulmonary fibrosis drugs in China. Has R&D locations in US and China.
4565	Sosei Group	15,569	22.1%	0.7%	A biotech start-up engaged in membrane protein GPCR-targeted drug discovery. Founded by Shinichi Tamura, former president of Genentech's Japanese subsidiary. The mainstay of its business is a UK acquisition, Heptares.
4571	NanoCarrier	264	-780.6%	-29.1%	Biotech start-up focused on oncology. Aims at new drugs with few side effects using its ultrafine micellar nanoparticle technology.
4572	Carna Biosciences	1,387	-91.6%	-26.4%	Revenue stable. Sells kinase proteins and provides early stage drug discovery support services such as screening under contract. Also engaged in drug discovery using BTK inhibitors.
4582	Symbio	10,008	19.6%	14.6%	Main focus on oncology, hematology, and rare diseases. In-licenses drug candidate compounds which it develops and commercializes.
4587	PeptiDream	26,852	33.4%	26.3%	Biopharmaceutical company using proprietary Peptide Discovery Platform System to produce specialty peptide drug candidates, which it creates with major drug companies and licenses technology for. Developing COVID-19 treatment drugs.
4597	Solasia Pharma	1,092	-226.1%	-97.1%	Biotech venture that in-licenses development rights for candidate substances and uses in clinical development, focusing on cancer. Fabless operations. Outsources manufacturing to overseas companies.
4883	Modalis	41	-5,094.3%	-63.8%	Biotech start-up that creates therapeutic drugs for rare genetic disorders through drug discovery using unique non-cleaving genome editing technology. Has research base in US.

Source: Shared Research based on company data

(JPYmn)	RaQualia (4579)			GNI group (2160)			Sosei Group (4565)		
	FY12/20 Cons.	FY12/21 Cons.	FY12/22 Cons.	FY12/20 IFRS, Cons.	FY12/21 IFRS, Cons.	FY12/22 IFRS, Cons.	FY12/20 IFRS, Cons.	FY12/21 IFRS, Cons.	FY12/22 IFRS, Cons.
Revenue	1,107	2,776	2,918	9,774	12,690	17,419	8,842	17,712	15,569
Gross profit	969	2,456	2,686	8,228	11,090	14,745	8,081	16,779	14,643
R&D expenses	932	1,127	1,249	1,243	2,016	2,545	3,793	5,931	7,454
SG&A expenses	523	620	572	5,181	7,959	10,966	3,435	3,940	4,377
Operating profit	-486	708	866	1,870	1,625	1,378	928	3,775	3,436
Recurring profit	-528	864	904	1,806	1,107	768	1,622	433	645
Net income	-607	756	723	1,366	55	-868	1,479	1,017	382
ROE	-14.1%	17.2%	14.1%	7.1%	12.8%	7.9%	3.0%	1.9%	0.7%

RaQualia Pharma 4579

ROA (RP-based)	-11.6%	18.2%	15.7%	8.2%	4.1%	2.4%	2.4%	0.5%	1.1%
Operating profit margin	-43.9%	25.5%	29.7%	19.1%	12.8%	7.9%	10.5%	21.3%	22.1%
Total assets	4,251	5,234	6,258	23,219	30,297	33,907	76,465	96,985	99,417
Net assets	4,011	4,788	5,497	12,769	19,266	19,811	52,381	57,468	57,936
Equity ratio	94.1%	91.3%	87.7%	47.4%	62.3%	61.8%	68.5%	59.3%	58.3%
Operating CF	-289	366	1,480	1,378	552	393	4,672	7,095	9,952
Investing CF	225	-279	-48	570	-261	-4,116	-150	278	1,043
Financial CF	-7	-16	-30	801	2,853	-646	20,278	11,123	-4,887
Cash and deposits	1,394	2,345	3,675	10,322	14,352	11,049	40,008	60,087	66,557
Interest-bearing debt	46	39	222	1,747	1,126	537	1,834	1,831	1,831
Net debt	-1,349	-2,306	-3,453	-8,575	-13,226	-10,512	-38,174	-58,256	-64,726
	NanoCarrier (4571)			Carma Biosciences (4572)			SymBio (4582)		
	FY03/20	FY03/21	FY03/22	FY12/20	FY12/21	FY12/22	FY12/20	FY12/21	FY12/22
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Revenue	553	313	264	1,133	2,018	1,387	2,987	8,257	10,008
Gross profit	475	275	223	941	1,882	1,215	867	5,800	7,600
R&D expenses	1,152	1,173	1,530	1,474	1,841	1,882	2,267	1,736	2,555
SG&A expenses	506	405	503	1,998	2,413	2,485	5,373	4,784	5,636
Operating profit	-1,106	-1,303	-2,061	-1,057	-531	-1,270	-4,506	1,016	1,964
Recurring profit	-1,144	-1,279	-1,925	-1,077	-523	-1,279	-4,616	1,001	2,000
Net income	-2,010	-2,836	-1,882	-1,111	-534	-1,350	-4,090	2,032	1,179
ROE	-27.8%	-35.2%	-29.1%	-21.1%	-10.2%	-26.4%	-104.7%	39.6%	14.6%
ROA (RP-based)	-13.1%	-15.3%	-25.7%	-29.0%	-13.2%	-34.0%	-79.9%	13.6%	19.2%
Operating profit margin	-200.0%	-415.9%	-780.6%	-93.3%	-26.3%	-91.6%	-150.9%	12.3%	19.6%
Total assets	8,945	7,821	7,136	4,835	5,433	4,266	6,275	8,453	10,433
Net assets	8,769	7,500	5,567	3,824	4,316	3,642	4,657	6,746	8,506
Equity ratio	97.0%	94.8%	77.6%	79.0%	79.3%	85.0%	74.2%	79.8%	77.6%
Operating CF	-1,139	-1,247	-1,753	-1,261	-1,537	-810	-4,122	140	1,614
Investing CF	-112	-872	-244	-70	-42	-126	-160	-71	-47
Financial CF	2,162	-11	1,146	724	1,065	367	4,222	-72	628
Cash and deposits	4,471	3,892	3,545	4,299	3,818	3,379	3,849	3,860	6,283
Interest-bearing debt	0	0	1,150	430	540	300	0	0	0
Net debt	-4,471	-3,892	-2,395	-3,869	-3,278	-3,079	-3,849	-3,860	-6,283
	PeptiDream (4587)			Solasia Pharma (4597)			Modalis (4883)		
	FY12/20	FY12/21	FY12/22	FY12/20	FY12/21	FY12/22	FY12/20	FY12/21	FY12/22
	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	Cons.	Cons.	Cons.
Revenue	11,677	9,422	26,852	454	559	1,092	342	1	41
Gross profit	9,529	7,029	18,113	244	373	662	-	-	-
R&D expenses	1,460	1,654	2,915	1,928	845	883	532	1,010	1,862
SG&A expenses	1,078	1,355	6,218	2,432	1,948	2,250	208	231	242
Operating profit	6,991	4,066	8,980	-4,116	-2,419	-2,470	-398	-1,239	-2,063
Recurring profit	6,976	3,804	6,653	-4,159	-2,442	-2,492	-440	-1,231	-1,996
Net income	4,448	2,573	7,554	-4,127	-2,478	-2,548	-448	-739	-2,703
ROE	23.4%	11.0%	26.3%	-78.1%	-79.4%	-97.1%	-8.9%	-12.6%	-63.8%
ROA (RP-based)	31.6%	14.3%	14.6%	-60.6%	-54.8%	-79.4%	-8.6%	-16.6%	-43.4%
Operating profit margin	59.9%	43.2%	33.4%	-906.6%	-432.7%	-226.1%	-116.5%	-112,676.7%	-5,094.3%
Total assets	26,267	27,035	63,865	5,775	3,144	3,134	6,277	6,069	3,130
Net assets	21,217	25,350	32,041	3,652	2,587	2,662	6,207	5,549	2,941
Equity ratio	80.5%	93.8%	50.2%	63.2%	82.3%	84.9%	98.9%	91.4%	93.4%
Operating CF	1,733	6,655	-83	-2,789	-2,473	-2,074	-377	-747	-1,896
Investing CF	-1,200	-2,283	-27,377	-171	-164	-418	-830	172	-186
Financial CF	-237	66	20,789	1,829	361	2,571	2,778	73	64
Cash and deposits	7,149	11,747	5,248	2,964	714	803	5,421	4,936	2,933
Interest-bearing debt	0	0	21,048	1,039	84	37	0	0	0
Net debt	-7,149	-11,747	15,801	-1,925	-630	-766	-5,421	-4,936	-2,933

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods. Pre-tax profit for companies that use IFRS is shown as recurring profit.

Strengths and weaknesses

Strengths

Focus on ion channel drug discovery based on research processes and operating procedures on par with pharmaceutical companies

The company took over drug discovery R&D expertise and methodologies from its predecessor, Pfizer's central research laboratory in Japan, following an employee buyout, and carried on with its research programs. It is able to create numerous drug candidates from its compound library, which includes hundreds of thousands of compounds. Advanced technological capabilities based on pharmaceutical company standard research processes and operating procedures have enabled it to discover drugs targeting ion channels with the potential to treat a wide range of diseases. It has already out-licensed five ion channel projects at an early stage.

Ion channels are widely expressed in vital organs needed for life, such as the heart and brain. There are over 100 types. Blocking one ion channel affects the entire body by simultaneously blocking ion channels in a different location, selective blocking is required to avoid strong side effects. Ion channel drug discovery is difficult as compound design expertise and systems enabling constant screening to evaluate compounds are necessary. As a result, drugs that target ion channels account for only 5% of all prescription drugs. According to the company, this is a niche territory with few companies operating in it, and RaQualia is the only company in the world to have out-licensed five drugs in the area.

The company has four products already commercialized by licensees, 10 pipelines (including those targeting ion channels) already out-licensed, and six at the pre-out-licensing stage. The value of biotech companies is generally considered to be the sum total of its pipelines. Shared Research thinks that RaQualia's corporate value is also backed by its alliances with major companies in Japan and overseas and joint research outcomes in both commercialized products and out-licensed projects, in addition to its ability to generate a series of candidate compounds.

Several hundred patents held

The company applies for basic patents (substance patents) and obtains rights in major countries around the world on an ongoing basis. It has several hundred patents (including peripheral patents) in various regions with different expiry dates (some effective until as late as 2040). After filing for a basic patent, the company aims to extend its life cycle of a compound it has created by seeking extensions and peripheral patents. Compound patents are effective for 20 years, and may be extended by up to five years, and peripheral patents (such as use patents and manufacturing process patents) can extend the exclusive period for a further 20 years. The company has extended patents that Pfizer originally applied for until the mid-2030s via extensions and peripheral patent applications.

Patent expirations are a matter of life and death for drug companies. Pfizer's major restructuring came about after its failure to develop a successor for its hyperlipidemia drug Lipitor® (which generated more than JPY1tn in revenue worldwide), despite investing JPY80bn. RaQualia's strategy aims to ensure revenue over the long term by delaying the launch of lower-priced generic drugs with the same ingredients and efficacy after the patent for a new drug has expired. In addition to obtaining strong patents with broad coverage, the timing of filing patent applications is important to avoid gaps. Some former Pfizer patent experts have come over to the company and are managing patent life cycles using pharmaceutical company expertise. This is a strength for the company.

Ability to efficiently identify candidate compounds from its massive compound library with SCARA robotic system

Many Japanese biotech startups find difficulty creating their next candidate compound seeds following establishment. RaQualia's ability to continuously create candidate compounds rests on its technology. The company screens compounds from its library of 800,000 on a daily basis using a robotics system called SCARA (Selective Compliance Assembly Robot Arm). It is able to evaluate 10,000 compounds a day using the system.

New compounds that will become the seeds of new drugs are synthesized by analyzing multidimensional data, with designs based on empirical rules and computational methods according to an efficient synthesis plan based on accumulated expertise. Synthetic samples (including impurities) synthesized by company chemists are delivered promptly to pharmacological evaluators in solution form with purity guaranteed through the company's CAP (Centralized Analysis & Purification) system, which automates the purification, weighing, dissolution, and dispensing processes. The company says that these technologies enhance the efficiency by roughly 10 times compared to chemists performing it manually, enabling it to supply 150 compounds per week.

All information concerning compounds is managed using two-dimensional barcodes in a database and used for structure-activity relationship (SAR) research. Barcode-controlled 384-hole plates conduct rapid, accurate pharmacological, safety, and metabolic studies. Results are promptly recorded in a database and reported to design and synthesis staff. This research cycle takes two weeks, which the company says is the fastest in the world.

Weaknesses

Drug discovery modality (methodology) relies on small molecule compounds

Small molecule drugs are generally less expensive to produce than biopharmaceuticals because they have a fixed chemical structural formula and are easy to mass-produce. Biopharmaceuticals have active ingredients derived from proteins, such as growth hormones, insulin, or antibodies, and are manufactured from cells, yeast, or bacteria. Their molecules are large and complex, and their properties and characteristics depend on the manufacturing process, boosting costs. Biopharmaceuticals launched as new drugs tend to be more expensive, and the market is also larger.

The company has an abundant development pipeline, with four products already commercialized, 10 pipelines (including those targeting ion channels) already out-licensed, and six at the pre-out-licensing stage. However, these are all small molecule drugs. The chances of launching a new drug are said to be one in 30,000, and developing a small molecule drug candidate compound takes about 72 months, and the market size in comparison to the time and cost involved is smaller than for biopharmaceuticals. The advantage of biopharmaceuticals is that they enable an approach to targets that are difficult for

small molecule drugs, but the disadvantage is that they cannot be administered orally. The share of small molecule drugs in FDA approvals remained greater than that of biopharmaceuticals at 59.5% of the total in 2022.

In its medium-term plan through FY12/24, the company is testing new modality concepts it hopes will drive the next generation of growth. However, Shared Research believes that it will take time to establish the necessary sophisticated platform technologies, as the development, manufacturing processes, and quality control for biopharmaceuticals are difficult.

Lack of control over amount or timing of revenue, because milestone and royalty payments depend on development and earnings at licensees

The company's revenue comes from: 1) upfront payments received when a contract is signed; 2) milestone payments that depend on pipeline progress such as launching clinical trials; 3) research cooperation payments when conducting joint research, and 4) royalty payments received once the drug under development is launched on the market. Upfront payments depend on the licensee's assessment of the company's development products, and are decided by negotiation. Milestone payments are sometimes delayed due to stalled development at the licensee. Research cooperation payments are insignificant compared to other payments. Finally, because royalty payments are based on a certain percentage of licensees' sales, the company's revenue depends on their marketing and sales capabilities.

The company has traditionally aimed at out-licensing at the preclinical preparation stage, and many of the out-licensing deals to date have been in the early development stages. However, due to the low likelihood of market launch for pipeline drugs in the early development stage, there is a tendency for upfront, milestone, and royalty payment rates to be lower. For this reason, the new management team has decided to carry on development of new drug candidate compounds until the proof of concept (POC) stage, which confirms usefulness and efficacy of a new drug candidate compound under development through administration to an animal or human, in a bid to enhance the value of its future pipelines. Obtaining POC confirmation generally requires reaching Phase II, entailing an investment of JPY2.0–5.0bn in general, which will require more funding than previously. If expenditures do not match the timing of revenue received from licensees, the company may need to raise funds.

Difficulty in recruiting and training specialist researchers

The company mainly hires researchers with abundant R&D experience at pharmaceutical companies. From FY12/22 onward, it plans to recruit holders of doctorates in a bid to stand shoulder to shoulder with the world's top companies. However, researchers in biopharmacology have high levels of expertise, and focus on specific disease areas. The company will need to hire personnel with experience in researching neurological diseases professionally as it branches out from its traditional areas of pain and gastrointestinal diseases. Per the Ministry of Education, Culture, Sports, Science and Technology, enrolments in graduate doctoral programs (typically five years) entered a downtrend after peaking in 2003, before a gentle uptrend since bottoming in 2015. In 2018 there were 15,000 doctoral students (up 0.9% YoY), including 6,000 specializing in health fields (medicine, dentistry, pharmacy, and health sciences). Furthermore, most biopharmaceutical drug discovery occurs overseas, and there are relatively few researchers in Japan. Shared Research thinks that the company's future growth will depend on its ability to hire personnel who match its particular requirements.

Historical results and financial statements

Income statement

Income statement (JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Operating revenue	228	154	146	705	1,419	745	1,703	1,107	2,776	2,918
YoY	687.0%	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.7%	-35.0%	150.7%	5.1%
Operating expenses	2,366	2,276	2,010	1,465	1,570	1,820	1,719	1,593	2,068	2,052
YoY	-11.2%	-3.8%	-11.7%	-27.1%	7.1%	15.9%	-5.5%	-7.3%	29.8%	-0.8%
Cost of revenue	0	3	-	118	150	89	263	138	321	232
YoY	-	731.3%	-	-	27.1%	-40.2%	193.9%	-47.5%	132.4%	-27.8%
R&D expenses	1,518	1,480	1,302	796	849	1,075	864	932	1,127	1,249
YoY	-15.9%	-2.5%	-12.0%	-38.9%	6.6%	26.6%	-19.6%	7.9%	20.9%	10.8%
R&D expense ratio	665.7%	961.7%	895.2%	112.9%	59.8%	144.3%	50.7%	84.2%	40.6%	42.8%
SG&A expenses	848	794	708	551	572	656	592	523	620	572
YoY	-1.6%	-6.3%	-10.9%	-22.1%	3.7%	14.7%	-9.7%	-11.6%	18.6%	-7.9%
SG&A ratio	371.7%	515.9%	486.4%	78.2%	40.3%	88.1%	34.8%	47.2%	22.3%	19.6%
Operating profit	-2,138	-2,123	-1,865	-760	-150	-1,075	-16	-486	708	866
YoY	-	-	-	-	-	-	-	-	-	22.4%
Operating profit margin	-	-	-	-	-	-	-	-	25.5%	29.7%
Non-operating income	327	187	99	94	85	45	49	35	177	77
Interest income	1	3	4	13	4	9	9	4	2	1
Interest on securities	-	31	78	52	35	32	35	28	21	13
Foreign exchange gains	55	27	14	-	1	-	-	-	146	44
Gain on valuation of compound financial instruments	-	20	-	8	-	-	4	1	0	-
Gain on sale of securities	-	-	1	-	-	-	-	-	-	-
Subsidy income	-	-	-	20	44	1	0	2	6	-
Dividend received	-	-	0	-	-	-	-	-	-	-
Reversal of allowance for investment loss	261	-	-	-	-	-	-	-	-	-
Other	10	6	1	2	1	3	1	1	3	6
Non-operating expenses	9	7	29	55	85	35	12	76	21	39
Interest expenses	-	-	-	-	-	-	0	1	6	-
Foreign exchange losses	-	-	-	55	-	33	0	76	-	-
Share issuance expenses	8	7	6	-	13	1	12	0	0	16
Loss on valuation of derivatives	-	-	-	-	-	-	-	-	10	-
Settlement package	-	-	-	-	-	-	-	-	10	-
Loss on valuation of compound financial instruments	-	-	21	-	2	1	-	-	-	11
Loss on redemption of securities	-	-	2	-	-	-	-	-	-	-
Other	1	-	-	-	0	-	-	-	-	-
Recurring profit	-1,820	-1,942	-1,795	-721	-81	-1,065	22	-528	864	904
YoY	-	-	-	-	-	-	-	-	-	4.7%
Recurring profit margin	-	-	-	-	-	-	1.3%	-	31.1%	31.0%
Extraordinary gains	801	1,549	66	-	21	5	6	9	17	14
Gain on sale of fixed assets	-	6	-	-	-	-	-	1	-	-
Gain on sale of investment securities	801	1,544	66	-	18	5	6	8	14	10
Gain on redemption of investment securities	-	-	-	-	-	-	-	-	2	4
Extraordinary losses	83	65	119	2	0	18	9	9	68	-
Impairment losses	58	-	-	-	-	-	-	3	-	-
Loss on sales of investment securities	-	-	-	-	0	-	-	0	-	-
Loss on redemption of investment securities	-	-	6	2	-	-	-	7	-	-
Special retirement expenses	-	10	69	-	-	-	-	-	-	-
Office relocation expenses	-	54	43	-	-	-	-	-	-	-
Loss on cancellation of lease contract	24	-	-	-	-	-	-	-	-	-
Other	1	-	-	-	-	-	-	-	-	-
Income taxes	6	7	6	5	-2	26	22	79	125	128
Implied tax rate	-0.6%	-1.5%	-0.3%	-0.7%	2.9%	-2.4%	80.4%	-15.0%	14.2%	15.0%
Net income attributable to owners of the parent	-1,108	-465	-1,854	-728	-58	-1,105	5	-607	756	723
YoY	-	-	-	-	-	-	-	-	-	-4.3%
Net margin	-	-	-	-	-	-	0.3%	-	27.2%	24.8%

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

In June 2008, the company received intellectual property rights from Pfizer covering a number of projects that were in the exploratory or development stages. When the company out-licenses rights for compounds transferred from Pfizer, it pays a certain percentage of the revenue it receives (upfront, milestone, and royalty payments) as royalties to Pfizer and record them under operating expenses.

The bulk of the upfront, milestone, and royalty payments the company receives from out-licensing is in US dollars, so it books foreign exchange gains or losses each fiscal year depending on currency fluctuations, which affect earnings.

Balance sheet

Balance sheet (JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Assets										

Cash and deposits	4,035	1,891	1,840	1,428	2,268	1,671	2,174	1,394	2,345	3,675
Notes and accounts receivable	60	20	73	58	449	1	747	531	1,205	602
Securities		1,184	503	9	329	168	26	719	314	251
Inventories	47	9	7	7	5	6	6	7	11	9
Advances paid		58	179	205	190	9	6	36	16	90
Prepaid expenses		55	65	56	62	72	69	50	90	109
Other	222	43	40	43	20	35	39	97	22	87
Total current assets	4,364	3,261	2,708	1,806	3,322	1,962	3,067	2,834	4,004	4,822
Buildings and structures	83	80	140	141	142	143	143	153	154	154
Tools, furniture, and fixtures	370	349	394	452	488	677	742	872	944	964
Lease assets						3	3	49	60	255
Accumulated depreciation	-464	-363	-273	-344	-415	-505	-639	-741	-859	-982
Machinery, equipment, and vehicles	17	2								
Total tangible fixed assets	7	85	261	249	216	318	249	333	299	391
Trademark	4	3	2	6	5	5	5	4	4	4
Software		6	8	7	4	28	27	28	29	20
Other	8	3	4	0	-	1	1	1	1	0
Total intangible assets	12	12	14	13	10	34	32	33	34	24
Investment securities	2,221	1,800	1,752	1,937	1,503	1,717	1,474	1,038	888	988
Long-term prepaid expenses		4	5	3	2	10	2	0	0	24
Deferred tax assets								3	-	
Other	45	39	12	11	11	12	12	10	9	8
Investments and other assets	2,266	1,844	1,769	1,951	1,516	1,738	1,488	1,051	897	1,020
Total fixed assets	2,284	1,941	2,044	2,213	1,742	2,090	1,769	1,417	1,230	1,436
Total assets	6,648	5,202	4,752	4,019	5,064	4,052	4,837	4,251	5,234	6,258
Liabilities										
Notes and accounts payable						2	34	42	46	128
Short-term debt	-	-	-	-	-	1	1	18	22	46
Accounts payable—other	142	119	123	126	63	99	67	53	113	206
Accrued expenses		63	57	40	44	48	50	50	63	60
Income taxes payable	17	16	15	1	21	14	20	21	80	31
Consumption taxes payable					14					37
Deferred tax liabilities				1						
Advances received		14		14	1		7			
Deposits		5	5	3	4	3	3	3	29	19
Other	74	46	-	5	-	-	-	-	10	4
Total current liabilities	233	262	200	190	149	164	183	187	401	494
Long-term debt	-	-	-	-	-	2	2	27	18	177
Asset retirement obligations			12	12	12	12	12	12	12	12
Deferred tax liabilities	669	109	26	29	16	16	19	14	16	3
Other	-	-	-	-	-	-	-	-	-	-
Total fixed liabilities	669	109	38	41	27	31	33	53	46	267
Total liabilities	902	371	238	231	176	195	216	240	446	761
Net assets										
Capital stock	8,628	8,952	9,806	2,238	2,741	2,793	2,255	2,255	2,257	2,266
Capital surplus	3,912	4,236	5,090	2,238	2,931	2,983	2,445	2,445	2,447	2,455
Retained earnings	-8,074	-8,567	-10,421	-728	-786	-1,890	-99	-706	50	773
Share subscription rights	33	11	11	15	17	13	12	12	11	8
Total net assets	5,746	4,831	4,514	3,788	4,888	3,857	4,621	4,011	4,788	5,497
Total liabilities and net assets	6,648	5,202	4,752	4,019	5,064	4,052	4,837	4,251	5,234	6,258
Working capital	107	29	80	65	452	7	718	496	1,170	483
Total interest-bearing debt	-	-	-	-	-	3	2	46	39	222
Net debt	-4,035	-1,891	-1,840	-1,428	-2,268	-1,668	-2,172	-1,349	-2,306	-3,453

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Cash flow statement

Cash flow statement (JPYmn)	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Cash flows from operating activities (1)	-2,179	-2,081	-2,117	-681	-307	-404	-531	-289	366	1,480
Pre-tax profit	-1,102	-632	-1,848	-723	-60	-1,078	27	-528	881	851
Depreciation	68	21	53	80	86	126	140	124	142	148
Impairment losses								3	-	
Gain and loss on sale and disposal of fixed assets								-1	-	
Change in working capital	-50	78	-51	15	-377	445	-711	223	-674	687
Cash flows from investing activities (2)	952	-796	666	-441	534	-368	216	225	-279	-48
Purchase of intangible/tangible fixed assets	-26	-101	-200	-37	-88	-221	-94	-156	-105	-32
Proceeds from sale of intangible/tangible fixed assets	4	2						1	-	
Free cash flow (1+2)	-1,227	-2,877	-1,451	-1,122	226	-772	-315	-64	87	1,432
Cash flows from financing activities	309	762	1,702	-	1,007	99	696	-7	-16	-30
Net change in short-term borrowings	-	-	-	-	-	-	-	-	-	-
Net change in long-term borrowings	-	-	-	-	-	-	-	-	-	12
Proceeds from issuance of, and redemption of, bonds	-	140	-	-	-	-	-	-	-	-
Proceeds from share issuance exercising share subscription rights	272	640	1,686		996	100	692	0	2	4
Proceeds from issuance of share subscription rights	38	15	15		11		4			
Repayments of lease obligations						-1	-1	-7	-18	-45
Change in cash and cash equivalents	-855	-2,031	252	-999	1,229	-644	371	-139	179	1,439
Cash and cash equivalents (year-end)	4,035	2,004	2,243	1,244	2,474	1,830	2,200	2,061	2,241	3,679

Source: Shared Research based on company data

Note: Figures may differ from company materials due to differences in rounding methods.

Cash flows from operating activities

In FY12/22, cash flows from operating activities increased by JPY1.1bn vs. FY12/21 inflows of JPY366mn to JPY1.5bn. This was mainly due to JPY851mn in pre-tax profit, JPY148mn in depreciation, and a JPY603mn decline in trade receivables.

Cash flows from investing activities

Cash outflows from investing activities came to JPY48mn, a decrease of JPY231mn versus cash outflows of JPY279mn in FY12/21. This was mainly attributable to JPY651mn used for the purchase of securities, JPY315mn for the purchase of investment securities, and JPY210mn in proceeds from sales of investment securities.

Cash flows from financing activities

Cash outflows from financing activities came to JPY30mn, an increase of JPY13mn versus cash outflows of JPY16mn in FY12/21. This was mainly attributable to repayments of lease obligations of JPY45mn.

Historical performance

FY12/22 results (out February 14, 2023)

Earnings summary

Full-year FY12/22 (January–December 2022) results

- Revenue: JPY2.9bn (+5.1% YoY)
- Operating profit: JPY866mn (+22.4% YoY)
- Recurring profit: JPY904mn (+4.7% YoY)
- Net income attributable to owners of the parent: JPY723mn (-4.3% YoY)
- R&D expenses: JPY1.2bn (+10.8% YoY)

Attainment versus the company's upwardly revised (on November 17, 2022) full-year FY12/22 forecast was revenue 94.9%, operating profit 105.1%, recurring profit 99.5%, and net income 99.9%. Operating expenses fell 0.8% YoY to JPY2.1bn, with R&D expenses up JPY122mn (+10.8%) YoY at JPY1.2bn but other SG&A expenses down 14.7% YoY at JPY803mn.

Operating revenue breakdown

Royalty revenue in FY12/22 came to JPY1.5bn (6.4% above the initial forecast), and other revenue including upfront and milestone revenue was JPY1.4bn (18.6% above).

In pet drugs, sales were firm for GALLIPRANT® and ENTyce®/ELURA®, and royalty revenue increased.

In human drugs, sales in South Korea remained strong for tegoprazan (K-CAB®), buoyed by the launch of an orally disintegrating tablet formulation and approval for a fifth indication (maintenance therapy for healed erosive esophagitis). In China, Shandong Luoxin Pharmaceutical Group Stock Co., Ltd. (SHE: 002793), a licensee of HK inno.N, obtained marketing approval for tegoprazan and began sales. In the Philippines, Metro Pharma Philippines, Inc. (unlisted) launched sales after obtaining approval.

With regard to the cyclooxygenase (COX-2) inhibitor, Ask At Inc. (to which RaQualia has out-licensed drug rights) has entered into a license and development support agreement with US-based Velo-1, Inc. (unlisted). RaQualia received a lump-sum payment from AskAt as a result. Eli Lilly, a sub-licensee of Asahi Kasei Pharma Corporation (unlisted; subsidiary of Asahi Kasei [TSE Prime: 3407]), initiated a Phase II clinical study of a novel P2X7 receptor antagonist discovered through joint research between the company and Asahi Kasei Pharma. The company received an upfront payment as a result.

Factors behind higher revenue and profits

While milestone revenue increased, the company did not book any upfront revenue due to the absence of new licensing agreements. The forex rate came in at JPY134.25/USD, versus the company assumption of JPY110.00/USD, which added JPY323mn to operating revenue. A change to development schedules resulted in a decline of JPY160mn in development

expenses, while the bringing forward of research investments increased depreciation by JPY30mn, for operating expenses JPY132mn below the initial forecast (down 0.8% YoY).

Milestone and upfront payments received in FY12/22

- Milestone payment of JPY115mn from Elanco on filing for approval of ELURA® in Europe
- Upfront payment of JPY300mn from HK inno.N on approval and launch of tegoprazan in China
- Upfront payment from HK inno.N on Brazil sublicense agreement
- Upfront payment from AskAt for license and development support agreements with US-based Velo-1
- Upfront payment from Asahi Kasei Pharma on Phase II clinical study of P2X7 receptor antagonist by Eli Lilly

Pipeline

Brisk royalties from four commercialized products

Pet drugs

In pet drugs, sales of GALLIPRANT® (generic name: grapiprant) for treatment of osteoarthritis in dogs and ENTYCE® (capromorelin) for treatment of anorexia in dogs, both out-licensed to Elanco, grew. Elanco also sells capromorelin under the brand name ELURA® as a drug for the management of weight loss in cats with chronic kidney disease in the US. Elanco applied for marketing approval for these drugs in Europe as well, and based on this development, RaQualia received a milestone payment of USD1mn from Elanco in Q1 (January–March 2022). According to RaQualia, sales of GALLIPRANT® continued double-digit growth five years after its launch in 2017. Since there is no official drug price system for pet drugs, which are basically free medical treatment, manufacturers have strong pricing power for products that pet owners rate highly. Sales royalties for the company are growing against this backdrop.

Development of tegoprazan in countries around the world

Sales of GERD treatment K-CAB® in South Korea by licensee HK inno.N continued to be robust, with sales from prescriptions outside hospitals amounting to KRW125.2bn (+14.2% YoY; roughly JPY12.5bn at JPY0.1/KRW) in FY12/22. Furthermore, in July 2022, HK inno.N received manufacturing and marketing approval in South Korea for the product as a maintenance therapy for healed erosive esophagitis. As a result, there are now five indications for which the product has received manufacturing and marketing approval in South Korea: erosive esophagitis, non-erosive reflux disease, gastric ulcer, adjuvant therapy for Helicobacter pylori eradication, and maintenance therapy for healed erosive esophagitis. K-CAB® has the most indications of P-CAB drugs used to suppress gastric acid secretion sold in South Korea.

HK inno.N aims to roll out the drug to 100 countries around the world. As of February 2023, it had done so in 36, and sub-licensees are starting to gain approval and launch sales. Prospects are for further growth in regions selling the drug over the next two years.

In April 2022, HK inno.N's Chinese licensee Luoxin received marketing approval from the Chinese authorities for tegoprazan. Just 15 days later, it started selling tegoprazan under the brand name Tai Xin Zan®. In China, it received Category 1 designation as an innovative drug, and is being sold in major hospitals, retail drugstores, and online. In January 2023, it was listed on the National Reimbursement Drug List (NRDL). Luoxin Pharmaceutical, the distributor, targets sales of CNY1.0bn (approximately JPY19.6bn, converted at JPY19.6/CNY) for 2023 and CNY3.0bn (JPY58.8bn) in the medium to long term. The company expects sales to grow in line with increasing prescription numbers as it is covered under insurance.

In May 2022, Metro Pharma Philippines, Inc. (unlisted), acquired approval in the Philippines and launched sales. In October 2022, PT Kalbe Pharma Tbk (KLBK) gained approval to market the drug for non-erosive reflux disease in Indonesia. Licensees have applied or are preparing to file for approval in another 28 countries.

HK inno.N is looking for licensees in other regions. In February 2022, HK inno.N reached a manufacturing supply agreement for Malaysia with the country's largest drug company, Pharmaniaga Logistics Sdn Bhd (PHARMA 7081), and in May 2022 it signed a licensing agreement covering India and six other countries with Dr. Reddy's Laboratories.

Upfront payments

In July 2022, AskAt (RaQualia's licensee) entered into a license agreement with US-based Velo-1 for global rights to cyclooxygenase-2 (COX-2) inhibitor RQ-00317076 as a drug for animals, as well as a two-year development support agreement with Velo-1. The company has the right to receive part of the royalty revenue for RQ-00317076 from AskAt and booked the upfront payment from this agreement as operating revenue in Q3.

In November 2022, sublicensee Eli Lilly, which acquired rights to P2X7 receptor antagonist from Asahi Kasei Pharma Corporation (unlisted, Asahi Kasei Pharma, a subsidiary of Asahi Kasei [TSE Prime: 3407]), started a Phase II trial for chronic pain. With the start of the trial, RaQualia reached the threshold for a milestone payment and received an upfront payment of USD4mn (JPY500mn based on JPY125/USD translation) from Asahi Kasei Pharma. P2X7 receptor inhibitors represent a potential market worth more than JPY1tn. The start of Phase II is a major step forward, given that the company is targeting first-in-class. Based on the licensing agreement with Asahi Kasei Pharma, RaQualia has rights to payments from Asahi Kasei Pharma for each developmental milestone reached by the P2X7 receptor inhibitor and a set percentage of sales as royalty income once commercialized.

Out-licensed and pre-out-licensing programs

Out-licensed programs are in the preclinical development stage or later at licensees. Xgene Pharmaceutical Co. Ltd. (unlisted) began preclinical studies of the TRPM8 blocker following a 2021 licensing agreement with RaQualia.

In pre-out-licensing programs, preclinical trials are underway on a ghrelin receptor agonist being developed in-house. With tegoprazan, the company is aiming at rapid approval in Japan and to that end is getting ready to launch clinical studies while also seeking potential out-licensing candidates.

At the exploratory research stage, RaQualia is steadily advancing joint research with ASKA Pharmaceutical Co., Ltd. (unlisted, subsidiary of ASKA Pharmaceutical Holdings Co., Ltd. [TSE Prime: 4886]), while also working on in-house discovery of development candidate compounds. In Q3 FY12/22, the company entered into a joint research agreement with STAND Therapeutics Co., Ltd. (unlisted) and started a joint research project to discover new drugs for intractable and rare diseases by utilizing the company's ion channel drug discovery technology and STAND's intracellular antibody production technology.

In May 2022, the company and Socium Inc. (unlisted) signed a joint research agreement to look for indications for RaQualia's compounds to treat intractable and rare diseases, using Socium's proprietary disease database and AI drug discovery platform. In Q3 FY12/22, the company entered into a joint research agreement with STAND Therapeutics Co., Ltd. (unlisted) and started a joint research project to discover new drugs for intractable and rare diseases by utilizing the company's ion channel drug discovery technology and STAND's intracellular antibody production technology. In December 2022, the company began joint research with Veritas In Silico Inc. (unlisted) and D. Western Therapeutics Institute (TSE Growth: 4576).

In addition, clinical trials for the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are under way in the US by Syros Pharmaceuticals Inc. (NASDAQ: SYRS) for a retinoic acid receptor alpha agonist (tamibarotene), which was discovered by consolidated subsidiary TMRC Co., Ltd. and licensed to Syros. In January 2023, tamibarotene received fast-track designation from the US Food and Drug Administration (FDA) for higher-risk myelodysplastic syndrome (HR-MDS).

Skip US Phase II trials for Tegoprazan

In October 2022, HK inno.N's sublicensee Braintree commenced US Phase III trials of tegoprazan for erosive esophagitis and non-erosive reflux disease. After consultations with the US Food and Drug Administration (FDA), Braintree obtained approval to skip Phase II and go directly to Phase III. Patients were enrolled in the Phase III study according to the FDA-approved clinical trial protocol, and the first patient was dosed.

In the Phase III study, proton pump inhibitors (PPIs) will be used as control drugs to evaluate the efficacy and safety of tegoprazan. Based on the licensing agreement with HK inno.N, the company is entitled to milestone payments based on the development progress of tegoprazan in the US and a predetermined percentage of US sales as royalties. While RaQualia will not receive a milestone payment for the start of Phase III, the company believes an accelerated US approval and launch will contribute to longer-term earnings growth.

Series 16 share subscription rights issued

In the medium-term management plan, RaQualia has outlined the total R&D investment of JPY2.4bn by the end of 2024 (JPY1.2bn for explorative research and JPY1.2bn for non-clinical and clinical studies, not including personnel expenses). In addition, the company plans to invest approximately JPY2.8bn over the next five years to enhance its R&D activities further and accelerate progress. It will use this fund to explore new modalities, promote AI-driven drug discovery, and revamp laboratory facilities. Because these funding needs cannot be covered by cash on hand (about JPY4.0bn) or expected income, the company determined that it needed to secure new funds to invest in development and decided to issue new shares and share subscription rights via third-party allotment.

Q3 FY12/22 results (out November 11, 2022)

Earnings summary

Q3 FY12/22 (January–September 2022) results

- Operating revenue: JPY1.9bn (+17.3% YoY)
- Operating profit: JPY501mn (+367.6% YoY)
- Recurring profit: JPY676mn (+183.8% YoY)
- Net income attributable to owners of the parent: JPY467mn (+175.9% YoY)
- R&D expenses: JPY840mn (+7.6% YoY)

Progress against the company's full-year forecast was operating revenue 73.1%, operating profit 119.3%, recurring profit 161.1%, and net income 136.6% (while progress against November 17 revised forecasts was 61.0% for operating revenue, 60.8% for operating profit, 74.4% for recurring profit, and 64.5% for net income).

Factors behind higher revenue and profits

Cumulative Q3 operating revenue increased 17.3% to JPY1.9bn, comprised of JPY1.1bn (+69.2% YoY) in royalty revenue and JPY820n (+16.6%) in other revenue.

In pet drugs, sales were firm for GALLIPRANT® and ENTYCE®/ELURA®. In human drugs, sales in South Korea remained strong for tegoprazan (K-CAB®), buoyed by the launch of an orally disintegrating tablet formulation and approval for a fifth indication (maintenance therapy for healed erosive esophagitis). In China, Shandong Luoxin Pharmaceutical Group Stock Co., Ltd. (SHE: 002793), a licensee of HK inno.N, obtained marketing approval for tegoprazan and began sales. With regard to the cyclooxygenase (COX-2) inhibitor, AskAt Inc. to which RaQualia has out-licensed the rights to the drug, has entered into a license and development support agreement with US-based Velo-1, Inc. (unlisted). RaQualia received a lump-sum payment from AskAt as a result.

Of the JPY1.4bn (-7.4% YoY) in total operating expenses, R&D expenses increased JPY60mn to JPY840mn (+7.6% YoY) while other SG&A expenses were JPY395mn (-15.3% YoY). R&D spending reached 57.0% of the full-year budget, showing no major change in R&D activity.

Pipeline

Launched products

In pet drugs, sales of GALLIPRANT® (generic name: grapiprant) for treatment of osteoarthritis in dogs and ENTYCE® (capromorelin) for treatment of anorexia in dogs, both out-licensed to Elanco, grew. Elanco also sells capromorelin under the brand name ELURA® as a drug for the management of weight loss in cats with chronic kidney disease in the US. Elanco applied for marketing approval for these drugs in Europe as well, and based on this development, RaQualia received a milestone payment of USD1mn from Elanco in Q1 (January–March 2022). According to RaQualia, sales of GALLIPRANT® continue to grow five years after its launch in 2017.

Development of tegoprazan in countries around the world

Sales of GERD treatment K-CAB® in South Korea by licensee HK inno.N continued to be robust, with sales from external prescriptions amounting to KRW31.6bn (+12.5% YoY) in Q3 FY12/22, and cumulative sales from external prescriptions of KRW92.2bn (+18.1%) year to date for FY12/22. Furthermore, in July 2022, HK inno.N received manufacturing and marketing approval in South Korea for the product as a maintenance therapy for healed erosive esophagitis. As a result, there are now five indications for which the product has received manufacturing and marketing approval in South Korea: erosive esophagitis, non-erosive reflux disease, gastric ulcer, adjuvant therapy for Helicobacter pylori eradication, and maintenance therapy for healed erosive esophagitis.

In China, Luoxin, a licensee of HK inno.N commenced sales of tegoprazan in April 2022 and has taken steps to obtain insurance reimbursement. Preparations are underway for its launch in Mongolia and the Philippines. In addition, the product is under review or in preparation for approval in 29 other countries, including Indonesia, Thailand, and Mexico.

Out-licensed programs under development

Out-licensed programs are in the preclinical development stage or later at licensees.

Out-licensed programs (humans)

- Tegoprazan: Launched in South Korea. Preparing for commercialization in Mongolia, the Philippines, and Indonesia. Braintree commenced Phase III in the US
- EP4 receptor antagonist: Ikena Oncology (NASDAQ: IKNA), a licensee of AskAt, had been conducting clinical trials but decided to suspend development in December 2022
- CB2 agonist: Oxford Cannabinoid Technologies, a licensee of AskAt, is conducting pre-clinical studies
- Selective sodium channel blocker: Under development by Maruho
- P2X7 receptor antagonist: Eli Lilly initiated Phase II (November 2022)
- Specific ion channel target: Under development by EA Pharma Co., Ltd (unlisted, EA Pharma, formerly Ajinomoto Pharmaceuticals Co., Ltd but now a consolidated subsidiary of Eisai [TSE Prime: 4523])
- TRPM8 blocker: Xgene Pharmaceutical Co., Ltd (unlisted) is conducting pre-clinical studies.
- Sodium channel blocker: Hisamitsu Pharmaceutical is preparing for pre-clinical studies.

Out-licensed programs (pets)

- COX-2 inhibitor: Velo-1, a licensee of AskAt, is preparing for development

Pre-out-licensing programs

In pre-out-licensing programs, preclinical trials are underway on a ghrelin receptor agonist being developed in-house. With tegoprazan, the company is aiming at rapid approval in Japan and to that end is getting ready to launch clinical studies while also seeking potential out-licensing candidates.

- Tegoprazan (Japan): Preparing for clinical development and looking for licensing partner candidates
- Ghrelin receptor agonist: Pre-clinical studies underway at contract research organization
- 5-HT4 partial agonist, 5-HT2B antagonist, motilin receptor agonist: Conducting out-licensing activities
- TRPM8 blocker: Considering pre-clinical studies

At the exploratory research stage, RaQualia is steadily advancing joint research with ASKA Pharmaceutical Co., Ltd. (unlisted, subsidiary of ASKA Pharmaceutical Holdings Co., Ltd. [TSE Prime: 4886]), while also working on in-house discovery of development candidate compounds. In Q3 FY12/22, the company entered into a joint research agreement with STAND Therapeutics Co., Ltd. (unlisted) and started a joint research project to discover new drugs for intractable and rare diseases by utilizing the company's ion channel drug discovery technology and STAND's intracellular antibody production technology.

In addition, clinical trials for the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are under way in the US by Syros Pharmaceuticals Inc. (NASDAQ: SYRS) for a retinoic acid receptor alpha agonist (tamibarotene), which was discovered by consolidated subsidiary TMRC Co., Ltd. and licensed to Syros. In November 2022, Syros presented data from the safety lead-in part of the AML Phase II trial and announced it is advancing the randomized part of the study.

1H FY12/22 results (out August 15, 2022)

Earnings summary

1H FY12/22 (January–June 2022) results

- Operating revenue: JPY1.4bn (+9.6% YoY)
- Operating profit: JPY551mn (+75.1% YoY)
- Recurring profit: JPY681mn (+57.4% YoY)
- Net income attributable to owners of the parent: JPY469mn (+55.0% YoY)
- R&D expenses: JPY497mn (+0.0% YoY)
- Progress against full-year forecast: Operating revenue 55.6%, operating profit 131.3%, recurring profit 162.2%, and net income 137.3%

Factors behind higher revenue and profits

In 1H FY12/22, operating revenue came to JPY1.4bn (+9.6% YoY), comprising royalty revenue of JPY699mn (+43.2% YoY), milestone payments of JPY434mn (-42.0% YoY), which included a one-time payment of JPY300mn from approval and launch of tegoprazan in China, and other revenue of JPY314mn (+XX% YoY).

In pet drugs, while sales of GALLIPRANT® were sluggish in Europe due to inclement weather among other factors, sales of the drug maintained double-digit growth in the US. ENTyce® and ELURA® also performed strong. In human drugs, orally disintegrating tablet formulation of tegoprazan (K-CAB®) was launched, and the drug was approved for its fifth indication, maintenance therapy for healed erosive esophagitis, with sales in South Korea remaining strong. In China, Luoxin, a licensee of HK inno.N, obtained marketing approval for tegoprazan and began sales, triggering a milestone payment of JPY300mn.

R&D expenses totaled JPY528mn (+6.4% YoY, 35.8% of the full-year plan), consisting of JPY481mn for discovery of development candidate compounds and JPY46mn for preclinical studies of a ghrelin receptor agonist and preparation of clinical pharmacological studies of tegoprazan. All profit categories exceeded their respective full-year targets as of end-1H, but the company maintained its forecast as it expects to incur R&D and other expenses in 2H.

Pipeline

Launched products

In pet drugs, sales of GALLIPRANT® (generic name: grapiprant) for treatment of osteoarthritis in dogs and ENTyce® (capromorelin) for treatment of anorexia in dogs, both out-licensed to Elanco, grew. Elanco also sells capromorelin under the brand name ELURA® as a drug for the management of weight loss in cats with chronic kidney disease in the US. Elanco applied for marketing approval for these drugs in Europe as well, and based on this development, RaQualia received a milestone payment of USD1mn from Elanco in Q1 (January–March 2022).

Development of tegoprazan in countries around the world

Sales of GERD treatment K-CAB® in South Korea by licensee HK inno.N continued to be robust, with sales amounting to KRW60.6bn (approximately JPY6.0bn, converted at JPY0.10/KRW; +21.2% YoY). HK inno.N obtained marketing approval for and launched the new orally disintegrating tablet formulation of tegoprazan in South Korea. In China, Luoxin, a licensee of HK inno.N in the country, obtained marketing approval for tegoprazan from the Chinese authorities in April 2022 and began sales in the same month. Luoxin targets sales of CNY1.0bn (approximately JPY19.6bn, converted at JPY19.6/CNY) for 2023 and CNY3.0bn (JPY58.8bn) in the medium to long term. The company will receive royalty payments from HK inno.N after the latter confirms its revenue from the drug.

In April 2022, HK inno.N completed Phase I clinical trial of tegoprazan in the US, and sublicensee Braintree had pre-clinical trial consultations with the US FDA with the goal of commencing clinical trials within 2022. In May 2022, HK inno.N entered into a license agreement with India-based Dr. Reddy's Laboratories (NSD: DRREDDY), covering marketing rights in seven countries including India in Asia, Eastern Europe, and Africa. Also in May 2022, Metro, a sublicensee of HK inno.N in the Philippines, obtained marketing approval for tegoprazan for erosive esophagitis and three other indications.

Out-licensed pipeline

Out-licensed programs are in the preclinical development stage or later at licensees.

- ▶ EP4 receptor antagonist: US-based Ikena Oncology (NASDAQ: IKNA), a sublicensee of the company's licensee AskAt Inc. (unlisted), is conducting a Phase Ib clinical trial of the pipeline drug as cancer immunotherapy in the US. In China, Ningbo NewBay Medical Technology Development Co., Ltd. (unlisted), a licensee of AskAt, is conducting a Phase I study in the oncology field.
- ▶ CB2 agonist: UK-based OCT, a licensee of AskAt, is conducting preclinical studies in the UK.
- ▶ P2X7 receptor antagonist: US-based Eli Lilly is preparing to conduct a Phase II study.
- ▶ TRPM8 blocker: Hong Kong-based Xgene Pharmaceutical commenced preclinical studies.
- ▶ Sodium channel blocker: Hisamitsu Pharmaceutical is preparing to conduct preclinical studies.

In addition to the above, although development stage is undisclosed, a selective sodium channel blocker is being developed by Maruho Co., Ltd. (unlisted), and a candidate compound targeting a specific ion channel is under development by EA Pharma.

Pre-out-licensing pipeline

- ▶ Tegoprazan (Japan): Consultations with PMDA and discussions with candidate licensing partners ongoing with an eye toward starting clinical development
- ▶ Ghrelin receptor agonist: Preclinical studies underway at a contract research organization
- ▶ 5-HT4 partial agonist, 5-HT2B antagonist, motilin receptor agonist: Out-licensing activities ongoing

Q1 FY12/22 results

Earnings summary

Q1 FY12/22 (January–March 2022) results

- Revenue: JPY339mn (-48.3% YoY)
- Operating loss: JPY120mn (profit of JPY149mn in Q1 FY12/21)
- Recurring loss: JPY70mn (profit of JPY268mn)
- Net loss attributable to owners of the parent: JPY121mn (net income of JPY189mn)
- R&D expenses: JPY264mn (+3.0% YoY)
- Progress against full-year forecast: Revenue 13.0%, R&D expenses 17.9%

In Q1 FY12/22, the company generated revenue of JPY339mn, comprising royalty revenue of JPY184mn (+36% YoY), milestone payments of JPY115mn accompanying the approval of ELURA® in Europe, and other revenue of JPY40mn. Revenue declined versus Q1 FY12/21, when the company received a total of JPY516mn in milestone payments from Asahi Kasei Pharma and Maruho.

The company spent JPY264mn on R&D, primarily exploratory research. It conducted preclinical studies into its ghrelin receptor agonist and prepared to start clinical pharmacological studies of tegoprazan.

Revenue came in at 13.0% of the full-year forecast. Royalty payments for tegoprazan are twice yearly, and booked in Q2 and Q4, so progress was largely in line with the company forecast. At the time of the Q1 results announcement, the company maintained its full-year FY12/22 forecast.

Pipeline

Launched products

Sales of K-CAB® (GERD treatment) in South Korea by licensee HK inno.N remained strong, with revenue from prescriptions outside hospitals up 23.5% YoY. HK inno.N received manufacturing and marketing approval for a new orally disintegrating tablet formulation of tegoprazan in South Korea. In China, HK inno.N's Chinese licensee Luoxin Pharmaceutical received manufacturing and marketing approval from Chinese authorities in April 2022. In Malaysia, HK inno.N signed a drug product supply agreement with Pharmaniaga.

In pet drugs, sales of GALLIPRANT® (grapiprant; treatment for osteoarthritis in dogs) and ENTyce® (capromorelin; treatment for anorexia in dogs) remained in an uptrend for licensee Elanco. Elanco also sells capromorelin under the brand name ELURA® as a drug for the management of weight loss in cats with CKD. Elanco filed for manufacturing and marketing approval for capromorelin in Europe, and the company received a milestone payment of USD1mn in Q1.

Out-licensed pipeline

Out-licensed programs are in the preclinical development stage or later at licensees.

Pre-out-licensing pipeline

The company plans to develop tegoprazan in Japan and aims at efficient development and approval in Japan using South Korean data. It decided to conduct clinical pharmacological studies to evaluate ethnic differences between Japanese and Korean people. In February 2022, by mutual consent, the company and Meiji Seika Pharma Co., Ltd. terminated a license agreement signed in March 2011 granting the latter exclusive rights to develop and market the schizophrenia drug ziprasidone in Japan. The company decided to return the license to the licensor, US-based Viatris Inc. (NASDAQ: VTRS).

News and topics

New share issuance as restricted stock compensation for directors

2023-03-24

RaQualia Pharma Inc. announced the issuance of new shares as stock compensation with transfer restrictions for directors.

The company announced that it had resolved to issue new shares as restricted stock compensation to directors at its Board of Directors meeting on March 24, 2023. The restricted stock compensation plan for the company's directors had been approved at the general meeting of shareholders held in March 2022.

Payment date	April 24, 2023
Type and number of shares to be issued	14,100 shares of common stock in the company
Issue price	JPY821 per share (closing price on March 23, 2023)
Total issue price	JPY11,576,100
Allottees	Three directors of the company, excluding Audit & Supervisory Committee members and outside directors

The purpose of the restricted stock compensation plan is to provide incentives for sustainable improvement of the company's corporate value while promoting value sharing with shareholders. Under the plan, the company will offer annual monetary compensation claims of up to JPY15mn to eligible directors, who will then receive an allotment of restricted shares by providing the full amount in cash. In order to implement value sharing with shareholders over the medium to long term, the transfer restriction period will be from the date of allotment until the eligible director cease to hold a directorship or other positions as determined by the Board of Directors.

Nav1.7 and Nav1.8 sodium channel blocker (amide derivative) approved for a patent in China

2023-03-03

RaQualia Pharma Inc. announced that its Nav1.7 and Nav1.8 sodium channel blocker (amide derivative) had been approved for a patent in China.

The company announced that it was notified of the decision to grant a substance patent to its Nav1.7 and Nav1.8 sodium channel blocker, which had been under review in China, from the Chinese patent office. An invention is approved for a patent when the patent office of a country determines that the invention is worth granting a patent right to after a review. The patent is registered once the patent fees are paid, and the patent right comes into effect in the relevant country. The granting of the patent to the sodium channel blocker indicates that the company's IP right to the drug has been recognized in China, following Japan, Europe, and the US.

The sodium channel blocker discovered and developed by the company specifically acts on Nav1.7 and Nav1.8 sodium channels, and has been shown to be highly effective in multiple animal models of pain. Also, because the drug exhibits strong selectivity for Nav1.5 sodium channels which play an important role in the heart, the company expects the drug to become a breakthrough therapy with the potential to suppress adverse effects on the cardiovascular system.

RaQualia says this development will have no impact on its FY12/23 earnings, but believes that the amide derivate, which has been approved for a patent, will contribute to increasing its corporate value in the medium to long term through future development.

Marketing approval in Mexico for GERD treatment tegoprazan

2023-02-14

RaQualia Pharma Inc. announced marketing approval in Mexico for tegoprazan, a treatment for gastroesophageal reflux disease (GERD).

RaQualia has an out-licensing agreement for tegoprazan with South Korea-based HK inno.N (South Korean brand name: K-CAB®). The company announced that Mexico-based sublicensee Laboratorios Carnot (unlisted) has received marketing approval for tegoprazan from the Mexican regulatory authorities. Carnot has been working toward gaining approval since 2019, when it entered into a sublicense agreement with HK inno.N. The drug has been approved in Mexico for four indications: erosive esophagitis, non-erosive reflux disease, gastric ulcer, and adjuvant therapy for Helicobacter pylori eradication (combination antibiotic therapy for peptic ulcer and chronic atrophic gastritis patients). Mexico is the seventh nation to approve tegoprazan, following South Korea, Mongolia, China, the Philippines, Indonesia, and Singapore.

Under its agreement with HK inno.N, Carnot has been granted the license for tegoprazan in 17 South and Central American countries, including Mexico. According to the company, the market for peptic ulcer drugs in the region is worth roughly JPY210bn. Following its approval in Mexico, the company expects moves to launch the drug in other parts of Latin America.

RaQualia has entered into a licensing agreement with HK inno.N, granting it an exclusive license with sublicensing rights for development, sales, and manufacturing of tegoprazan. Based on the agreement, RaQualia is entitled to receive a certain percentage of the revenue that HK Inno.N receives from sublicensees. RaQualia will receive an upfront payment from HK Inno.N for the approval of tegoprazan in Mexico, which it will book as operating revenue in Q1 FY12/23.

Establishment of new research center in Shonan Health Innovation Park and fast track designation of tamibarotene for MDS by US FDA

2023-01-27

RaQualia Pharma Inc. announced that it had established a new research center in Shonan Health Innovation Park.

The company has up to now conducted drug discovery research primarily at RaQualia Industry-Academia Collaborative Research Center located on the premise of Higashiyama Campus, Nagoya University. It announced on the date of this release that it would open a new research center in Shonan Health Innovation Park (Fujisawa, Kanagawa Prefecture; Shonan iPark) and commence research activities there. Established in April 2018, Shonan iPark is Japan's first pharma-led science park, where more than 2,000 persons belonging to over 150 companies and organizations (as of January 2023), including pharmaceutical companies, experts and researchers on next-generation medicine and AI, startups, and administrative agencies, make up an ecosystem.

Through the establishment of the new research center, RaQualia plans to build networks with a diverse array of partners, including those already operating in Shonan iPark. The company looks to capture opportunities to collaborate with companies conducting cutting-edge clinical trials or possessing advanced technologies related to novel modalities, target molecule searches, and AI-driven drug discovery, and in doing so further enhance its drug discovery value chain and portfolio. The company says this development will have minimal impact on its FY12/23 earnings.

The company announced that US-based Syros Pharmaceuticals Inc. obtained fast track designation from the US FDA for tamibarotene for the treatment of myelodysplastic syndrome (MDS).

RaQualia announced that retinoic acid receptor alpha (tamibarotene), which consolidated subsidiary TMRC Co., Ltd. had out-licensed to US-based Syros Pharmaceuticals Inc. (NASDAQ: SYRS), was granted fast track designation from the US Food and Drug Administration (FDA) for the treatment of higher-risk MDS.

Fast track is a program initiated by the FDA to expedite the approval review process and promote development of drug candidates that aim to treat serious diseases and have demonstrated potential to address unmet medical needs through non-clinical and clinical studies. Developers of drug candidates that have received fast track designation can frequently consult the FDA regarding their development plan. Further, provided that their efficacy and safety are sufficiently supported by clinical data, these drug candidates may be eligible for priority review or expedited approval.

Tamibarotene is a selective retinoic acid receptor alpha (RAR α) agonist, that, due to its exhibition of strong differentiation-inducing activity, is expected to have a synergistic effect when used in combination with other antitumor agents. Syros is currently conducting a Phase III clinical trial of tamibarotene + azacitidine combination therapy in RARA-positive, newly diagnosed HR-MDS patients. Patient enrollment is ongoing at over 75 clinical research facilities in 12 countries. Syros expects to complete enrollment of 190 patients by Q4 FY12/23, and obtain data for regulatory approval filing by Q3 FY12/24.

*RARA-positive patients are those with overexpressed RARA, a gene that codes for RAR α .

*MDS is a condition that occurs when hematopoietic stem cells in the bone marrow become abnormal, preventing the production of healthy blood cells.

In September 2015, TMRC entered into a license agreement with Syros, granting Syros development and marketing rights to the anticancer agent tamibarotene in North America and Europe, in return for the right to receive milestone payments in accordance with development progress and royalties after the product goes on sale. TMRC will not receive any one-time payment as a result of this development, i.e., the fast track designation of tamibarotene, and accordingly no change will be made to the consolidated earnings forecast for FY12/23. Nonetheless, the company believes the fast track designation of tamibarotene will significantly contribute to steady and consistent progress of clinical development and regulatory approval processes.

Sublicensing of GERD treatment tegoprazan in Brazil

2023-01-26

RaQualia Pharma Inc. announced the sublicensing of its GERD treatment tegoprazan in Brazil.

The company announced that HK inno.N, to which RaQualia out-licensed tegoprazan, a gastroesophageal reflux disease (GERD) treatment (marketed as K-CAB[®] in South Korea), had entered a license agreement covering Brazil. The sublicensee, Eurofarma Laboratories S.A. (EUFA-BR), is Brazil's leading pharmaceutical company and was established in 1972. In 2021, Eurofarma booked operating revenue of BRL8.3bn (about JPY199bn, converted at JPY24/BRL). Under the agreement, HK inno.N will transfer tegoprazan manufacturing technologies to Eurofarma, and Eurofarma will use these to produce and market the tegoprazan formulation in Brazil.

According to the company, the market for peptic ulcer drugs in Brazil is about JPY80bn, which is the largest in Latin America and sixth largest in the world. Over 3,100 Eurofarma group employees interact with medical professionals on 630,000 occasions per month, comprising the largest sales and marketing organization in the industry, so the company hopes for swift penetration of tegoprazan in the Brazilian market.

RaQualia has a licensing agreement with HK inno.N, granting it an exclusive license with sublicensing rights for development, sales, and manufacturing of tegoprazan. Based on its licensing agreement with HK Inno.N, RaQualia is entitled to receive a certain percentage of the revenue that HK Inno.N receives from sublicensees. The company will receive an upfront payment from HK inno.N under the agreement, which will be booked as operating revenue in Q4 FY12/22, but this will not have a material impact on FY12/22 results.

Insurance coverage of GERD treatment tegoprazan in China

2023-01-19

On January 19, 2023, RaQualia Pharma Inc. announced the inclusion of tegoprazan, a treatment for gastroesophageal reflux disease (GERD), in the health insurance reimbursement list in China.

RaQualia out-licensed GERD treatment tegoprazan (marketed as K-CAB[®] in South Korea and Tai Xin Zan[®] in China) to HK inno.N, which then entered into a sublicense agreement for the drug with Shandong Luoxin Pharmaceutical Group Stock Co., Ltd. (SHE: 002793, "Luoxin") in China. The company announced that tegoprazan has been approved for reimbursement under the China's national health insurance system, the basic medical insurance.

Luoxin filed for regulatory approval of tegoprazan in China, and in April 2022, obtained approval from the nation's regulatory authorities. In a mere 15 days after obtaining the approval, Luoxin began sales of tegoprazan. In a notice dated January 18, 2023 regarding the issue of the National Reimbursement Drug List (NRDL) 2022 released by the National Healthcare Security Administration, China's regulatory agency, the agency indicated that tegoprazan will be listed in the NRDL, in less than a year after its launch. Prices of drugs fall when they are listed in the NRDL (an average price fall of 60.1% for those listed in 2022 NRDL), but the company believes insurance coverage will increase access to tegoprazan as the cost of the drug, which was fully borne by patients previously, will be covered by the national insurance, and lead to higher sales.

RaQualia, based on its license agreement with HK inno.N, is entitled to receive milestone payments based on development progress and a predetermined percentage of revenue HK inno.N generates from the drug, such as royalties on sales after the drug's launch. The company will not receive any payment as a result of this development, i.e., the addition of tegoprazan

to NRDL, but factored in its earnings forecast for FY12/22 some royalties on sales of the drug in China as it was launched a half-year ahead of schedule.

Marketing approval for GERD treatment tegoprazan in Singapore

2023-01-13

RaQualia Pharma Inc. announced marketing approval in Singapore for tegoprazan, a treatment for gastroesophageal reflux disease (GERD).

RaQualia has formed an out-licensing agreement for tegoprazan with South Korea-based HK inno.N (South Korean brand name: K-CAB®). Singapore-based sublicensee United Italian Trading Corporation (Pte) Ltd. (UITC; unlisted) has now obtained marketing authorization for tegoprazan from the Health Sciences Authority of Singapore. UITC has been working toward gaining approval since 2020 when it entered into a sublicense agreement with HK inno.N. The drug has been approved in Singapore for five indications: erosive esophagitis, non-erosive reflux disease, gastric ulcer, adjuvant therapy for Helicobacter pylori eradication, and maintenance therapy for healed erosive esophagitis. Singapore is the sixth nation to issue an approval for tegoprazan, following South Korea, Mongolia, China, the Philippines, and Indonesia.

RaQualia had entered into a licensing agreement with HK inno.N, granting it an exclusive license with sublicensing rights for development, sales, and manufacturing of tegoprazan. Based on its licensing agreement with HK Inno.N, RaQualia is entitled to receive a certain percentage of the revenue that HK Inno.N receives from sublicensees. However, there is no one-time payment accompanying this approval for tegoprazan in Singapore.

Concludes joint research agreement with Veritas In Silico

2022-12-27

RaQualia Pharma Inc. announced that it had concluded a joint research agreement with Veritas In Silico Inc.

The company announced that it will embark on joint research with Veritas In Silico (unlisted) to discover breakthrough small-molecule drugs targeting messenger RNAs (mRNA). Veritas In Silico possesses proprietary platform technologies specialized for mRNA-targeted drug discovery. To pioneer a new area of drug discovery that can replace the conventional approach focused on protein targets, Veritas In Silico has developed its original mRNA-targeted drug discovery platform ibVIS® that enables the identification of target mRNA structures and development of small-molecule drugs that bind to the identified target structures.

ibVIS® has a series of cutting-edge platform technologies necessary for mRNA-targeted drug discovery, including structural analysis of RNA, quantitative screening of RNA-binding low-molecular-weight compounds, experimental techniques for measuring the binding of target RNA structures with low-molecular-weight compounds, 3-D structural analysis of RNA and low-molecular-weight compound complexes, and structure-based drug design* based on molecular orbital calculations.

*Structure-based drug design (SBDD) is a method of design based on structural information on the binding site of receptor proteins.

Through the joint research, which will span multiple years, the company and Veritas In Silico will target a number of genes associated with cancer specified by the company and identify target structures on corresponding mRNA; identify hit compounds by high-throughput screening; identify lead compounds by synthesizing analogues (hit expansion); and determine development candidate compounds through lead optimization. The company will acquire exclusive, worldwide rights to develop, manufacture, distribute, and sell development compounds identified from the joint drug discovery research. In return, it will pay Veritas In Silico an upfront payment and research collaboration fees. Further, if the candidate compounds reach the development stage and are launched, the company may pay milestone payments in accordance with development progress and royalties.

The company says this development will have only a marginal impact on its earnings for FY12/22, and hence has made no change to the full-year earnings forecast. In the medium to long term, however, the company believes the joint research will lead to enhancing its R&D portfolio and fortifying its development pipeline.

Issue of new shares and series 16 share subscription rights via third-party allotment

2022-12-20

RaQualia Pharma Inc. announced the issue of new shares and series 16 share subscription rights via third-party allotment.

In the medium-term management plan, RaQualia has outlined the total R&D investment of JPY2.4bn by the end of 2024 (JPY1.2bn for explorative research and JPY1.2bn for non-clinical and clinical studies, not including personnel expenses). In addition, the company plans to invest approximately JPY2.8bn over the next five years to enhance its R&D activities further and accelerate progress. It will use this fund to explore new modalities, promote AI-driven drug discovery, and revamp laboratory facilities. Because these funding needs cannot be covered by cash on hand (about JPY4.0bn) or expected income, the company determined that it needed to secure new funds to invest in development and decided to issue new shares and share subscription rights via third-party allotment.

The company plans to allocate funds raised from the issue of new shares, combined with its own funds, to necessary expenditures through December 2024 and use funds raised from the exercise of share subscription rights to fund necessary activities through December 2027.

Shares	
Pay-in date	January 5, 2023
Number of new shares to be issued	625,000 common shares of the company
Issue price	JPY1,258 per share
Funds to be raised	JPY786,250,000
Allottee	CVI Investments, Inc.
Share subscription rights	
Allotment date	January 15, 2023
Total number of share subscription rights to be issued	12,500
Issue price	Total JPY19,362,500 (JPY1,549 per share subscription right)
Dilutive shares	1,250,000 shares (100 shares per share subscription right)
Funds to be raised	JPY1,945mn*
Exercise price	JPY1,556 (not subject to revision)
Exercise period	January 6, 2023–January 5, 2028
Allottee	CVI Investments, Inc.

*Actual funds raised may be less than the amount expected if the share subscription rights are not exercised within the exercise period or if the company acquires and retires the rights.

Intended use of funds raised from the issue of new shares		
Existing programs and clinical development of new candidate compounds	JPY232mn	January 2023–December 2024
Explorative research to discover new modalities and investment in AI-driven drug discovery	JPY365mn	January 2023–December 2024
Revamping of laboratory facilities	JPY181mn	January 2023–December 2024
	Total JPY778mn	
Intended use of funds raised from the issue of series 16 share subscription rights		
Existing programs and clinical development of new candidate compounds	JPY815mn	January 2025–December 2027
Explorative research to discover new modalities and investment in AI-driven drug discovery	JPY623mn	January 2025–December 2027
Revamping of laboratory facilities	JPY507mn	January 2025–December 2027
	Total JPY1,945mn	

The company says this fundraising will have minimal impact on its FY12/22 earnings and has made no revisions to its earnings forecast for the fiscal year. See company release for details.

Joint research agreement with DWTI; progress in clinical trials of tamibarotene in AML patients being conducted by Syros (US) and development plans going forward

2022-12-13

On December 12, 2022, RaQualia Pharma Inc. announced the signing of a joint research agreement with D. Western Therapeutics Institute, Inc.

The company and D. Western Therapeutics Institute (TSE Growth: 4576, "DWTI") will utilize each other's technologies, resources, and know-hows in pharmaceutical R&D in joint research aimed at discovery and development of therapeutic

agents for specific optic nerve disorders.

In the joint research, the company will draw on its ion channel drug discovery technology to synthesize a group of compounds that target specific ion channels ("the group of compounds"). DWTI, on the other hand, will utilize its evaluation technology in the field of ophthalmology to verify the potential of the group of compounds as therapeutic agents for eye diseases through pharmacological tests and other methods. Technological achievements and intellectual properties obtained from the joint research will be jointly owned by the company and DWTI, and even after the conclusion of the joint research, the two companies will hold discussions with an eye to the next stage of collaboration.

The company says this development will have only a marginal impact on its FY12/22 earnings, and hence it made no change to its earnings forecast. In the longer term, however, the company believes the joint research with DWTI will contribute to enhancing its R&D portfolio and fortifying its development pipeline.

On the same day, the company announced progress in clinical trials of tamibarotene in acute myeloid leukemia patients being conducted by Syros Pharmaceuticals Inc. (US) and development plans going forward.

Tamibarotene is a selective retinoic acid receptor alpha (RAR α) agonist, that, due to its exhibition of strong differentiation-inducing activity, is expected to have a synergistic effect when used in combination with other antitumor agents. Consolidated subsidiary TMRC Co., Ltd. out-licensed RAR α agonist (tamibarotene) to Syros Pharmaceuticals Inc. (NASDAQ: SRY, "Syros"). Syros is currently conducting clinical trials of the study compound in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) patients in the US.

Syros commenced a Phase II clinical trial of tamibarotene + venetoclax + azacitidine three-drug combination therapy in RAR α -positive newly diagnosed unfit AML patients (patients who are not suitable for standard chemotherapy, e.g., the elderly). Syros recently presented data from the safety lead-in part of the Phase II study at the 64th American Society of Hematology (ASH) Annual Meeting. According to Syros, the results of the study suggested that the use of tamibarotene in combination with existing standard of care can improve outcomes for approximately 30% of AML patients who are positive for RAR α overexpression, and demonstrated 83% composite complete response rate*. Syros also announced that based on the data obtained, it will advance the study to the randomized part*². The randomized part of the study is scheduled to commence in Q1 FY12/23, with data expected in 2023 or 2024.

TMRC entered into a license agreement with Syros in September 2015, granting Syros development and marketing rights to tamibarotene in North America and Europe. Based on the terms of the agreement, TMRC is entitled to receive milestone payments in accordance with development progress and royalties after tamibarotene is launched. The progress in clinical studies in AML patients outlined above will not trigger any one-time payment, and hence the company made no change to its consolidated earnings forecast for FY12/22. That being said, the company believes the progress will lead to enhancing the value of tamibarotene in the longer term.

*Composite complete response rate: total of complete response (CR) rate and CR with incomplete hematologic recovery (CRi) rate

*²In a randomized trial, trial subjects are randomly assigned to two or more groups using a method that is not associated with any specific intention, and the effects of treatment, etc. are verified. Also called randomized controlled trial or randomized control trial.

The start of a Phase II clinical trial on a P2X7 receptor antagonist and accompanying receipt of an upfront payment from Asahi Kasei Pharma; revisions to items related to its business plan and growth potential; revisions to consolidated earnings forecast for full-year FY12/22

2022-11-18

On November 17, 2022, RaQualia Pharma Inc. announced the start of a Phase II clinical trial on a P2X7 receptor antagonist and accompanying receipt of an upfront payment from Asahi Kasei Pharma.

In March 2018, RaQualia entered into a license agreement with Asahi Kasei Pharma Corporation (unlisted; subsidiary of Asahi Kasei [TSE Prime: 3407]) for a novel P2X7 receptor antagonist (RQ-00466479). Eli Lilly (NYSE LLY), with whom Asahi Kasei Pharma in turn has a license agreement, has initiated a Phase II clinical study in patients with chronic pain, signifying that a milestone has been met. With this, RaQualia will receive a USD4mn (JPY500mn) milestone payment from Asahi Kasei Pharma, which will be booked as operating revenue in Q4 FY12/22.

Under the terms of its license agreement with Asahi Kasei Pharma, RaQualia receives milestone payments corresponding to stages of development for the P2X7 receptor antagonist, and royalty payments in proportion to sales amounts after launch.

On the same day, RaQualia announced revisions to items related to its business plan and growth potential.

Based on recent changes in its business climate and business progress, the company revised its business plan as follows. As the main reasons for the revision, RaQualia cited changes in projected milestone revenue in FY12/22 and FY12/23, and the impact of revising its exchange rate assumption from JPY125/USD to JPY135/USD to factor in recent exchange rates.

	FY12/21	FY12/22	FY12/23	FY12/24	FY12/23	FY12/24	3-year
(JPYmn)	Cons.	Revised forecast	Previous target	Previous target	Revised target	Revised target	CAGR
Operating revenue	2,776	3,075	3,069	3,645	2,957	3,752	
YoY	150.7%	10.8%	-0.2%	18.8%	-3.6%	26.9%	10.6%
Operating expenses	2,068	2,251	2,675	2,478	2,691	2,504	
YoY	29.8%	8.8%	18.8%	-7.4%	0.6%	-6.9%	6.6%
Operating expense ratio	74.5%	73.2%	87.2%	68.0%	91.0%	66.7%	
Operating profit	708	824	393	1,167	266	1,248	
YoY	-	16.4%	-52.3%	196.9%	-32.3%	369.2%	20.8%
Operating profit margin	25.5%	26.8%	12.8%	32.0%	9.0%	33.3%	
Recurring profit	864	909	403	1,174	256	1,238	
YoY	-	5.2%	-55.7%	191.3%	-36.5%	383.6%	12.7%
Recurring profit margin	31.1%	29.6%	13.1%	32.2%	8.7%	33.0%	
Net income	756	724	327	970	204	990	
YoY	-	-4.2%	-54.8%	196.6%	-37.6%	385.3%	9.4%
Net margin	27.2%	23.5%	10.7%	26.6%	6.9%	26.4%	

Source: Shared Research based on company data

RaQualia also announced revisions to its consolidated earnings forecast for full-year FY12/22.

Revisions to full-year FY12/22 forecast

- Revenue: JPY3.1bn (+10.8% YoY, previous forecast was JPY2.6bn)
- Operating expenses: JPY2.3bn (+8.8% YoY, JPY2.2bn)
- Operating profit: JPY824mn (+16.4% YoY, JPY420mn)
- Recurring profit: JPY909mn (+5.2% YoY, JPY420mn)
- Net income attributable to owners of the parent: JPY724mn (-4.2% YoY, JPY342mn)
- Earnings per share: JPY34.55 (JPY16.34)

Reasons for revisions

Taking probability of achievement into account, RaQualia assumed in its initial forecast that entry of the P2X7 receptor antagonist into Phase II clinical trials would generate milestone revenue of JPY250mn each in FY12/22 and FY12/23. RaQualia's revised forecast for FY12/22 assumes the entire USD4mn (JPY500mn) will be booked in FY12/22 and also factors in a JPY147mn boost from yen depreciation. The company revised its exchange rate assumption from JPY125/USD to JPY135/USD.

Phase III study of GERD treatment tegoprazan commences in the US

2022-10-21

On October 20, 2022, RaQualia Pharma Inc. announced the commencement of a Phase III clinical trial of tegoprazan, a drug indicated for gastroesophageal reflux disease (GERD), in the US.

The company announced that US-based Braintree Laboratories, Inc. (unlisted; hereafter "Braintree"), a sublicensee of HK inno.N to which the company out-licensed GERD treatment tegoprazan (being marketed under the band name K-CAB® in South Korea), initiated a Phase III study of tegoprazan in patients with erosive esophagitis and non-erosive reflux disease (NERD).

HK inno.N signed a sublicensing agreement with Braintree in December 2021, and since then, Braintree has worked toward conducting late stage clinical trials. Before initiating the Phase III study, Braintree consulted with the US Food and Drug

Administration (FDA) and obtained the agency's approval to skip Phase II and proceed straight to the Phase III study. Patients were enrolled in the Phase III study according to the FDA-approved clinical trial protocol, and the first patient has been dosed.

In the Phase III study, proton pump inhibitors (PPIs) will be used as control drugs to evaluate the efficacy and safety of tegoprazan. The company believes that the commencement of the Phase III study without conducting a Phase II study is significant in that it can lead to shortening of the clinical development period, and accordingly shorten the time required to launch the drug in the US.

According to the company, the US market for peptic ulcer drugs is one of the largest in the world, valued at roughly JPY400bn (as of 2021). In the US, P-CABs (potassium-competitive acid blockers) are currently not being marketed, and PPIs are primarily used to treat GERD. In terms of P-CAB competitor drugs, VOQUENZA™ (generic name: vonoprazan) was approved as a treatment for helicobacter pylori infection in 2022.

Based on the licensing agreement with HK inno.N, the company is entitled to milestone payments based on development progress of tegoprazan in the US and a predetermined percentage of the drug's sales in the country as royalties. While RaQualia will receive no one-off payment as a result of the commencement of the Phase III study, the company believes that if the study does lead to shortening of the time required to launch tegoprazan in the US, it will contribute to expanding the company's earnings in the medium to long term. This development will have no impact on the company's earnings forecast for FY12/22.

Marketing approval in Indonesia for GERD treatment tegoprazan

2022-10-13

On October 12, 2022, RaQualia Pharma Inc. announced marketing approval in Indonesia for tegoprazan, a treatment for gastroesophageal reflux disease (GERD).

RaQualia Pharma has out-licensed its GERD treatment tegoprazan to South Korea's HK inno.N Corporation, which markets the drug as K-CAB and has sublicensed it to Indonesia's PT Kalbe Pharma Tbk. Kalbe has obtained marketing approval for tegoprazan from the Indonesian National Agency of Drug and Food Control (NADFC), for the indication of non-erosive GERD. This makes Indonesia the fifth nation to issue approval, following South Korea, Mongolia, China, and the Philippines.

RaQualia had entered into a licensing agreement with HK inno.N, granting it an exclusive license with sublicensing rights for development, sales, and manufacturing of tegoprazan. HK inno.N has been marketing tegoprazan as K-CAB since 2019, and in 2021 the drug generated South Korean domestic sales (out-of-hospital prescription) of KRW109.6bn (about JPY10.96bn at JPY0.1/KRW), affording it the No. 1 market share for gastric ulcer drugs in South Korea.

In Indonesia, HK Inno.N entered into a sublicensing agreement with Kalbe in 2019, since which time Kalbe has been working to obtain marketing approval. According to HK Inno.N, the Indonesian market for gastric ulcer drugs was worth approximately USD170mn (about JPY21.3bn at JPY125/USD), making it the 19th largest market in the world.

Based on its licensing agreement with HK Inno.N, RaQualia is entitled to receive a certain percentage of the revenue that HK Inno.N receives from Kalbe. With this approval for tegoprazan in Indonesia, the company received a one-time payment from HK Inno.N, which will be recorded as operating revenue for Q4 FY12/22. At this juncture, there is no change to RaQualia's full-year consolidated earnings forecast for FY12/22.

Other information

History

Feb 2008	Company established in Chita, Aichi to conduct R&D into pharmaceuticals
Jul 2008	Accompanying the closure of Pfizer's central research laboratory in Japan, RaQualia's business launched with the transfer of some employees and purchase of laboratory equipment
Sep 2010	Reached out-licensing agreement for marketing potassium-competitive acid blocker (P-CAB) in South Korea, China including Hong Kong, and Taiwan with South Korea's CJ CheilJedang Corporation (currently HK inno.N Corporation)
Dec 2010	Reached agreement to grant global rights to commercialize EP4 receptor antagonist and ghrelin receptor agonist as veterinary drugs to US-based Aratana Therapeutics Inc. (currently Elanco Animal Health Inc.)
Jul 2011	Listed shares on Osaka Securities Exchange JASDAQ Growth market (currently Tokyo Stock Exchange Growth)
Feb 2014	Signed agreement with Nagoya University to establish joint industry-academia research department
Sep 2014	Biological Research Department, Drug Discovery Research Division was moved to the premises of Nagoya University
Nov 2014	Signed out-licensing agreement with CJ HealthCare Corporation (currently HK inno.N Corporation) for marketing P-CAB in Southeast Asia
Aug 2015	Scientific Research Department, Drug Discovery Research Division was moved to the premises of Nagoya University
Jan 2017	Aratana Therapeutics, Inc. (currently Elanco Animal Health Inc.) began marketing EP4 receptor antagonist (GALLIPRANT®, veterinary drug) in the US
Dec 2017	Out-licensed selective sodium channel blocker to Maruho Co., Ltd.
Mar 2018	Signed out-licensing agreement with Asahi Kasei Pharma for P2X7 receptor antagonist targeting peripheral neuropathic pain
Mar 2019	CJ CheilJedang Corporation (currently HK inno.N Corporation) began marketing P-CAB (tegoprazan, K-CAB®) in South Korea
Mar 2019	Aratana Therapeutics, Inc. (currently Elanco Animal Health Inc.) began marketing ghrelin receptor agonist (ELURA®, veterinary drug) in the US
Nov 2019	Signed agreement with CJ CheilJedang Corporation (currently HK inno.N Corporation) on expanding global partnership
Sep 2021	Signed out-licensing agreement with Hong Kong-based Xgene Pharmaceutical Co. Ltd. covering TRPM8 blocker
Dec 2021	Signed out-licensing agreement with Hisamitsu Pharmaceutical Co., Inc., covering sodium channel blocker
Apr 2022	Listed on Growth market under new Tokyo Stock Exchange classifications

Source: Shared Research based on company data

New R&D base established at Shonan iPark

The company conducts drug discovery research primarily at the RaQualia Industry-Academia Collaborative Research Center located on the premises of the Higashiyama Campus of Nagoya University. In January 2023, the company opened a new research center at Shonan Health Innovation Park (Fujisawa, Kanagawa Prefecture; Shonan iPark) and commenced research activities there. Established in April 2018, Shonan iPark is Japan's first pharma-led science park, where more than 2,000 people from over 150 companies and organizations (as of January 2023), including pharmaceutical companies, experts and researchers in next-generation medicine and AI, startups, and administrative agencies, form an ecosystem. The Park hosts a variety of networking events, and the company seeks opportunities to collaborate with companies conducting cutting-edge clinical trials or possessing advanced technologies for novel modalities, target search, and AI-driven drug discovery, further enhancing its drug discovery value chain and portfolio.

Top management and corporate governance

Form of organization and capital structure	
Form of organization	Company with Audit & Supervisory Committee
Controlling shareholder and parent company	None
Directors and Audit & Supervisory Committee members	
Number of directors under Articles of Incorporation	1200.00%
Number of directors	7
Directors' term of office under Articles of Incorporation	1 year
Chairperson of Board of Directors	President
Number of outside directors	4
Number of independent outside directors	3
Number of Audit & Supervisory Committee members under Articles of Incorporation	3
Number of Audit & Supervisory Committee members	3
Number of outside directors on Audit and Supervisory Committee	3
Chairperson of Audit & Supervisory Committee	Outside director
Other	
Participation in electronic voting platform	In place
Providing convocation notice in English	In place
Implementation of measures regarding director incentives	Performance-linked remuneration
Eligible for stock option	Employees
Disclosure of directors' compensation	None
Policy to determine amount and calculation method of remuneration	In place
Corporate takeover defenses	None

Source: Shared Research based on company data

Top management

President and CEO: Hirobumi Takeuchi (born December 21, 1971)

Apr 1994	Joined Kyowa Co., Ltd.
Feb 2004	Joined Skylight Biotech Inc as general manager of sales department
Sep 2005	Director in charge of business promotion and finance, Skylight Biotech Inc.
Jul 2006	Director and CFO in charge of administrative division, Skylight Biotech Inc.
May 2009	Joined Sumisho Realty Management Co., Ltd. as manager of administration department
Jan 2013	Joined Cyfuse Biomedical K.K. as director in charge of corporate planning and business administration
Jan 2014	Joined RaQualia Pharma Inc. as deputy general manager of accounting department
Apr 2014	General manager of accounting department, RaQualia Pharma Inc.
Oct 2014	General manager of finance and accounting department, finance and corporate planning division, RaQualia Pharma Inc.
Apr 2018	President and CEO, UBIENCE Inc.
Mar 2021	President and CEO, RaQualia Pharma Inc. (current position)
Jun 2021	Director, UBIENCE Inc. (current position)

Corporate governance

RaQualia Pharma employs a company with Audit & Supervisory Committee structure, and has a board of directors, an Audit & Supervisory Committee, and a corporate internal audit office. The board of directors has seven members (including four outside directors). In order to strengthen the board's monitoring functions, the company chooses outside board members who are familiar with the pharmaceutical industry and corporate management. Furthermore, the company has an executive officer system in order to separate the management and execution functions and strengthen and invigorate execution.

In March 2023, the company established a nomination and remuneration committee to enhance the fairness, transparency, and objectivity of procedures related to the nomination and remuneration of directors and strengthen corporate governance.

Dividends

The company sees returning profits to shareholders as an important management issue, but it has continued to make upfront investments since its establishment and recorded net losses, so has not yet paid a dividend. In FY12/21, it posted an operating profit for the first time and will consider paying a dividend in the future if it is able to maintain business profits, depending on the strength of its financial position.

Top shareholders

Top shareholders	Shares held (000 shares)	Shareholding ratio
Yuichi Kakinuma	2,385	11.37%
SBI Securities Co., Ltd.	830	3.95%
Pfizer Japan Inc.	743	3.54%
MSIP CLIENT SECURITIES (Standing proxy: Morgan Stanley MUFG Securities Co., Ltd.)	495	2.36%
MORGAN STANLEY & CO.LLC (Standing proxy: Mitsubishi UFJ Morgan Stanley Securities Co., Ltd.)	312	1.48%
The Tokyo Tanshi Co., Ltd.	270	1.29%
Advanced Media, Inc.	224	1.07%
JPMorgan Securities Japan Co., Ltd.	207	0.99%
au Kabucom Securities Co., Ltd.	202	0.96%
BNYM SAINV FOR BNYM FOR BNY GCM CLIENT ACCOUNTS LSCB RD (Standing proxy: MUFG Bank, Ltd.)	189	0.90%
SUM	5,855	27.91%

Source: Shared Research based on company data (as of December 31, 2022)

Number of employees

	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22
Number of employees (consolidated)	74	72			60	63	68	70	67	65
Number of employees (parent)	70	70	64	50	55	58	62	64	62	62
Average age	43	43.6	44.1	44.8	45.5	45.5	46.3	47.3	46.5	47.5
Average years of service	4.7	5.5	5.9	6.6	7.0	6.9	7.4	8.1	8.7	10.7
Average annual salary (JPY'000)	8,024	7,971	8,124	7,242	7,391	7,408	7,237	7,510	7,369	7,033

Source: Shared Research based on company data

In FY12/22, roughly 50 of the parent's 62 employees were involved in research and development, and over 10 were involved in out-licensing and other business development and management duties.

Profile

Company Name

RaQualia Pharma Inc.

Phone

052-446-6100

Established

2008-02-19

IR Contact

<https://www.raqualia.com/contact/>

Head Office

**Meieki Southside Square, 1-21-19 Meieki Minami, Nakamura-ku,
Nagoya City**

Listed On

Tokyo Stock Exchange, Growth Market

Exchange Listing

2011-07-20

Fiscal Year-End

Dec

About Shared Research Inc.

We offer corporate clients comprehensive report coverage, a service that allows them to better inform investors and other stakeholders by presenting a continuously updated third-party view of business fundamentals, independent of investment biases. Shared Research can be found on the web at <https://sharedresearch.jp>.

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