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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 FY12/23, operating revenue was JPY1.9bn (-34.8% YoY), comprising royalty revenue (approximately 70%) and upfront and milestone payments (approximately 30%).

The company started as an independent entity when US-based Pfizer Inc. (NYSE: PFE; ranked third in terms of pharmaceuticals sales globally in 2023) 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 it 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®), 13 compound programs already out-licensed, and seven 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 Healthcare 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. Sublicensees of HK inno.N are working on development, manufacturing, and sales of tegoprazan in 45 countries outside South Korea. As of May 2024, tegoprazan was being sold in eight countries: South Korea, Mongolia, China, the Philippines, Indonesia, Singapore, Mexico, and Peru, and was newly approved in Chile, Dominican Republic, Nicaragua, and Honduras. In 24 other countries including Argentina, HK inno.N is in various stages of bringing tegoprazan to market, including clinical development, regulatory review by local authorities, and pre-marketing activities.

* 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 obtained approval for ELURA®, a weight loss management drug for cats with CKD, in Europe in 2023 and launched it in France in August 2024. It obtained approval in Japan in February 2024 and expects to launch the drug domestically in 2024. The company plans to expand ELURA® into other markets, having already secured approvals in the UK, several European countries, Brazil, and Canada. While the pet drug market is smaller than the human pharmaceuticals market, the absence of regulated drug prices in Japan and other regions allows the company to maintain or increase prices more easily. Shared Research thinks this pricing flexibility supports stable royalty revenue and earnings.

RaQualia initially planned 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 markets excluding Japan by FY12/21. The company originally planned to complete clinical studies (equivalent to Phase I) in FY12/23, hoping to out-license tegoprazan in FY12/24 or later. However, during FY12/23, in order to launch the drug at the earliest possible date, the company decided to out-license the drug within the same year without conducting clinical pharmacological studies. However, due to lengthy negotiations with the potential licensee, the closing of the agreement is expected to be delayed until 1H FY12/24. 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 commence clinical studies in 2025.

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 (clinical 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 under 10% of all drugs. RaQualia says it is the only company in the world to have out-licensed five drugs in the area.

In March 2024, the company acquired all shares in FIMECS, Inc. (unlisted) and made it a subsidiary (see the "Medium-term business plan" section below). FIMECS advances the research and development of new pharmaceuticals using targeted protein degradation (TPD) inducers, a new modality in drug discovery. Based on its unique drug discovery platform technology RaPPIDS™, it conducts joint research with Astellas Pharma Inc. (TSE Prime: 4503) and may receive milestone payments according to progress with development and royalties after product launch. The company expects to strengthen its drug discovery value chain, increase its earnings through a hybridized business model, and strengthen the cancer disease area by making FIMECS a subsidiary.

Earnings trends

In FY12/23, RaQualia reported revenue of JPY1.9bn (-34.8% YoY), operating loss of JPY337mn (compared to a profit of JPY866mn in the previous year), a recurring loss of JPY293mn (compared to a profit of JPY904mn), and a net loss attributable to owners of the parent of JPY324mn (compared to a net income of JPY723mn). Although revenue came in slightly below the company's revised forecast, which was adjusted downward delays in the out-licensing of tegoprazan in Japan and the milestone achievement associated with the approval and launch of ELURA® in Europe into FY12/24, losses were narrower than projected. Expanding global earnings of the gastric acid secretion inhibitor 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.

For FY12/24, the company forecasts revenue of JPY4.5bn (+138.5% YoY), operating profit of JPY313mn (compared to a loss of JPY337mn in the previous year), recurring profit of JPY290mn (compared to a loss of JPY293mn), and net income

attributable to owners of the parent of JPY236mn (compared to a loss of JPY324mn). The company anticipates stable royalty income from tegoprazan, GALLIPRANT®, ENTYCE®, and ELURA®, as well as upfront payments from new licensing deals and milestone payments based on R&D progress of out-licensed programs. Additionally, the results of a newly consolidated subsidiary FIMECS will be included from Q2. The assumed exchange rate is JPY135.0/USD (compared to JPY138.0/USD in the previous year). The earnings forecast remains unchanged as of the 1H results announcement.

The company unveiled its medium-term management plan for the three-year period from FY12/24 to FY12/26, alongside its FY12/23 earnings. Due to delays in revenue recognition and the acquisition of FIMECS, the operating revenue target for FY12/24 has been increased by JPY1.6bn. Additionally, the target for FY12/25 has been raised by JPY201mn, reflecting FIMECS's contributions and the altered timing for the out-licensing of a ghrelin receptor agonist. The business model, competitive edges, and investment strategy remain unchanged. For the final year, FY12/26, the company targets operating revenue of JPY5.5bn (a CAGR of 42.7% over three years), operating profit of JPY1.1bn, recurring profit of JPY1.1bn, and net income of JPY834mn. Aiming for stable royalty income, increased upfront and milestone payments, and contributions from a newly integrated subsidiary, the company seeks to achieve operating profit across three consecutive periods. The forecasted exchange rate for FY12/26 is JPY120.00/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	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23	FY12/24
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Company forecast
Operating revenue	**154**	**146**	**705**	**1,419**	**745**	**1,703**	**1,107**	**2,776**	**2,918**	**1,901**	**4,535**
YoY	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.7%	-35.0%	150.7%	5.1%	-34.8%	138.5%
Operating expenses	**2,276**	**2,010**	**1,465**	**1,570**	**1,820**	**1,719**	**1,593**	**2,068**	**2,052**	**2,239**	**4,222**
YoY	-3.8%	-11.7%	-27.1%	7.1%	15.9%	-5.5%	-7.3%	29.8%	-0.8%	9.1%	88.6%
Operating profit	**-2,123**	**-1,865**	**-760**	**-150**	**-1,075**	**-16**	**-486**	**708**	**866**	**-337**	**313**
YoY	-	-	-	-	-	-	-	-	22.4%	-	-
Operating profit margin	-	-	-	-	-	-	-	25.5%	29.7%	-	6.9%
Recurring profit	**-1,942**	**-1,795**	**-721**	**-81**	**-1,065**	**22**	**-528**	**864**	**904**	**-293**	**290**
YoY	-	-	-	-	-	-	-	-	4.7%	-	-
Recurring profit margin	-	-	-	-	-	1.3%	-	31.1%	31.0%	-	6.4%
Net income	**-465**	**-1,854**	**-728**	**-58**	**-1,105**	**5**	**-607**	**756**	**723**	**-324**	**236**
YoY	-	-	-	-	-	-	-	-	-4.3%	-	-
Net margin	-	-	-	-	-	0.3%	-	27.2%	24.8%	-	5.2%
Per-share data (JPY, Split-adjusted)											
Shares issued (year-end; '000)	14,857	18,767	18,767	20,295	20,388	20,950	20,952	20,955	20,977	21,623	
EPS (JPY)	-45.7	-116.5	-38.8	-3.0	-54.2	0.3	-29.0	36.1	34.5	-15.0	10.9
EPS (fully diluted; JPY)	-	-	-	-	-	0.3	-	36.0	34.5	-	
Dividend per share (JPY)	-	-	-	-	-	-	-	-	-	-	-
Book value per share (JPY)	315	240	201	240	189	220	191	228	262	282	
Balance sheet (JPYmn)											
Cash and cash equivalents	1,891	1,840	1,428	2,268	1,671	2,174	1,394	2,345	3,675	3,715	
Total current assets	**3,261**	**2,708**	**1,806**	**3,322**	**1,962**	**3,067**	**2,834**	**4,004**	**4,822**	**4,957**	
Tangible fixed assets	85	261	249	216	318	249	333	299	391	574	
Investments and other assets	1,844	1,769	1,951	1,516	1,738	1,488	1,051	897	1,020	1,311	
Intangible assets	12	14	13	10	34	32	33	34	24	30	
Total assets	**5,202**	**4,752**	**4,019**	**5,064**	**4,052**	**4,837**	**4,251**	**5,234**	**6,258**	**6,872**	
Short-term debt	-	-	-	-	1	1	18	22	46	77	
Total current liabilities	**262**	**200**	**190**	**149**	**164**	**183**	**187**	**401**	**494**	**389**	
Long-term debt	-	-	-	-	2	2	27	18	177	291	
Total fixed liabilities	**109**	**38**	**41**	**27**	**31**	**33**	**53**	**46**	**267**	**362**	
Total liabilities	**371**	**238**	**231**	**176**	**195**	**216**	**240**	**446**	**761**	**752**	
Shareholders' equity	4,821	4,503	3,773	4,871	3,845	4,608	3,999	4,777	5,489	6,095	
Total net assets	**4,831**	**4,514**	**3,788**	**4,888**	**3,857**	**4,621**	**4,011**	**4,788**	**5,497**	**6,120**	
Total interest-bearing debt	-	-	-	-	3	2	46	39	222	368	
Cash flow statement (JPYmn)											
Cash flows from operating activities	-2,081	-2,117	-681	-307	-404	-531	-289	366	1,480	-719	
Cash flows from investing activities	-796	666	-441	534	-368	216	225	-279	-48	-135	
Cash flows from financing activities	762	1,702	-	1,007	99	696	-7	-16	-30	793	
Financial ratios											
ROA (RP-based)	-32.8%	-36.1%	-16.4%	-1.8%	-23.4%	0.5%	-11.6%	18.2%	15.7%	-4.5%	
ROE	-8.8%	-39.8%	-17.6%	-1.3%	-25.3%	0.1%	-14.1%	17.2%	14.1%	-5.6%	
Equity ratio	92.7%	94.8%	93.9%	96.2%	94.9%	95.3%	94.1%	91.3%	87.7%	88.7%	

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

Approval of GERD treatment tegoprazan in Malaysia

2024-09-26

RaQualia Pharma Inc. announced that its potassium-competitive acid blocker (P-CAB), tegoprazan, has received marketing approval in Malaysia.

The company stated that Pharmaniaga Logistics Sdn Bhd (KLSE: 7081), a sublicensee of HK inno.N Corporation (KOSDAQ: 195940), obtained marketing approval for tegoprazan from the National Pharmaceutical Regulatory Agency (NPRA) of Malaysia.

Tegoprazan, developed by RaQualia, represents a novel acid suppressant that operates via the P-CAB mechanism. Unlike proton pump inhibitors (PPIs), which are currently the first-line therapy for gastroesophageal reflux disease (GERD), P-CABs offer more rapid and sustained suppression of gastric acid secretion, providing a more advanced treatment option.

RaQualia holds an exclusive license agreement with HK inno.N, granting them sublicensing rights for the development, manufacture, and marketing of tegoprazan worldwide, excluding Japan. Under this agreement, HK inno.N and its sublicensees have been advancing the development and commercialization of tegoprazan, which is currently available in nine countries, including South Korea, Mongolia, China, the Philippines, Indonesia, Singapore, Mexico, Peru, and Chile. Marketing preparations, regulatory approvals, and clinical trials are underway in 37 additional countries, including the US.

In Malaysia, HK inno.N entered into a product supply agreement with Pharmaniaga in 2021, and Pharmaniaga has since worked toward obtaining marketing approval. Following the regulatory review, the NPRA approved the marketing of tegoprazan for four indications: erosive esophagitis, non-erosive esophagitis, peptic ulcers, and as an adjunct therapy for the eradication of Helicobacter pylori. The product will be sold under the brand name K-CAB®, with sales scheduled to commence in 1H FY12/25.

The peptic ulcer market in Southeast Asia is valued at USD520mn (JPY72.0bn, at an exchange rate of JPY140/USD), with further growth anticipated. Tegoprazan is currently marketed in the Philippines, Singapore, and Indonesia, with regulatory reviews ongoing in Thailand and Vietnam. With the addition of Malaysia, the drug is expanding into the six largest markets in Southeast Asia.

Under the license agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns from Pharmaniaga. The company expects no milestone payments from the approval in Malaysia. RaQualia believes that the expansion of tegoprazan's sales territories will contribute to operating revenue growth and enhance its corporate value over the medium to long term. The company remains committed to strengthening its collaboration with HK inno.N, supporting development and sublicense agreements, and expanding treatment options for acid-related disorders to improve quality of life for patients.

Issuance of stock options (share acquisition rights)

2024-09-13

Raqualia Pharma Inc. has decided to issue share acquisition rights as stock options.

At the Board of Directors meeting held on September 13, 2024, the company resolved to issue share acquisition rights as stock options to its employees and those of its subsidiaries, as detailed below. The stock options will be issued without charge, aiming to incentivize employees to drive earnings growth and enhance corporate value, and to promote value-sharing with shareholders. The company will finalize any undecided matters by the planned allocation date of September 30, 2024.

Overview

Type and number of shares	209,000 shares of the company's common stock
Allottees and the number of share acquisition rights to be allotted	66 employees of the company: 1,570 rights 21 employees of the company's subsidiaries: 520 rights
Allotment date	September 30, 2024
Exercise period	From September 14, 2026, to September 13, 2034

Approval of GERD Treatment tegoprazan in Colombia

2024-09-02

RaQualia Pharma Inc. announced the approval of its gastroesophageal reflux disease (GERD) treatment, tegoprazan, for sale in Colombia.

Laboratorios Carnot (unlisted), RaQualia's sublicensee, obtained marketing approval for tegoprazan from the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), the Colombian regulatory authority. RaQualia has out-licensed tegoprazan, a gastric anti-secretory drug, to HK inno.N Corporation (KOSDAQ: 195940), which subsequently sublicensed it to Carnot.

Tegoprazan, developed by RaQualia, is a novel potassium-competitive acid blocker (P-CAB). It offers a distinct mechanism compared to traditional proton pump inhibitors (PPIs), which are typically the first treatment for GERD. Unlike PPIs, P-CABs inhibit gastric acid secretion more rapidly and sustainably, positioning them as a new generation of GERD therapy.

RaQualia has signed an exclusive license agreement with HK inno.N, granting HK inno.N sublicensing rights for the development, manufacture, and sale of tegoprazan worldwide, excluding Japan. Under this agreement, HK inno.N and its sublicensees are actively conducting business activities involving tegoprazan across various countries. In Latin America, HK inno.N has sublicensed tegoprazan to two companies, including Carnot, for commercialization in 18 countries.

With the approval from INVIMA, tegoprazan is now approved for sale in nine Latin American countries: Mexico, Peru, Chile, the Dominican Republic, Honduras, Nicaragua, Guatemala, El Salvador, and Colombia. Tegoprazan was launched under the brand name Ki-CAB® in Mexico and Peru in 2023 and in Chile in 2024. Carnot aims to commence sales in the remaining six approved countries within this year.

RaQualia reports that the market for ulcer drugs in the 17 Latin American countries where Carnot sells tegoprazan is approximately KRW574.0bn (approximately JPY63.1bn, converted at JPY0.11/KRW). To expand tegoprazan's reach in Latin America, HK inno.N and Carnot have been conducting intensive promotional activities, including hosting academic conferences for healthcare professionals. Tegoprazan has garnered significant attention, particularly in Mexico, where it is ranked top 10 anti-ulcer drugs within seven months of its launch and is expected to rank among the top five this year. The recent update to Mexico's gastroenterology guidelines, recommending P-CABs as a first treatment for GERD, is anticipated to further enhance tegoprazan's market presence in Latin America.

Under the license agreement with HK inno.N, RaQualia is set to receive a percentage of the revenue generated by HK inno.N from Carnot. Additionally, RaQualia will receive a lump sum payment from HK inno.N following the product launch in Colombia, which the company plans to recognize as operating revenue in Q3 FY12/24. RaQualia has already incorporated the impact of this approval into its full-year consolidated forecast for FY12/24, with no current plans to revise the full-year earnings forecast. However, should a revision become necessary, RaQualia will promptly disclose any changes.

Milestone payment received following the launch of Eluracat, a ghrelin receptor agonist by Elanco in France

2024-08-29

Raqualia Pharma Inc. announced that Elanco Animal Health Inc. (NYSE: ELAN) has notified them of the launch in France of Eluracat® (capromorelin/RQ-00000005/AT-002), a ghrelin receptor agonist, for treating weight loss in cats with chronic medical conditions. As a result of the launch of the product licensed to Elanco by Raqualia in France, the company has confirmed that it will receive a milestone payment.

This medication is an oral solution containing capromorelin, the active ingredient that mimics ghrelin, the hunger hormone responsible for stimulating appetite and promoting gastrointestinal motility. The weight gain in cats treated with this medication is believed to result from a combination of enhanced food intake and metabolic changes due to its mechanism of action. In the US, it has been marketed since 2021 under the product name Elura® for the management of weight loss in cats with chronic kidney disease. In Europe, Elanco secured manufacturing and marketing authorization for the drug in 2023 and had been preparing for its launch. Recently, Elanco released it in France under the product name Eluracat®. With the launch in France, this medication is now available in two countries. It has also received approval in Japan, the UK, other European countries, Brazil, and Canada, and the company anticipates further expansion into additional markets.

In 2010, the company entered into an out-licensing agreement with Aratana Therapeutics Inc. (now Elanco) for the global commercialization of capromorelin as a veterinary drug. As a result of this agreement, the company will receive a milestone payment of USD2mn, which will be recorded as operating revenue in Q3 FY12/24.

The company stated that it will not revise its earnings forecast for FY12/24, which was announced on February 14, 2024, at this time. However, if any changes become necessary, it will promptly disclose an updated forecast.

Syros suspends enrollment of new patients in clinical trials for AML in the US

2024-08-14

RaQualia Pharma Inc. announced today that Syros Pharmaceuticals, Inc. (NASDAQ: SYRS, "Syros"), a licensee of its consolidated subsidiary TMRC Co., Ltd., has decided to end the enrollment of new patients in its ongoing Phase II clinical trial of tamibarotene (TM-411/SY-1425), a retinoic acid receptor alpha (RAR alpha) agonist, for the treatment of acute myeloid leukemia (AML).

Tamibarotene, a selective activator of the RAR alpha subtype, which was licensed out by TMRC to Syros, exhibits strong differentiation-inducing activity and is expected to have synergistic effects when combined with other anti-tumor agents to enhance the effectiveness of anti-tumor therapies. Since September 2021, Syros has been conducting the SELECT-AML-1 Phase II clinical trial, a triplet regimen study involving venetoclax and azacitidine in patients with AML and RAR alpha positivity, including elderly patients and others for whom standard chemotherapy is unsuitable.

On August 9, 2024, an interim analysis of the SELECT-AML-1 trial was conducted using data from 51 patients. As a result of this analysis, which included a non-binding futility analysis, Syros decided to stop enrolling new patients, as the probability of demonstrating superiority in the final analysis with data from 80 patients was considered low. A futility analysis statistically predicts the outcome of a study based on prespecified hypotheses and evaluation criteria to determine whether the study should continue. Importantly, no new safety concerns were identified with tamibarotene in combination with venetoclax and azacitidine. Syros plans to present data from the SELECT-AML-1 study at the 12th annual meeting of the Society of Hematology and Oncology (SOHO) in September 2024.

Meanwhile, Syros is advancing its Phase III SELECT-MDS-1 trial of tamibarotene in combination only with azacitidine, the standard of care, the standard treatment for high-risk myelodysplastic syndrome (MDS) patients with RARA gene overexpression. The trial is progressing on schedule, with a futility analysis cleared in Q1 FY12/24 and pivotal CR data expected by mid-Q4.

In September 2015, TMRC entered into a license agreement granting Syros the rights to develop and commercialize tamibarotene for the treatment of cancer in North America and Europe, with the right to receive milestone payments and post-marketing royalties based on the development stage. According to the company, this agreement will have no impact on its full-year consolidated results for FY12/24.

Patent review in Japan for XIAP inhibitor (heterocyclic compound)

2024-07-22

RaQualia Pharma Inc. announced the receipt of notification for a Japanese substance patent application (application number: JP-A2020-534723) for a X-linked inhibitor of apoptosis (XIAP) inhibitor (heterocyclic compound) developed by its consolidated subsidiary, FIMECS, Inc.

A patent is granted when a country's patent office determines that an invention is worthy of a patent. Upon payment of the patent fee, the patent becomes registered in that country. The recently patented heterocyclic derivative is an XIAP inhibitor with a novel structure designed by FIMECS, that is expected to bind to XIAP, an E3 ligase, and exhibit antitumor activity. XIAP belongs to the inhibitor of apoptosis protein (IAP) family. XIAP is up-regulated in many cancers and is positively correlated with malignant transformation and poor prognosis. Therefore, inhibition of XIAP is expected to exhibit anti-cancer activity. XIAP is widely known as one of the E3 ligases, along with VHL and CRBN, that can be used as inducers of target protein degradation.

FIMECS focuses on techniques that induce target protein degradation by utilizing E3 ligase binding compounds. FIMECS is developing these inducers using this group of compounds.

This is the second patent issued to FIMECS, following the issuance of a patent in the US last year (application number: 17/263,580). Currently, similar patents have been filed or are pending in Europe, China, and other countries. The company expects FIMECS's intellectual property rights to continue to strengthen in the future.

The company does not expect this patent decision to impact its consolidated results for FY12/24. However, the company believes that the XIAP inhibitor (heterocyclic compound) for which the patent decision was issued will contribute to its corporate value in the medium to long term through future development and related activities.

Patent review in the US for Nav1.7 and Nav1.8 sodium channel blockers (heterocyclic derivatives)

2024-07-17

RaQualia Pharma Inc. has announced that it received a notice of patent review (a decision for patent grant) on the same day for its Nav1.7 and Nav1.8 sodium channel blockers (heterocyclic derivatives), which the company developed and were under review in the US (Application No. 17/417,182).

The heterocyclic derivatives that received this patent review are a novel group of compounds with blocking effects on Nav1.7 and Nav1.8 sodium channels, based on a new molecular framework different from those previously granted patents by the company. A patent review is an evaluation indicating that the patent office of the relevant country has determined that a patent should be granted for the applied invention. Upon payment of the patent fees, the patent is registered, and patent rights are created in the respective country. With this patent review, the company's intellectual property rights have been strengthened in the US.

Sodium channels are a type of ion channel predominantly expressed on the surface of the cell membrane in excitable cells such as muscle and nerve cells. They open in response to changes in membrane potential, selectively allowing sodium ions to pass into the cell. The opening of sodium channels generates action potentials, responsible for pain transmission in sensory nerves. To date, nine types (Nav1.1–Nav1.9) of sodium channels have been reported, and sodium channel blockers are anticipated to be therapeutic agents for various diseases, including pain.

The sodium channel blockers created by the company specifically target the Nav1.7 and Nav1.8 sodium channels and have demonstrated high efficacy in multiple animal models of pain. Furthermore, due to their good selectivity for the Nav1.5 sodium channel, which is critical for cardiac function, they are expected to be revolutionary new drugs capable of suppressing side effects in the cardiovascular system, thus meeting various medical needs.

According to the company, the patent review will have no impact on the financial results for FY12/24. The company believes that the heterocyclic derivatives that have received patent review will contribute to improving its corporate value over the medium to long term through future development.

Trends and outlook

Quarterly trends and results

Earnings (cumulative)	FY12/22				FY12/23				FY12/24		FY12/23	
(JPYmn)	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2	% of forecast	FY forecast
Operating revenue	339	1,447	1,904	2,918	370	1,014	1,495	1,901	649	1,411	31.1%	4,535
YoY	-48.3%	9.6%	17.3%	5.1%	9.2%	-29.9%	-21.5%	-34.8%	75.1%	39.1%		138.5%
Operating expenses	459	896	1,403	2,052	479	1,037	1,604	2,239	604	1,565	61.7%	2,538
YoY	-9.4%	-10.9%	-7.4%	-0.8%	4.4%	15.8%	14.3%	9.1%	26.0%	50.9%		13.4%
Operating expense ratio	135.3%	61.9%	73.7%	70.3%	129.4%	102.3%	107.2%	117.7%	93.1%	110.9%		56.0%
R&D expenses	264	528	840	1,249	268	603	934	1,373	359	833		
YoY	3.0%	6.4%	7.6%	10.8%	1.7%	14.2%	11.2%	9.9%	33.8%	38.0%		
R&D expense ratio	77.7%	36.5%	44.1%	42.8%	72.4%	59.5%	62.5%	72.2%	55.4%	59.0%		
Operating profit	-120	551	501	866	-109	-23	-108	-337	45	-154	-	313
YoY	-	75.1%	367.6%	22.4%	-	-	-	-	-	-		-
Operating profit margin	-	38.1%	26.3%	29.7%	-	-	-	-	6.9%	-		6.9%
Recurring profit	-70	681	676	904	-110	37	-36	-293	-77	-278	-	290
YoY	-	57.4%	183.8%	4.7%	-	-94.6%	-	-	-	-		-
Recurring profit margin	-	47.1%	35.5%	31.0%	-	3.6%	-	-	-	-		6.4%
Net income	-121	469	467	723	-148	25	-118	-324	-78	-324	-	236
YoY	-	55.0%	175.9%	-4.3%	-	-94.6%	-	-	-	-		-
Net margin	-	32.4%	24.5%	24.8%	-	2.5%	-	-	-	-		5.2%

Earnings (quarterly)	FY12/22				FY12/23				FY12/24	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Operating revenue	339	1,108	457	1,014	370	644	481	406	649	762
YoY	-48.3%	66.6%	51.1%	-12.1%	9.2%	-41.9%	5.3%	-60.0%	75.1%	18.5%
Operating expenses	459	437	507	649	479	558	566	635	604	961
YoY	-9.4%	-12.5%	-0.6%	17.4%	4.4%	27.8%	11.6%	-2.1%	26.0%	72.2%
Operating expense ratio	135.3%	39.4%	111.0%	64.0%	129.4%	86.7%	117.6%	156.5%	93.1%	126.1%
R&D expenses	264	265	312	409	268	335	331	438	359	474
YoY	3.0%	10.0%	9.8%	17.8%	1.7%	26.6%	6.2%	7.2%	33.8%	41.4%
R&D expense ratio	77.7%	23.9%	68.2%	40.3%	72.4%	52.0%	68.8%	108.0%	55.4%	62.1%
Operating profit	-120	671	-50	365	-109	85	-85	-229	45	-199
YoY	-	304.5%	-	-39.2%	-	-87.3%	-	-	-	-
Operating profit margin	-	60.6%	-	36.0%	-	13.3%	-	-	6.9%	-
Recurring profit	-70	751	-5	228	-110	147	-73	-257	-77	-200
YoY	-	356.5%	-	-63.6%	-	-80.5%	-	-	-	-
Recurring profit margin	-	67.8%	-	22.5%	-	22.8%	-	-	-	-
Net income	-121	590	-2	256	-148	174	-143	-206	-78	-246
YoY	-	416.8%	-	-56.3%	-	-70.6%	-	-	-	-
Net margin	-	53.3%	-	25.3%	-	27.0%	-	-	-	-

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

1H FY12/24 results (out August 14, 2024)

Earnings summary

1H FY12/24 (January–June 2024) results

- Operating revenue: JPY1.4bn (+39.1% YoY)
- Operating loss: JPY154mn (vs. loss of JPY23mn in 1H FY12/23)
- Recurring loss: JPY278mn (vs. JPY37mn)
- Net loss attributable to owners of the parent: JPY324mn (vs. JPY25mn)
- R&D expenses: JPY833mn (+38.0% YoY)

In 1H, operating revenue was 31.1% of the full-year forecast. In March 2024, the company acquired all outstanding shares and stock options of FIMECS, making it a consolidated subsidiary. As a result, FIMECS's financial performance has been reflected in the company's results from Q2. According to the company, both revenue and expenses were largely in line with forecasts.

Factors behind higher revenue and lower profits

In 1H, royalty income from three pet products, along with the steady global expansion of tegoprazan, generated royalty income of JPY998mn (+36.3% YoY). Other income, including upfront and milestone payments, totaled JPY413mn (+46.5% YoY). Other revenue includes a lump-sum payment related to the sublicensing of tegoprazan in the Middle East and North Africa, as well as a JPY200mn milestone payment FIMECS received from Astellas Pharma in May 2024.

Total operating expenses were JPY1.6bn (+50.9% YoY), including cost of revenue at JPY227mn (+85.6% YoY), R&D expenses at JPY833mn (+38.0% YoY), and other SG&A expenses at JPY506mn (+62.1% YoY). The increase in expenses, driven by higher R&D expenses and the consolidation cost of FIMECS, resulted in operating loss of JPY154mn. The company also

recorded non-operating income, including foreign exchange gains of JPY75mn. However, it booked non-operating expenses such as derivative valuation losses of JPY52mn and arrangement fees of JPY140mn related to a syndicated loan, resulting in a recurring loss and a net loss.

Breakdown of operating revenue

Earnings (cumulative)	FY12/22				FY12/23				FY12/24	
(JPYmn)	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2	Q1–Q3	Q1–Q4	Q1	Q1–Q2
Operating revenue	339	1,447	1,904	2,918	370	1,014	1,495	1,901	649	1,411
YoY	-48.3%	9.6%	17.3%	5.1%	9.2%	-29.9%	-21.5%	-34.8%	75.1%	39.1%
Royalties	184	698	1,083	1,487	350	732	1,198	1,605	551	998
YoY	35.3%	43.0%	69.2%	-	90.2%	4.9%	10.6%	7.9%	57.4%	36.3%
% of total	54.2%	48.2%	56.9%	51.0%	94.5%	72.2%	80.1%	84.4%	85.0%	70.7%
Other(Upfront and milestone payments)	155	748	820	1,431	20	282	297	297	97	413
YoY	-70.2%	-10.1%	-16.6%	-	-87.1%	-62.3%	-63.8%	-79.3%	385.0%	46.5%
% of total	45.7%	51.7%	43.1%	49.0%	5.4%	27.8%	19.9%	15.6%	15.0%	29.3%
R&D expenses	264	528	840	1,249	268	603	934	1,373	359	833
YoY	3.0%	6.4%	7.6%	10.8%	1.7%	14.2%	11.2%	9.9%	33.8%	38.0%
Research	255	482	761	1,024	219	485	780	-	-	-
YoY	-	-	-	-	-14.1%	0.6%	2.5%	-	-	-
% of total	96.7%	91.2%	90.6%	82.0%	81.6%	80.4%	83.5%	-	-	-
Development	8	46	79	225	49	118	154	-	-	-
YoY	-	-	-	-	512.5%	156.5%	94.9%	-	-	-
% of total	3.0%	8.7%	9.4%	18.0%	18.3%	19.6%	16.5%	-	-	-
Earnings (quarterly)(three months)	**FY12/22**				**FY12/23**				**FY12/24**	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Operating revenue	339	1,108	457	1,014	370	644	481	406	649	762
YoY	-48.3%	66.6%	51.1%	-12.1%	9.2%	-41.9%	5.3%	-60.0%	75.1%	18.5%
Royalties	184	514	385	404	350	382	466	-	551	447
YoY	35.3%	46.0%	153.3%	-	90.2%	-25.7%	21.0%	-	57.4%	17.0%
% of total	54.2%	46.4%	84.2%	39.9%	94.5%	59.4%	96.8%	-	85.0%	58.6%
Other(Upfront and milestone payments)	155	593	72	611	20	262	15	-	97	316
YoY	-70.2%	90.1%	-52.3%	-	-87.1%	-55.8%	-79.2%	-	385.0%	20.6%
% of total	45.7%	53.5%	15.8%	60.3%	5.4%	40.7%	3.1%	-	15.0%	41.4%
R&D expenses	263	265	312	634	268	335	331	438	359	474
YoY	76.5%	59.7%	-250.1%	5.5%	1.9%	26.4%	6.1%	-30.9%	34.0%	41.4%
Research	255	227	279	392	219	266	295	-	-	-
YoY	-	-	-	-	-14.1%	17.2%	5.7%	-	-	-
% of total	97.0%	85.7%	89.4%	61.8%	81.7%	79.4%	89.1%	-	-	-
Development	8	38	33	242	49	69	36	-	-	-
YoY	-	-	-	-	512.5%	81.6%	9.1%	-	-	-
% of total	3.0%	14.3%	10.6%	38.2%	18.3%	20.6%	10.9%	-	-	-

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Pipeline

Brisk royalties from four commercialized products

Pet drugs

Sales of GALLIPRANT® (generic name: grapiprant), a treatment for osteoarthritis in dogs, ENTYCE® (generic name: capromorelin), a treatment for anorexia in dogs, and ELURA® (generic name: capromorelin), a treatment for weight management in cats with chronic kidney disease (CKD), continue to perform well. In February 2024, Elanco obtained manufacturing and marketing approval for ELURA® from Japan's Ministry of Agriculture, Forestry, and Fisheries, and is now preparing for its launch. In Europe, Elanco secured manufacturing and marketing approval in 2023 and launched the product in France in August 2024, resulting in the confirmation of a milestone payment to RaQualia.

Development of tegoprazan in countries around the world

Sales of the GERD treatment K-CAB® in South Korea by licensee HK inno.N remained robust. K-CAB® held a 14% share of the anti-ulcer drug market in South Korea, maintaining its top position. Prescription sales outside hospitals reached KRW91.9bn (+24.1% YoY; approximately JPY10.1bn at JPY0.11/KRW) in 1H FY12/24. Notably, sales of orally disintegrating tablets (OD tablets) grew, accounting for about 27% of total sales. In July 2024, HK inno.N launched a low-dose (25 mg) OD tablet for maintenance therapy following the treatment of erosive GERD, and the company expects the share of OD tablet sales to increase further.

In South Korea, a negative patent scope confirmation trial* was filed against tegoprazan's compound patents, but all claims were dismissed in June 2024. The company believes that this outcome will strengthen the protection of K-CAB®'s exclusive commercialization rights.

*A negative scope confirmation trial in South Korea is a legal proceeding requested by a third party who is not the patent holder. The third party seeks confirmation that the technology or actions it implements do not fall within the scope of the patent. The patent term for tegoprazan in South Korea is 20 years from the application date, with a possible extension of up to five years. As a result, HK inno.N holds exclusive marketing rights until 2031.

The company holds an exclusive license agreement with HK Inno.K to develop, market, and manufacture tegoprazan, including sublicense rights. HK Inno.K aims to expand tegoprazan's reach to 100 countries by 2028 and is actively pursuing this goal. During 1H, Laboratories Carnot (unlisted) obtained marketing approvals in Chile, the Dominican Republic, Honduras, and Nicaragua. As a result, RaQualia received a lump-sum payment from HK Inno.K in accordance with their agreement.

As of end-1H, tegoprazan was available or in preparation in 46 countries worldwide. It is currently marketed in eight countries: South Korea, China, the Philippines, Mongolia, Mexico, Indonesia, Singapore, and Peru. Regulatory reviews are underway in several Southeast Asian and Latin American countries, including Thailand, Vietnam, and Argentina. Additionally, clinical development is ongoing in the United States, Canada, and other countries.

The company records royalties from tegoprazan sales on a quarterly basis in South Korea and semi-annually in China, with sales from July to December of the previous year recorded in Q1, and sales from January to June of the current year recorded in Q3. Although contributions from other countries remain small, sales in these markets are steadily increasing.

Out-licensed and pre-out-licensing programs

For the out-licensed programs, RaQualia's partners are advancing development in the preclinical or later stages.

For the TRPM8 antagonist (RQ-00434739/XG2002), the company's licensee, Xgene Pharmaceutical Co. Ltd. (unlisted), received approval from the local research ethics committee in Australia to conduct a Phase I clinical trial. Consequently, RaQualia received a milestone payment from Xgene. The Phase I trial will evaluate the tolerability and pharmacokinetics of TRPM8 blockade in a dose-escalation study in healthy volunteers.

In April 2024, the company entered into an option and license agreement with Velovia Pharma, LLC (unlisted) for the development of animal health products using four compounds with potential applications in gastrointestinal, metabolic, and fibrotic diseases. If Velovia Pharma exercises its option on one or more of the compounds, the company will receive an option exercise fee. Additionally, the company is eligible to receive milestone payments based on subsequent development progress, as well as royalties and sales milestone payments from Velovia Pharma once the animal health products containing the compounds become commercially available.

Sublicensee Eli Lilly completed Phase II clinical trials in the US for a P2X7 receptor antagonist targeting three diseases and has published the results. While the safety profile was favorable with no major concerns, the efficacy failed to meet the primary endpoints. Eli Lilly is currently reviewing its future development plans.

Status of the out-license preparation pipeline:

In its pre-out-licensing programs, the company is advancing preclinical trials for a ghrelin receptor agonist in-house. Following the completion of these preclinical trials by end-2024, the company expects to launch Phase I clinical trials in 2H FY12/25. Regarding tegoprazan, the company retains the rights for development, manufacturing, and sales in Japan and is actively negotiating with potential licensing partners. For other pre-out-licensing programs, the company has conducted business development activities aimed at acquiring partners, utilizing a flexible combination of in-person meetings and online conferences.

Programs in the exploratory research stage

In the exploratory research phase, RaQualia is concentrating on research programs aimed at creating new development compounds. The company seeks to establish its next-generation drug discovery value chain by leveraging synergies between existing technologies and new initiatives, approached from four perspectives: modality, drug discovery targets, disease areas, and foundational technologies. In addition to its independent research efforts, RaQualia is also expanding collaborations with startups and drug discovery ventures.

To strengthen its expertise in small molecule drug discovery, the company is conducting joint research with Veritas In Silico Co., Ltd. (TSE Growth: 130A) to develop small molecule drugs targeting mRNA for cancer treatment, leveraging

technologies such as AI-driven compound design and iPS cell-derived neural cells. In 1H, the company made significant progress in exploring compounds, resulting in the discovery of several small molecules exhibiting the desired properties at the cellular level. The company is focusing on drug discovery using novel modalities at its new research facility, established in 2023 at the Shonan Health Innovation Park (Fujisawa, Kanagawa Prefecture). Additionally, it is collaborating with STAND Therapeutics Co., Ltd. (unlisted) to apply intracellular antibody technology in developing treatments for intractable and rare diseases.

Tamibarotene

Regarding the retinoic acid receptor α agonist (tamibarotene), which was out-licensed from subsidiary TMRC Co., Ltd. to Syros Pharmaceuticals Inc. (NASDAQ: SYRS), clinical trials are underway in the US targeting myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In Q1, Syros completed the patient enrollment required for the primary endpoint analysis in the Phase III clinical trial (SELECT-MDS-1), which targets patients with high-risk myelodysplastic syndromes (HR-MDS) exhibiting an overexpression of the RAR alpha gene. Complete remission rate data are expected to be available by mid-Q4.

In August 2024, Syros announced it would halt patient enrollment in the Phase II clinical trial (SELECT-AML-1) for untreated AML patients who overexpress the RAR alpha gene and are ineligible for conventional chemotherapy. The decision was based on an interim analysis of 51 patients, which indicated a low likelihood that the final analysis of 80 patients would demonstrate significantly superior efficacy of the investigational drug. Syros presented the results at the 12th Annual Meeting of the Society of Hematology and Oncology (SOHO) in September 2024.

Acquisition of FIMECS

In March 2024, the company acquired all issued shares and share subscription rights of FIMECS Inc., making it a wholly owned subsidiary. FIMECS is a drug discovery startup that advances the R&D of new pharmaceuticals using targeted protein degradation inducers, a novel modality in drug discovery. Leveraging its unique E3 ligase-binding molecules and the RaPPIDS™ drug discovery platform technology, FIMECS aims to develop innovative medicines for diseases previously considered "undruggable."

The figures include FIMECS' results from Q2 FY12/24, following its consolidation. In line with the joint research agreement for targeted protein degraders, FIMECS received JPY200mn from Astellas Pharma Inc., which was recorded as operating revenue in Q2 FY12/24.

FIMECS's business model is a hybrid that combines revenue generation from out-licensing its in-house developed pipeline with collaborative research partnerships with pharmaceutical companies. The acquisition of FIMECS not only strengthens the company's drug discovery value chain through the acquisition of platform technologies but also enhances earnings through the hybridization of its business model, and the expansion and strengthening of its oncology business.

When the company converted FIMECS into a subsidiary, the closing consideration amounted to JPY4.5bn, funded in part by a JPY3.5bn syndicated loan, with disbursement completed in March 2024. The acquisition significantly increased the company's assets and liabilities, resulting in an equity ratio of 55.6%, a decrease of 33.1pp from end-FY12/23.

FY12/24 company forecast

	FY12/22			FY12/23			FY12/24		
(JPYmn)	1H results	2H results	FY results	1H results	2H results	FY results	1H results	2H forecast	FY forecast
Operating revenue	**1,447**	**1,471**	**2,918**	**1,014**	**887**	**1,901**	**1,411**	**3,124**	**4,535**
YoY	9.6%	1.1%	5.1%	-29.9%	-39.7%	-34.8%	39.1%	252.1%	138.5%
Operating expenses	**896**	**1,156**	**2,052**	**1,037**	**1,201**	**2,239**	**1,565**		**4,222**
YoY	-10.9%	8.8%	-0.8%	15.8%	3.9%	9.1%	50.9%		88.6%
Cost of revenue	105	127	232	122	123	245	227		
YoY	-40.2%	-12.9%	-27.8%	16.9%	-3.3%	5.8%	85.6%		
R&D expenses	528	720	1,249	603	769	1,373	833		
YoY	6.4%	14.2%	10.8%	14.2%	6.8%	9.9%	38.0%		
R&D expense ratio	36.5%	49.0%	42.8%	59.5%	86.7%	72.2%	59.0%		
SG&A expenses	263	309	572	312	309	621	506		
YoY	-21.4%	8.0%	-7.9%	18.7%	0.1%	8.6%	62.1%		
SG&A ratio	18.2%	21.0%	19.6%	30.8%	34.8%	32.7%	35.8%		
Operating profit	**551**	**315**	**866**	**-23**	**-314**	**-337**	**-154**	**467**	**313**
YoY	75.1%	-19.9%	22.4%	-	-199.7%	-138.9%	-	-248.8%	-
Operating profit margin	38.1%	21.4%	29.7%	-2.3%	-35.4%	-17.7%	-10.9%	15.0%	6.9%
Recurring profit	**681**	**223**	**904**	**37**	**-330**	**-293**	**-278**	**568**	**290**
YoY	57.4%	-48.2%	4.7%	-94.6%	-248.0%	-132.4%	-	-271.9%	-
Recurring profit margin	47.1%	15.2%	31.0%	3.6%	-37.2%	-15.4%	-19.7%	18.2%	6.4%
Net income	**469**	**254**	**723**	**25**	**-349**	**-324**	**-324**	**560**	**236**
YoY	55.0%	-43.9%	-4.3%	-94.6%	-237.5%	-144.7%	-	-260.4%	-
Net margin	32.4%	17.3%	24.8%	2.5%	-39.4%	-17.0%	-23.0%	17.9%	5.2%

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.

Full-year FY12/24 consolidated earnings forecast (out February 14, 2024)

- Operating revenue: JPY4.5bn (+138.5% YoY)
- Operating profit: JPY313mn (compared to a loss of JPY337mn in the previous year)
- Recurring profit: JPY290mn (compared to a loss of JPY293mn)
- Net income attributable to owners of the parent: JPY236mn (compared to a loss of JPY324mn)
- Earnings per share: JPY10.91 (compared to a loss of JPY14.98 per share)

In 1H, the company achieved 31.1% of its full-year operating revenue forecast. This figure includes the results of FIMECS from Q2 FY12/24, following its consolidation. At the time of the Q2 (interim) earnings announcement, the company made no changes to its earnings forecast.

In addition to royalty income, the company confirmed the receipt of a milestone payment following the launch of Eluracat® in France in August 2024, with USD2mn to be recorded as operating revenue in Q3. Additionally, in September 2024, the company will receive a milestone payment from HK inno.N after a sublicensee obtained marketing approval for tegoprazan in Colombia, which will also be recorded as Q3 operating revenue.

The company has resolved all three key issues in its out-licensing negotiations for tegoprazan in Japan. The potential partner is currently evaluating development risks and future revenue projections. The company believes that major terms of the outlicensing contract, including upfront payments, milestones, and royalty rates, are generally within acceptable ranges, and will finalize the economic terms upon selecting the partner.

Assumptions for initial forecast

For FY12/24, the company anticipates stable royalty revenue from tegoprazan, GALLIPRANT®, ENTYCE®, and ELURA®, as well as upfront payments from new licensing deals (including out-licensing of tegoprazan in Japan) and milestone payments based on R&D progress of out-licensed programs. Additionally, the results of a newly consolidated subsidiary FIMECS will be included from Q2. Revenue from joint research currently underway or newly initiated by FIMECS is projected at JPY1.1bn. The assumed exchange rate is JPY135.0/USD (compared to JPY138.0/USD in the previous year).

The company applied for marketing approval of ELURA® (indication: weight loss management in cats) in Europe in March 2022. In May 2023, the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA) adopted a positive opinion. Although the review is progressing smoothly, RaQualia has determined that the milestone achievement (i.e., product approval), originally anticipated in FY12/23, will be delayed until the following year. The company expects to achieve the milestone of launching the product in FY12/24. Approval was granted in Japan in February 2024.

The company unveiled its medium-term management plan for the three-year period from FY12/24 to FY12/26, alongside its FY12/23 earnings. Due to delays in revenue recognition and the acquisition of FIMECS, the operating revenue target for FY12/24 has been increased by JPY1.6bn. Additionally, the target for FY12/25 has been raised by JPY201mn, reflecting

FIMECS's contributions and the altered timing for the out-licensing of a ghrelin receptor agonist. The business model, competitive edges, and investment strategy remain unchanged. For the final year, FY12/26, the company targets operating revenue of JPY5.5bn (a CAGR of 42.7% over three years), operating profit of JPY1.1bn, recurring profit of JPY1.1bn, and net income of JPY834mn. Aiming for stable royalty income, increased upfront and milestone payments, and contributions from a newly integrated subsidiary, the company seeks to achieve operating profit across three consecutive periods. The forecasted exchange rate for FY12/26 is JPY120.00/USD.

Key progress events expected in FY12/24

ELURA® (weight loss in cats)

Obtained approval in Europe and Japan. Launched in France in August 2024 and scheduled to be launched in Japan in FY12/24.

Tegoprazan (gastric acid secretion inhibitor)

- US: Phase III clinical trials in progress, expects to conclude the study in 2024
- Japan: Licensing activities are ongoing, with an out-licensing agreement expected in FY12/24

Tamibarotene (antitumor drug)

- MDS: Phase III clinical trials in progress, with the completion of patient enrollment expected in Q1 FY12/24 and results to be released in mid-Q4
- AML: Phase II clinical trial ongoing; stopped new patient admission, announced the results of randomized part of Phase II clinical trials in September 2024 (SOHO2024)

P2X7 receptor antagonist (pain)

Analysis of Phase II clinical trial data ongoing, with results of the Phase II study scheduled to be released in FY12/24
*Having failed to meet the primary endpoints, Eli Lilly is reviewing future development plans.

CB2 agonist (pain associated with CIPN/IBS)

Phase I clinical trials in progress, with the start of the next phase of clinical trials expected in FY12/24.

TRPM8 blocker (chronic pain)

Preclinical trials completed; expects to commence Phase I clinical trials in Australia in FY12/24, receive milestone payments from Xgene (Q1), and disclose results of Phase I study in FY12/24

Ghrelin receptor agonist (constipation, cachexia)

Preclinical trials and investigational drug manufacturing in progress, expects to conclude preclinical trials in FY12/24 with the start of Phase I clinical trials expected in FY12/25 (overseas, including the US).

Difference between initial company forecasts and results

Results vs. initial forecast	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Operating revenue (initial forecast)	300	600	950	1,100	1,388	2,022	2,129	2,738	2,605	2,799
Operating revenue (Results)	154	146	705	1,419	745	1,703	1,107	2,776	2,918	1,901
Results vs. initial forecast	**-48.7%**	**-75.8%**	**-25.8%**	**29.0%**	**-46.4%**	**-15.8%**	**-48.0%**	**1.4%**	**12.0%**	**-32.1%**
Operating profit (initial forecast)	-1,684	-1,395	-819	-760	-698	187	70	420	420	260
Operating profit (Results)	-2,123	-1,865	-760	-150	-1,075	-16	-486	708	866	-337
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**68.5%**	**106.2%**	**-**
Recurring profit (initial forecast)	-1,685	-1,415	-819	-761	-680	195	85	427	420	242
Recurring profit (Results)	-1,942	-1,795	-721	-81	-1,065	22	-528	864	904	-293
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-88.9%**	**-**	**102.3%**	**115.3%**	**-**
Net income (initial forecast)	-282	-1,661	-825	-767	-686	153	13	343	342	183
Net income (Results)	-465	-1,854	-728	-58	-1,105	5	-607	756	723	-324
Results vs. initial forecast	**-**	**-**	**-**	**-**	**-**	**-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.

In FY12/23, the company revised its earnings forecast downward on December 8, 2023, due to expected delays in finalizing the licensing agreement for the development, manufacture, and sale of tegoprazan in Japan, and the postponement of the approval and launch of ELURA®, a weight loss treatment for cats with CKD, in Europe until FY12/24. The company estimated these delays would negatively impact earnings by JPY900mn.

Medium-term business plan

	FY12/21	FY12/22	FY12/23	FY12/24	FY12/25	FY12/26	3-year
(JPYmn)	Cons.	Cons.	Cons.	Company forecast	Revised target	Targets	CAGR
Operating revenue	**2,776**	**2,918**	**1,901**	**4,535**	**4,386**	**5,524**	
YoY	150.7%	5.1%	-34.8%	138.5%	-3.3%	25.9%	42.7%
Existing businesses				3,435	3,036	3,574	
YoY				80.7%	-11.6%	17.7%	
% of total				75.7%	69.2%	64.7%	
FIMECS revenue				1,100	1,350	1,950	
YoY				-	22.7%	44.4%	
% of total				24.3%	30.8%	35.3%	
Operating expenses	**2,068**	**2,052**	**2,538**	**4,222**	**3,995**	**4,437**	
YoY	29.8%	-0.8%	23.7%	66.4%	-5.4%	11.1%	20.5%
Operating expense ratio	74.5%	70.3%	133.5%	93.1%	91.1%	80.3%	
Operating profit	**708**	**866**	**-337**	**313**	**391**	**1,086**	
YoY	-	22.4%	-	-	24.9%	177.7%	-
Operating profit margin	25.5%	29.7%	-	6.9%	8.9%	19.7%	
Recurring profit	**864**	**904**	**-293**	**290**	**371**	**1,072**	
YoY	-	4.7%	-	-	27.9%	188.9%	-
Recurring profit margin	31.1%	31.0%	-	6.4%	8.5%	19.4%	
Net income	**756**	**723**	**-324**	**236**	**295**	**834**	
YoY	-	-4.3%	-	-	25.0%	182.7%	-
Net margin	27.2%	24.8%	-	5.2%	6.7%	15.1%	

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Review of previous medium-term management plan (FY12/21–FY12/23)

The company adopted a new management structure in March 2021 and formulated its three-year medium-term management plan (FY12/21–FY12/23) in June 2021. It partially attained its three-year earnings target, research target (one out of two compounds discovered), failed to achieve its development target, and partially attained the out-licensing target.

Status of achievement of previous medium-term management plan and future plans

	Three-year targets starting in FY12/23	Achievements through FY12/23	Future plans
Revenue	1) Maintain profitability for three fiscal years through FY12/25 2) Total operating revenue of JPY9.9bn in three years	Not attained	Aim to turn profitable in FY12/24 onward
Research	Discover one development candidate compound by FY12/24	0 compounds discovered	To discover two candidate drug compounds by FY12/26
Development	In-house development of ghrelin receptor agonist: Completed preclinical trials in FY12/23, started clinical trials in FY12/24	Clinical trial commencement delayed until FY12/25	Completion of preclinical trials delayed until FY12/24
Out-licensing	Out-licensing one program each year	One agreement concluded	Out-licensing of tegoprazan in Japan delayed until FY12/24

Source: Shared Research based on company data

New medium-term management plan (FY12/24–FY12/26)

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 FY12/24 to FY12/26. The plan targets FY12/26 operating revenue of JPY5.5bn (three-year CAGR of

42.7%), operating profit of JPY1.1bn, recurring profit of JPY1.1bn, and net income attributable to owners of the parent JPY834mn. The company targets operating profit in three consecutive years due to a doubling of operating revenue as a result of increased upfront and milestone payments and making FIMECS a subsidiary (see below). It assumes a forex rate of JPY135/USD in FY12/24, JPY125/USD in FY12/25, and JPY120/USD in FY12/26.

Three priority measures to improve corporate value and shareholder value

The company breaks down its price-to-book ratio (PBR) into price-per-earnings ratio (PER) and return on equity (ROE), and implements the three priority measures for improving corporate value and shareholder value outlined below to raise PER through growth expectations and increase PBR by recovering its investment.

1. Strengthen drug discovery value chain

Seek to improve growth potential (PER) by taking on new modalities and expanding focus disease areas

2. Expand development pipeline

Aim to improve growth potential (PER) by discovering new development candidate compounds and progressing clinical development to increase value

3. Expand scale of operating revenue

Improve growth potential (PER) and profitability (ROE) through a platform business and moving into areas with potential for large-scale licensing agreements

Key points of new business plan

- M&A: Acquired FIMECS, which holds targeted protein degradation (TPD) technologies, to gain a platform business
- Revenue: Forecasts total operating revenue of JPY14.4bn in FY12/24–FY12/26, up 45.5% from the previously announced forecast. The company expects a steady increase in royalty revenue, new out-licensing agreements and upfront payments in FIMECS' platform business.
- Out-licensing: The company expects at least one out-licensing agreement per year from its pre-out-licensing program. For tegoprazan in Japan, it aims to conclude an out-licensing agreement in 1H FY12/24. It also expects at least one joint research agreement in FIMECS' platform business.
- R&D: To accelerate the strengthening of its drug discovery value chain centered on open innovation. Plans to discover two pipeline candidates by FY12/26, including new modalities.
- Ghrelin receptor agonist: Clinical trials scheduled for FY12/25

Outlook for operating revenue: Three-year total of JPY14.4bn

- FY12/24: The company looks for increased royalty revenue on solid sales of tegoprazan and pet drugs. It expects upfront payments and milestone payments from the launch of tegoprazan in Japan. Combined with revenue from newly acquired and ongoing joint research projects in FIMECS' platform business, the company forecasts total operating revenue of JPY4.5bn (+138.5% YoY).

- FY12/25: The company expects growth in global sales of tegoprazan and solid sales of pet drugs. It forecasts a total of JPY4.4bn (-3.3% YoY) in revenue including royalty revenue and upfront and milestone payments, and revenue from FIMECS' platform business.

- FY12/26: The company expects royalty revenue to remain stable, due to continued solid sales of tegoprazan and pet drugs. It also looks for upfront payments and milestone payments from ghrelin receptor agonist and other drugs. It forecasts a total of JPY5.5bn in revenue (+25.9% YoY), including revenue from FIMECS' platform business.

Growth strategy

M&A to raise corporate value and shareholder value

In February 2024, the company announced it would acquire all shares in FIMECS, Inc. (unlisted) and make it a subsidiary, because it needs to create a new source of earnings to follow tegoprazan and pet drugs. FIMECS advances the research and development of new pharmaceuticals using targeted protein degradation (TPD) inducers, a new modality in drug discovery. Based on its unique drug discovery platform technology RaPPIDS™, it conducts joint research with Astellas Pharma Inc. (TSE Prime: 4503) and may receive milestone payments according to progress with development and royalties after product

launch. The company expects to strengthen its drug discovery value chain, increase its earnings through a hybridized business model, and strengthen the cancer disease area by making FIMECS a subsidiary.

Synergies expected from M&A

Management resources	• Acquire pipelines • Acquire skilled personnel • New corporate cultures and innovation engines
Increased growth potential	• Strengthen drug discovery value chain • Acquire new modalities • Further advance into cancer disease area
Increased profitability	• Increase earnings opportunities • Expand into platform businesses

Source: Shared Research based on company data

Taking on untouched drug discovery targets

Existing small molecule drugs treat diseases by binding to disease-related proteins, which are the drug discovery targets, and inhibiting their function. Proteins with structures that prevent binding have been considered "undruggable" (impossible to discover drugs to treat the condition). However, new modalities and application of new technologies such as informatics and AI in drug discovery have opened up the possibility of creating new candidate drugs that target disease-related proteins that were previously believed to be "undruggable."

Founded in 2018, FIMECS is a drug discovery bio-venture engaged in research and development of new pharmaceuticals using targeted protein degradation (TPD) inducers, a new modality in drug discovery. TPD works by directly breaking down "undruggable" target proteins. The human body naturally breaks down and removes unnecessary proteins through metabolism, but TPD stimulates the breaking down of the target protein by bringing E3 ligase, an enzyme that adds ubiquitin to mark the target protein to help break it down.

Based on its unique E3 ligase binding molecule and drug discovery platform technology RaPPIDS™, it aims to create innovative medicines for diseases that have been considered extremely difficult to treat using medications ("undruggable"). FIMECS has established a technology to identify the optimal E3 ligase for each target from over 600 known E3 ligases and acquire novel E3 ligase binders by improving and evolving RaPPIDS™.

In 2022, FIMECS entered into a research collaboration agreement with Astellas Pharma Inc. (TSE Prime: 4503) on multiple targets. Based on this agreement, FIMECS received an upfront payment of JPY500mn and research funding. After the identification of candidate compounds, Astellas Pharma will conduct development, and FIMECS will receive milestone payments based on the progress of development for each target program. Furthermore, after commercialization, FIMECS may receive sales milestones and royalties at a single-digit rate based on sales revenue.

FIMECS is also advancing several first-in-class new drug development programs targeting proteins associated with cancer diseases as its main in-house pipeline. The most advanced program, the IRAK-M program (compound code: FIM-001), aims to develop a new cancer immunotherapy based on the mechanism of action of immune suppression relief and is currently in the preclinical stage.

FIMECS' pipeline

Target	Target disease	Research stage	Partner
IRAK-M	Non-small cell lung cancer, pancreatic cancer, other	Preclinical studies	
TRIB1	Cancer	Exploratory	
Undisclosed	Undisclosed	Exploratory	Astellas Pharma
Undisclosed	Undisclosed	Exploratory	Astellas Pharma

Source: Shared Research based on FIMECS website

Reason for the acquisition

RaQualia is focused on enhancing corporate and shareholder value by reinforcing its growth foundation, while aiming to improve profitability through the signing of large contracts. In pursuit of growth enhancement, updating the drug discovery value chain and M&A are positioned as key strategies. By making FIMECS a subsidiary, RaQualia expects business expansion in the following three areas:

1. Enhancing the drug discovery value chain to improve growth potential and competitiveness

Traditionally, RaQualia has specialized in drug discovery research of small molecules targeting ion channels and GPCRs, generating many drug candidate compounds. Since 2022, aiming to establish the next-generation in-house drug discovery value chain from four perspectives: modality, drug discovery target, disease area, and core technology, RaQualia has been advancing collaborations with several startups and drug discovery companies. Acquiring FIMECS's RaPPIDS™ platform technology to venture into new modalities such as targeted protein degradation inducers allows targeting molecules and disease areas previously considered undruggable. The acquisition of FIMECS is expected to significantly advance the strengthening of RaQualia's next-generation in-house drug discovery value chain.

2) Adopt a hybridized business model: Increase its earnings through platform business

The company is a "pipeline-type" drug discovery company, which discovers new drug candidate compounds and develops them in-house, and undertakes the later stages of clinical development by out-licensing, through joint research, or independently. FIMECS is a "platform-type" drug discovery company, which focuses on exploratory research, with technology that it out-licenses and ability to create drug discovery seeds. The company that in-licenses its technology undertakes development from the preclinical studies stage onward. The earnings structure of platform-type companies is based on joint research from the exploratory research stage to obtain upfront payments, research cooperation payments, and milestone payments early on, as well as receiving royalty revenue. For pipeline-type companies on the other hand, exploratory research through to out-licensing is an investment phase, and the investment recovery phase comes after out-licensing in the form of upfront and milestone payments and royalty revenue. By making FIMECS a subsidiary, the company has hybridized its business model so it can earn revenue from the exploratory research stage.

Currently, FIMECS is conducting joint research with Astellas Pharma on multiple targets, which may yield milestone payments, royalties, and sales milestones based on the progress of these joint research projects. The interest in targeted protein degradation inducers is particularly high abroad, with similar companies in the US (e.g., Arvinas [NASDAQ: ARVN], C4 Therapeutics [NASDAQ: CCCC], Kymera Therapeutics [NASDAQ: KYMR], Nurix Therapeutics [NASDAQ: NRIX]) building their platforms and securing substantial contracts from the early stages of collaboration. FIMECS plans to continuously acquire new joint research partners both domestically and internationally around its core platform technology, RaPPIDS™, expecting further expansion of revenue opportunities.

3. Further strengthening and expansion in the oncology field

RaQualia has developed marketed pharmaceuticals such as the gastric acid secretion inhibitor tegoprazan (brand name: K-CAB®) and the dog osteoarthritis treatment grapiprant (brand name: GALLIPRANT®). While many of its out-licensed programs are being developed by pharmaceutical companies and belong mainly to the pain and gastrointestinal disease areas, the company has initiated exploratory research targeting cancer as part of strengthening its drug discovery value chain. The acquisition of FIMECS, adding pipelines including the IRAK-M program, will strengthen the group's pipeline targeting cancer.

Consideration and method for the acquisition

RaQualia plans to acquire all issued shares of FIMECS from the current shareholders on March 26, 2024, making FIMECS a consolidated subsidiary. The consideration for the acquisition consists of an upfront payment (the closing consideration) paid at the time of the share acquisition and payments based on future revenues earned by FIMECS (the earn-out consideration).

1. Closing consideration

RaQualia will pay a closing consideration of JPY4.5bn in cash to the sellers on March 26, 2024. In March 2024, the company decided to borrow a syndicated loan of JPY3.5bn (loan period: seven years) to fund the share acquisition.

2. Earn-out consideration

From FY12/24 to FY12/28, based on contract upfront payments, milestone payments, royalty income, and revenue from commissioned work generated from contracts with third parties, an amount calculated using a predetermined calculation method will be paid to the sellers.

This arrangement mitigates the risk of RaQualia paying an undue consideration by not paying the entire consideration at the time of the acquisition execution but paying part of it as earn-out consideration based on the revenue of FIMECS. It also serves as an incentive for some sellers involved in FIMECS's operations to continue contributing to research and development activities and revenue expansion.

Establishing drug discovery value chain through open innovation

The company thinks that it must organically combine basic technologies with drug discovery technologies if it is to continually create its development pipeline, and thus has a policy of actively working in collaboration with startups, drug discovery ventures, and academia to solve problems. Creating a drug development pipeline by combining its own technologies is possible with a plentiful supply of funds and human resources, but carries the risk of being limited by existing technologies and frameworks. Relationships of trust and ensuring rights are protected are important in open innovation between multiple companies and collaborations with academia, but this approach allows the application of technologies that a company does not own. The company seeks to establish a next-generation in-house drug discovery value chain by harnessing synergies between its own existing technologies and strengthened collaboration with startups and drug discovery ventures (see the "Business" section below).

1) Initiatives to expand drug discovery targets: Joint research with Veritas In Silico Inc. (TSE Growth: 130A)

2) Initiatives to harness AI: Joint research with Socium Inc.

3) Initiatives to expand modalities: Joint research with STAND Therapeutics Co., Ltd.

4) Initiatives to maximize value of pipeline: Joint research with D. Western Therapeutics Institute (TSE Growth: 4576)

5) Initiatives to utilize structural biology in ion channel drug discovery: Collaboration with leadXpro AG (Switzerland)

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; ranked third in terms of pharmaceuticals sales worldwide in 2023) 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 2023 it held about 3.44%.

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-HT_4, 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

	Process		Duration	Details	RaQualia's business territory
Research	Exploratory (basic) research		3–5 years	Development of therapeutic concepts, compound synthesis and evaluation	✔
Development	Preclinical (nonclinical) studies		2–3 years	Evaluation of efficacy and safety mainly in animals	✔
	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	24

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 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

Out-licensing

- 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. (TSE GRT: 130A) 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.

Licensees have already launched four products, providing the company with stable long-term royalty revenue, its main source of earnings. In FY12/23, operating revenue was JPY1.9bn (-34.8% YoY), comprising royalty revenue (approximately 70%) and upfront and milestone payments (approximately 30%).

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

	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Total	154	146	705	1,419	745	1,703	1,107	2,776	2,918	1,901
YoY	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.6%	-35.0%	150.7%	5.1%	-34.8%
US	-	-	646	818	278	761	549	1,004	1,142	1,091
YoY	-	-	-	26.5%	-66.0%	173.8%	-27.8%	82.7%	13.8%	-4.5%
% of total	-	-	91.6%	57.6%	37.3%	44.7%	49.6%	36.2%	39.1%	57.4%
Japan	131	106	50	471	349	196	28	1,187	742	6
YoY	86.9%	-19.4%	-52.6%	841.1%	-25.8%	-43.7%	-85.9%	4175.6%	-37.5%	-99.2%
% of total	85.0%	72.5%	7.1%	33.2%	46.8%	11.5%	2.5%	42.8%	25.4%	0.3%
Asia	20	40	9	131	121	746	530	585	1,034	801
YoY	-	100.0%	-77.5%	1355.0%	-7.8%	517.9%	-28.9%	10.3%	76.8%	-22.6%
% of total	13.0%	27.5%	1.3%	9.2%	16.2%	43.8%	47.9%	21.1%	35.4%	42.1%
Europe	-	-	-	-	-	-	-	-	-	-
YoY	-	-	-	-	-	-	-	-	-	-
% of total	-	-	-	-	-	-	-	-	-	-
Other	3	-	-	-	-	-	-	-	-	4
YoY	-84.7%	-	-	-	-	-	-	-	-	-
% of total	2.0%	-	-	-	-	-	-	-	-	-

Source: Shared Research based on company data
Note: Revenue is based on customer location, and classified by country or region

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: 13 project compounds already out-licensed, including ion channel projects, and seven at the pre-out-licensing stage.

It also had nine programs in its exploratory research pipeline as of February 2024, and in addition to in-house research, it is conducting joint research with other companies and academia. 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. The company thinks that it can continually discover innovative compounds as development candidates by always having 7–10 exploratory research programs underway.

Out-licensed pipeline (human)

Out-licensed programs (human)

Program name	Generic nameCompound code	Key indication	Out-licensing region	Development stage
Tegoprazan (potassium-competitive acid blocker [P-CAB]; K-CAB®)	RQ-00000004 (tegoprazan)	GERD	South Korea	On market(Mar 2019)
			China	On market(Apr 2022)
			Philippines	On market (Oct 2022)
			Mongolia	On market (Oct 2022)
			Mexico	On market (May 2023)
			Indonesia	On market (Jul 2023)
			Singapore	On market (Sep 2023)
			Peru	On market (Oct 2023)
			Thailand, Vietnam, Malaysia	Application under review
			15 countries in Latin America	Preparing for approval filing, obtained approval in four countries, including Chile
			Brazil	Preparing for approval filing
			US, Canada	Phase III underway in US (2022-)
			7 countries including India	Phase III underway, preparations underway
Retinoic acid receptor alpha agonist	TamibaroteneTM-411/SY-1425	High-risk MDS	North America, Europe	Phase III underway(US)
		Acute myeloid leukemia (AML)		Phase II underway(US)
EP4 receptor antagonist	RQ-00000007 (grapiprant)	Pain	Worldwide	Phase II complete (US)
				Phase I complete (China)
		Cancer	Worldwide	Phase I complete (US)
				Phase I underway (China)
	RQ-00000008	Osteoarthritis, autoimmune disorders, etc.	Worldwide	Preclinical trials completed
5-HT4 partial agonist	RQ-00000009	Alzheimer's disease	Worldwide	Phase I complete (US)
COX-2 inhibitor	RQ-00317076	Pain	Worldwide	Phase IIa complete (US)
				Phase I underway (China)
CB2 agonist	RQ-00202730	Pain relief, etc.	Worldwide	Phase I underway (UK)
Selective sodium channel blocker	Not disclosed	Analgesic and antipruritic	Worldwide	Not disclosed
P2X7 receptor antagonist	RQ-00466479 AK1780	Neuropathic pain	Worldwide	Phase II underway (US and others)
Specific ion channel target	Not disclosed	Gastroenterology	Worldwide	Not disclosed
TRPM8 blocker	RQ-00434739	Chronic pain	Worldwide, except Japan	Phase I underway (Australia)
Sodium channel blocker	RQ-00350215	Chronic pain	Worldwide	Preclinical trials ongoing
IRAK-M degradation inducer	FIM-001	Cancer	Worldwide	Preclinical trials ongoing

Source: Shared Research based on company data (as of May 2025)

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. Sales of TAKECAB® in 2023 totaled JPY115.6mn (+3.3% YoY), the fifth highest among domestic drugs.

Maintained 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 2023 (non-hospital prescription data) remained brisk in 2023, totaling KRW158.2bn (+19.8% YoY, roughly JPY17.4bn converted at KRW/JPY0.11), with the total number of prescriptions in 2019–2013 reaching KRW508.5bn (JPY55.9bn) and top market share in South Korea for gastrointestinal disease treatments at 14% as of June 2024.

As of end-August 2024, HK Inno.N's sublicensees are advancing the development, manufacturing, and sales of tegoprazan in 45 countries. Tegoprazan is marketed in eight countries, namely South Korea, China, Mongolia, the Philippines, Mexico, Indonesia, Singapore, and Peru. In February 2024, the sublicensee in Chile receivied approval to market tegoprazan for four conditions, including erosive reflux disease. Moreover, regulatory reviews are in progress in over 20 countries, including Argentina. In the US, Braintree, a sublicensee, is conducting Phase III clinical trials of tegoprazan, with the study scheduled to be completed in 2024.

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 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.

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. 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.

As of August 2024, tegoprazan is marketed in eight countries, namely South Korea, China, Mongolia, the Philippines, Mexico, Indonesia, Singapore, and Peru, has obtained marketing approval in four Latin American countries including Chile, and has been rolled out in 36 countries (under development, in the marketing approval process, or preparing for launch). 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. 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

Potential global market size		Share captured		Royalty rate		Maximum royalties company can receive
JPY2bn	×	11% in South Korea	×	Generally 1–10%	=	

Source: Shared Research based on company data

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

Country/region	Licensee*	Sales and development status	Market size (JPYmn)
South Korea	HK inno.N	Launched in 2019, maintaining No. 1 market share	120,000
China	Luoxin	Launched in April 2022	450,000
Philippines	MPPI	Launched in October 2022	5,000
Mongolia	Monos	Launched in October 2022	-
Mexico	Carnot	Launched in May 2023	66,000
Indonesia	Kalbe	Launched in July 2023	50,000
Singapore	UITC	Launched in September 2023	50,000
Peru	Carnot	Launched in October 2023	66,000
Thailand, Vietnam, Malaysia	Pond's, Lyhn farma, Pharmaniaga	Application under review	50,000
Argentina and 15 other Latin American countries	Carnot	Application under review, approval obtained in four Latin American countries, including Chile	66,000
Brazil	Eurofarma	Filing in preparation	88,000
US, Canada	Braintree	Phase III study in progress	460,000
7 countries including India	Dr.Reddy	Phase III study in progress/preparation	140,000

Source: Shared Research based on company data (as of May 2024)
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), is a business partner since November 2015. 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). After receiving approval, it started dosing patients in July 2023. OCTP's Phase I clinical trial for the CB2 agonist mainly targets chemotherapy induced peripheral neuropathy (CIPN). OCTP plans to proceed with clinical development of the CB2 agonist, and commenced the Phase I trial in the UK in Q3 FY12/23.

The human body has cannabinoid receptors known as CB1 and CB2, but targeting CB1 entails risks of central nervous system side effects on behavior or psychology. However, CB2 is attracting interest as a target for drugs to treat pain, inflammatory diseases, and cancer. Because the company's CB2 agonist is a compound that selectively acts on CB2, it avoids side effects via CB1, and is thought promising as a highly tolerable treatment. The global CIPN market is worth about USD1.6bn (roughly JPY225.0bn at JPY140/USD), and is expected to grow to USD2.4bn (roughly JPY330.0bn) by 2027.

P2X7 receptor antagonist (RQ-00466479)

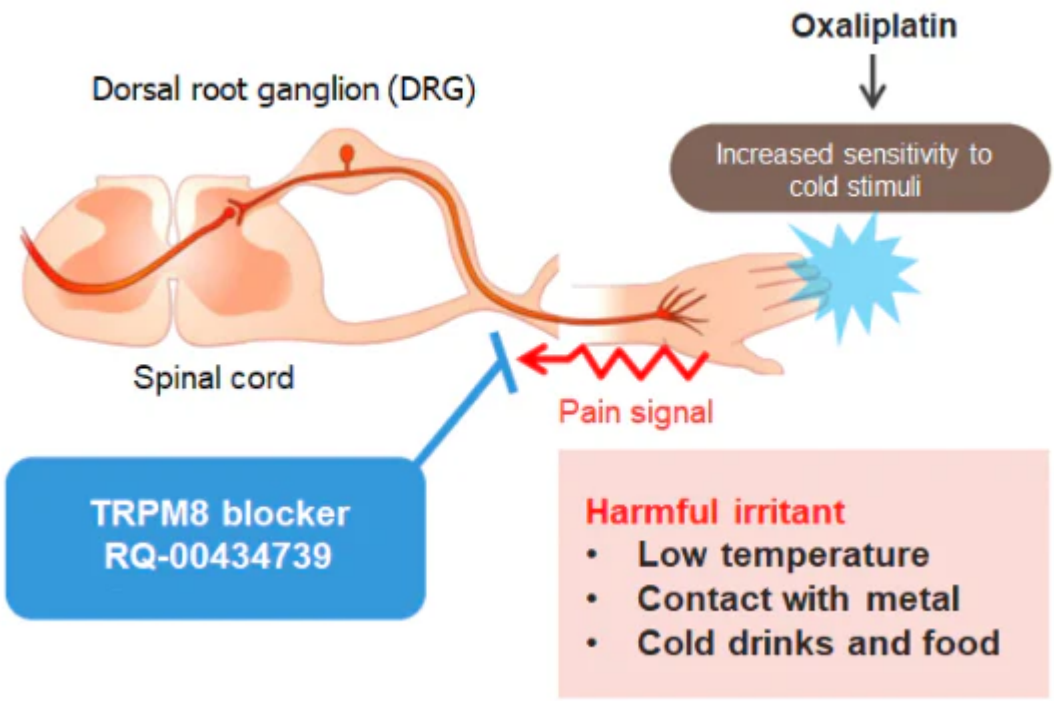
The company created a P2X7 receptor antagonist through joint research with Asahi Kasei Pharma (a license agreement signed in March 2018). Phase I clinical trials targeting peripheral neuropathic pain have been completed. Eli Lilly, with whom Asahi Kasei Pharma has a license agreement, will take over 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).

In August 2024, sublicensee Eli Lilly announced the results of Phase II clinical trials conducted in the US for three diseases. Although the safety profile of the investigational drug was favorable with no major concerns, its efficacy did not meet the primary endpoints. Eli Lilly is currently reviewing future development plans.

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.

TRPM8 blocker and pain mechanisms



Source: Company data

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 In March 2024, it received approval to begin Phase I clinical trials from the Australian Therapeutic Goods Administration (TGA). 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).

In May 2024, Xgene initiated a Phase I clinical trial in Australia. The trial involves a dose-escalation study in healthy volunteers to evaluate the tolerability and pharmacokinetics of a TRPM8 antagonist, with the aim of gathering critical information for subsequent clinical trials.

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 to 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 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.

Out-licensed to US-based Syros Pharmaceuticals

In September 2015, TMRC granted development and marketing rights in Europe and North America for tamibarotene as a cancer therapy to US-based Syros 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 patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Tamibarotene is a selective retinoic acid receptor alpha (RARα) agonist. The company aims to file a new drug application for tamibarotene as a precision medicine* using RAR alpha as a biomarker. Consolidated subsidiary TMRC has licensed it to US-based Syros Pharmaceuticals Inc. (NASDAQ: SYRS), which is conducting clinical trials for the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in the US.

* Precision medicine: Also known as cancer gene therapy, it is cutting-edge medicine that entails analyzing cancer at the genetic level to provide the optimal treatment for that particular cancer. It is most advanced in the field of oncology, but can be used for all diseases. It 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.

Analysis shows that approximately 50% of MDS patients and 30% of AML patients have RAR alpha overexpression. When tamibarotene is used in combination with an anticancer agent, tamibarotene binds to RAR alpha, controlling the expression of differentiation factor genes, for an anti-tumor effect inducing cancer cell death. A patent review regarding the use of tamibarotene with anticancer drugs in Japan was conducted in July 2023.

Syros plans to complete registration of 190 patients for primary analysis of 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. It also plans to release pivotal data by Q4 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. Syros announced the results of the randomized part of the study in December 2023.

In August 2024, an interim analysis, including a non-binding futility analysis, was conducted using data from 51 patients enrolled in the SELECT-AML-1 trial. A futility analysis is a statistical assessment that predicts trial outcomes based on prespecified hypotheses and evaluation criteria to determine whether the trial should continue. The interim analysis concluded that the likelihood of the investigational drug's demonstrating superiority in the final analysis with data from 80 patients was low, leading Syros to halt new patient enrollment. No new safety concerns were identified with the combination of tamibarotene, venetoclax, and azacitidine.

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.

Tamibarotene received fast-track designation from the US Food and Drug Administration for higher-risk myelodysplastic syndrome (HR-MDS) in January 2023, and for acute myeloid leukemia (AML) in April 2024. The company hopes it will be eligible for priority and expedited review. 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.

Separately, a clinical research/investigator-initiated clinical trial of tamibarotene for pancreatic cancer and upper urinary tract cancer (led by Nagoya University) has been underway since March 2023, as a Japan Agency for Medical Research and Development (AMED) project. 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)
Licensor	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. The three products on the market are currently sold by Elanco.

Out-licensed programs (veterinary)

Program name	Generic name/compound code	Key indication	Rollout area	Development stage
EP4 antagonist GALLIPRANT®	RQ-00000007 (grapiprant)	Osteoarthritis in dogs	US	On market
			Europe	On market
			Japan	On market
Ghrelin receptor agonistENTYCE®	RQ-00000005 (capromorelin)	Anorexia in dogs	US	On market
Ghrelin receptor agonistELURA®		Weight loss in cats with CKD	US	On market
			Europe	Approved, on market
			Japan	Approved, preparing for launch
COX-2 inhibitor	RQ-00317076	Pain	—	Exploratory research completed
EP4 receptor antagonist	RQ-00000008	Osteoarthritis, etc.	Worldwide	Preclinical trial ongoing
5-HT4 agonist	RQ-00000010	Intestinal motility disorder (dogs, cats)	Worldwide (Veterinary)	POC trial ongoing
Four specific compounds	Not disclosed	Under evaluation	Worldwide	Under evaluation

Source: Shared Research based on company data (as of August 2024)

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. The company filed for approval of ELURA® in March 2022, and the Committee for Veterinary Medicinal Products (CVMP) of the European Medical Agency (EMA) indicated that it was in favor of approval in May 2023. Approval was granted in 2023; the company expects to launch the product and attain a milestone in FY12/24. ELURA® was also approved in Japan in February 2024.

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.

New licensing agreement

In April 2024, the company entered into an option and license agreement with US-based Velovia Pharma, LLC (unlisted) for the development of veterinary drugs containing the company's four pipeline compounds. Based on the terms of the agreement, the company granted Velovia option for the exclusive rights to evaluate, develop, manufacture, and sell veterinary drugs containing its four pipeline compounds. If Velovia exercises its option right for one or more of the compounds, the company is entitled to receive option exercise fees as well as milestone payments based on Velovia's subsequent development progress. Further, if veterinary drugs containing the compounds reach the market, the company may receive sales royalties and sales milestone payments based on product sales from Velovia.

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 2024 round of price revisions, the price was cut by 1.18% on a medical fee basis and reduced and by 5.51% on a drug fee basis 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 pet 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
Curtailing 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 seven 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
tegoprazan	tegoprazan RQ-00000004	GERD, others	Japan	
5-HT4 partial agonist	RQ-00000010	Gastroparesis, functional dyspepsia, chronic constipation	Worldwide (human)	Phase I completed
5-HT28 agonist	RQ-00310941	Irritable bowel syndrome with diarrhea (IBS-D)	Worldwide	Phase I completed (UK)
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, contipation from spinal cord	Worldwide	Preclinical trials underway
IRAK-K degradation inducer	FIM-001	Cancer (NSCLC, pancreatic cancer)	-	Preclinical trials underway
TRPM8 blocker	RQ-00434739	Pain	Japan	Preclinical trials underway

Source: Shared Research based on company data (as of May 2024)

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).

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.

Extended negotiations for out-licensing tegoprazan in Japan

The the company retains the rights for Japan for tegoprazan, which was out-licensed to HK inno.N in September 2010. It had planned to complete pharmacological studies as part of Phase I clinical trials in FY12/23 and out-license in FY12/24 onward. However, having been approached by a licensee candidate, the company decided not to conduct its own pharmacological studies and out-license in FY12/23 so that the product could go on sale as soon as possible. It began negotiations with the

licensee candidate in FY12/23 and expected to conclude an agreement by the end of the year, but the following issues have required more time to resolve.

In the negotiations with the licensee candidate for tegoprazan in Japan, RaQualia identified three primary discussion points: 1) accelerating and reducing the risk of development, 2) ensuring the supply of APIs and formulations, and 3) addressing concerns about potential drug price cuts.

To expedite and de-risk the development process (item 1), the company decided to leverage overseas clinical information by acquiring data from its partners, HK Inno.N and Braintree. Consequently, RaQualia will recognize a one-time payment in FY12/24 for utilizing overseas clinical trial data. Regarding the supply of APIs and formulations (item 2), the company will utilize partnerships. These two issues were resolved early in 2023. However, discussions on the third issue persist. To maintain price elasticity in anticipation of future drug price reductions, negotiations with the licensee candidate continue. The focus is on determining various conditions such as license fees and supply costs, and these negotiations are still ongoing. The company is still negotiating with the licensee candidate and aims to conclude a license agreement by end-FY12/24.

Use of South Korean and US 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. As noted above, the company has decided to use overseas clinical information, and plans to record a one-time payment for the use of data in FY12/24.

5-HT4 partial agonist (RQ-00000010)

This compound is under development for target indications of gastrointestinal dysmotility including gastroparesis, functional dyspepsia, and chronic constipation. 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. However, the company plans to conduct clinical trials in 2025, because preclinical studies are taking a long time.

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.

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.

IRAK-M degradation inducer (FIM-001)

A targeted protein degradation inducer developed by FIMECS, FIM-001 serves as a caner immunotherapy that operates by degrading IRAK-M to disrupt immunosuppressive mechanisms. It negates a systemic immunosuppressive mechanism by a mechanism distinct from immune checkpoint inhibitors. For this reason, the company believes the investigational drug may help overcome resistance to immune checkpoint inhibitors. Preclinical studies are ongoing for the main expected indications of non-small cell lung cancer and pancreatic cancer.

Exploratory and discovery phase pipeline

As of February 2024, the company had nine programs in exploratory and discovery research, six of which were joint research with companies or academia.

	Collaboration partner	Target diseases	Target molecule	Notes	Beginning of 2023	Beginning of 2024
Company	ASKA Pharmaceutical	Not disclosed	Ion channels		✔	Ended
	Socium	Rare diseases	Not disclosed	AI drug discovery	✔	✔
	STAND	Rare diseases	Ion channels	New modality	✔	Ended
	STAND	Rare diseases	Not disclosed	New modality		✔
	DWTI	Ocular ciseases	Ion channels		✔	✔
	VIS	Cancers	Not disclosed	New modality	✔	✔
	leadXpro	Not disclosed	Ion channels	Structural biology		✔
Academia	Gifu Pharmaceutical University	Ocular ciseases	Not disclosed		✔	✔
In-house (independent)		Not disclosed	Ion channels		✔	✔
		Not disclosed	Ion channels		✔	✔
		Not disclosed	Ion channels			✔

Source: Shared Research based on company data

Drug discovery research targeting specific ion channel

The company has been conducting joint research with ASKA Pharmaceutical Co., Ltd. (unlisted; subsidiary of ASKA Pharmaceutical Holdings Co., Ltd. [TSE Prime: 4886]) 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.

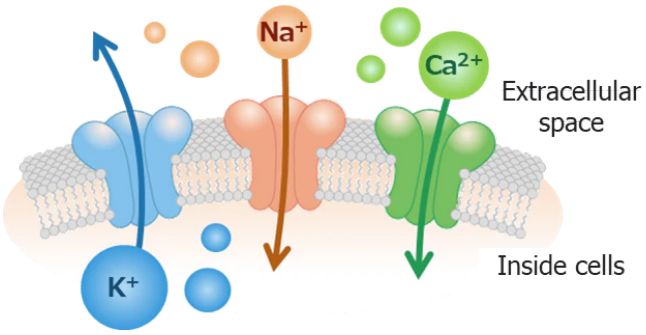
Ion channel drug discovery

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 under 10% 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
				Xgene (Hong Kong) running Phase I trials
Sodium channel blocker	RQ-00350215	Chronic pain	Hisamitsu	Out-licensed in 2021
				Preclinical trials underway

Source: Shared Research based on company data (as of August 2024)

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 of main target diseases

Disease	Number of patients	Market size	Region	Existing therapies	RaQualia's development pipeline
GERD	58mn (US), 17mn (Japan)	JPY2tn JPY450bn JPY250bn	Worldwide US Japan	H2RA, PPI, vonoprazan	Tegoprazan
Pain	50mn (US), 23mn (Japan)	JPY2.4tn JPY300bn	Worldwide Japan	Pregabalin, duloxetine, celecoxib, etc.	EP4 receptor antagonist , COX-2 inhibitor, TRPM8 blocker, P2X7 receptor antagonist, sodium channel blocker
Cancer immunity	Approx. 12% of cancer patients respond to cancer immunotherapy	JPY10tn	Worldwide	Nivolumab, pembrolizumab, etc.	EP4 antagonist
Chronic constipation	42mn (US)	JPY660bn JPY60bn	Worldwide Japan	Linaclotide, lubiprostone, etc.	5-HT_4 partial agonist
Gastroparesis	80,000-400,000	JPY200bn	Worldwide	Metoclopramide, etc.	5-HT_4 partial agonist, motilin receptor agonist
Irritable bowel syndrome	5-20% of Japanese/Western adults	JPY100bn	Worldwide	Rifaximin, ramosetron, etc.	5-HT_{2B} 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), 20,000 new cases annually (US, Europe)	JPY100bn	Worldwide	Azacitidine, etc.	Tamibarotene
Acute myeloid leukemia	160,000 (worldwide), 25,000 new cases annually (US, Europe), 7,000 (Japan)	JPY1tn	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 2023 reached JPY11.3tn (+3.1% YoY), the ninth consecutive year above JPY10tn. Sales of antacids, flatulence agents, and ulcer agents came to JPY278.4bn (-16.1% YoY) with sales of Takeda's antiulcer drug TAKECAB® at JPY115.6bn (+3.3% YoY), the fifth highest among domestic drugs.

Prescription drug sales in Japan

(JPYmn)	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
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
YoY	0.0%	3.8%	1.2%	4.1%	2.1%	7.5%	-0.6%	4.6%	2.6%	7.2%
Antacids, flatulence/ulcer agents	391,242	400,632	383,713	392,301	395,660	418,112	408,593	422,148	427,027	446,651
YoY	-1.0%	2.4%	-4.2%	2.2%	0.9%	5.7%	-2.3%	3.3%	1.2%	4.6%
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Prescription drug sales in Japan	8,873,623	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
YoY	0.2%	6.9%	0.7%	3.1%	1.4%	6.2%	0.2%	-1.0%	-1.7%	2.8%
Antacids, flatulence/ulcer agents	429,890	434,997	408,604	418,289	397,394	389,788	376,365	377,550	349,783	351,329
YoY	-3.8%	1.2%	-6.1%	2.4%	-5.0%	-1.9%	-3.4%	0.3%	-7.4%	0.4%
	2020	2021	2022	2023						
Prescription drug sales in Japan	10,371,733	10,599,031	10,939,481	11,280,631						
YoY	-2.4%	2.2%	3.2%	3.1%						
Antacids, flatulence/ulcer agents	347,142	351,640	331,675	278,425						
YoY	-1.2%	1.3%	-5.7%	-16.1%						

Source: Shared Research based on IQVIA 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 2024 price revisions, the price was cut by 1.18% on a medical fee basis and reduced and by 5.51% on a drug fee basis 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 1.35% 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).

The April 2024 NHI drug price revision calls for cuts of 0.97% on a medical fee basis and 4.67% on a drug fee basis, with the expectation of a JPY120.0bn reduction in healthcare spending. The 2024 price revision reviewed the drug reimbursement price system to resolve the issue of drug lag and drug loss as well as ensure a stable supply. It overhauled the Drug Price Standard, including the way it drugs are evaluated for early adoption in Japan and the way premiums such as innovation premium, value premium (for usefulness), pediatric premium (to encourage development of pediatric drugs), and repricing for market expansion are calculated by doing away with corporate indicators and increasing the number of items for evaluation.

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	2019	2020	2022	2024	
NHI price revisions (drug fee basis)	-6.00%	-5.64%	-5.57%	-7.48%	-4.35%	-4.38%	-6.69%	-4.67%	
NHI price revisions (medical fee basis)	-1.26%	-1.22%	-1.22%	-1.65%	-0.93%	-0.99%	-1.35%	-0.97%	
Average deviation	8.2%	8.8%	9.1%	7.2%	8.0%	8.0%	7.0%		

Source: Shared Research based on MHLW "NHI drug price revisions"
* The average differential between the NHI drug price and prevailing market price was around 6.0%.

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. Although the market for pet drugs is smaller than that of human pharmaceuticals, the company can maintain or increase prices more easily in the absence of regulated drug prices in Japan and elsewhere, which means royalty revenue is less likely to decline and thus provides stable earnings.

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	○	○		○
	Nucleic acid (DNA/RNA)	○		○	○
Target molecule location	Intracellular	○	○	○	
	Extracellular	○	○	○	○
Administration route	Oral	○			
	Other	○	○	○	○

Source: Shared Research based on company data

Number of approvals by FDA (US)

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
New Molecular Entities (NMEs)	19	28	47	34	25	33	25	19	11	15	31	18	18	16	21
% of total	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%	87.5%
Biologics License Applications (BLAs)	2	1	6	5	5	2	2	5	6	6	5	2	4	2	3
% of total	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%	12.5%
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**
New Molecular Entities (NMEs)	20	15	24	33	25	30	33	15	34	42	38	40	36	22	34
% of total	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%	61.8%
Biologics License Applications (BLAs)	6	6	6	6	2	11	12	7	12	17	10	13	14	15	21
% of total	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%	38.2%

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 increased in 2023 from 2022, and remained the most common at 61.8% 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	1,901	-17.7%	-5.6%	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	26,011	50.4%	29.6%	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	12,766	-74.6%	-11.5%	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	202	-616.3%	-27.0%	Biotech start-up focused on oncology. Aims at new drugs with few side effects using its ultrafine micellar nanoparticle technology.
4572	Carna Biosciences	1,626	-68.7%	-30.7%	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	5,590	-14.5%	-26.1%	Main focus on oncology, hematology, and rare diseases. In-licenses drug candidate compounds which it develops and commercializes.
4587	PeptiDream	28,712	23.6%	8.4%	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. Many alliances with major overseas drug companies. Moved into radiopharmaceuticals by M&A.
4597	Solasia Pharma	617	-184.6%	-49.0%	Biotech venture that in-licenses development rights for candidate substances and uses in clinical development, focusing on cancer. Re-out-licenses drug candidates it has in-licensed and developed, and sells pharmaceutical products. Fabless operations. Outsources manufacturing to overseas companies.
4883	Modalis	0	-	-111.9%	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)		
	FY12/21	FY12/22	FY12/23	FY12/21	FY12/22	FY12/23	FY12/21	FY12/22	FY12/23
	Cons.	Cons.	Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.
Revenue	2,776	2,918	1,901	12,690	17,419	26,011	17,712	15,569	12,766
Gross profit	2,456	2,686	1,670	11,090	14,745	22,431	16,779	14,643	9,664
R&D expenses	1,127	1,249	1,373	2,016	2,545	2,558	5,931	7,454	10,075
SG&A expenses	620	572	621	7,959	10,966	15,293	3,940	4,377	9,965
Operating profit	708	866	-337	1,625	1,378	13,109	3,775	3,436	-9,526
Recurring profit	864	904	-293	1,107	768	12,613	433	645	-10,680
Net income	756	723	-324	55	-868	9,504	1,017	382	-7,193
ROE	17.2%	14.1%	-5.6%	2.3%	2.0%	29.6%	1.9%	0.7%	-11.5%
ROA (RP-based)	18.2%	15.7%	-4.5%	4.1%	2.4%	26.2%	0.5%	1.1%	-8.3%
Operating profit margin	25.5%	29.7%	-17.7%	12.8%	7.9%	50.4%	21.3%	22.1%	-74.6%
Total assets	5,234	6,258	6,872	30,297	33,907	63,394	96,985	99,417	157,198
Net assets	4,788	5,497	6,120	19,266	19,811	36,053	57,468	57,936	66,810
Equity ratio	91.3%	87.7%	88.7%	62.3%	61.8%	54.2%	59.3%	58.3%	42.5%
Operating CF	366	1,480	-719	552	393	6,549	7,095	9,952	-5,273
Investing CF	-279	-48	-135	-261	-4,116	-9,843	278	1,043	-63,791
Financial CF	-16	-30	793	2,853	-646	10,687	11,123	-4,887	48,329
Cash and deposits	2,345	3,675	3,715	14,352	11,049	21,633	60,087	66,557	49,065
Interest-bearing debt	39	222	368	1,126	537	3,699	1,831	1,753	73,973
Net debt	-2,306	-3,453	-3,347	-13,226	-10,512	-17,934	-58,256	-64,804	24,908
	NanoCarrier (4571)			Carna Biosciences (4572)			SymBio (4582)		
	FY03/21	FY03/22	FY03/23	FY12/21	FY12/22	FY12/23	FY12/21	FY12/22	FY12/23
	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Revenue	313	264	202	2,018	1,387	1,626	8,257	10,008	5,590
Gross profit	275	223	160	1,882	1,215	1,451	5,800	7,600	4,411
R&D expenses	1,173	1,530	1,120	1,841	1,882	1,903	1,736	2,555	2,638
SG&A expenses	405	503	1,406	2,413	2,485	2,568	4,784	5,636	5,223
Operating profit	-1,303	-2,061	-1,246	-531	-1,270	-1,117	1,016	1,964	-812
Recurring profit	-1,279	-1,925	-1,105	-523	-1,279	-1,126	1,001	2,000	-736
Net income	-2,836	-1,882	-1,311	-534	-1,350	-1,153	2,032	1,179	-1,963
ROE	-35.2%	-29.1%	-27.0%	-10.2%	-34.0%	-30.7%	39.6%	14.6%	-26.1%
ROA (RP-based)	-15.3%	-25.7%	-17.0%	-13.2%	-26.4%	-26.1%	13.6%	19.2%	-7.9%
Operating profit margin	-415.9%	-780.6%	-616.3%	-26.3%	-91.6%	-68.7%	12.3%	19.6%	-14.5%
Total assets	7,821	7,136	5,784	5,433	4,266	4,350	8,453	10,433	8,170
Net assets	7,500	5,567	4,253	4,316	3,642	3,878	6,746	8,506	7,210
Equity ratio	94.8%	77.6%	73.5%	79.3%	85.0%	89.1%	79.8%	77.6%	84.9%
Operating CF	-1,247	-1,753	-1,087	-1,537	-708	-1,677	140	1,614	-195
Investing CF	-872	-244	1,208	-42	-126	-11	-71	-47	-377
Financial CF	-11	1,146	0	1,065	367	1,182	-72	628	680
Cash and deposits	3,892	3,545	2,812	3,818	3,379	2,889	3,860	6,283	6,517
Interest-bearing debt	0	1,150	0	540	300	183	0	0	0
Net debt	-3,892	-2,395	-2,812	-3,278	-3,079	-2,706	-3,860	-6,283	-6,517
	PeptiDream (4587)			Solasia Pharma (4597)			Modalis (4883)		
	FY12/21	FY12/22	FY12/23	FY12/21	FY12/22	FY12/23	FY12/21	FY12/22	FY12/23
	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	IFRS, Cons.	Cons.	Cons.	Cons.
Revenue	9,422	26,852	28,712	559	1,092	617	1	41	0
Gross profit	7,029	18,113	17,218	373	662	337	-	-	-
R&D expenses	1,654	2,915	3,155	845	883	403	1,010	1,862	2,103
SG&A expenses	1,355	6,218	7,256	1,948	2,250	1,073	231	242	268
Operating profit	4,066	8,980	6,773	-2,419	-2,470	-1,139	-1,239	-2,063	-2,371
Recurring profit	3,804	6,653	4,353	-2,442	-2,492	-1,135	-1,231	-1,996	-2,352
Net income	2,573	7,554	3,036	-2,478	-2,548	-1,112	-739	-2,703	-2,392
ROE	11.0%	26.3%	8.4%	-79.4%	-97.1%	-49.0%	-12.6%	-63.8%	-111.9%
ROA (RP-based)	14.3%	14.6%	6.5%	-54.8%	-79.4%	-42.3%	-16.6%	-43.4%	-91.2%
Operating profit margin	43.2%	33.4%	23.6%	-432.7%	-226.1%	-184.6%	-112676.7%	-5094.3%	-
Total assets	27,035	63,865	69,464	3,144	3,134	2,229	6,069	3,130	2,026
Net assets	25,350	32,041	40,350	2,587	2,662	1,875	5,549	2,941	1,380
Equity ratio	93.8%	50.2%	58.1%	82.3%	84.9%	84.1%	91.4%	93.4%	66.8%
Operating CF	6,655	-83	12,421	-2,473	-2,074	-359	-747	-1,896	-2,254
Investing CF	-2,283	-27,377	1,303	-164	-418	0	172	-186	-40
Financial CF	66	20,789	264	361	2,571	275	73	64	1,216
Cash and deposits	11,747	5,248	19,508	714	803	728	4,936	2,933	1,883
Interest-bearing debt	0	21,048	22,221	84	37	33	0	0	0
Net debt	-11,747	15,801	2,713	-630	-766	-695	-4,936	-2,933	-1,883

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 under 10% 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 61.8% of the total in 2023.

In its medium-term plan through FY12/24, the company will continue 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.

According to the Ministry of Education, Culture, Sports, Science and Technology data, the number of students starting PhD programs (usually five years) at graduate schools peaked in 2003 and continued to decline until bottoming in 2015. The number has since increased slightly, reaching 15,000 (+0.9% YoY) in 2018, of which 6,000 specialized in health (medicine, dentistry, pharmaceutical science, and health science). The number in 2021 was flat at 15,000, but the overall trend is downward. We also note that bio-pharma drug discovery mostly takes place overseas and the number of researchers in Japan is small. In the most recent fiscal year, the US has the largest number of PhD holders in this field (92,000), followed by China (66,000) and Germany (26,000), and numbers have doubled in South Korea, China, and the US since 2000. Shared Research thinks that attracting personnel that fit the company's needs holds the key to its future growth.

Historical results and financial statements

Income statement

Income statement	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Operating revenue	**154**	**146**	**705**	**1,419**	**745**	**1,703**	**1,107**	**2,776**	**2,918**	**1,901**
YoY	-32.5%	-5.5%	384.7%	101.2%	-47.5%	128.7%	-35.0%	150.7%	5.1%	-34.8%
Operating expenses	**2,276**	**2,010**	**1,465**	**1,570**	**1,820**	**1,719**	**1,593**	**2,068**	**2,052**	**2,239**
YoY	-3.8%	-11.7%	-27.1%	7.1%	15.9%	-5.5%	-7.3%	29.8%	-0.8%	9.1%
Cost of revenue	3	-	118	150	89	263	138	321	232	245
YoY	731.3%	-	-	27.1%	-40.2%	193.9%	-47.5%	132.4%	-27.8%	5.8%
R&D expenses	1,480	1,302	796	849	1,075	864	932	1,127	1,249	1,373
YoY	-2.5%	-12.0%	-38.9%	6.6%	26.6%	-19.6%	7.9%	20.9%	10.8%	9.9%
R&D expense ratio	961.7%	895.2%	112.9%	59.8%	144.3%	50.7%	84.2%	40.6%	42.8%	72.2%
SG&A expenses	794	708	551	572	656	592	523	620	572	621
YoY	-6.3%	-10.9%	-22.1%	3.7%	14.7%	-9.7%	-11.6%	18.6%	-7.9%	8.6%
SG&A ratio	515.9%	486.4%	78.2%	40.3%	88.1%	34.8%	47.2%	22.3%	19.6%	32.7%
Operating profit	**-2,123**	**-1,865**	**-760**	**-150**	**-1,075**	**-16**	**-486**	**708**	**866**	**-337**
YoY	-	-	-	-	-	-	-	-	22.4%	-
Operating profit margin	-	-	-	-	-	-	-	25.5%	29.7%	-
Non-operating income	187	99	94	85	45	49	35	177	77	88
Interest income	3	4	13	4	9	9	4	2	1	3
Interest on securities	31	78	52	35	32	35	28	21	13	7
Foreign exchange gains	27	14		1			-	146	44	52
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										
Other	6	1	2	1	3	1	1	3	6	
Non-operating expenses	7	29	55	85	35	12	76	21	39	44
Interest expenses							0	1	6	7
Commitment fees									6	9
Foreign exchange losses			55		33	0	76	-		
Share issuance expenses	7	6		13	1	12	0	0	16	4
Loss on valuation of derivatives							-	10	-	25
Settlement package							-	10		
Loss on valuation of compound financial instruments		21		2	1				11	
Loss on redemption of securities		2								
Other	-	-	-	0	-	-	-	-	-	-
Recurring profit	**-1,942**	**-1,795**	**-721**	**-81**	**-1,065**	**22**	**-528**	**864**	**904**	**-293**
YoY	-	-	-	-	-	-	-	-	4.7%	-
Recurring profit margin	-	-	-	-	-	1.3%	-	31.1%	31.0%	-
Extraordinary gains	1,549	66		21	5	6	9	17	14	-
Gain on sale of fixed assets	6						1	-		
Gain on sale of investment securities	1,544	66		18	5	6	8	14	10	
Gain on redemption of investment securities								2	4	
Extraordinary losses	65	119	2	0	18		9		68	1
Impairment losses							3			
Loss on sales of investment securities				0			0			
Loss on redemption of investment securities		6	2				7		50	-
Retirement benefits for officers									18	-
Special retirement expenses	10	69								
Office relocation expenses	54	43								
Loss on cancellation of lease contract										
Other	-	-	-	-	-	-	-	-	-	-
Income taxes	7	6	5	-2	26	22	79	125	128	30
Implied tax rate	-1.5%	-0.3%	-0.7%	2.9%	-2.4%	80.4%	-15.0%	14.2%	15.0%	-10.1%
Net income attributable to owners of the parent	**-465**	**-1,854**	**-728**	**-58**	**-1,105**	**5**	**-607**	**756**	**723**	**-324**
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	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23

(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Assets										
Cash and deposits	1,891	1,840	1,428	2,268	1,671	2,174	1,394	2,345	3,675	3,715
Notes and accounts receivable	20	73	58	449	1	747	531	1,205	602	603
Securities	1,184	503	9	329	168	26	719	314	251	50
Inventories	9	7	7	5	6	6	7	11	9	148
Advances paid	58	179	205	190	9	6	36	16	90	67
Prepaid expenses	55	65	56	62	72	69	50	90	109	188
Other	43	40	43	20	35	39	97	22	87	186
Total current assets	**3,261**	**2,708**	**1,806**	**3,322**	**1,962**	**3,067**	**2,834**	**4,004**	**4,822**	**4,957**
Buildings and structures	80	140	141	142	143	143	153	154	154	158
Tools, furniture, and fixtures	349	394	452	488	677	742	872	944	964	1,125
Lease assets					3	3	49	60	255	398
Accumulated depreciation	-363	-273	-344	-415	-505	-639	-741	-859	-982	-1,107
Machinery, equipment, and vehicles	2									
Total tangible fixed assets	**85**	**261**	**249**	**216**	**318**	**249**	**333**	**299**	**391**	**574**
Trademark	3	2	6	5	5	5	4	4	4	5
Software	6	8	7	4	28	27	28	29	20	26
Other	3	4	0	-	1	1	1	1	0	0
Total intangible assets	**12**	**14**	**13**	**10**	**34**	**32**	**33**	**34**	**24**	**30**
Investment securities	1,800	1,752	1,937	1,503	1,717	1,474	1,038	888	988	1,231
Long-term prepaid expenses	4	5	3	2	10	2	0	0	24	64
Deferred tax assets							3	-		6
Other	39	12	11	11	12	12	10	9	8	11
Investments and other assets	**1,844**	**1,769**	**1,951**	**1,516**	**1,738**	**1,488**	**1,051**	**897**	**1,020**	**1,311**
Total fixed assets	**1,941**	**2,044**	**2,213**	**1,742**	**2,090**	**1,769**	**1,417**	**1,230**	**1,436**	**1,915**
Total assets	**5,202**	**4,752**	**4,019**	**5,064**	**4,052**	**4,837**	**4,251**	**5,234**	**6,258**	**6,872**
Liabilities										
Notes and accounts payable				2		34	42	46	128	54
Short-term debt	-	-	-	-	1	1	18	22	46	77
Accounts payable–other	119	123	126	63	99	67	53	113	206	159
Accrued expenses	63	57	40	44	48	50	50	63	60	54
Income taxes payable	16	15	1	21	14	20	21	80	31	20
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	4
Other	46	-	5	-	-	-	-	10	4	22
Total current liabilities	**262**	**200**	**190**	**149**	**164**	**183**	**187**	**401**	**494**	**389**
Long-term debt	-	-	-	-	2	2	27	18	177	291
Asset retirement obligations		12	12	12	12	12	12	12	12	12
Deferred tax liabilities	109	26	29	16	16	19	14	16	3	-
Other	-	-	-	-	-	-	-	-	75	59
Total fixed liabilities	**109**	**38**	**41**	**27**	**31**	**33**	**53**	**46**	**267**	**362**
Total liabilities	**371**	**238**	**231**	**176**	**195**	**216**	**240**	**446**	**761**	**752**
Net assets										
Capital stock	8,952	9,806	2,238	2,741	2,793	2,255	2,255	2,257	2,266	2,668
Capital surplus	4,236	5,090	2,238	2,931	2,983	2,445	2,445	2,447	2,455	2,857
Retained earnings	-8,567	-10,421	-728	-786	-1,890	-99	-706	50	773	449
Share subscription rights	11	11	15	17	13	12	12	11	8	26
Total net assets	**4,831**	**4,514**	**3,788**	**4,888**	**3,857**	**4,621**	**4,011**	**4,788**	**5,497**	**6,120**
Total liabilities and net assets	**5,202**	**4,752**	**4,019**	**5,064**	**4,052**	**4,837**	**4,251**	**5,234**	**6,258**	**6,872**
Working capital	29	80	65	452	7	718	496	1,170	483	697
Total interest-bearing debt	-	-	-	-	3	2	46	39	222	368
Net debt	-1,891	-1,840	-1,428	-2,268	-1,668	-2,172	-1,349	-2,306	-3,453	-3,347

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	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
(JPYmn)	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.	Cons.
Cash flows from operating activities (1)	-2,081	-2,117	-681	-307	-404	-531	-289	366	1,480	-719
Pre-tax profit	-632	-1,848	-723	-60	-1,078	27	-528	881	851	-294
Depreciation	21	53	80	86	126	140	124	142	148	176
Impairment losses							3	-		
Gain and loss on sale and disposal of fixed assets							-1	-		
Change in working capital	78	-51	15	-377	445	-711	223	-674	687	-214
Cash flows from investing activities (2)	-796	666	-441	534	-368	216	225	-279	-48	-135
Purchase of intangible/tangible fixed assets	-101	-200	-37	-88	-221	-94	-156	-105	-32	-222
Proceeds from sale of intangible/tangible fixed assets	2						1	-		
Free cash flow (1+2)	-2,877	-1,451	-1,122	226	-772	-315	-64	87	1,432	-854
Cash flows from financing activities	762	1,702	-	1,007	99	696	-7	-16	-30	793
Net change in short-term borrowings							-	-		
Net change in long-term borrowings	-	-	-	-	-	-	-	-	12	40
Proceeds from issuance of, and redemption of, bonds	140	-	-	-	-	-	-	-	-	-
Proceeds from share issuance exercising share subscription rights	640	1,686		996	100	692	0	2	4	4
Proceeds from issuance of share subscription rights	15	15		11		4				783
Repayments of lease obligations					-1	-1	-7	-18	-45	-52
Change in cash and cash equivalents	-2,031	252	-999	1,229	-644	371	-139	179	1,439	-15
Cash and cash equivalents (year-end)	2,004	2,243	1,244	2,474	1,830	2,200	2,061	2,241	3,679	3,665

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 FY12/23, cash outflows from operating activities decreased by JPY2.2bn versus FY12/22 inflows of JPY1.5bn to JPY719mn. This was mainly due to JPY294mn in pre-tax loss, JPY175mn in depreciation, an increase of JPY139mn in inventories, and JPY121mn in income taxes paid.

Cash flows from investing activities

Cash outflows from investing activities came to JPY135mn, a decrease of JPY87mn versus cash outflows of JPY48mn in FY12/22. This was mainly attributable to JPY204mn used for the purchase of tangible fixed assets, JPY160mn for the purchase of investment securities, and JPY250mn in proceeds from sales of investment securities.

Cash flows from financing activities

Cash inflows from financing activities came to JPY793mn, an increase of JPY823mn versus cash outflows of JPY30mn in FY12/22. This was mainly attributable to inflows of JPY50mn from long-term borrowings and JPY782mn proceeds from share issuance and outflows of JPY52mn for repayments of lease obligations.

Historical performance

Q1 FY12/24 results (out May 15, 2024)

Earnings summary

Q1 FY12/24 (January–March 2024) results

- Operating revenue: JPY649mn (+75.1% YoY)
- Operating profit: JPY45mn (vs. loss of JPY109mn in Q1 FY12/23)
- Recurring loss: JPY0.77mn (vs. loss of JPY110mn)
- Net loss attributable to owners of the parent: JPY78mn (vs. loss of JPY148mn)
- R&D expenses: JPY359mn (+33.8% YoY)

In Q1, the company's rate of progress toward its full-year forecast was 14.3% for operating revenue and 14.2% for operating profit.

Factors behind higher revenue and profits

In Q1, the company received one-time payments in addition to royalties of JPY551mn (+57.4% YoY) from its four marketed products. The one-time payments were for the approval of tegoprazan in four countries in Latin America and the approval to conduct a Phase I clinical trial of a TRPM8 blocker in Australia. Other revenue, including the one-time payments, was JPY97mn (+385.0% YoY).

Total operating expenses were JPY604mn (+26.0% YoY), including cost of revenue at JPY61mn (+1.9% YoY), R&D expenses at JPY359mn (+33.8% YoY), and other SG&A expenses at JPY185mn (+21.8% YoY). The increase in R&D expenses was mainly due to progress in preclinical studies of ghrelin receptor agonist and manufacture of APIs. Despite the increase in costs, the rise in operating revenue led to an operating profit of JPY44mn. The company also recorded non-operating income, including foreign exchange gains of JPY42mn. However, it booked non-operating expenses such as derivative valuation losses of JPY27mn and arrangement fees of JPY140mn related to a syndicated loan, resulting in a recurring loss and a net loss for the quarter.

Pipeline

Brisk royalties from four commercialized products

Pet drugs

Sales of GALLIPRANT® (generic name: grapiprant), a treatment for osteoarthritis in dogs, ENTYCE® (generic name: capromorelin), a treatment for anorexia in dogs, and ELURA® (generic name: capromorelin), a treatment for weight

management in cats with chronic kidney disease (CKD), continue to perform well. In February 2024, Elanco secured manufacturing and marketing approval from the Ministry of Agriculture, Forestry, and Fisheries in Japan for ELURA®. Following the approval received in Europe in 2023, Elanco is progressing with preparations to launch the product.

In April 2024, the company entered into an option and license agreement with US-based Velovia Pharma, LLC (unlisted) for the development of veterinary drugs containing the company's four pipeline compounds. Based on the terms of the agreement, the company granted Velovia option for the exclusive rights to evaluate, develop, manufacture, and sell veterinary drugs containing its four pipeline compounds. If Velovia exercises its option right for one or more of the compounds, the company is entitled to receive option exercise fees as well as milestone payments based on Velovia's subsequent development progress. Further, if veterinary drugs containing the compounds reach the market, the company may receive sales royalties and sales milestone payments based on product sales from Velovia.

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 KRW45.2bn (+26.8% YoY; roughly JPY5.0bn at JPY0.11/KRW) in FY12/23. Co-promotions with Boryung Pharmaceutical Co., Ltd. (KRX: 003850) initiated in January 2024 and a change in sales channels proved successful. HK inno.N's continues to lead the anti-ulcer drug market in South Korea with a share of 14%.

In April 2024, HK inno.N entered into an exclusive license agreement with Tabuk Pharmaceutical Manufacturing Company (unlisted) of Saudi Arabia, granting the latter sublicensing rights to tegoprazan in 10 countries. As of end-Q1, companies licensed by HK Inno.N (sublicensees) are advancing development, manufacturing, and sales initiatives for tegoprazan in 46 countries, including South Korea. During Q1, the sublicensee, Laboratories Carnot (unlisted), obtained marketing approvals in Chile, the Dominican Republic, Honduras, and Nicaragua. Consequently, RaQualia received a lump-sum payment from HK Inno.N based on their agreement. As of May 2024, tegoprazan was being marketed in eight countries: South Korea, China, Mongolia, the Philippines, Mexico, Indonesia, Singapore, and Peru.

Out-licensed and pre-out-licensing programs

For the out-licensed programs, RaQualia's partners are advancing development in the preclinical or later stages.

For the TRPM8 antagonist (RQ-00434739/XG2002), the company's licensee, Xgene Pharmaceutical Co. Ltd. (unlisted), received approval from the local research ethics committee in Australia to conduct a Phase I clinical trial in March 2024. Consequently, RaQualia received a milestone payment from Xgene. In April the same year, Xgene announced the enrollment of the first patient and commenced the Phase I trial. Based on the license agreement with Xgene, the company is entitled to receive milestone payments in accordance with development progress and royalties on product sales after the product's launch.

In its pre-out-licensing programs, the company is advancing preclinical trials for a ghrelin receptor agonist in-house. Regarding tegoprazan, the company retains the rights for development, manufacturing, and sales in Japan and is actively negotiating with potential licensing partners. For other pre-out-licensing programs, the company has conducted business development activities aimed at acquiring partners, utilizing a flexible combination of in-person meetings and online conferences.

In the exploratory research phase, RaQualia is concentrating on research programs aimed at creating new development compounds. The company seeks to establish its next-generation drug discovery value chain by leveraging synergies between existing technologies and new initiatives, approached from four perspectives: modality, drug discovery targets, disease areas, and foundational technologies. In addition to its independent research efforts, RaQualia is also expanding collaborations with startups and drug discovery ventures.

Development status of tamibarotene

Regarding the retinoic acid receptor α agonist (tamibarotene), which was out-licensed from subsidiary TMRC Co., Ltd. to Syros Pharmaceuticals Inc. (NASDAQ: SYRS), a Phase III clinical trial in myelodysplastic syndromes (MDS) patients and a Phase II trial in acute myeloid leukemia (AML) patients are ongoing in the US. In Q1, Syros completed the patient enrollment required for the primary endpoint analysis in the Phase III clinical trial (SELECT-MDS-1), which targets patients with high-risk myelodysplastic syndromes (HR-MDS) exhibiting an overexpression of the RARA gene. Syros expects to disclose pivotal data on complete remission (CR) by mid-Q4 FY12/24.

In April 2024, tamibarotene was awarded a fast-track designation by the US FDA for the treatment of AML. In December 2023, Syros released data from the randomized part of the Phase II clinical trial being conducted in AML patients (SELECT-

AML-1). Complete remission/complete remission with incomplete blood cell recovery (CR/CRi) rate was 70% (seven out of 10 patients) for the current standard of care, the venetoclax/azacitidine combination therapy, whereas the CR/CRi rate was 100% (nine out of all nine patients enrolled in the study) for the three-drug combination therapy including tamibarotene (venetoclax/azacitidine/tamibarotene) in a short time. Syros plans to release additional data in Q4 FY12/24.

Acquisition of FIMECS

In March 2024, the company acquired all issued shares and share subscription rights of FIMECS Inc., making it a subsidiary. FIMECS is a drug discovery startup that advances the R&D of new pharmaceuticals using targeted protein degradation inducers, a novel modality in drug discovery. Leveraging its unique E3 ligase-binding molecules and the RaPPIDS™ drug discovery platform technology, FIMECS aims to develop innovative medicines for diseases previously considered "undruggable." Its business model is a hybrid that combines revenue generation from out-licensing its in-house developed pipeline with collaborative research partnerships with pharmaceutical companies.

The company believes that the acquisition of FIMECS not only strengthens the company's drug discovery value chain through the acquisition of platform technologies but also enhances earnings through the hybridization of its business model, and the expansion and strengthening of its oncology business. The company financed this acquisition by raising JPY3.5bn through a syndicated loan. As a result, the equity ratio fell 32.8pp from end-FY12/23 to 55.9%. FIMECS's financial results will be reflected in the consolidated income statement starting Q2. The balance sheet was consolidated from the deemed acquisition date of March 31, 2024, resulting in assets expanding 55.6% from end-FY12/23 and liabilities ballooning 524.8%.

Full-year FY12/23 results (out February 14, 2024)

Earnings summary

Full-year FY12/23 (January–December 2023) results

- Revenue: JPY1.9bn (-34.8% YoY)
- Operating loss: JPY337mn (compared to a profit of JPY866mn in the previous year)
- Recurring loss: JPY293mn (compared to a profit of JPY904mn)
- Net loss attributable to owners of the parent: JPY324mn (compared to a net income of JPY723mn)
- R&D expenses: JPY1.4bn (+9.9% YoY)

On December 8, 2023, the company revised its earnings forecast for FY12/23 downward, attributing this to anticipated delays in finalizing the license agreement for developing, manufacturing, and selling tegoprazan in Japan, as well as postponement of the approval and launch of ELURA®, a weight loss treatment for cats with CKD, in Europe until FY12/24. Against this revised forecast, full-year sales reached 98.1%.

Factors behind lower revenue and operating loss

In the previous fiscal year, the company reported royalty revenue of JPY1.5bn and other revenue (mainly from upfront and milestone payments) totaling JPY1.4bn. In comparison, FY12/23 revenue decreased by 34.8%, primarily due to the deferral of tegoprazan's out-licensing in Japan and the milestone achievement related to ELURA® to FY12/24. Royalty revenue also fell short of the company's assumption due to the delayed launch of tegoprazan in China and slowing growth of sales in South Korea, where tegoprazan has been on the market for over five years. Revenue for Q4 alone (October–December 2023) was JPY406mn, which did not meet the revised forecast of JPY443mn for combined royalty and other revenues.

Operating expenses totaled JPY2.2bn (+9.1% YoY), with cost of revenue increasing by JPY13mn to JPY245mn (+5.8% YoY), R&D expenses increasing by JPY124mn to JPY1.4bn (+9.9% YoY), and other SG&A expenses amounting to JPY621mn (+8.6% YoY). The increase in costs amid declining operating revenue resulted in an operating loss of JPY337mn. Operating expenses were below the initial forecast of JPY2.5bn due to the delayed booking of outsourcing expenses for a ghrelin receptor agonist and reduced personnel expenses associated with the company's hiring plan. However, with a 9.1% YoY increase in operating expenses and lower operating revenue, the company recorded a JPY337mn operating loss. Although the company recorded non-operating income including foreign exchange gains of JPY52mn, this was offset by an increase in non-operating expenses, including derivative valuation losses of JPY25mn. As a result, the company recorded a recurring loss and a net loss.

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. All three products are out-licensed to Elanco.

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 KRW158.2bn (+19.8% YoY; roughly JPY17.4bn at JPY0.11/KRW) in FY12/23. HK inno.N's leads the anti-ulcer drug market in South Korea with a share of 13%.

As of end-December 2023, HK Inno.K's sublicensees are advancing the development, manufacturing, and sales of tegoprazan in 35 countries. In China, which became the second country to launch tegoprazan in 2022 following South Korea, the product is now available across 31 provinces and administrative regions. Additionally, in Peru, the sublicensee has received marketing approval for tegoprazan for four conditions, including erosive reflux esosophagitis. Tegoprazan is marketed in eight countries, namely South Korea, China, Mongolia, the Philippines, Mexico, Indonesia, Singapore, and Peru. Moreover, regulatory reviews are in progress in over 20 countries, including Argentina. In the US, Braintree, a sublicensee, is conducting Phase III clinical trials of tegoprazan, with plans to apply for approval in 2024.

Out-licensed and pre-out-licensing programs

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

In FY12/23, Oxford Cannabinoid Technologies Ltd. (LSE: OCTP, hereafter "OCT") initiated Phase I clinical trials of a cannabinoid CB2 receptor agonist (RQ-00202730/AAT-730/OCT46120), which was out-licensed to OCT from AskAt Inc. (unlisted), a licensee of RaQualia. With plans to develop the CB2 agonist for the lead indication of chemotherapy-induced peripheral neuropathy (CIPN), OCT began dosing patients in July 2023.

Xgene Pharmaceutical Co., Ltd. (unlisted) completed preclinical trials for the TRPM8 antagonist (RQ-00434739/XG2002), which was out-licensed from RaQualia, and had been preparing for Phase I clinical trials. In March 2024, it received approval to begin clinical trials from the Australian Therapeutic Goods Administration (TGA). Additionally, the company's licensees are engaged in both preclinical and clinical trials for other out-licensed programs.

In April 2023, RaQualia signed an option and license agreement with Vetbiolix SAS, an unlisted French company, for the development of pet drugs using the company's 5-HT$_4$ agonist (RQ-10). Under the agreement, the company grants Vetbiolix an exclusive option for a sublicensable license to develop, manufacture, and sell veterinary drugs containing RQ-10 with worldwide exclusivity. If Vetbiolix exercises the exclusive option, RaQualia will receive an option fee from Vetbiolix and will also be eligible to receive development milestones and sales royalties.

In pre-out-licensing programs, the company has engaged in business development activities, flexibly combining in-person and online meetings to seek potential licensing partners. As for tegoprazan, the company holds the rights for development, manufacturing, and sales in Japan, and continues to negotiate with potential licensing partners. In addition, RaQualia is advancing the development of its ghrelin receptor agonist with the goal of securing a major licensing agreement. Preclinical studies and API manufacturing has been underway for the ghrelin receptor agonist.

In the exploratory research phase, RaQualia is focusing on research programs to create new development compounds, while also working on strengthening its drug discovery research capabilities. The company is aiming to establish its own next-generation drug discovery value chain by creating synergies between existing technologies and new initiatives. This approach is taken from four perspectives: modality, drug discovery targets, disease areas, and basic technology. In addition to its own independent research, the company is also advancing collaborations with startups and drug discovery companies. As part of these efforts, from December 2022, the company has been advancing joint research with Veritas In Silico Inc. (unlisted) aimed at creating mRNA-targeted small molecule drugs that target multiple genes related to cancers. In December 2023, a predetermined milestone was achieved.

In the US, Syros Pharmaceuticals Inc. (NASDAQ: SYRS) is conducting clinical trials for a retinoic acid receptor alpha agonist (tamibarotene), aimed at treating myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). This compound,

discovered by TMRC Co., Ltd., a consolidated subsidiary, has been licensed to Syros. Currently, a Phase III clinical trial is in progress, focusing on patients with high-risk myelodysplastic syndromes (HR-MDS) that show overexpression of the RARA gene. In December 2023, Syros published preliminary results from the randomized segment of a Phase II clinical trial for AML patients. As a result, the company earned fees related to the clinical development conducted by Syros.

Cumulative Q3 FY12/23 results (out November 10, 2023)

Earnings summary

Cumulative Q3 FY12/23 (January–September 2023) results

- Operating revenue: JPY1.5bn (-21.5% YoY)
- Operating loss: JPY108mn (versus a profit of JPY501mn in cumulative Q3 FY12/22)
- Recurring loss: JPY36mn (versus a profit of JPY676mn)
- Net loss attributable to owners of the parent: JPY118mn (versus a profit of JPY467mn)
- R&D Expenses: JPY934mn (+11.2% YoY)

Operating revenue for cumulative Q3 reached 53.4% of the company's consolidated forecast for FY12/23. RaQualia revised its earnings outlook downward on December 8, 2023, and the progress rate against the revised operating revenue forecast was 77.2%.

Factors behind lower revenue and operating loss

In standalone Q3 (July–September 2023), operating revenue was JPY481mn, up 5.3% YoY. This comprised royalties amounting to JPY466mn (+21.0% YoY) and a one-time payment related to a milestone achievement totaling JPY15mn (-79.2% YoY). However, Q3 revenue fell short of the JPY561mn projected by the company at end-Q2. The primary reason for the shortfall was lower-than-expected sales of tegoprazan due to a change in the distribution channel following the drug's inclusion in China's National Reimbursement Drug List. In the same period of the previous year, the company recorded royalty revenue of JPY1.1bn and other revenues of JPY820mn, including a one-time payment of JPY300mn for the approval and launch of tegoprazan in China. In comparison, the one-time payments received in cumulative Q3 FY12/23 were minimal, resulting in a 21.5% YoY decline in operating revenue.

Operating expenses totaled JPY1.6bn (+14.3% YoY), with cost of revenue increasing by JPY21mn to JPY189mn (+12.8% YoY), R&D expenses increasing by JPY94mn to JPY934mn (+11.2% YoY), and other SG&A expenses amounting to JPY479mn (+21.4% YoY). R&D expenses were 55.8% of the full-year budget as a result of conducting preclinical studies on a ghrelin receptor agonist based on exploratory research and manufacturing APIs for clinical trials. The increase in costs amid declining operating revenue resulted in an operating loss of JPY108mn. Although the company recorded non-operating income including foreign exchange gains of JPY112mn, this was offset by a threefold YoY increase in non-operating expenses, including derivative valuation losses of JPY47mn. As a result, the company recorded a recurring loss and a net loss.

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. All three products are out-licensed to Elanco.

Development of tegoprazan in countries around the world

Sales of GERD treatment tegoprazan (brand name: K-CAB®) in South Korea by licensee HK inno.N continued to be robust, with sales from prescriptions outside hospitals amounting to KRW114.1bn (+18.7% YoY; roughly JPY11.4bn at JPY0.1/KRW) in cumulative Q3 FY12/23. K-CAB®'s market share in the anti-ulcer drug market reached 13%. The sales growth was driven by OD tablets, which accounted for 17.9% of total K-CAB® sales.

As of end-Q3, sublicensees of HK Inno.K are pursuing development, manufacturing, and sales efforts for tegoprazan in 35 countries. The drug was newly launched in Indonesia and Singapore in Q3, and following the launch in Peru in October

2023, tegoprazan is now available in eight countries, including South Korea, China, Mongolia, the Philippines, and Mexico. Royalties on sublicensee sales are received semi-annually through HK Inno.K, and RaQualia expects to record royalties on sales in Indonesia, Singapore, and Peru from FY12/24.

In China, the second country after South Korea to launch tegoprazan in 2022, tegoprazan products are now marketed in 31 provinces and administrative regions. In December 2023, the Chinese sublicensee filed for approval of an additional indication of Helicobacter pylori eradication therapy. If approved, this would mark the third indication approved in China after erosive esophagitis and duodenal ulcers. The development of injectable tegoprazan is also underway in China, and RaQualia expects tegoprazan sales to further expand in the country. Furthermore, in Peru, the sublicensee obtained marketing approval for four indications, including erosive esophagitis. In addition, local regulatory reviews are underway in over 20 countries, including Argentina.

Tegoprazan global rollout

Country/region	Licensee*	Sales and development status	Market size (JPYmn)
South Korea	HK inno.N	Launched in 2019, maintaining No. 1 market share	100,000
China	Luoxin	Launched in April 2022	410,000
Philippines	MPPI	Launched in October 2022	8,000
Mongolia	Monos	Launched in October 2022	-
Mexico	Carnot	Launched in May 2023	57,000 *2
Indonesia	Kalbe	Launched in July 2023	20,000
Singapore	UITC	Launched in September 2023	1,600
Peru	Carnot	Launched in October 2023	57,000 *2
Thailand, Vietnam, Malaysia	Pond's, Lyhn farma, Pharmaniaga	Application under review	27,000
Argentina and 15 other Latin American countries	Carnot	Application under review	57,400 *2
7 countries including India	Dr. Reddy	Filing and development in preparation	130,000
Brazil	Eurofarma	Filing in preparation	80,000
US, Canada	Braintree	Clinical trials underway, approval expected in 2025	370,000

Source: Shared Research based on company materials (as of November 2023)
Note: Licensees include sublicensees of HK inno.N
Note: Market size of JPY57.0bn is aggregate of 17 Latin American countries including Mexico, Argentina, and Peru

Out-licensed and pre-out-licensing pipeline programs

Out-licensed pipeline programs

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

In cumulative Q3 FY12/23, Oxford Cannabinoid Technologies Ltd. (LSE: OCTP, hereafter "OCT") initiated UK-based Phase I clinical trials of a cannabinoid CB2 receptor agonist (RQ-00202730/AAT-730/OCT46120), which was out-licensed to OCT from AskAt Inc. (unlisted), a licensee of RaQualia. With plans to develop the CB2 agonist for the lead indication of chemotherapy-induced peripheral neuropathy (CIPN), OCT began dosing patients in July 2023. CIPN, a side effect of specific anticancer drugs, is believed to impact around 60% of patients undergoing chemotherapy, leading to diminished quality of life with symptoms like pain and numbness. Following the completion of administration in all cohorts in the Phase I clinical trial, no safety or tolerability concerns were identified. OCT is confident in advancing to the next stage of clinical trials.

Pre-out-licensing pipeline programs

In pre-out-licensing programs, the company has engaged in business development activities, flexibly combining in-person and online meetings to seek potential licensing partners. As for tegoprazan, the company holds the rights for development, manufacturing, and sales in Japan, and continues to negotiate with potential licensing partners for an early launch.

In addition, RaQualia is advancing the development of its ghrelin receptor agonist with the goal of securing a major licensing agreement. The company is conducting various preclinical trials and also manufacturing APIs for clinical trials. The ghrelin receptor agonist acts on the parasympathetic ganglia in the spinal cord's defecation center, inducing bowel movements by promoting increased peristalsis in the colon. Over 300,000 individuals worldwide who have spinal cord injuries experience defecation disorders due to autonomic nerve impairment. Existing constipation medications are prone to causing diarrhea, so RaQualia's ghrelin receptor agonist aims to improve quality of life by promoting autonomous bowel movements.

Exploratory research phase pipeline programs

In the exploratory research phase, RaQualia is focusing on research programs to create new development compounds, while also working on strengthening its drug discovery research capabilities. The company is aiming to establish its own next-generation drug discovery value chain by creating synergies between existing technologies and new initiatives. This

approach is taken from four perspectives: modality, drug discovery targets, disease areas, and basic technology. In addition to its own independent research, the company is also advancing collaborations with startups and drug discovery companies.

Development progress at TMRC

In addition, clinical trials for the treatment of myelodysplastic syndrome (MDS; currently in Phase III) and acute myeloid leukemia (AML; in Phase II) 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 the Phase III clinical trial for untreated high-risk MDS, Syros plans to complete patient enrollment in Q1 FY12/24 and report results in Q4.

In December 2023, Syros announced early data from the randomized trial part of the Phase II clinical trial targeting AML. The randomized trial part is the second part conducted following the safety lead-in part. Syros reported that the complete response rate (CR) and complete response rate with incomplete hematologic recovery (CRi) were observed in 100% of patients who received a triple combination therapy of tamibarotene, venetoclax, and azacitidine, compared to 70% for the control group who received a dual combination therapy of venetoclax and azacitidine. Additionally, the early safety data of the triple combination therapy indicated good tolerance. Syros continues to enroll patients and plans to report updated data in 2024.

In addition to this, clinical research and investigator-led trials for pancreatic cancer and urothelial cancer are also underway, and the search for the next candidate compound following tamibarotene is being conducted.

Funding status and investment plans

In December 2022, RaQualia announced its plan to raise funds through the issuance of new shares and Series 16 share subscription rights through a third-party allotment. The primary objective is to secure additional capital to support investments in exploratory research, preclinical and clinical development, as outlined in its medium-term management plan. Also, the funds will cover additional investments needed to accelerate growth. The company has assessed that its existing funds and revenue stream, characterized by some degree of uncertainty, would be insufficient for these purposes.

The company plans to finance the necessary investments until December 2024 through the use of existing cash reserves and the funds raised through the issuance of new shares (approximately JPY786mn). In addition, the funding required until December 2027 will be allocated from the cash raised through the exercise of share subscription rights (approximately JPY1.9bn). In January 2023, the company received payment for the capital increase through a third-party allotment, increasing both capital stock and capital surplus by approximately JPY393mn. Furthermore, owing to the exercise of share subscription rights and the issuance of new shares as restricted stock compensation for directors, both capital stock and capital surplus increased by approximately JPY399mn. As a result, as of end-Q3, the capital stock was JPY2.7bn, and the capital surplus was JPY2.9bn.

Funding status and allocation

(JPYmn)

Funding status		Investments to maximize corporate value	
Operating income forecast for 2023–2025	10,000	Investment in exploratory research (expansion of existing fields)	4,200
Borrowing capacity (commitment line)	1,700	Three-year investment in preclinical/clinical development (project value enhancement)	1,200
On-hand cash (as of end-Q3 FY03/23)	5,200	Capital investment (expansion of existing facilities, digital transformation investments, etc.)	
Equity financing (common stock)	Secured	Strategic investments (acquisition of drug discovery technology, including M&A)	
Equity financing (share subscription rights: plan)	2,000		

Source: Shared Research based on company data (as of December 2023)
Note: Investments in exploratory research and pre-clinical/clinical development are planned for three years and include personnel expenses.

1H FY12/23 results (out August 10, 2023)

Earnings summary

1H FY12/23 (January–June 2023) results

- Operating revenue: JPY1.0bn (-29.9% YoY)
- Operating loss: JPY23mn (JPY551mn profit in 1H FY12/22)
- Recurring profit: JPY37mn (-94.6% YoY)

- Net income attributable to owners of the parent: JPY25mn (-94.6% YoY)
- R&D Expenses: JPY603mn (+14.2% YoY)

Progress versus the company's full-year FY12/23 forecast was 36.2% for operating revenue, 15.2% for recurring profit, and 13.9% for net income attributable to owners of the parent. The company said that its initial forecast for FY12/23 was skewed toward 2H, and progress was slightly ahead of plan.

Factors behind lower revenue and operating loss

In Q2 (April–June 2023), the company booked JPY382mn in royalty revenue (-25.7% YoY), and milestone revenue and fee payment from Syros Pharmaceuticals of a combined JPY262mn (-55.8% YoY), for a total of JPY644mn (-41.9% YoY). In Q2 FY12/22, the company booked JPY699mn in royalty revenue, plus a milestone revenue of JPY434mn, including a one-time payment of JPY300mn for the approval and launch of tegoprazan in China. Although operating revenue declined YoY in 1H FY12/23, operating revenue in Q2 (April–June 2023) reached JPY644mn, exceeding the JPY425mn forecast at end-Q1 for combined royalty and other revenues. Operating revenue came in ahead of plan because the fee from Syros for clinical development was not factored into the initial forecast.

Operating expenses totaled JPY1.0bn (+15.8% YoY), with cost of revenue increasing by JPY18mn to JPY122mn (+16.9% YoY), R&D expenses increasing by JPY75mn to JPY603mn (+14.2% YoY), and other SG&A expenses amounting to JPY312mn (+18.7% YoY). R&D expenses were 36.0% of the full-year forecast due to preclinical studies and API manufacturing for a ghrelin receptor agonist candidate. The increase in costs amid declining operating revenue resulted in an operating loss. However, non-operating income, including a foreign exchange gain of JPY90mn, exceeded non-operating expenses, resulting in recurring profit and net income being in the black.

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. All three products are out-licensed to Elanco.

K-CAB®: Sales of tegoprazan in South Korea maintain double-digit growth

Sales of orally disintegrating (OD) tablets drove growth of tegoprazan (K-CAB®), as sales in South Korea remained strong. OD tablets comprised 16% of sales. 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 KRW74.1bn (+22.2% YoY; roughly JPY7.4bn at JPY0.1/KRW) in Q2 FY12/23. HK inno.N kept its position as the market leader in the anti-ulcer drug market in South Korea, with a market share of 12%.

Development of tegoprazan in countries around the world

As of end-1H (end-June 2023), sublicensees of HK Inno.K were pursuing development, manufacturing, and sales efforts for tegoprazan in 35 countries. Following South Korea, China, the Philippines, and Mongolia, sales of tegoprazan sales began in Mexico in Q2. In July, tegoprazan was also launched in Indonesia and received marketing authorization for four indications in Peru. Peru is the eighth country to approve tegoprazan following South Korea, Mongolia, China, the Philippines, Indonesia, Singapore, and Mexico. Sales began in Singapore (September 2023), and regulatory reviews are ongoing in more than 20 countries, including Argentina.

In China, tegoprazan is sold as an erosive esophagitis treatment in 31 provinces and administrative regions. Royalties from sales in 1H FY12/23 are expected to be booked in Q3 FY12/23.

In the US, Braintree skipped Phase II trials and is conducting a Phase III study, aiming at filing for approval in 2024 and market launch in 2025.

In Japan the company is in discussions with potential licensees with a view to early market launch and is in talks aimed at out-licensing the manufacturing and sales rights in 2023. It plans to conduct speedy and efficient Phase II and Phase III clinical trials using overseas data.

Out-licensed programs

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

Sublicensee Oxford Cannabinoid Technologies launches Phase I trial

In 1H FY12/23, Oxford Cannabinoid Technologies Ltd. (LSE: OCTP) received UK regulatory and research ethics committee approval to conduct Phase I clinical trials of a cannabinoid CB2 receptor agonist (RQ-00202730/AAT-730/OCT461201) out-licensed to Oxford Cannabinoid Technologies from AskAt Inc. (unlisted), a licensee of RaQualia. With plans to develop the CB2 agonist for the lead indication of chemotherapy-induced peripheral neuropathy (CIPN), OCTP began dosing patients in July 2023. OCTP expects results from the Phase I study in Q3 FY12/23.

According to the company, CIPN is a side effect of some anticancer drugs, with symptoms of pain and numbness reducing quality of life. The human body has cannabinoid receptors known as CB1 and CB2, but targeting CB1 entails risks of central nervous system side effects on behavior or psychology. However, CB2 is attracting interest as a target for drugs to treat pain, inflammatory diseases, and cancer. Because the company's CB2 agonist is a compound that selectively acts on CB2, it avoids side effects via CB1, and is thought promising as a highly tolerable treatment. The global CIPN market is worth about USD1.6bn (roughly JPY225.0bn at JPY140/USD), and is expected to grow to USD2.4bn (roughly JPY330.0bn) by 2027.

Pet drug option and license agreement

In April 2023, RaQualia signed an option and license agreement with Vetbiolix SAS, an unlisted French company, for the development of pet drugs using the company's 5-HT_4 agonist (RQ-10). Under the agreement, the company grants Vetbiolix an exclusive option for a sublicensable license to develop, manufacture, and sell veterinary drugs containing RQ-10 with worldwide exclusivity. If Vetbiolix exercises the exclusive option, RaQualia will receive an option fee from Vetbiolix and will also be eligible to receive development milestones and sales royalties.

Pre-out-licensing pipeline

In pre-out-licensing programs, the company aiming for rapid commercialization of tegoprazan in Japan and is in talks with potential licensing partners. In addition, RaQualia is advancing the development of its ghrelin receptor agonist with the goal of securing a major licensing agreement. Preclinical studies and API manufacturing are underway for the ghrelin receptor agonist, with a view to starting clinical trials in FY12/24. 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.

In-house R&D

In the exploratory research phase, the company is focusing on exploratory research programs to generate new development compounds and is working to strengthen its drug discovery research infrastructure. By leveraging synergies between existing technologies and new initiatives, RaQualia aims to establish next-generation proprietary drug discovery value chains and is strengthening collaborations with startups and drug discovery companies. In 1H, the company initiated a partnership with the Swiss company leadXpro AG (unlisted). The collaboration with leadXpro aims to accelerate drug discovery projects targeting ion channels through 3D structural analysis of membrane proteins. The joint research project with Aska Pharmaceutical, which had been ongoing since July 2019, was terminated by mutual agreement.

Tamibarotene

Tamibarotene is a selective retinoic acid receptor alpha (RARα) agonist. The company aims to file a new drug application for tamibarotene as a precision medicine* using RAR alpha as a biomarker. Consolidated subsidiary TMRC Co., Ltd. has licensed it to US-based Syros Pharmaceuticals Inc. (NASDAQ: SYRS), which is conducting clinical trials for the treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in the US.

* Precision medicine: Also known as cancer gene therapy, it is cutting-edge medicine that entails analyzing cancer at the genetic level to provide the optimal treatment for that particular cancer. It is most advanced in the field of oncology, but can be applied to all diseases.

Analysis shows that approximately 50% of MDS patients and 30% of AML patients have RAR alpha overexpression. The use of tamibarotene in combination with an anticancer agent is expected to strengthen the effect of the anticancer agent due to tamibarotene binding to RAR alpha, for a more effective anti-tumor effect inducing cancer cell death. A patent review regarding the use of tamibarotene with anticancer drugs in Japan was conducted in July 2023.

Syros is conducting a Phase II clinical trial in the US in AML patients, and plans to report results of the randomized part in Q4 2023. It plans to announce results of the US MDS Phase III clinical trial in Q3 2024, and file for approval during 2024. In Q2 FY12/23, the company received clinical development fees from 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.

Separately, a clinical research/investigator-initiated clinical trial of tamibarotene for pancreatic cancer and upper urinary tract cancer (led by Nagoya University) has been underway since March 2023, as a Japan Agency for Medical Research and Development (AMED) project.

News and topics

Subsidiary FIMECS achieves initial milestone in joint research with Astellas Pharma and receives lump-sum payment

2024-05-13

RaQualia Pharma Inc. announced that its subsidiary, FIMECS Inc., has achieved an initial milestone in joint research with Astellas Pharma Inc. (TSE Prime: 4503). As a result, FIMECS will receive a lump-sum payment from Astellas.

In 2022, FIMECS signed a contract with Astellas for joint research on targeted protein degraders. Based on this contract, FIMECS has been collaborating with Astellas to discover protein degraders for multiple targets related to oncology, utilizing its proprietary RaPPIDS™ platform. The milestone achieved pertains to one specific program within this collaboration.

As a result of the milestone achievement, FIMECS will receive JPY200mn from Astellas, which will be recorded as operating revenue for Q2 FY12/24. Moving forward, both companies will accelerate the search for development compounds through further optimization by FIMECS and technological collaboration from Astellas. Should a development candidate be identified and lead to the commercialization of a new drug, FIMECS may receive more than JPY15bn in milestone payments based on the progress of development, regulatory approvals, and sales, as well as royalties in the single-digit percentage range of product sales.

RaQualia acquired all shares in FIMECS on March 26, 2024, making it a wholly-owned subsidiary. The impact of this event on the consolidated financial results for FY12/24 has been accounted for in the company's initial earnings forecast.

RaQualia's novel TRPM8 blocker enters Phase I trial in Australia

2024-05-08

RaQualia Pharma Inc. announced that its licensee, Xgene Pharmaceutical Co. Ltd., (headquartered in Hong Kong; unlisted) has announced the enrollment of the first subject in the Phase I clinical trial in Australia for a novel TRPM8 blocker.

In September 2021, RaQualia entered into an exclusive license agreement with Xgene to grant the exclusive rights for development, manufacturing, and sales of the TRPM8 blocker (RQ-00434739/XG2002) globally, excluding Japan.

TRPM8 is an ion channel expressed in peripheral sensory neurons and is highly expressed in various pain conditions and cancer cells. Preclinical studies conducted by Xgene have shown that this compound inhibits TRPM8 and exhibits significant analgesic effects while maintaining a favorable safety profile. Xgene is hopeful that this compound will serve as a potential treatment for various types of acute and chronic pain, including neuropathic pain such as migraine and diabetic pain. The Phase I clinical trial aims to evaluate the tolerability and pharmacokinetics of the compound in a dose-escalation study in healthy volunteers, providing essential information for subsequent clinical trials.

Based on the license agreement with Xgene, RaQualia has the right to receive milestone payments and royalties based on the product's sales after launch. There are no upfront payments associated with the initiation of the Phase I trial and it will not impact the financial results for FY12/24, but RaQualia believes that the development progress by Xgene will contribute to the long-term value enhancement of the compound.

Sublicensing of tegoprazan in the Middle East and North Africa

2024-04-24

RaQualia Pharma Inc. announced a sublicense agreement established between licensee HK inno.N of South Korea and Tabuk Pharmaceutical Manufacturing Company in Saudi Arabia. This agreement concerns the company's gastric acid secretion inhibitor, tegoprazan (marketed in South Korea under the brand name K-CAB®) and applies to the Middle East and North Africa region.

Tabuk Pharmaceutical, a leading pharmaceutical company in Saudi Arabia, distributes pharmaceuticals across 17 countries in the Middle East and North Africa. Through this agreement, Tabuk Pharmaceutical has acquired the rights to sell tegoprazan products in these regions. Due to Tabuk's strong market presence, RaQualia anticipates significant acceleration in the deployment of tegoprazan in this emerging market with high growth potential.

RaQualia has an exclusive license agreement (including sublicensing rights) with HK inno.N for the development, manufacture, and sale of tegoprazan worldwide, excluding Japan. Under this agreement, HK inno.N and sublicensees conduct business activities related to tegoprazan in various countries. The conclusion of this new sublicense agreement with Tabuk Pharmaceutical has enabled tegoprazan to be introduced into 46 countries. Currently, tegoprazan is marketed in eight countries: South Korea, China, the Philippines, Mongolia, Mexico, Indonesia, Singapore, and Peru. The drug has also received approval in Chile, the Dominican Republic, Honduras, and Nicaragua, with regulatory reviews underway in other Latin American countries. Clinical development is in progress in countries such as the US and Canada. HK inno.N aims to roll out tegoprazan to 100 countries worldwide by 2028.

Under its license agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns through Tabuk Pharmaceutical. RaQualia will also receive a lump sum payment from HK inno.N as a result of the sublicense agreement, which it will recognize as operating revenue in Q2 FY12/24. The company has already incorporated the impact of this agreement into its full-year consolidated earnings forecast for FY12/24.

Tamibarotene receives the FDA Fast Track designation for AML treatment

2024-04-10

RaQualia Pharma Inc. announced that tamibarotene, a drug candidate it has out-licensed to Syros Pharmaceuticals Inc. (NASDAQ: SYRS) in the US through its subsidiary TMRC Co., Ltd., has been granted Fast Track designation by the US Food and Drug Administration (FDA) for the treatment of acute myeloid leukemia (AML).

The FDA's Fast Track designation was awarded for a triple combination therapy of tamibarotene with venetoclax and azacitidine, intended for newly diagnosed, untreated AML patients. Tamibarotene acts as a selective agonist of the retinoic acid receptor alpha (RARα), and synergistic effects are expected when combined with other antitumor agents due to its strong differentiation-inducing activity.

Syros Pharmaceuticals is currently advancing a Phase II clinical trial (SELECT-AML-1). Initial data from the randomized part of this trial, released in December 2023, showed that while 70% (seven out of 10 cases) in the standard treatment group achieved complete remission or complete remission with incomplete blood recovery (CR/CRi) with a dual combination of venetoclax and azacitidine, 100% (nine out of nine cases) in the triple combination group including tamibarotene achieved CR/CRi within a short duration. Syros Pharmaceuticals anticipates releasing further data in 2024.

* Fast Track is a process established by the FDA to facilitate the development and expedite the review of drug candidates aimed at treating serious conditions and filling unmet medical needs. Fast Track designation is awarded to drug candidates demonstrating potential to address these needs based on nonclinical or clinical evidence. Benefits of this designation for a drug candidate include increased communication with the FDA regarding development plans, and, with supportive clinical data, may qualify for priority review or accelerated approval.
*2 Complete remission with incomplete blood recovery (CRi) refers to a condition in which the percentage of leukemia cells among the cells in the patient's bone marrow is less than 5%, but with incomplete recovery of neutrophil or platelet counts, or both.

Additionally, with the FDA's Fast Track designation, Syros Pharmaceuticals has initiated a Phase III clinical trial to evaluate the efficacy of tamibarotene in combination with azacitidine as a treatment for high-risk myelodysplastic syndromes (HR-MDS) in patients with untreated HR-MDS with RARA gene overexpression (note: azacitidine is the standard treatment for high-risk HR-MDS). The enrollment of patients required for the primary endpoint analysis (190 patients) was completed in Q1 FY12/24, and interim data on complete remission is expected by mid-Q4.

RaQualia is entitled to milestone payments from Syros Pharmaceuticals based on the development progress of tamibarotene, in addition to receiving royalties post-commercialization. MDS and AML significantly impact life expectancy, and the global market size for drugs for their treatment is projected by Syros Pharmaceuticals to reach approximately USD7.5bn (about JPY1.0tn, at an exchange rate of USD/JPY135) for MDS and USD4.7bn (about JPY630mn) for AML by 2028. RaQualia will not receive any lump sum payments in connection with this designation and there is no impact on the consolidated earnings forecast for FY12/24. Nonetheless, RaQualia views the Fast Track designation as a potential accelerator for the development and approval processes of tamibarotene for AML, which could enhance the drug's value in the medium to long term.

RaQualia partners with Velovia Pharma for veterinary drug development

2024-04-03

RaQualia Pharma Inc. announced that it has entered into an option and license agreement with Velovia Pharma, LLC (unlisted) for the development of veterinary drugs using four compounds in RaQualia's development pipeline.

Under the agreement, RaQualia grants Velovia Pharma an option for an exclusive license to evaluate, develop, manufacture, and market veterinary drugs containing these four compounds. Velovia Pharma, which is engaged in the development of veterinary drugs, has expressed interest in the potential application of these compounds for pet medications. If Velovia Pharma exercises its option for one or more compounds, RaQualia will receive an option exercise fee from Velovia Pharma and will be entitled to milestone payments as development progresses. Furthermore, if the veterinary drugs containing these compounds reach the market, RaQualia will receive sales royalties and sales milestone payments from Velovia Pharma.

RaQualia notes that this agreement is not expected to impact its financial results for FY12/24 and has thus maintained its earnings forecast. Nevertheless, the company views this partnership as an opportunity to bolster its development pipeline and enhance its operating revenue and corporate value over the longer term.

Approval to initiate Phase I clinical trial in Australia for a novel TRPM8 blocker

2024-03-11

RaQualia Pharma Inc. announced that its licensee, Xgene Pharmaceutical Co. Ltd. (unlisted), has received approval from the Australian Bellberry Human Research Ethics Committee (HREC) to conduct a Phase I clinical trial in Australia for a novel TRPM8 blocker.

In September 2021, RaQualia entered into a license agreement with Xgene, based in Hong Kong, granting Xgene exclusive rights to develop, manufacture, and sell the company's novel TRPM8 blocker worldwide, excluding Japan. In preclinical studies conducted by Xgene, the TRPM8 blocker (RQ-00434739/XG2002) demonstrated potent analgesic effects in several animal models of pain and a favorable safety profile. Xgene believes this compound has the potential to be a treatment for various types of acute and chronic pain, including neuropathic pain such as migraine and diabetic neuropathy. The HREC-approved Phase I clinical trial is designed to assess tolerability and pharmacokinetics through a dose-ascending study in healthy volunteers, gathering important information for future clinical trials.

RaQualia has received an upfront payment from Xgene upon signing the license agreement and is entitled to milestone payments based on development progress and royalties on sales. With this approval, RaQualia will receive a milestone payment from Xgene, which will be recorded as operating revenue in Q1 FY12/24. The company has already reflected the financial impact of this matter in its consolidated earnings forecast for FY12/24, which was released on February 14, 2024.

Fundraising for the acquisition of a subsidiary

2024-03-08

RaQualia Pharma Inc. announced its plan to raise funds for the acquisition of shares in FIMECS, Inc. (unlisted).

At its Board of Directors meeting held on March 8, 2024, the company resolved to borrow funds necessary for the acquisition of FIMECS. RaQualia had previously announced on February 14, 2024, its plan to acquire all shares of FIMECS and make it a subsidiary. According to the company, the impact of this fundraising on the consolidated financial results for FY12/24 has already been factored into the earnings forecast published on February 14, 2024.

Overview of the loan

Lenders	A syndicate led by Mizuho Bank, Ltd. as arranger, with The Shoko Chukin Bank, Ltd. as co-arranger
Loan amount	JPY3.5bn
Date of execution	March 25, 2024 (scheduled)
Loan term	Seven years (84 months)
Interest rate	Base rate + spread
Repayment method	Initial repayment on June 30, 2024, followed by equal principal repayments every three months
Major financial covenants	From FY12/24 onward, EBITDA, calculated based on the figures presented in the parent income statement for each fiscal year, shall not be negative for two consecutive periods. (EBITDA = operating profit + depreciation and amortization expenses)

Approval of GERD treatment tegoprazan in Chile

2024-02-20

RaQualia Pharma Inc. announced that its gastroesophageal reflux disease (GERD) treatment, tegoprazan, has been approved for sale in Chile.

The company announced that its sublicensee, Laboratories Carnot (unlisted), has received marketing approval for tegoprazan from the Chilean Agencia Nacional de Medicamento (ANAMED) for four indications, including erosive esophagitis. Carnot has a sublicense agreement for tegoprazan with HK inno.N, which markets the drug in South Korea under the brand name K-CAB®.

RaQualia has an exclusive license agreement (including sublicense rights) with HK inno.N for the development, manufacture, and sale of tegoprazan worldwide, excluding Japan. Under this agreement, HK inno.N and sublicensees conduct business activities related to tegoprazan in various countries. Chile is the ninth country to approve tegoprazan, following South Korea, Mongolia, China, the Philippines, Indonesia, Singapore, Mexico, and Peru.

In 2019, HK inno.N and Carnot signed a sublicense agreement for 17 countries in Latin America, including Mexico, Peru, and Chile. Since then, Carnot has been actively seeking marketing authorization across these nations. Approval was secured in Chile after local authorities completed their review. The approved indications are erosive esophagitis, non-erosive reflux disease, peptic ulcer disease, and adjuvant therapy for Helicobacter pylori eradication. According to RaQualia, the market for ulcer drugs in the 17 Latin American countries, including Chile, is approximately KRW574.0bn (approximately JPY63.1bn, converted at KRW/JPY0.11). In May 2023, tegoprazan was launched in Mexico, the second-largest pharmaceutical market in Latin America. RaQualia is expecting progress toward product launches in other countries in Latin America following Mexico, Peru, and Chile.

Under the license agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns from Carnot. RaQualia will also receive a lump sum payment from HK inno.N as a result of the product launch in Chile, which it will recognize as operating revenue in Q1 FY12/24. The company has already incorporated the impact of this approval into its full-year consolidated results for FY12/24.

RaQualia acquires FIMECS

2024-02-14

RaQualia Pharma Inc. announced the acquisition of shares in FIMECS, Inc., making it a wholly owned subsidiary.

Founded in 2018, FIMECS, Inc. is a biotech company advancing the research and development of new pharmaceuticals using targeted protein degradation inducers, a new modality in drug discovery. Based on its unique E3 ligase binding molecule and drug discovery platform technology RaPPIDS™, it aims to create innovative medicines for diseases that have been considered extremely difficult (undruggable) to treat. FIMECS has established a technology to identify the optimal E3 ligase for each target from over 600 known E3 ligases and acquire novel E3 ligase binders by improving and evolving RaPPIDS™.

In 2022, FIMECS entered into a research collaboration agreement with Astellas Pharma Inc. (TSE Prime: 4503) on multiple targets. Based on this agreement, FIMECS received an upfront payment of JPY500mn and research funding. After the identification of candidate compounds, Astellas Pharma will conduct development, and FIMECS will receive milestone payments based on the progress of development for each target program. Furthermore, after commercialization, FIMECS may receive sales milestones and royalties at a single-digit rate based on sales revenue.

FIMECS is also advancing several first-in-class new drug development programs targeting proteins associated with cancer diseases as its main in-house pipeline. The most advanced program, the IRAK-M program (compound code: FIM-001), aims to develop a new cancer immunotherapy based on the mechanism of action of immune suppression relief and is currently in the preclinical stage.

Reason for the acquisition

RaQualia is focused on enhancing corporate and shareholder value by reinforcing its growth foundation, while aiming to improve profitability through the signing of large contracts. In pursuit of growth enhancement, updating the drug discovery value chain and M&A are positioned as key strategies. By making FIMECS a subsidiary, RaQualia expects business expansion in the following three areas:

1. Enhancing the drug discovery value chain to improve growth potential and competitiveness

Traditionally, RaQualia has specialized in drug discovery research of small molecules targeting ion channels and GPCRs, generating many drug candidate compounds. Since 2022, aiming to establish the next-generation in-house drug discovery value chain from four perspectives: modality, drug discovery target, disease area, and core technology, RaQualia has been advancing collaborations with several startups and drug discovery companies. Acquiring FIMECS's RaPPIDS™ platform technology to venture into new modalities such as targeted protein degradation inducers allows targeting molecules and disease areas previously considered undruggable. The acquisition of FIMECS is expected to significantly advance the strengthening of RaQualia's next-generation in-house drug discovery value chain.

2. Increased revenue through a platform business

Currently, FIMECS is conducting joint research with Astellas Pharma on multiple targets, which may yield milestone payments, royalties, and sales milestones based on the progress of these joint research projects. The interest in targeted protein degradation inducers is particularly high abroad, with similar companies in the US (e.g., Arvinas [NASDAQ: ARVN], C4 Therapeutics [NASDAQ: CCCC], Kymera Therapeutics [NASDAQ: KYMR], Nurix Therapeutics [NASDAQ: NRIX]) building their platforms and securing substantial contracts from the early stages of collaboration. FIMECS plans to continuously acquire new joint research partners both domestically and internationally around its core platform technology, RaPPIDS™, expecting further expansion of revenue opportunities.

Further strengthening and expansion in the oncology field

RaQualia has developed marketed pharmaceuticals such as the gastric acid secretion inhibitor tegoprazan (brand name: K-CAB®) and the dog osteoarthritis treatment grapiprant (brand name: GALLIPRANT®). While many of its out-licensed programs are being developed by pharmaceutical companies and belong mainly to the pain and gastrointestinal disease areas, the company has initiated exploratory research targeting cancer as part of strengthening its drug discovery value chain. The acquisition of FIMECS, adding pipelines including the IRAK-M program, will strengthen the group's pipeline targeting cancer.

Consideration and method for the acquisition

RaQualia plans to acquire all issued shares of FIMECS from the current shareholders on March 26, 2024, making FIMECS a consolidated subsidiary. The consideration for the acquisition consists of an upfront payment (the closing consideration) paid at the time of the share acquisition and payments based on future revenues earned by FIMECS (the earn-out consideration).

1. Closing consideration

RaQualia will pay a closing consideration of JPY4.5bn in cash to the sellers on March 26, 2024.

2. Earn-out consideration

From FY12/24 to FY12/28, based on contract upfront payments, milestone payments, royalty income, and revenue from commissioned work generated from contracts with third parties, an amount calculated using a predetermined calculation method will be paid to the sellers.

This arrangement mitigates the risk of RaQualia paying an undue consideration by not paying the entire consideration at the time of the acquisition execution but paying part of it as earn-out consideration based on the revenue of FIMECS. It also serves as an incentive for some sellers involved in FIMECS's operations to continue contributing to research and development activities and revenue expansion.

Shares acquired, acquisition price, and share ownership before and after the acquisition

Shares owned before the transaction	None (number of voting rights: 0, percentage of voting rights owned: 0%)
Number of shares to be acquired	Issued shares: 35,352 shares, stock acquisition rights: 1,141
Total acquisition price at closing	JPY4.5bn Advisory fees and other estimated costs: JPY17mn
Shares owned after the transaction	35,352 (number of voting rights: 35,352, percentage of voting rights owned: 100%)
Breakdown of the acquisition price	A cash payment of JPY4.5bn at the time of the share transfer. In addition, as earn-out consideration, payments based on contract upfront payments, milestone payments, royalty income, and revenue from commissioned work generated from contracts with third parties, calculated using a predetermined method, will be paid to the sellers.
Date of share transfer	March 26, 2024 (planned)

RaQualia expects to recognize goodwill from this acquisition, with the amount currently under review. FIMECS's performance will be reflected in the consolidated performance from Q2 FY12/24. The impact of this transaction on the consolidated performance for FY12/24 has already been factored into the consolidated performance forecast.

Extension of committed credit line agreement

2024-02-01

RaQualia Pharma Inc. announced the extension of its committed credit line agreement.

The company signed the committed credit line agreement with MUFG Bank, Ltd. in February 2022. It decided to extend the agreement to secure a flexible and stable funding source to meet temporary capital needs arising from future business activities, thereby strengthening and stabilizing its financial foundation.

Details of the committed credit line agreement

Contract partner	MUFG Bank, Ltd.
Contract amount	JPY1.0bn
Contract date	February 22, 2022
Contract duration	On year
Expiry date before extension	February 27, 2024
New expiry date	February 27, 2025
Collateral	Unsecured

The impact of this matter on the consolidated financial performance of the company group for FY12/24 is expected to be minimal.

Helicobacter pylori eradication added to indications for tegoprazan in China

2023-12-15

RaQualia Pharma Inc. has announced the addition of Helicobacter pylori eradication therapy as an indication for the gastric acid secretion inhibitor tegoprazan in China.

Shandong Luoxin Pharmaceutical Group Stock Co., Ltd., a sublicensee of RaQualia in China, has received regulatory approval to include combined therapy for the treatment of Helicobacter pylori infection as an indication for tegoprazan (trade name in China: Tai Xin Zan®).

RaQualia has out-licensed tegoprazan to HK inno.N in South Korea, and Luoxin develops, manufactures, and sells tegoprazan in China under a sublicense agreement with HK inno.N. Luoxin began selling tegoprazan just 15 days after receiving approval for the indication of erosive esophagitis in April 2022. In March 2023, tegoprazan was included in China's National Reimbursement Drug List (NRDL), making it eligible for reimbursement by health insurance companies. Furthermore, in November 2023, Luoxin obtained approval to manufacture and sell tegoprazan for the treatment of duodenal ulcers.

Tegoprazan is a gastric acid secretion inhibitor with a new mechanism of action, classified as a potassium-competitive acid blocker (P-CAB), developed by RaQualia. Characteristic of P-CABs is their suppression of gastric acid secretion through a mechanism different, faster and more persistent than proton pump inhibitors (PPIs), which are the first-line drugs for gastric acid secretion inhibition. Luoxin has announced that in the Phase III clinical trial with a primary efficacy endpoint of a 14-day eradication rate in Chinese patients with Helicobacter pylori infection, the tegoprazan-containing bismuth-based quadruple therapy showed a statistically significant higher eradication rate compared to the esomeprazole-containing bismuth-based quadruple therapy in the control group. Esomeprazole, included in the control group, is a typical PPI.

In Helicobacter pylori eradication therapy, it is important to maintain a high pH level in the stomach and prevent a decrease in antibiotic activity. According to the company, the characteristics of P-CABs provide an advantage over PPIs in this regard. Helicobacter pylori is implicated in the development of various diseases such as peptic ulcers and gastric cancer. Therefore, Chinese and international guidelines and consensus recommend Helicobacter pylori eradication therapy in cases of confirmed infection.

With the approval for Helicobacter pylori infection, tegoprazan is now approved in China for three indications, including erosive esophagitis and duodenal ulcers. Epidemiological studies indicate that the infection rate of Helicobacter pylori in the Chinese population is between 40% and 60%. The development of injectable tegoprazan is also underway in China, and RaQualia expects tegoprazan sales to further expand in the country.

Under the licensing agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns from royalties and other sources upon commercialization. Although RaQualia will not receive any upfront payments in connection with this matter, and the impact on the consolidated results for FY12/23 is expected to be immaterial, the company believes that the expanded use of tegoprazan in China will contribute to future sales growth and thus improve operating revenue and corporate value in the medium to long term.

Milestone achieved in joint research with Veritas In Silico

2023-12-14

RaQualia Pharma Inc. announced that it has achieved a milestone outlined in the joint drug discovery research agreement signed with Veritas In Silico Inc. (unlisted) in December 2022.

In December 2022, the company announced its commitment to creating small molecule drugs targeting messenger RNA (mRNA) through joint research with Veritas In Silico. This collaborative effort involves several years of drug discovery research, with a focus on multiple genes associated with cancer as specified by RaQualia. The research aims to identify target structures on the corresponding mRNAs, acquire hit compounds via high-throughput screening, synthesize lead compounds from the hit compounds, and optimize lead compounds to generate candidate compounds for development.

As a result of the joint research outcomes exceeding the pre-defined standard, RaQualia will pay a milestone fee to Veritas In Silico. According to RaQualia, the impact of this matter on the FY12/23 results is minor and has already been factored into the full-year consolidated earnings forecast announced on December 8, 2022. Over the medium to long term, the company believes that the joint research findings will contribute to strengthening its R&D portfolio and expanding its development pipeline.

Revision to consolidated earnings forecast for FY12/23

2023-12-08

RaQualia Pharma Inc. announced a revision to its consolidated earnings forecast for FY12/23.

Revision to the company's full-year FY12/23 consolidated earnings forecast

- Revenue: JPY2.0bn (-33.6% YoY; previous forecast: JPY2.8bn)
- Operating loss: JPY409mn (versus a profit of JPY866mn in FY12/22; previous forecast: profit of JPY260mn)
- Recurring loss: JPY340mn (versus a profit of JPY904; profit of JPY242mn)
- Net loss attributable to owners of the parent: JPY426mn (versus a profit of JPY723mn; profit of JPY183mn)
- Net loss per share: JPY19.73 (versus a profit of JPY34.50; profit of JPY8.74)

Reason for the revision

The revision was made because the license agreement under negotiation for the rights to develop, manufacture, and sell the gastric acid secretion inhibitor tegoprazan in Japan and the approval and launch of ELURA® (generic name: capromorelin), a treatment for weight loss in cats with CKD, are now expected to be pushed back to FY12/24.

The company estimates the negative impact of these delays on its earnings for FY12/23 to be JPY900mn. The impact of currency fluctuations on the company's earnings is anticipated to be positive JPY84mn for the full year. This is because the average exchange rate was about JPY138/USD during the fiscal year, compared with the initial assumption of JPY125/USD. Operating expenses are expected to decrease 7.5% from the previous forecast to JPY191mn.

Revision to business plan and growth potential

RaQualia Pharma also announced a revision to its three-year medium-term business plan, covering FY12/23 to FY12/25.

	FY12/21	FY12/22	FY12/23	FY12/23	FY12/24	FY12/24	FY12/25	3-year
(JPYmn)	Cons.	Cons.	Initial forecast	Revised forecast	Previous target	Revised target	Targets	CAGR
Operating revenue	**2,776**	**2,918**	**2,799**	**1,938**	**2,966**	**3,924**	**4,185**	
YoY	150.7%	5.1%	-4.1%	-33.6%	6.0%	102.5%	6.7%	12.8%
Operating expenses	**2,068**	**2,052**	**2,538**	**2,538**	**2,657**	**3,721**	**2,860**	
YoY	29.8%	-0.8%	23.7%	23.7%	4.7%	46.6%	-23.1%	11.7%
Operating expense ratio	74.5%	70.3%	90.7%	131.0%	89.6%	94.8%	68.3%	
Operating profit	**708**	**866**	**260**	**-409**	**309**	**203**	**1,325**	
YoY	-	22.4%	-70.0%	-	18.8%	-	552.7%	15.2%
Operating profit margin	25.5%	29.7%	9.3%	-	10.4%	5.2%	31.7%	
Recurring profit	**864**	**904**	**242**	**-340**	**317**	**193**	**1,330**	
YoY	-	4.7%	-73.2%	-	31.0%	-	589.1%	13.7%
Recurring profit margin	31.1%	31.0%	8.6%	-	10.7%	4.9%	31.8%	
Net income	**756**	**723**	**183**	**-426**	**248**	**90**	**1,166**	
YoY	-	-4.3%	-74.7%	-	35.5%	-	1195.6%	17.2%
Net margin	27.2%	24.8%	6.5%	-	8.4%	2.3%	27.9%	

Source: Shared Research based on company data

As a result of a review of recent business performance, the company made revisions to its Medium-Term Management Plan 2023–2025 announced on February 14, 2023, regarding its business plan and growth potential for FY12/23–FY12/25.

Main factors for the revision

For FY12/23, the company made a downward revision due to the expected delays of the license agreement for the development, manufacture, and sale of tegoprazan in Japan and of the approval and launch of ELURA®, a treatment for weight loss in cats with CKD, in Europe until FY12/24. The company estimates the negative impact of these delays to be JPY900mn and the positive impact of exchange rate fluctuations to be JPY84mn. It also anticipates a JPY191mn decrease in operating expenses compared with the previous forecast.

For FY12/24, the company expects operating revenue to be JPY958mn higher than the previous forecast. This is mainly due to the deferral of a total of JPY900mn in upfront and milestone payments that were expected to be recorded in FY12/22 for tegoprazan. Operating expenses are expected to be JPY1.1bn higher than the previous forecast. This is primarily due to the cost of upfront payments for new license agreements of about JPY500mn and an increase in research expenses of roughly JPY370mn due to increased outsourcing for discovery of new development compounds in FY12/23. The company assumes this to be a one-time increase.

As there are no changes to the business plan, including the company's business model, source of competitiveness, and investment strategy, the targets for FY12/25, the final year of the medium-term business plan, remain unchanged.

Progress in clinical trials for treatment of acute myeloid leukemia using tamibarotene by Syros Pharmaceuticals of the US

2023-12-07

TMRC Co., Ltd., a consolidated subsidiary of RaQualia Pharma Inc., announced that its US-based licensee Syros Pharmaceuticals, Inc. (NASDAQ: SYRS, hereafter "Syros") has reported preliminary data from the randomized part of the Phase II clinical trial of retinoic acid receptor alpha (RARα) agonist (tamibarotene/TM-411/SY-1425, hereafter "tamibarotene"), which had been licensed from Syros to Syros, for acute myeloid leukemia (AML).

Tamibarotene is a selective retinoic acid receptor (RARα) agonist, that, due to its exhibition of strong differentiation-inducting activity, is expected to have a synergistic effect when used in combination with other antitumor agents. Syros has been conducting a Phase II clinical trial (SELECT-AML-1) of tamibarotene + venetoclax + azacitidine three-drug combination

therapy in elderly and other patients who are RARA-positive and not suitable for standard chemotherapy since September 2021.

The randomized part from which data was released followed the safety lead-in part, as the second part of the trial. In this announcement, Syros reported that the primary endpoint of the study, complete response rate (CR)/ complete response rate with incomplete hematologic recovery (CRi), was 100% in patients (nine out of nine) treated with the three-drug therapy of tamibarotene, venetoclax, and azacitidine. In contrast, the rate was 70% in patients (seven out of ten) treated with the venetoclax and azacitidine combination therapy. Syros also reported initial data showing good tolerability regarding the safety of the three-drug therapy. Syros continues to enroll patients in the SELECT-AML-1 trial and plans to report the top-line data in 2024.

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.

*[1] RARA-positive patients are those with overexpressed RARA, a gene that codes for RARα.

Indication expansion for tegoprazan in China

2023-11-22

RaQualia Pharma Inc. has announced the expansion of the indications for tegoprazan, a gastric acid secretion inhibitor, in China.

According to the company, Shandong Luoxin Pharmaceutical Group Stock Co., Ltd. (SHE: 002793), a sublicensee in China, has received approval to manufacture and sell tegoprazan (trade name in China: Tai Xin Zan®) for the treatment of duodenal ulcer.

RaQualia has out-licensed tegoprazan to HK inno.N in South Korea, and Luoxin develops, manufactures, and sells tegoprazan in China under a sublicense agreement with HK inno.N. In April 2022, Luoxin received approval to market tegoprazan for the indication of erosive esophagitis. Luoxin began selling the product just 15 days after approval, distributing the drug through hospitals, retail pharmacies, and the internet. In March 2023, tegoprazan was included in China's National Reimbursement Drug List (NRDL) for 2022, making it eligible for reimbursement by health insurance companies.

With this indication expansion, there are now two approved indications for tegoprazan in China: erosive esophagitis and duodenal ulcer. According to RaQualia, duodenal ulcer is one of the most common and frequent chronic diseases in China, accounting for approximately 70% of all peptic ulcers. In addition, Phase III clinical trials have been completed in China for the use of the drug in adjuvant therapy for Helicobacter pylori eradication, and development of an injectable product is underway.

Under the licensing agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns from royalties and other sources upon commercialization. Although RaQualia will not receive any upfront payments in connection with this matter and the impact on the consolidated results for FY12/23 is expected to be immaterial, the company believes that the expanded use of tegoprazan in China will contribute to future sales growth and thus improve operating revenue and corporate value in the medium to long term.

GERD treatment tegoprazan launched in Peru

2023-10-16

RaQualia Pharma Inc. has announced the launch of its gastroesophageal reflux disease (GERD) treatment, tegoprazan, in Peru.

The company announced that Laboratories Carnot (unlisted), a Mexican sublicensee of the company, has commenced sales of tegoprazan in Peru. The drug is sublicensed to Carnot through RaQualia's licensee HK inno.N Corporation (KOSDAQ:

195940). The product will be marketed in Peru under the name Ki-CAB®. The launch date of October 12th is commemorated in Peru as the day Columbus reached America.

RaQualia has entered into an exclusive license agreement with HK inno.N, which includes sublicensing rights and covers the development, manufacture, and sale of tegoprazan worldwide, excluding Japan. In South Korea, where sales of tegoprazan (sold as K-CAB®) started in 2019, domestic sales (based on hospital prescriptions) for 2022 amounted to KRW132.1bn (approximately JPY13.2bn, calculated at KRW0.10/JPY). Cumulative sales from January to September 2023 were KRW114.0bn (approximately JPY11.4bn, +19% YoY), indicating steady growth. Based on the licenses granted by HK inno.N and RaQualia, sublicensees are conducting business activities related to tegoprazan in various countries.

In 2019, HK inno.N and Carnot signed a sublicense agreement targeting 17 countries in Latin America, including Peru. Since then, Carnot has advanced its product launch initiatives. In July 2023, Carnot received marketing authorization from the Peruvian General Directorate of Medicines, Supplies and Drugs for four indications: erosive esophagitis, non-erosive reflux disease, peptic ulcers, and adjuvant therapy for the eradication of Helicobacter pylori.

In Latin America, Carnot already launched tegoprazan in Mexico in May 2023. With the start of sales in Peru, tegoprazan is now available in eight countries: South Korea, China, Mongolia, the Philippines, Mexico, Indonesia, and Singapore. Clinical development, regulatory review, and pre-marketing activities are ongoing in an additional 29 countries.

Under the license agreement with HK inno.N, RaQualia has the right to receive a percentage of the revenue that HK inno.N earns from Carnot. The company will not receive any upfront payments in connection with this matter and the impact on the consolidated results for FY12/23 is expected to be immaterial.

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®, pet 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®, pet 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
Other	
Participation in electronic voting platform	In place
Providing convocation notice in English	In place
Implementation of measures regarding director incentives	Performance-linked compensation system
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	11.03%
Pfizer Japan Inc.	743	3.44%
BOFAS INC SEGREGATION ACCOUNT (Standing proxy: BofA Securities Japan Co., Ltd.)	630	2.91%
Ueda Yagi Tanshi Co., Ltd.	286	1.32%
The Tokyo Tanshi Co., Ltd.	270	1.25%
Advanced Media, Inc.	224	1.03%
SBC Co., Ltd.	206	0.95%
Takahiro Tanago	180	0.83%
Yukio Uemura	145	0.67%
Ikuyoshi Koumoto	137	0.63%
SUM	5,207	24.06%

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

Number of employees

	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20	FY12/21	FY12/22	FY12/23
Number of employees (consolidated)	72	-	-	60	63	68	70	67	65	67
Number of employees (parent)	70	64	50	55	58	62	64	62	62	64
Average age	43.6	44.1	44.8	45.5	45.5	46.3	47.3	46.5	47.5	46.4
Average years of service	5.5	5.9	6.6	7.0	6.9	7.4	8.1	8.7	10.7	8.9
Average annual salary (JPY'000)	7,971	8,124	7,242	7,391	7,408	7,237	7,510	7,369	7,033	7,264

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

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Phone

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Established

2008-02-19

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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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