Basic Information

Basic Information on the Pharmaceutical Industry

Drug Discovery Research

Research and Development Aims

Drug discovery research is the activity of creating new drugs by first identifying target molecules and then developing them into drug candidates. To respond to unmet medical needs,* Chugai aims to successively create innovative new drugs that can achieve first-in-class*/best-in-class* status. This series of pre-clinical processes is said to normally require five to eight years. Chugai conducts its research activities making efficient use of its research infrastructure, including unique drug discovery and AI technologies, its external networks, including links with academia, and the infrastructure of the Roche Group.

Unmet medical needs
Medical need that is not adequately met due to a lack of effective treatments.

First-in-class
An original drug that is highly novel and useful, and will significantly change the therapeutic system.

Best-in-class
A drug that offers clear advantages over other existing drugs in the same category, such as those with the same molecular target.

Drug Discovery Modalities

Modality refers to the material classification of a drug. Until the 1990s, small molecule drugs were virtually the only modality, but the options are now increasing. New modalities open up new approaches in areas of disease where there is no effective treatment. To add to its world-leading therapeutic antibodies* and small molecule drugs,* Chugai is therefore working to establish mid-size molecule drugs* as a third modality.

Therapeutic antibody
A type of biopharmaceutical, which is a drug created by applying biotechnology such as genetic recombination. It is an artificially created antibody used as a medicine to prevent or treat diseases. Therapeutic antibodies are designed to act only on the specific molecule (antigen) that causes the disease, and therefore can be expected to provide high therapeutic efficacy and reduce side effects.

Small molecule drug
A drug created by chemical synthesis with a low molecular weight of 500 or less.

Mid-size molecule drug
This modality is thought to offer a promising new approach to reaching intracellular targets inaccessible with antibodies and small molecules.

Clinical Drug Development

Basic Clinical Development Process

In clinical development, the efficacy and safety* of drug candidates are demonstrated based on the evidence obtained in the research stage. To do this, clinical trials* with an optimal design based on the latest scientific findings are conducted to gather the data required for regulatory approval. Chugai achieves efficient and speedy clinical development by contributing from Japan to joint multinational clinical studies as part of global development projects sponsored by the Roche Group.

PoC / Early PoC
Proof of concept (PoC) is confirmation that the therapeutic effect conceived in the research stage is effective in humans. Early PoC means that in addition to safety, signs of efficacy or pharmacological effect have been confirmed in a limited number of cases.

Clinical trial
A study to verify the safety, efficacy, and other characteristics of a drug in human subjects. Studies conducted for the purpose of filing an application for approval are called clinical trials.

Phase I: Performed on a small number of healthy volunteers (or, for certain disease areas and diseases, on patients) to assess the drug's safety and the process by which it is absorbed, distributed, metabolized, and eliminated by the body.

Phase II: Performed on a small number of consenting patients to determine the safest and most effective dosage and the dosing regimen.

Phase III: Performed on a large number of consenting patients to verify the efficacy and safety of the new drug in comparison with existing drugs or placebo.

Phase IV: Post-marketing clinical surveillance. Performed on a larger number of consenting patients than in phase III studies to verify the drug's safety and efficacy for its approved indication(s).

Application for Approval

When a new drug candidate has demonstrated efficacy and safety in a range of clinical trials, pharmaceutical companies file an application for manufacturing and marketing approval with the regulatory authorities. In Japan, the Minister of Health, Labour and Welfare grants manufacturing and marketing approval to substances deemed appropriate as pharmaceuticals based on reviews by the Pharmaceutical and Medical Devices Agency (PMDA) as well as academic and other experts in the Pharmaceutical Affairs and Food Sanitation Council. To expedite the practical application of a drug, there is a system* in place enabling breakthrough therapies and other drugs that fulfill certain conditions to be given priority in consultation and review for regulatory approval.

Breakthrough therapy designations
This is a designation granted by the U.S. Food and Drug Administration (FDA) to expedite the development and review of drugs for the treatment of serious or life-threatening diseases and symptoms. A drug must be highly innovative to receive the designation, but receiving it is valuable for various reasons. For example, a drug with this designation receives priority review, which shortens the development period, bringing the drug to patients as quickly as possible. Chugai has received this designation for five products and eight projects originating from in-house research (as of February 4, 2021), an indication of the strength of its drug discovery capabilities.

Drug Lifecycle Management

Basic Lifecycle Management System

Chugai operates an integrated lifecycle management (LCM) system. In this process, customer needs and product management perspectives are incorporated from the early stage of each clinical development project. The management process continues as the product is launched and matures right through to the end of the lifecycle. To maximize the product's value potential, Chugai pursues a range of objectives, from shortening the development period, expanding sales, and extending product lifespan to acquiring additional indications,* ensuring appropriate cost management, and implementing an appropriate patent strategy.

Additional indication
A new indication for a previously approved drug.

Drug Patents

Patents are crucial to the value of a drug. As they operate in combination with the regulatory system, relatively few patents are required for product protection compared to other industries. Patent rights are normally valid for 20 years from the date of application, but to compensate for the length of the pharmaceutical R&D period, some governments may allow an extension of patent rights for a maximum of five years. As the market release of generics is not permitted during the term of the

patent, it is an important part of the LCM strategy to progressively acquire patents for additional indications, additional dosing and administration options, and others.

Overview of Domestic Pharmaceutical Market and National Health Insurance (NHI) Drug Prices

Trends in National Medical Expenses

Without medical system reforms, Japan's national medical expenses will increase at an annual rate of approximately 2 to 4 percent going forward. In fiscal 2019 (the year ended March 2020), national medical expenses[1] totaled ¥43.6 trillion, a ¥1.0 trillion or 2.4 percent increase from the previous year. The accelerating pace of aging of Japan's society presents serious challenges to efficiently managing the increase in medical expenses for the elderly.

1. Source: Trends of recent medical expenditure (fiscal 2019) by Ministry of Health, Labour and Welfare

Promotion of the Use of Generics

The Japanese government is promoting the use of generics with the primary objective of reducing the cost burden on patients and improving the finances of the health insurance system. Various measures have been carried out under the action program announced in October 2007 to promote the worry-free use of generics. In April 2013, the new "Roadmap to Further Promote the Use of Generics" was formulated. A Cabinet decision in June 2017 set the new goal of raising the volume market share of generics, which was 78.3 percent[2] as of September 2020, to 80 percent by the end of September 2020. Based on the result achieved, a new target for promoting the use of generics is now being considered. For biosimilars, the government aims to double the number of items in use by the end of 2023 compared to July 2010, based on the number of active ingredients.[3]

2. Preliminary results of 2020 Drug Price Survey
3. New Economic and Fiscal Revitalization Plan, 2020 Reform Schedule

NHI Drug Price Revision

The Ministry of Health, Labour and Welfare (MHLW) generally reviews drug reimbursement prices every two years and sets new standard prices (reimbursement prices) so that the official prices of pharmaceuticals prescribed under the health insurance system approximate their actual market price. The MHLW does this by investigating the prices and volumes of all prescription drug transactions during a given period.

Due to the growing public financial burden caused by the situation at the time, in which drug prices were maintained for up to two years even if the actual market price fell, it was decided in the fiscal 2018 fundamental reform of the NHI drug pricing system that drug price survey and revision should also take place in interim years, when, ordinarily, there would be no revision. The government has since been considering the specific details of this policy.

Fiscal 2021 will be the first year in which the interim price revision is conducted. With the aim of achieving a wide-ranging reduction of the public financial burden, the revision will be applied to all product items showing a price difference from the market average of more than 0.625 times (5 percent). Moreover, to take into account the impact of COVID-19 infection, the drug price revision will be based on actual market prices so as to soften by 0.8 percent the extent of the price reduction.

In concrete terms, it has been decided that the revision of April 2021 should bring a drug price reduction of ¥100.1 billion when measured in terms of government spending.

NHI Drug Price Revision Rate (%) 4. Adjusted to account for consumption tax increase 5. Pending release by the MHLW Source: Chugai data

	2008	2010	2012	2014[4]	2016	2018	2019/10[4]	2020	2021
Industry average	(5.2)	(6.5)	(6.25)	(2.65)	(7.8)	(7.48)	(2.4)	(4.38)	—[5]
Chugai	(7.2)	(6.8)	(6.0)	+0.8	(5.5)	(6.7)	(0.2)	(9.2)	(2.5–3.0)

Repricing Based on Market Expansion

Under this repricing rule introduced in 1994, drugs priced by the cost calculation method with annual sales exceeding ¥10.0 billion and more than 10 times the original forecast at the time of price revision, or with annual sales exceeding ¥15.0 billion and more than two times the original forecast, are subject to a price reduction of up to 25.0 percent. Drugs priced by methods other than the cost calculation method (including the similar efficacy comparison method) with annual sales exceeding ¥15.0 billion and more than two times the original forecast at the time of the price revision are subject to a price reduction of up to 15.0 percent. In addition, the prices of drugs that have pharmacological action similar to a drug subject to this repricing rule are reduced by the same rate. In the NHI drug pricing system fundamental reforms of fiscal 2018, it was decided to use the NHI listing of new drugs that takes place four times a year as an opportunity for repricing of drugs with annual sales exceeding ¥35.0 billion. The purpose of this change is to respond more quickly when sales expand rapidly due to an additional indication or other reasons.

Special Market-Expansion Repricing

In the reforms to the drug pricing system in fiscal 2016, an additional repricing rule for drugs with very high annual sales was introduced as a special measure from the standpoint of balancing reward for innovation with the sustainability of the NHI system. This rule lowers prices by up to 25.0 percent for drugs with annual sales of ¥100.0–150.0 billion and more than 1.5 times the original forecast, and lowers prices by up to 50.0 percent for drugs with annual sales exceeding ¥150.0 billion and more than 1.3 times the original forecast. In addition, the prices of drugs that have pharmacological action similar to a drug subject to the special repricing rule and were comparator drugs at the time of the NHI price listing are reduced by the same rate. In the NHI drug pricing system fundamental reforms of fiscal 2018, it was decided to use the NHI listing of new drugs that takes place four times a year as an opportunity for repricing under this scheme.

Premium to Promote the Development of New Drugs and Eliminate Off-Label Use

As part of the NHI drug pricing system reforms of fiscal 2010 (the year ended March 2011), a new pricing scheme was implemented on a trial basis to promote the creation of innovative medical products and solve the drug lag[6] problem. In this scheme, at the time of the NHI drug price revisions, prices are maintained on drugs for which no generics are available (provided that they have been in the NHI price list for no more than 15 years), and which satisfy certain conditions.

This premium pricing for new drugs was continued on a trial basis in subsequent NHI drug pricing system reforms. However, in the NHI drug pricing system fundamental reforms of fiscal 2018, the decision was made to revise the requirements for

companies and products and list them in the drug repricing rules. Companies that do not respond appropriately to development requests from the MHLW will continue to be excluded from eligibility for premium pricing. In addition, indicators have been set for (A) creation of innovative drugs and treatments for antimicrobial-resistant bacteria, (B) drug lag countermeasures, and (C) development of novel drugs ahead of other countries, and the pricing premiums may vary according to the level of achievement or fulfillment of these indicators. Healthcare-related ventures are expected to play an important role in the creation of innovative drugs, and will be evaluated accordingly, irrespective of the company indicators.

Regarding the product requirements, the percentage price difference requirement will be abolished, and the price premium will be limited to novel drugs during their patent period, and drugs that are truly innovative and useful. More specifically, it will be limited to orphan drugs; drugs for which development was publicly requested; drugs to which the premium was applied because of their usefulness, such as at the time they were newly listed; drugs with novel mechanisms of action that are innovative or useful (limited to the top three first-in-class drugs within three years from listing) or that have newly added efficacy or effectiveness deemed equivalent to novel modes of action; drugs that have Sakigake designation; and treatments for antimicrobial-resistant bacteria.

Among new drugs subject to premium pricing, including those for which generics (including biosimilars) have been launched or 15 years have elapsed since their drug price listing, the cumulative amount of premium pricing is deducted from the NHI drug price in the subsequent initial drug price revision. Furthermore, a reduction or other adjustment due to the actual market price of the new drug during the fiscal year is made to the NHI drug price less the cumulative amount.

6. The inability of Japanese patients to gain access to global standard or most advanced treatments because the drugs are not developed in Japan

Solving the Drug Lag Problem

In January 2005, the MHLW established the Investigational Committee for Usage of Unapproved Drugs as one means of helping solve the drug lag problem. The committee is charged with investigating the clinical necessity and the appropriateness of usage of drugs already approved in Europe and the United States, but not yet approved in Japan. The aim of these investigations is to promote the development of those drugs in Japan. In February 2010, the MHLW established the Review Committee on Unapproved Drugs and Indications with High Medical Needs. This committee evaluates the medical necessity of drugs and indications that are not yet approved in Japan and investigates matters such as the applicability of filings for approval based on evidence in the public domain. As a result of continuous efforts to strengthen the review function of the PMDA, an independent administrative institution responsible for reviewing drugs and medical devices for approval, the median total review time for new drugs in fiscal 2019 was 11.8 months. In fiscal 2019, the difference between Japan and the United States in the median total review period for approved new drugs was 0.1 years, while for new drug applications filed in Japan, the median lag compared to the time of filing in the United States was 0.5 years. Based on the total of these two figures, the fiscal 2019 drug lag amounted to 0.6 years.

Response to Requests from the MHLW Review Committee on Unapproved Drugs and Indications with High Medical Needs
(As of January 30, 2021)

Development Request	Product	Indication	Development Status
First development request	Xeloda	Advanced or recurrent gastric cancer	Approved in February 2011
	Tarceva	Advanced or recurrent pancreatic cancer	Approved in July 2011
	Avastin	Advanced or recurrent breast cancer	Approved in September 2011
	CellCept	Pediatric renal transplant	Approved in September 2011
	Herceptin	Q3W dosage metastatic breast cancer overexpressing HER2	Approved in November 2011
		Neoadjuvant breast cancer overexpressing HER2	
	Kytril	Gastrointestinal symptoms associated with radiotherapy	Approved in December 2011
	Pulmozyme	Improvement of pulmonary function in patients with cystic fibrosis	Approved in March 2012
	Bactramin	Treatment and prevention of pneumocystis pneumonia	Approved in August 2012
	Avastin	Ovarian cancer	Approved in November 2013
Second development request	Avastin	Recurrent glioblastoma	Approved in June 2013 (Malignant glioma)
	Herceptin	Q1W dosage postoperative adjuvant breast cancer overexpressing HER2	Approved in June 2013
	CellCept	Lupus nephritis	Approved in May 2016
Third development request	Tamiflu	Additional dosage for neonates and infants younger than 12 months	Approved in March 2017
	Xeloda	Adjuvant chemotherapy in rectal cancer	Approved in August 2016
	Avastin	Additional Q2W dosage and administration for ovarian cancer	Submitted company opinion and waiting for evaluation by committee

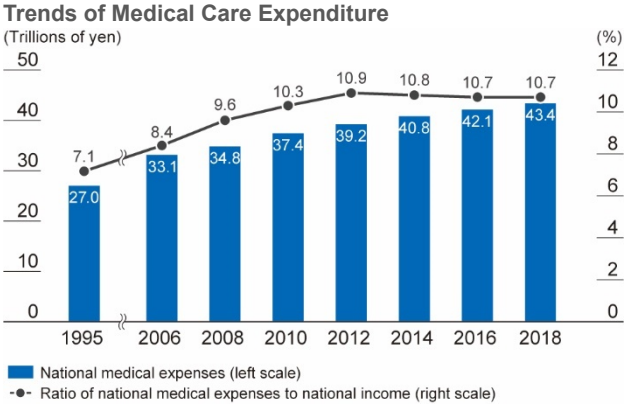
Fourth development request	Copegus	Improvement of viraemia associated with genotype 3 chronic hepatitis C or compensated cirrhosis related to hepatitis C when administered in combination with sofosbuvir	Approved in March 2017
	Xeloda	Neuroendocrine tumor	Submitted company opinion and waiting for evaluation by committee
	Avastin	Cerebral edema induced by radiation necrosis	Submitted company opinion and waiting for evaluation by committee
	Neutrogin	Combination therapy with chemotherapy including fludarabine for relapsed/refractory acute myeloid leukemia	Submitted company opinion and waiting for evaluation by committee
	CellCept	Prevention of graft-versus-host disease in hematopoietic stem cell transplantation	Evaluated by the Review Committee in December 2020 as eligible for public knowledge-based application; application approved January 27, 2021, by the First Committee on New Drugs, Pharmaceutical Affairs and Food Sanitation Council

Creation of a System for Cost-Effectiveness Assessments

A system of price adjustments based on cost-effectiveness assessments has been approved by Chuikyo, and was implemented in April 2019. The system primarily applies to products that meet the requirements of the selection criteria at the time of their NHI price listing. Cost-effectiveness assessments will be conducted for a certain period after the listing, and the price will be adjusted according to the results. The extent of the price adjustment is the portion corresponding to the amount of the corrective premium for usefulness applied at the time of the drug's initial pricing (for products with a degree of disclosure under 50 percent, as calculated by the cost calculation method, the portion corresponding to operating profit is also subject to adjustment). Price adjustments will be made according to the incremental cost effectiveness ratio (ICER).[7] The corrective premium will be maintained if the ICER is less than ¥5 million (less than ¥7.5 million for anticancer agents), but will be reduced in stages by up to 90 percent if the ICER is ¥5 million or more. The price adjustment will be limited to 10–15 percent of the total drug price.

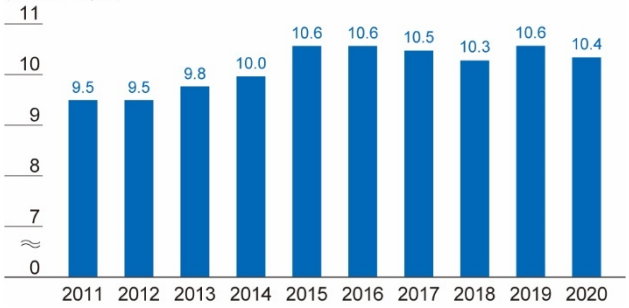
7. The ICER indicates the extent to which additional investment would be necessary to obtain the additional benefit from replacing existing drug (technology) B with new drug A.

Trends of Medical Care Expenditure



Source: Overview of Estimates of National Medical Care Expenditure, FY2018 by Ministry of Health, Labour and Welfare
Note: National income is based on the actual results of the System of National Accounts announced by the Cabinet Office.

Prescription Drug Market



Source: JPM, based on 2011–2020 (calendar year). Reprinted with permission.

Note: The status of products and drug candidates under development is as of February 4, 2021.

Oncology

Overview of Disease and Treatment Methods

Leading Cause of Death in Japan

Cancer has been the single most common cause of death in Japan since 1981.

In 2019, 376,425 people[1] died of cancer, accounting for 27.3 percent[1] of all deaths in that year and the highest number since government surveys began in 1899.

1. Source: Outline of Vital Statistics (2019) by Ministry of Health, Labour and Welfare

Establishment of the Basic Act for Anticancer Measures and Improvement in the Healthcare Environment

The Cancer Control Act was enacted in June 2006 to establish a system so that patients can receive appropriate treatment based on scientific knowledge regardless of the region in which they reside and with respect paid to their wishes, as well as to implement the Basic Plan to Promote Cancer Control Programs (the "Basic Plan"). Since the enactment of the Cancer Control Act, some results have been obtained, including establishment of designated cancer hospitals and a reduction of the cancer mortality rate and improvement of the five year survival rate owing to advances in cancer treatment. The goal of reducing the age-adjusted cancer mortality rate by 20 percent over the 10-year period from fiscal 2007 was judged difficult to achieve, and therefore, in December 2015, the Plan for Acceleration of Cancer Control Programs was formulated. This plan specified concrete measures that should be implemented intensively in a short period of time.

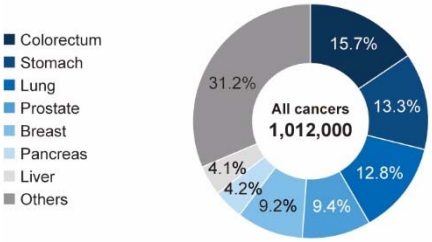
In recent years, it has become apparent that new measures are

necessary to fight rare cancers, difficult-to-treat cancers, childhood cancers, and cancers in adolescents and young adults (AYA); to promote new treatments such as genomic medicine; and to address societal problems including employment. The principles of the Cancer Control Act revised in 2016 require that the national and local governments make effective use of healthcare and welfare resources and implement cancer control measures from the viewpoint of serving the public in order to achieve the stated goal of creating a society in which cancer patients can live with peace of mind and dignity. In the 3rd Basic Plan to Promote Cancer Control Programs released in March 2018, measures are being implemented to educate the public, including patients, about cancer and help them to overcome it. These measures are based on four pillars: cancer prevention, improvement of cancer care, living with cancer, and deployment of infrastructure to support those measures.

Changes in Treatment Methods

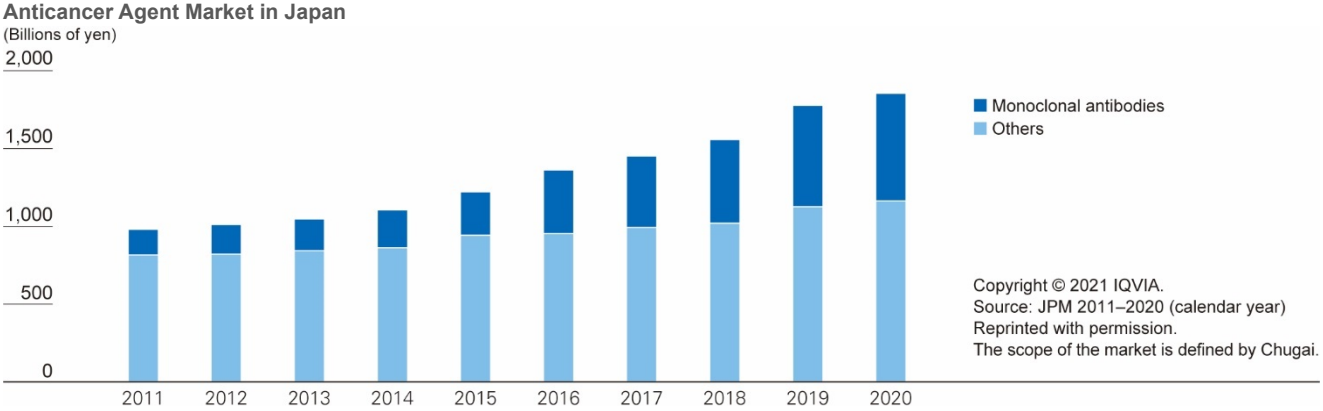
Cancer treatment is increasingly being based on a multidisciplinary approach that combines surgery, radiation therapy, and drug therapy. In particular, the field of anticancer agents is evolving, and highly innovative medicines such as molecular targeted drugs have been introduced. This has brought dramatic improvement in treatment outcomes for various types of cancer. Advances are being made in personalized healthcare (PHC), which involves testing patients with companion diagnostics when administering molecular targeted drugs to identify patients who are likely to benefit with minimal strain on the body and few side effects. In addition to enabling physicians to propose the optimal treatment tailored to each patient, this approach offers a number of other benefits. For example, it can reduce national healthcare expenditures by reducing the administration of drugs when their effect cannot be determined. Diagnosis with comprehensive genomic profiling (CGP), such as genomic testing using next-generation sequencing, is also becoming important. In improvement of cancer care, one of the pillars of the abovementioned Basic Plan, cancer genomic medicine heads the list of measures, and practical application of CGP testing was promoted as an important government-led initiative. As a result, in June 2019 CGP, which entails comprehensive analysis and profiling of genes in a single test using solid tumor tissue from the patient, became eligible for health insurance coverage. The provision of optimal treatments based on each patient's genomic profile has thus become a reality. Genomic medicine started in the oncology field, but is now being promoted for intractable diseases and other diseases, in line with the "Action Plan of the Growth Strategy," "Follow-up on the Growth Strategy," and "Action Plan for Innovative Business Activities in Fiscal 2019," which were approved by the Cabinet in June 2019. This is expected to further advance precision medicine in ways such as promoting the development of treatment approaches that utilize genomic information obtained not only through genomic analysis of cancer tissue, but through entire genome analysis. Cancer immunotherapy, which takes advantage of the body's own immune cells to fight cancer, is another important emerging field of treatment. Immune checkpoint inhibitors, one type of immunotherapy now in use, are a promising new direction in cancer treatment. Cancer has the ability to suppress (apply brakes to) immune functions to avoid attack from the immune system, but immune checkpoint inhibitors block the immune "brakes" (the binding of PD-1 to PD-L1, etc.) known as the immune checkpoint, thereby awakening immune cells to attack cancer cells. In clinical study results, immune checkpoint inhibitors have shown promise for long-term survival and cure, even in advanced cancer. Their high therapeutic efficacy is recognized in clinical settings, and they are increasingly used as treatments for a wide range of cancers. However, some patients do not respond to cancer immunotherapy, so screening to select patients for whom this therapy is likely to be effective is also being examined, as are various combinations with existing anticancer agents and development candidates, and development for use in early-stage cancer. CAR T-cell therapy, another immunotherapy using gene delivery technology, is also in use in Japan. In this approach, T cells collected from the patient are engineered to produce chimeric antigen receptors (CAR) that recognize specific cancer cell antigens. The T cells are then multiplied and returned to the patient to attack the cancer cells.

Projected Cancer Incidence (2020)



Source: National Cancer Center Cancer Information Service, "Cancer Registries/Statistics"
* Intraepithelial cancer not included in projection.
Note: The projection of cancer incidence was calculated by using future estimates of population by age bracket for 2020 to adjust the incidence by age bracket and cancer type according to the national cancer register (2017 recorded statistics). The total may not add up because projections have been performed by cancer type and figures have been rounded.
Reference: Japanese Journal of Clinical Oncology 2014, 44: 36-41

Anticancer Agent Market in Japan



Source: JPM 2011–2020 (calendar year)

The scope of the market is defined by Chugai.

FoundationOne CDx Cancer Genomic Profile

FoundationOne CDx Cancer Genomic Profile (F1CDx), developed by U.S.-based Foundation Medicine, Inc., is a next-generation sequencing-based diagnostic device. It detects substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB). The program is available as a companion diagnostic for multiple molecular-targeted drugs approved in Japan. Chugai launched the program and began providing testing services in June 2019. In March 2021, Chugai received approval for FoundationOne Liquid CDx Cancer Genomic Profile, a liquid biopsy test for solid tumors using blood samples. As it detects tumor DNA circulating in blood (ctDNA), it can be used in cases where tumor tissue is difficult to sample. The product is expected to bring further advances in PHC, including by allowing tissue samples and blood samples to be used selectively at different stages of treatment.

Tecentriq (RG7446)

Engineered anti-PD-L1 monoclonal antibody
(Generic name: atezolizumab)
Launch in Japan: April 2018

Tecentriq is an engineered anti-PD-L1 monoclonal antibody in-licensed from Roche. One way that tumor cells evade the immune system is by expressing a protein called programmed death-ligand (PD-L1) on their surface, which is believed to shield them from immune system attacks by binding to T cells. Tecentriq restores and maintains the immune response of T cells by binding to PD-L1, and is expected to demonstrate efficacy against cancer cells. Its mode of action differs from conventional treatments that attack cancer cells directly. Since it takes advantage of the patient's own immune response, it is also promising for use in combination with existing drugs and for various cancer types. Chugai obtained approval in January 2018 for the treatment of unresectable, advanced, or recurrent nonsquamous non-small cell lung cancer (NSCLC), and obtained approval in December 2018 for the treatment of chemotherapy-naïve people with unresectable, advanced, or recurrent nonsquamous NSCLC in combination with Avastin and chemotherapy. In 2019, Chugai obtained approval for the additional indications of extensive-stage small cell lung cancer (SCLC) in August, PD-L1-positive inoperable or recurrent triple-negative breast cancer (TNBC) in September, and unresectable, advanced, or recurrent NSCLC (new dosage/form) in November. Characterized by rapid progression and poor prognosis, SCLC and metastatic TNBC are diseases with high unmet medical needs. SCLC is an area that has long had limited therapeutic options, and Tecentriq received orphan drug designation as the first new drug in 17 years that improved treatment outcomes. The additional dosage forms for NSCLC, some of them approved for the first time worldwide, enable a regimen that does not limit combination with other anticancer agents in first-line treatment. In September 2020, approval was received for use in combination with Avastin for unresectable hepatocellular carcinoma (HCC). The MHLW had granted priority review designation on the grounds of improved prognosis and gave approval seven months after filing. Additionally, in December of the same year, Tecentriq was approved for monotherapy in chemotherapy-naïve cases of PD-L1-positive unresectable, advanced, or recurrent NSCLC. Tecentriq is the first immune checkpoint inhibitor to be approved in Japan, the United States, and Europe in the areas of SCLC, breast cancer, and HCC. Chugai is also participating in global phase III studies for a range of further indications: neoadjuvant and adjuvant therapy for NSCLC; urothelial carcinoma; renal cell carcinoma; renal cell carcinoma (adjuvant therapy); early breast cancer; ovarian cancer; HCC (adjuvant therapy); head and neck carcinoma (maintenance therapy); and esophageal cancer. A number of these studies involve the co-development with Takeda Pharmaceutical Company Limited, of combination therapy with CABOMETYX® tablets. Chugai is also engaged in global phase I studies for pancreatic cancer.

Review of 2020 Performance

Sales of Tecentriq increased ¥16.9 billion, or 82.0 percent, year on year to ¥37.5 billion, substantially higher than expected. This result was driven partly by expansion of the product's use in prescription for unresectable, advanced, or recurrent NSCLC, extensive SCLC, PD-L1-positive, inoperable, or recurrent TNBC, and unresectable HCC.

Avastin (RG435)

Anti-VEGF humanized monoclonal antibody
(Generic name: bevacizumab)
Launch in Japan: June 2007

Avastin is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). It is the first therapeutic agent in the world that inhibits angiogenesis, which is the growth of the network of blood vessels that supply nutrients and oxygen to the cancer. Unlike conventional anticancer agents that act directly on cancer cells, Avastin acts on the cancer microenvironment. In Japan, Avastin was launched in 2007 for the treatment of unresectable, advanced, or recurrent colorectal cancer. In 2009, Chugai obtained approval for a new dosage and administration for colorectal cancer and the additional indication of unresectable, advanced, or recurrent NSCLC, followed in 2011 by inoperable or recurrent breast cancer. Chugai also obtained approval for the additional indications of malignant glioma and ovarian cancer in 2013, and advanced or recurrent cervical cancer in May 2016. In September 2020, Chugai obtained approval for the additional indication of unresectable HCC in combination with Tecentriq.

Review of 2020 Performance

Sales of Avastin decreased ¥14.1 billion, or 14.7 percent, year on year to ¥81.5 billion. Performance was impacted by a 15.7 percent drug price reduction in April due to the loss of premium pricing status and by the launch of biosimilars in some of its indications. Development is progressing in global phase III studies of combination therapy with Tecentriq in HCC (adjuvant therapy) and SCLC.

Perjeta (RG1273)

HER2 dimerization inhibitory humanized monoclonal antibody
(Generic name: pertuzumab)
Launch in Japan: September 2013

Perjeta is a humanized monoclonal antibody and is the first molecular targeted therapy that inhibits the dimerization of HER2. The combination of Perjeta and Herceptin, which also targets HER2, provides a more comprehensive blockade of HER signaling pathways associated with the proliferation of tumor cells. Chugai launched Perjeta for the indication of HER2-positive inoperable or recurrent breast cancer in September 2013, after obtaining approval in June 2013. In 2018, Perjeta obtained approval for the additional indication of neoadjuvant and adjuvant therapy for HER2-positive breast cancer.

Review of 2020 Performance

Sales of Perjeta increased ¥2.8 billion, or 9.1 percent, year on year to ¥33.5 billion. Although repricing based on market expansion led to a 15 percent price reduction in April 2020, the combination of Perjeta and Herceptin with a chemotherapy agent

as neoadjuvant and adjuvant therapy for HER2-positive early breast cancer, an additional indication approved in October 2018, achieved good market penetration. Chugai is also engaged in a global phase III study of RG6264 (subcutaneous injection), a fixed-dose combination of Herceptin and Perjeta for HER2-positive breast cancer.

Alecensa (AF802/RG7853) (In-house development)

ALK inhibitor
(Generic name: alectinib)
Launch in Japan: September 2014

Alecensa, an oral, small molecule targeted molecular therapy created by Chugai, inhibits the activity of the tyrosine kinase anaplastic lymphoma kinase (ALK) with *EML4-ALK* fusion gene expressed in about 2 to 5 percent of NSCLC. It was designated as an orphan drug in Japan in September 2013 for the treatment of *ALK* fusion gene-positive unresectable, advanced, or recurrent NSCLC. In October 2013, Chugai filed an application for approval. Following approval in July 2014, Alecensa was launched first in Japan in September 2014. In addition to being the first product from Chugai research to be granted breakthrough therapy designation by the U.S. FDA as a second-line treatment in 2013, Alecensa received the same designation as a first-line treatment in 2016, and it is contributing to the treatment of patients around the world. Outside Japan, after obtaining approval in the United States in December 2015 and in Europe in February 2017 for the indication of ALK-positive metastatic (advanced) NSCLC in patients whose disease has progressed or who are intolerant to crizotinib, Alecensa obtained approval as a first-line treatment in the United States in November 2017 and Europe in December 2017.

In February 2020, Alecensa obtained approval for the additional indication of recurrent or refractory *ALK* fusion gene-positive anaplastic large cell lymphoma (ALK-positive ALCL).

Review of 2020 Performance

Market penetration proceeded further with the announcement of positive results that led to the early stopping for benefit of a study comparing the efficacy and safety of Alecensa and a competing product on patients in Japan (J-ALEX study). Sales of Alecensa in Japan increased ¥3.0 billion, or 13.0 percent, year on year to ¥26.0 billion, due to a high rate of continuation of treatment. Overseas sales of Alecensa (including exports to Roche) decreased ¥1.0 billion, or 2.2 percent, year on year to ¥44.3 billion due to a reduction in the export price. In development, a global phase III study for adjuvant therapy of ALK-positive NSCLC is under way.

Herceptin

Anti-HER2 humanized monoclonal antibody
(Generic name: trastuzumab)
Launch in Japan: June 2001

Herceptin is a humanized monoclonal antibody that targets human epidermal growth factor receptor type 2 (HER2),[8] which contributes to tumor cell growth. The earliest PHC-based anticancer agent, Herceptin has built a solid reputation as an essential treatment for HER2-positive breast cancer since its launch in 2001.

Overexpression of HER2 is found in about 15 to 20 percent of breast cancers. Such cancer is diagnosed as HER2-positive. HER2-positive breast cancer progresses rapidly, and has been associated with a poor prognosis. However, treatment outcomes have improved significantly with the emergence of Herceptin and other medicines that target HER2. In 2011, Herceptin obtained approval for the additional indication of advanced or recurrent gastric cancer overexpressing HER2, not amenable to curative resection, bringing PHC to the field of gastric cancer.

8. A diagnostic test can determine if a patient's breast or gastric cancer cells have overexpression of a protein called HER2. Herceptin, Perjeta, and Kadcyla target HER2 and are administered only to patients whose tumors are identified as HER2-positive.

Review of 2020 Performance

Sales of Herceptin decreased ¥10.8 billion, or 40.4 percent, year on year to ¥15.9 billion due to the impact of biosimilars. It is used in combination with Perjeta for HER2-positive advanced or recurrent breast cancer. Since October 2018, it has been widely used in combination with Perjeta, after Perjeta became available as a neoadjuvant and adjuvant therapy in HER2-positive breast cancer. For gastric cancer, although Herceptin maintained its established position in first-line treatment, sales decreased slightly due to competition in second-line treatment.

Kadcyla (RG3502)

Anti-HER2 antibody-tubulin polymerization inhibitor conjugate
(Generic name: trastuzumab emtansine)
Launch in Japan: April 2014

Kadcyla is an antibody-drug conjugate of the anti-HER2 humanized monoclonal antibody trastuzumab (product name: Herceptin) and the potent chemotherapeutic agent DM1, joined together with a stable linker. Chugai filed an application for approval for HER2- positive inoperable or recurrent breast cancer in January 2013, obtained approval in September 2013 after priority review, and launched the product in April 2014.

Review of 2020 Performance

Sales of Kadcyla increased ¥1.2 billion, or 13.3 percent, year on year to ¥10.2 billion. Kadcyla is widely used as a second-line treatment for HER2-positive advanced or recurrent breast cancer that has progressed following first-line treatment with Herceptin and Perjeta plus chemotherapy. In August 2020, it was approved for adjuvant therapy of HER2-positive breast cancer.

Rituxan

Anti-CD20 monoclonal antibody
(Generic name: rituximab)
Launch in Japan: September 2001

Rituxan is a monoclonal antibody targeting the CD20 antigen found on the surface of lymphocytes. As a standard therapy for CD20-positive, B-cell non-Hodgkin's lymphoma (hematological cancer), it has substantially improved clinical outcomes in combination with chemotherapy or in monotherapy. In Japan, Rituxan is marketed jointly by Chugai and Zenyaku Kogyo Co., Ltd. In recent years, the usefulness of Rituxan has been recognized in treating CD20-positive, B-cell lymphoma in immunosuppressed patients, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), refractory nephrotic syndrome with frequent relapses or steroid dependence, suppression of antibody-mediated rejection in ABO-incompatible kidney and liver transplantation, and idiopathic thrombocytopenic purpura (ITP). It has also become a valuable treatment option for patients with autoimmune diseases and other conditions. Rituxan obtained approval for the additional indications of CD20-positive chronic lymphocytic leukemia (CLL) in 2019 and acquired thrombotic thrombocytopenic purpura in February 2020.

Review of 2020 Performance

Sales of Rituxan decreased ¥4.7 billion, or 39.5 percent, year on year to ¥7.2 billion. The decrease was due to more intense competition resulting from the launch of biosimilars.

Gazyva (GA101)

Glycoengineered type II anti-CD20 monoclonal antibody
(Generic name: obinutuzumab)
Launch in Japan: August 2018

Gazyva is a glycoengineered type II monoclonal antibody in-licensed from Roche that, like Rituxan, targets CD20. A study that directly compared its efficacy and safety with Rituxan, currently the most widely used monoclonal antibody, in patients in Japan and overseas (the GALLIUM study) was terminated early for benefit after positive results were reported. Gazyva obtained approval for the indication of CD20-positive follicular lymphoma in July 2018, and was launched in August 2018. In November 2012, Chugai entered into an agreement with Nippon Shinyaku Co., Ltd. to co-develop and co-market this agent in Japan.

Review of 2020 Performance

Sales of Gazyva increased ¥1.0 billion, or 27.8 percent, year on year to ¥4.6 billion, reflecting steady sales expansion on market penetration for both initial and recurrent disease.

Xeloda

Antimetabolite, 5-FU derivative
(Generic name: capecitabine)
Launch in Japan: June 2003

Xeloda is a 5-fluorouracil (5-FU) anticancer agent developed at the research laboratories of the former Nippon Roche. Orally administered Xeloda is absorbed by the body, then gradually metabolized by certain highly active enzymes in liver and tumor tissue, and is eventually converted into active 5-FU within tumor tissue. Xeloda has obtained approval for the treatment of inoperable or recurrent breast cancer, colorectal cancer, and gastric cancer.

Review of 2020 Performance

Sales of Xeloda decreased ¥4.4 billion, or 55.0 percent, year on year to ¥3.6 billion. The sharp decline in sales resulted partly from the loss of premium pricing status, which led to a drug price cut of 27.4 percent in April 2020. Additionally, the uptake of a generic launched in January 2019 was greater than expected. However, in adjuvant therapy performed to inhibit recurrence after surgery for colon cancer, Xeloda is the most prescribed drug because of its recommendation in the guidelines for the treatment of colorectal cancer and the results of a large-scale global study.

Rozlytrek (RG6268)

ROS1/TRK inhibitor
(Generic name: entrectinib)
Launch in Japan: September 2019

Rozlytrek, in-licensed from Roche, is an orally bioavailable central nervous system (CNS)-active tyrosine kinase inhibitor that potently and selectively inhibits ROS1 and the TRK family, and also acts on brain metastases. Targeting *NTRK* fusion gene-positive solid tumors, RG6268 has been granted breakthrough therapy designation in the United States, PRIorityMEdicines (PRIME) designation in the EU, and Sakigake designation in Japan. Chugai obtained the world's first approval for the treatment of *NTRK* fusion gene-positive advanced/recurrent solid tumors in Japan in June 2019, and launched the product in September 2019. Rozlytrek is a tumor-agnostic therapy that uses a next-generation sequencing-based companion diagnostic to identify target genomic alterations that drive cancer, thus embodying the advanced PHC that Chugai is promoting. F1CDx obtained approval in June 2019 as a companion diagnostic for Rozlytrek. Chugai obtained approval for *ROS1* unresectable, advanced, or recurrent fusion gene-positive NSCLC in February 2020.

Review of 2020 Performance

Sales of Rozlytrek totaled ¥0.4 billion. Although market penetration was delayed by the spread of COVID-19 infection, sales expanded steadily following the start of its administration for *ROS1* fusion gene-positive unresectable, advanced, or recurrent NSCLC.

Neutrogin (In-house development)

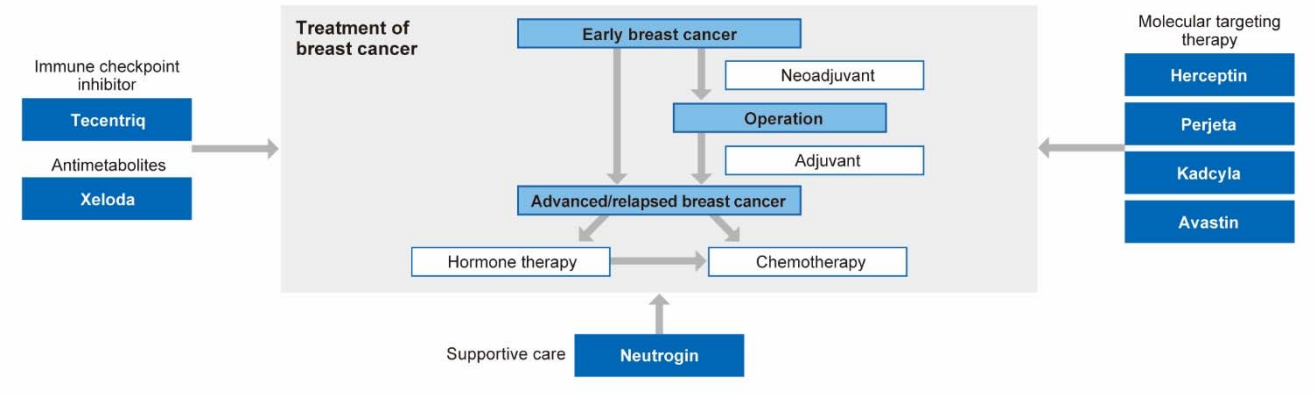
Recombinant human granulocyte colony-stimulating factor (G-CSF)
(Generic name: lenograstim;
overseas product name: Granocyte)
Launch in Japan: December 1991

Neutrogin is a recombinant human granulocyte colony-stimulating factor (G-CSF) created by Chugai. One common side effect of anticancer drugs is neutropenia, a decrease in the white blood cell count that heightens the risk of developing serious infections. Neutrogin stimulates the differentiation and growth of neutrophils, enabling the safer use of chemotherapy, thus helping to improve treatment outcomes. Neutrogin is also essential in hematopoietic stem cell transplantation, which is performed for illnesses that affect production of normal blood cells, such as leukemia.

Review of 2020 Performance

Overseas sales of Neutrogin decreased ¥0.9 billion, or 9.1 percent, year on year to ¥9.0 billion due to intensified competition.

Extensive Contribution to Cancer Treatment (Breast Cancer)



RG7596 Development project

Anti-CD79b antibody-drug conjugate
(Generic name: polatuzumab vedotin)

RG7596 is an antibody-drug conjugate of an anti-CD79b monoclonal antibody and the microtubule inhibitor MMAE, joined together with a linker. In-licensed from Roche, the conjugate is designed to deliver MMAE directly into B cells via CD79b, which is expressed on B cells, so that the inhibitor can act. To demonstrate a cytostatic effect on tumor cells, a global phase III study for previously untreated diffuse large B-cell lymphoma (DLBCL) started in November 2017. In addition, a phase II clinical study for relapsed or refractory DLBCL started in Japan in October 2018 and achieved a primary endpoint in February 2020.

In November 2019, RG7596 received orphan drug designation for the treatment of DLBCL, and in June 2020 Chugai filed an approval application for the treatment of recurrent or intractable DLBCL.

RG7440 Development project

AKT inhibitor
(Generic name: ipatasertib)

RG7440 is an AKT inhibitor in-licensed from Roche. Global phase III studies started in June 2017 for prostate cancer and in January 2018 for breast cancer.

Of the various breast cancer studies, global phase III studies for triple-negative breast cancer and hormone-positive breast cancer, begun in 2018, failed to meet the primary endpoint, while a global phase III study of combination therapy with atezolizumab for triple-negative breast cancer, initiated in 2020, was discontinued before completion. In progress at present is a global phase III study in hormone-positive breast cancer launched in 2019.

RG6058 Development project

Anti-TIGIT fully humanized monoclonal antibody
(Generic name: tiragolumab)

RG6058 is an anti-TIGIT monoclonal antibody in-licensed from Roche. TIGIT is an immune checkpoint expressed on the surface of NK cells and T cells that binds to poliovirus receptors (PVR) expressed on tumor cell surfaces. This binding is thought to allow the cancer cells to evade attack by immune cells. RG6058 restores and maintains the immune response of NK cells and T cells by blocking the binding of TIGIT to PVR, and is thus expected to demonstrate efficacy against cancer cells. In November 2019, Chugai began a phase I clinical trial of RG6058 for solid tumors in Japan. Additionally, Chugai launched a series of global phase III studies: for SCLC in February 2020, for NSCLC in March, for NSCLC (Stage III) in August, and for esophageal cancer in September.

RG6171 Development project

SERD
(Generic name: giredestrant)

RG6171 is a selective estrogen receptor degrader (SERD) in-licensed from Roche. In October 2020, Chugai initiated a global phase III study for the treatment of breast cancer.

OBP-301 Development project

Oncolytic type 5 adenovirus
(Generic name: undetermined)

OBP-301 is a type 5 adenovirus genetically engineered to specifically replicate within and thereby destroy cancer cells. The type 5 adenovirus is also present in the natural world, where it causes cold-like symptoms. It is expected to display powerful antitumor activity by specifically proliferating within cancer cells to dissolve them and also to demonstrate clinical safety due to its very low ability to proliferate within normal cells. In April 2019, Chugai acquired exclusive licensing rights in Japan and Taiwan in an agreement with Oncolys BioPharma Inc. In March 2020, Chugai began a phase II clinical study of combination with radiotherapy for esophageal cancer, followed in January 2021 by the start of a phase I clinical study of combination therapy with Tecentriq and Avastin for hepatocellular carcinoma. In April 2019, OBP-301 received Sakigake designation from the MHLW.

GC33 (RG7686) Development project (In-house development)

Anti-glypican-3 humanized monoclonal antibody
(Generic name: codrituzumab)

GC33, a humanized monoclonal antibody created by Chugai, targets glypican-3 (GPC3), which is specifically expressed in hepatocellular carcinoma. GC33 did not meet the primary endpoint in a global phase II monotherapy study started in March 2012. A phase I clinical study for hepatocellular carcinoma in combination with Tecentriq has been under way since August 2016, and the study results were presented at the European Society of Medical Oncology (ESMO) 2018 Congress.

ERY974 Development project (In-house development)
Anti-glypican-3/CD3 bispecific antibody

ERY974 is the first T-cell redirecting antibody (TRAB) developed by Chugai. TRAB is a bispecific antibody that creates a short bridge between CD3 on T cells and tumor antigen on tumor cells to activate T cells in a tumor antigen-dependent manner, and is expected to demonstrate strong cytotoxicity against tumor cells.

GPC3, a tumor antigen targeted by ERY974, is reported to be expressed in multiple types of tumor cells including hepatocellular carcinoma, lung cancer, gastric cancer, and esophageal cancer. A phase I clinical trial is under way.

RG7421 Development project
MEK inhibitor
(Generic name: cobimetinib fumarate)

RG7421 is an MEK inhibitor in-licensed from Roche. Chugai started a phase I clinical study for the treatment of solid tumors in Japan in July 2017.

RG7802 Development project
Anti-CEA/CD3 bispecific antibody
(Generic name: cibisatamab)

RG7802, a bispecific antibody in-licensed from Roche, is expected to activate T cells and attack tumor cells by cross-linking CD3 on T-cells to carcinoembryonic antigen (CEA) on tumor cells. Chugai started a phase I clinical study of RG7802 for the treatment of solid tumors in Japan in January 2018.

RG7828 Development project
Anti-CD20/CD3 bispecific antibody
(Generic name: mosunetuzumab)

RG7828 is a bispecific antibody in-licensed from Roche. It is expected to activate T cells and attack tumor cells by cross-linking CD3 on T cells to CD20 on B cells. Chugai started a phase I clinical study for the treatment of hematologic tumors in Japan in March 2018.

RG6026 Development project
Anti-CD20/CD3 bispecific antibody
(Generic name: glofitamab)

RG6026 is a bispecific antibody in-licensed from Roche. By cross-linking CD3 on T cells with CD20 on B cells, it is expected to cause T-cell activation and proliferation and attack on the target B cells through cytokine release, resulting in antitumor effect. Chugai started a phase I clinical study for the treatment of hematologic tumors in Japan in March 2020.

AMY109 Development project (In-house development)

AMY109 is the third therapeutic antibody to apply the recycling antibody engineering technology created by Chugai. In March 2020, Chugai began a phase I clinical study for solid tumors.

STA551 Development project (In-house development)
Anti-CD137 agonist switch antibody

STA551, a “switch antibody,” is the first application of switch antibody technology, which was developed by Chugai. Switch antibodies bind to the target antigen only where there is a high concentration of a certain “switch” molecule, which is concentrated specifically at the diseased site. STA551 binds to CD137 and activates T cells in the presence of the switch molecule ATP, but not in the absence of ATP. It therefore promises to act selectively on tumors. Chugai started a phase I clinical study for the treatment of solid tumors in March 2020.

SPYK04 Development project (In-house development)

SPYK04 is a small molecule drug developed in-house by Chugai. In September 2020, Chugai began a phase I clinical study for solid tumors.

RG6194 Development project
Anti-HER2/CD3 bispecific antibody
(Generic name: undetermined)

RG6194, an anti-HER2/CD3 bispecific antibody in-licensed from Roche, is expected to act against HER2-expressing cancer cells by inducing and activating T cells. In November 2020, Chugai began participation in a global phase I study for the treatment of solid tumors.

Bone and Joint Diseases / Autoimmune Diseases

Osteoporosis

Osteoporosis is a disease in which the bones become weak due to advanced age or other factors, increasing the risk of fractures. Osteoporosis patients may incur fractures through normal daily activities. Among these, compression fractures of the spine and femoral neck fractures can decrease QoL by leaving patients bedridden and can also increase mortality risk. About 13 million people in Japan suffer from osteoporosis. However, the treatment rate stands at around only 20 percent of the estimated number of sufferers because there are usually no symptoms until a fracture occurs. The availability of superior new drugs that have higher efficacy, safety and convenience has brought promise for improvement in the QoL of patients.

Treatment Methods

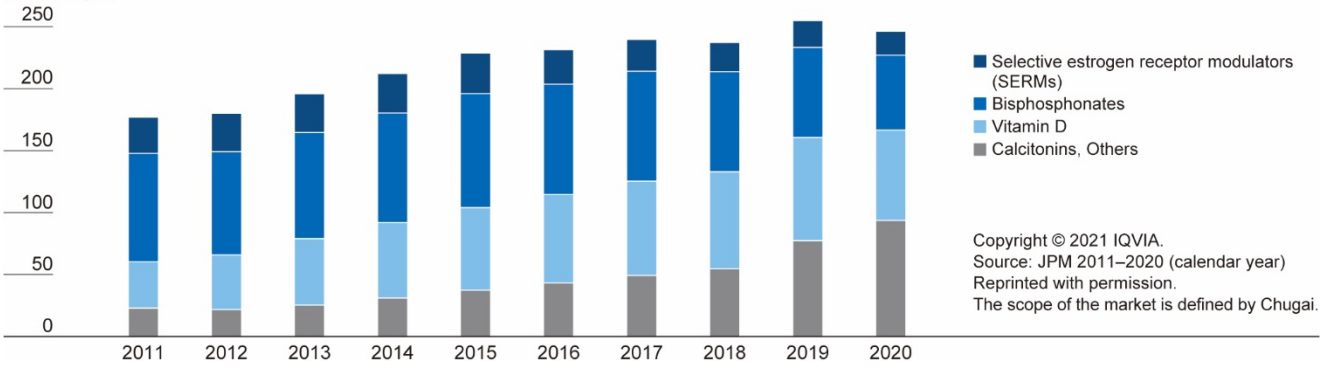
Osteoporosis drug therapies include active vitamin D_3 derivatives, which improve bone metabolism, bisphosphonates, which are bone resorption inhibitors, an anti-RANKL antibody, selective estrogen receptor modulators (SERMs), human parathyroid hormone (PTH), which is a bone formation agent, anti-sclerostin antibodies, and calcitonins.

Regulatory Trends

National prevention and treatment guidelines for osteoporosis were revised in October 2006. Subsequently, advances have been made in basic and clinical research into osteoporosis; evaluation of fracture risk and criteria for the initiation of drug treatment have been reviewed; and osteoporosis caused by lifestyle-related diseases has been addressed. In the interim, Edirol and other medicines have been approved for insurance coverage. Revisions issued in December 2011 added preventive and diagnostic items in light of the importance of early prevention to broaden the overall scope of osteoporosis treatment. Since then, the 2012 revised Diagnostic Criteria for Primary Osteoporosis and Management and Treatment Guidelines of Steroid-induced Osteoporosis have been adopted. Bonviva IV Injection and other medicines have been launched and covered by insurance, and revised guidelines were issued in July 2015.

Recently, an osteoporosis liaison service (OLS) initiated by the Japan Osteoporosis Society was introduced for the purpose of preventing osteoporosis and inhibiting bone fractures by coordinating the efforts of various healthcare professionals, including doctors, nurses, pharmacists, and physical therapists. Medical staff involved in liaison and possessing extensive knowledge related to osteoporosis are called osteoporosis managers. This education program has been ongoing since 2012, and approximately 3,600 osteoporosis managers were active as of April 2020.

Osteoporosis Market in Japan



Edirol (In-house development)

Active vitamin D_3 derivative
(Generic name: eldecalcitol)
Launch in Japan: April 2011

Edirol, a vitamin D_3 preparation born out of Chugai's many years of research in vitamin D, is an agent that improves bone metabolism in addition to calcium metabolism. Chugai started sales of Edirol in April 2011 as the successor drug to Alfarol for the indication of osteoporosis. Under an agreement signed in May 2008, Edirol was co-developed and co-marketed with Taisho Pharmaceutical Co., Ltd. Clinical trials have confirmed that Edirol has a similar safety profile to alfacalcidol with a statistically significant greater effect in preventing fractures. In the 2015 osteoporosis prevention and treatment guidelines, Edirol received a Grade A recommendation, the only one for an active vitamin D_3 derivative, for its effectiveness in increasing bone density and preventing vertebral fractures. The marketing alliance with Taisho Pharmaceutical terminated on April 10, 2021.

Review of 2020 Performance

Sales of Edirol decreased ¥8.9 billion, or 24.3 percent, year on year to ¥27.8 billion. Performance was impacted by the temporary reduction in medical consultations caused by the COVID-19 pandemic and by intensified competition due to the launch of generics.

In December 2020, Edirol received approval for the treatment of osteoporosis in China. Chugai is promoting its appropriate use by alerting to hypercalcemia as an adverse reaction.

Bonviva

Bisphosphonate anti-resorptive agent
(Generic name: ibandronate)
Launch in Japan: August 2013

Bonviva is a bisphosphonate in-licensed from Roche. Bonviva IV Injection was launched in August 2013. Under an agreement signed in September 2006, Bonviva is being co-developed and co-marketed with Taisho Pharmaceutical. Bonviva IV Injection can be given as a rapid intravenous injection once a month, and

thus may significantly reduce the burden on patients. It is also expected to benefit patients who have difficulty taking oral formulations or who tend to forget to take their medication. In addition, Bonviva Tablet, a once-monthly oral formulation, demonstrated non-inferiority to Bonviva IV Injection in a phase III clinical trial, and Chugai began sales in April 2016. By enabling drug selection according to patient lifestyle, monthly Bonviva IV Injection and Bonviva Tablet are expected to help improve patient adherence, convenience for healthcare providers, and the rate of continuation of treatment.

Review of 2020 Performance

Sales of Bonviva decreased ¥0.8 billion, or 8.2 percent, year on year to ¥8.9 billion, due partly to the reduction in medical consultations caused by the COVID-19 pandemic. The intravenous injection and oral formulations have the same high level of efficacy, and the ability to select the formulation according to the patient's condition has helped to differentiate Bonviva from other bisphosphonates.

Rheumatoid Arthritis/Osteoarthritis

Rheumatoid arthritis (RA) is a systemic disease characterized by painful inflammation and deformation of joints leading to dysfunction. Without appropriate treatment, the patient's condition deteriorates over time. There are currently an estimated 700,000 to 800,000 patients in Japan suffering from RA, of whom some 330,000 are currently receiving drug treatment. The aging of the patient population has also become a problem in recent years. On the other hand, there are about 8,000 patients in Japan with juvenile idiopathic arthritis (JIA), a form of RA suffered by children under 16 years of age.

Treatment Methods and Market Conditions

In drug therapy for RA, the introduction of biologics has made high remission rates a realistic treatment goal. Research in recent years suggests that the administration of biologics at the early onset stage is effective in inhibiting bone and joint damage. The global market for these agents is forecast to reach U.S.$56.7 billion[9] by 2024. The continuing change in the market is illustrated by the launch in the United States and Japan in 2013 of biological DMARDs, a new class of oral drugs, and the launch of biosimilars in Japan in 2014 following their earlier release in Europe. Actemra and other drugs are greatly expanding the therapeutic options for RA.

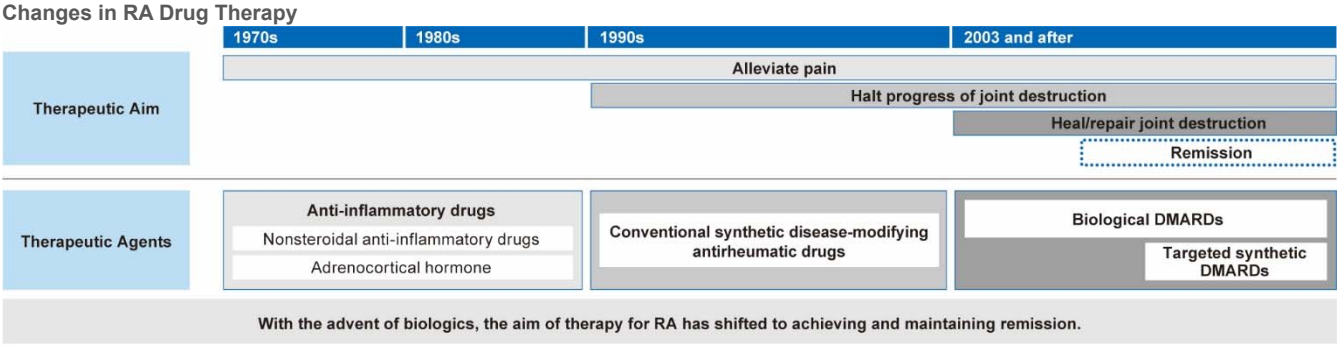
Systemic juvenile idiopathic arthritis (sJIA) accounts for 30 to 40 percent of all JIA cases, but steroids, the main treatment for sJIA, can cause growth impairment and other adverse reactions. Consequently, Actemra, approved for the additional indication of sJIA in April 2008, has provided a significant advance in therapy.

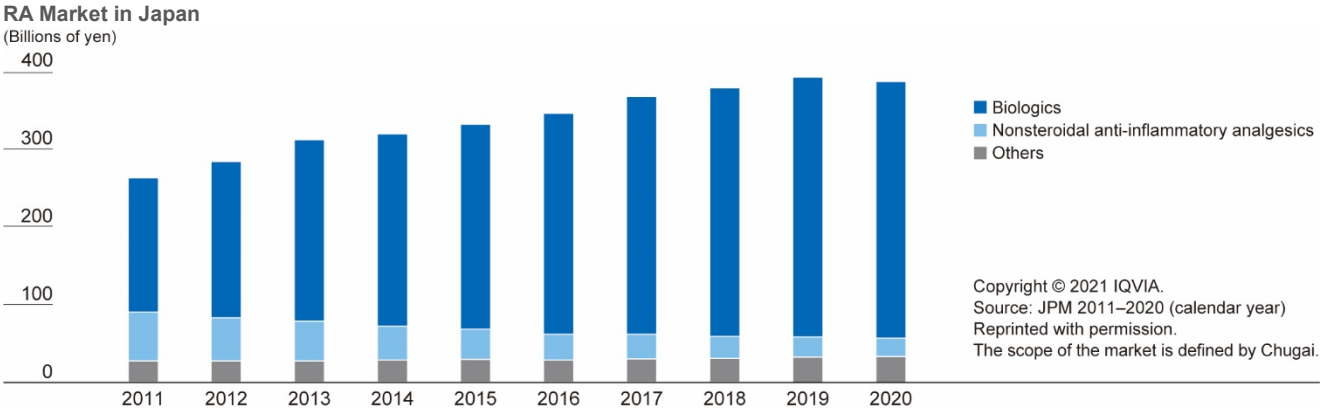
9. Source: Evaluate Pharma

Regulatory Trends

In November 2018, the MHLW released an update of the Report of the Rheumatism and Allergy Countermeasure Committee, which was previously issued in 2005 and 2011. To maximize long-term QoL of RA patients through appropriate treatment that controls disease activity, and to provide comprehensive support in daily life at workplaces and schools, and for life events such as pregnancy and childbirth, the report calls for (1) enhancement of medical service systems, (2) improvement of the patient environment, including consultation opportunities and access to information, and (3) promotion of research and development and other activities. In Europe, revised treatment recommendations in 2013 added Actemra and Abatacept to the biologic drugs recommended in first-line therapy, which were previously limited to anti-TNF agents. In 2015, a proposed update of clinical practice guidelines was announced at the American College of Rheumatology, with biologics including Actemra added as first-line therapy along with anti-TNF agents. Moreover, the updated European League Against Rheumatism (EULAR) recommendations that were announced in June 2016 state the superiority of interleukin-6 (IL-6) inhibitor therapy over other biologics in cases where MTX and other therapies cannot be used. In Japan, April 2021 saw the release of the Guidelines for the Management of Rheumatoid Arthritis, Japan College of Rheumatology 2020, which recommend regimens to reflect the advances in drug therapies of recent years and other factors such as Japan's falling birth rate and aging population.

Changes in RA Drug Therapy





Castleman's Disease

Castleman's disease is a lymphoproliferative disease characterized by symptoms such as systemic lymphadenopathy, fever, and general fatigue, as well as various abnormal laboratory test values including anemia, hypergammaglobulinemia, and hypoalbuminemia. It has been confirmed that these manifestations result from the excessive production of IL-6, one of the cytokines that causes inflammation. Castleman's disease is very rare, affecting approximately 1,500 people in Japan.

Large-Vessel Vasculitis

Large-vessel vasculitis belongs to a group of autoimmune diseases called vasculitis syndromes. It refers to vasculitis in the aorta and the major aortic branches to the limbs and head and neck, and includes Takayasu arteritis and giant cell arteritis (temporal arteritis).

Takayasu arteritis leads to inflammation of the aortic arch and its branch vessels. It affects women more than men, at a ratio of 9:1, and age of onset is between 20 and 50 years. It occurs most commonly in Asia, including Japan, and the Middle East. Initial symptoms are reduced head and cerebral blood flow related conditions, primarily dizziness, lightheadedness and headaches, as well as neck pain, chest pain, and vascular pain along the limb arteries.

Giant cell arteritis is a granulomatous vasculitis occurring primarily in the aorta and aortic branches, mainly the temporal arteries. It also affects women more than men, at a ratio of 1.6:1, and the age of onset is 55 years or older. It occurs most commonly in Western countries and is rare in Japan. Common initial symptoms include headache, systemic conditions such as fever, and loss of vision.

Adult Still's Disease

Adult Still's disease is an autoimmune disease that typically presents with a high spiking fever, aching joints, and a light-pink rash. Leukocytosis, increased C-reactive protein (CRP) levels, and elevated erythrocyte sedimentation rates are frequently observed in laboratory findings. Inflammation suppression with corticosteroids is the standard therapy, but until recently, no drug covered by the NHI was available for steroid-resistant patients.

Interstitial Lung Disease Associated with SSc

Systemic sclerosis (SSc), also known as scleroderma, is a progressive and potentially life-threatening disease. It is estimated to affect approximately 138,000 people worldwide, but with large regional differences in incidence. In SSc, abnormalities in the immune system cause fibrosis of the skin and various other organs. Of the organ damage accompanying SSc, interstitial lung disease (ILD) is the most frequently occurring and is the main cause of death related to SSc. ILD is a broad term covering more than 200 widely varying rare lung syndromes. ILD is characterized by coughing, shortness of breath, and other common symptoms, but the causes, treatment, and prognosis differ widely.

Actemra (MRA/RG1569) (In-house development)

Humanized anti-human IL-6 receptor monoclonal antibody
(Generic name: tocilizumab)
Launch in Japan: June 2005

Actemra, created by Chugai and the first therapeutic antibody originating in Japan, blocks the activity of IL-6, a type of cytokine. It was launched in Japan in June 2005 as a treatment for Castleman's disease. In April 2008, Chugai obtained approval in Japan for the additional indications of RA, polyarticular juvenile idiopathic arthritis (pJIA), and sJIA. In May 2013, Chugai launched a new subcutaneous formulation in addition to the existing intravenous infusion formulation with the aim of improving convenience. This subcutaneous formulation includes the first auto-injector in the Japanese RA market.

Actemra is marketed globally through Roche. In Europe, where the medicine is known as RoActemra, sales for the treatment of RA started in 2009. Chugai's marketing subsidiary co-promotes RoActemra with Roche in the United Kingdom, France, and Germany. In the United States, Actemra obtained approval in January 2010 for the treatment of adult patients with moderate to severe active RA who have had an inadequate response to one or more anti-TNF agents, and obtained approval in October 2012 as a first-line biologic treatment. In Taiwan and South Korea, where Chugai has marketing rights, Actemra obtained approval in July 2011 and April 2012, respectively. Following its launch in Japan, the subcutaneous formulation obtained approval in the United States in October 2013 and in Europe in April 2014, and has been launched in both markets. RoActemra was also approved for early RA in Europe in September 2014.

Furthermore, Actemra obtained approval for the additional indication of treatment of sJIA in the United States in April 2011 and in Europe in August 2011. Actemra also received breakthrough therapy designation from the U.S. FDA in 2016 for giant cell arteritis. In Japan, it became possible in June 2017 to reduce the dose interval of Actemra from two weeks to one week in patients with an inadequate response to use of the subcutaneous formulation for RA. Actemra obtained approval in Japan for the additional indications of Takayasu arteritis and giant cell arteritis in August 2017, and in the United States, in

November 2018 an autoinjector obtained approval as an additional formulation for the treatment of RA, giant cell arteritis, sJIA, and pJIA. Actemra also obtained approval in the United States in August 2017 and in Europe in August 2018 for the additional indication of chimeric antigen receptor (CAR) T-cell-induced cytokine release syndrome, and in Japan in March 2019 for the additional indication of cytokine release syndrome induced by tumor-specific T-cell infusion therapy. In May 2019, Chugai obtained approval for the additional indication of adult Still's disease where existing treatments provide insufficient efficacy.

In February 2020, Actemra obtained approval in the United States for the additional indication of interstitial lung disease associated with SSc.

Review of 2020 Performance

Sales of Actemra in Japan decreased ¥2.5 billion, or just 6.0 percent, year on year to ¥39.3 billion. This was despite an 18.5 percent price reduction due to repricing based on market expansion. Sales levels were maintained by the growth in new prescriptions for RA and by the strong performance of the subcutaneous formulation, which accounted for more than 60 percent of the total, following its approval for additional dosage and administration options with shorter dose interval and for the additional indications of Takayasu arteritis and giant cell arteritis.

Overseas sales of Actemra (including exports to Roche) increased ¥46.1 billion, or 52.2 percent, year on year to ¥134.4 billion on increased demand due to the COVID-19 pandemic. Roche's global sales also expanded by a considerable 30 percent.

RG7880 Development project
Human IL-22 fusion protein
(Generic name: efmarodocokin alfa)
RG7880 is a human IL-22 fusion protein in-licensed from Roche. It is expected to demonstrate efficacy in treating inflammatory bowel disease by directly promoting the regenerative and protective functions of IL-22 in epithelial tissue. A phase I clinical trial began in July 2019.

Renal Diseases

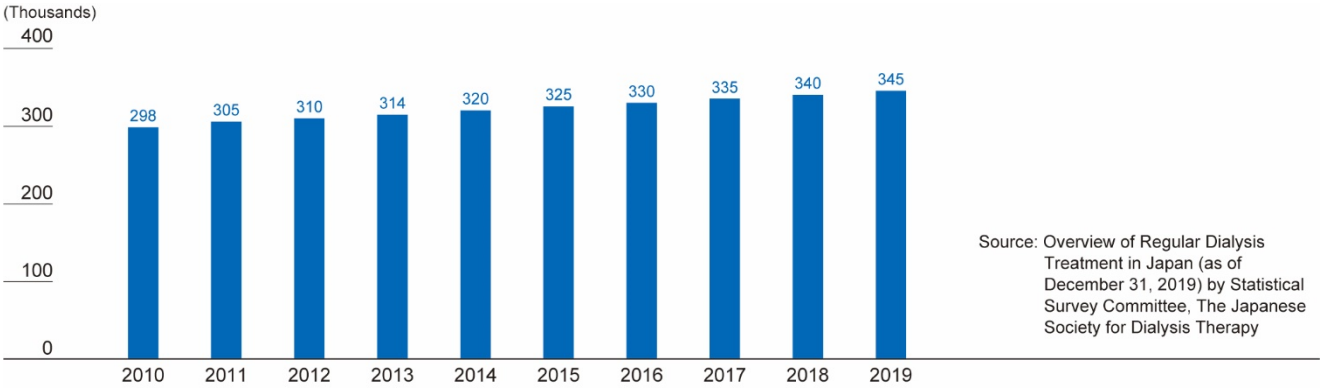
Renal Anemia

Complications of Renal Dysfunction

In dialysis patients and end-stage chronic kidney disease (CKD) patients, a key issue is treating the various complications of advanced renal dysfunction, such as renal anemia, secondary hyperparathyroidism, and abnormal calcium and phosphorus metabolism. Of these complications, renal anemia is one of the most frequent, occurring not only in renal disease patients undergoing dialysis but also in pre-dialysis CKD patients. Renal anemia is associated with reduced QoL, and is also a factor in the progress of organ damage, including decreased cardiac function and renal function.

The importance of treatment and the appropriate management of renal anemia and chronic kidney disease - mineral and bone disorder (CKD-MBD) were indicated in the Guidelines for Renal Anemia in Chronic Kidney Disease (2015) and the Clinical Practice Guidelines for the Management of CKD-MBD (2012) issued by the Japanese Society for Dialysis Therapy and in the Evidence-based Practice Guidelines for the Treatment of CKD (2018) issued by the Japanese Society of Nephrology.

Number of Dialysis Patients in Japan



Source: Overview of Regular Dialysis Treatment in Japan (as of December 31, 2019) by Statistical Survey Committee, The Japanese Society for Dialysis Therapy

ESA
Erythropoietin (EPO) is a hemopoietic factor produced mainly in the kidneys. It stimulates erythrocyte production by binding to EPO receptors on erythroid progenitor cells in bone marrow. An erythropoiesis-stimulating agent (ESA) is effective in treating renal anemia caused primarily by the decline in EPO production due to CKD, and is thought to help improve QoL. ESAs are currently used by approximately 80 percent of dialysis patients as well as by some predialysis CKD patients with renal anemia. ESAs are thus an essential drug for the treatment of renal anemia.

Flat-Sum Reimbursement System for ESAs
Since the 2006 revisions of medical fees, ESAs have been included in medical fee points for hemodialysis (artificial kidney). The integrated fee points are reviewed with each revision of medical fees, and were reduced in 2020, which has led to intensified price competition for ESAs in the dialysis market.

Mircera
Long-acting erythropoiesis-stimulating agent
(Generic name: epoetin beta pegol)
Launch in Japan: July 2011
Mircera is a drug that raises the stability of epoetin beta in the bloodstream through pegylation. It is a new type of renal anemia treatment with the longest serum half-life among ESAs, enabling stable and sustained control of anemia. It stimulates erythropoiesis through a different interaction with the EPO receptor on burst-forming unit erythroid (BFU-E) cells in the bone marrow. Mircera was launched in Japan in July 2011 as a treatment for renal anemia. Outside Japan, Mircera obtained approval in Europe in 2007 and is currently sold in more than 100 countries, including the United States.

The serum half-life of Mircera is virtually the same for intravenous or subcutaneous administration, and the drug demonstrates efficacy in relieving the symptoms of anemia when administered at four-week intervals during the maintenance period. Consequently, it is expected to reduce the burden of hospital visits on the aging population of patients with pre-dialysis CKD and to contribute to better treatment adherence. Furthermore, as a dialysis-related treatment, Mircera is expected to reduce the burden on medical staff and improve medical safety by dramatically reducing administration frequency, and is one of the options for the treatment of renal anemia.

Review of 2020 Performance
Sales of Mircera decreased ¥4.7 billion, or 21.2 percent, year on year to ¥17.5 billion. Despite its wide use in pre-dialysis CKD patients, it was impacted by the drug price revision and competition from authorized generics and biosimilars. There was also intensified price competition in the dialysis market after a medical fee revision that reduced the integrated fee points for hemodialysis (artificial kidney).

Others

Oxarol (In-house development)
Agent for secondary hyperparathyroidism
(Generic name: maxacalcitol)
Launch in Japan: September 2000
Originated by Chugai, Oxarol is the first intravenous active vitamin D_3 derivative agent in Japan. It treats secondary hyperparathyroidism, a result of conditions such as impaired vitamin D activation associated with renal dysfunction, by acting directly on the parathyroid gland to control parathyroid hormone synthesis and secretion, and by improving bone metabolic conditions. With its short serum half-life, Oxarol shows efficacy and enables treatment in patients who previously could not be treated adequately with oral active vitamin D_3 derivatives due to the onset of hypercalcemia.

Review of 2020 Performance
Sales of Oxarol, impacted by the market penetration of generics and the drug price revision, decreased ¥0.5 billion, or 7.2 percent, year on year to ¥6.4 billion.

EOS789 Development project (In-house development)
EOS789 is an oral drug created by Chugai with a molecular weight of over 500 g/mol. A phase I clinical trial of EOS789 for hyperphosphatemia has been completed.

Neurology

NMOSD
Neuromyelitis optica spectrum disorder (NMOSD) is a neurological autoimmune disorder characterized by severe optic neuritis and transverse myelitis. The disease affects 0.3 to 4.4 in 100,000 people, and there are about 4,000 patients in Japan. It is an incurable disease that typically appears around the age of 40 years and affects women more than men, at a ratio of 9:1. Symptoms include loss of vision (in some cases progressing to blindness) and impairment of motor function and sensation. In some cases, the disease results in death. NMOSD is an orphan disease with high unmet medical need. It is believed to occur mainly when aquaporin-4 (AQP4) in the central nervous system is attacked by autoantibodies called anti-AQP4 antibodies. Formerly, the diagnostic criteria of neuromyelitis optica (NMO) accompanied by optic neuritis and myelitis, and NMOSD accompanied by either optic neuritis or myelitis were proposed. Recently, however, it was proposed to reorganize and unify the definitions of both disorders under the term NMOSD. This term is now widely used to refer to a broader spectrum of disease.

Enspryng SA237/RG6168 (In-house development)
pH-dependent binding humanized anti-IL-6 receptor monoclonal antibody
(Generic name: satralizumab)
Launch in Japan: August 2020
Enspryng is a next-generation therapeutic antibody that has shown success in blocking IL-6 receptors with a longer duration of action. Chugai created Enspryng by applying its novel antibody engineering technology (Recycling Antibody engineering technology) that enables a single antibody molecule to block the target antigen repeatedly. As a result, a prolonged

serum half-life has been demonstrated in clinical trials, which will make a lower dosing frequency possible. Because IL-6 promotes the production of the anti-AQP4 antibodies that are the primary cause of NMOSD, this drug is expected to improve (reduce recurrence of) the symptoms of these diseases as it inhibits the production of those antibodies by blocking the IL-6 signal. Chugai has licensed exclusive rights to Roche for the development and marketing of Enspryng worldwide, with the exception of Japan and Taiwan. Enspryng has received orphan drug designation in Japan, the United States, and Europe. In the United States, it received breakthrough therapy designation for the treatment of NMOSD from the U.S. FDA in December 2018 and was approved in August 2020. It has now been approved in more than 10 countries including Japan, the United States, Canada, Switzerland, and Taiwan. In Europe, the marketing application was accepted by the European Medicines Agency in 2019.

Review of 2020 Performance
Enspryng achieved sales of ¥1.3 billion. The effects of the COVID-19 pandemic delayed its uptake by hospitals following its launch in Japan on August 26. It has however been introduced for certain patients, mainly those awaiting the development of a new drug because existing therapies (oral steroids and immunosuppressants) did not prevent recurrence and those in whom the existing therapies did control recurrence but were accompanied by side effects.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a lower motor neuron disease characterized by amyotrophy and progressive muscle weakness caused by degeneration of anterior horn cells in the spinal cord. The estimated number of patients in Japan is reported to be around 1,000. The disease is caused by a defect in the *SMN1* gene, and onset usually occurs in childhood. In severe cases it is fatal.

RG7916 Development project

SMN2 splicing modifier
(Generic name: risdiplam)

RG7916 is an SMN2 splicing modifier that increases generation of a protein derived from the *SMN2* gene. This protein is nearly identical to the protein made from the *SMN1* gene, which is not functional in SMA patients. RG7916 shows promise in improving neural and muscular function. Global phase II/III studies are under way, and RG7916 met its primary endpoint in the SUNFISH study in patients with Type 2 or 3 SMA and the FIREFISH study in patients with Type 1 SMA, respectively. RG7916 was granted PRIME designation by the European Medicines Agency in December 2018, and received orphan drug designation in Japan in March 2019. In October 2020, Chugai filed a regulatory application in Japan for RG7916 as the first oral therapy for SMA.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia. Pathologically, it is a progressive neurodegenerative disease that causes neuron death in the brain and brain atrophy. It leads to a general and progressive loss of memory and other cognitive functions, which can interfere with daily life. While existing AD treatments have some effect in slowing the progression of dementia symptoms, they do not slow pathological progress and are unable to stop neuron death, and a treatment for the underlying cause does not yet exist. Consequently, unmet medical needs are high, and there is strong demand for a more effective drug.

RG1450 Development project

Anti-amyloid-beta human monoclonal antibody
(Generic name: gantenerumab)

RG1450 targets aggregate amyloid beta, with a high binding affinity to plaques in particular. It is expected to reduce cognitive deterioration by removing amyloid beta in the brain. Global phase III studies of RG1450 for AD began in June and July 2018.

RG6100 Development project

Anti-tau humanized monoclonal antibody
(Generic name: semorinemab)

RG6100 binds to tau proteins found in the extracellular space of the brain, and is expected to slow the deterioration of cognitive functions in AD by halting the propagation of tau via neurons. A phase I clinical trial for AD began in April 2019.

Huntington's Disease

Huntington's disease is an intractable, progressive neurodegenerative disease that causes nerve cells in the brain to break down. Characterized mainly by involuntary movements (most commonly chorea), neuropsychiatric symptoms, and dementia, this disease profoundly affects the lives of affected individuals. As the disease progresses, people with Huntington's disease may develop walking and swallowing difficulties, personality changes and loss of cognitive functions.

The prevalence of Huntington's disease varies by ethnicity and geographical location. It is reported to affect 4 to 8 out of every 100,000 people in Western countries, but in Japan it is a rarer disease, affecting 0.7 out of every 100,000 people, about 1/10 the rate in Western countries. Existing drug therapies treat chorea and other involuntary movements, as well as neuropsychiatric symptoms, but a treatment for the underlying cause does not yet exist.

RG6042 Development project

Antisense oligonucleotide (ASO) targeting
human huntingtin messenger ribonucleic acid (*HTT* mRNA)
(Generic name: tominersen)

RG6042 is an ASO targeting human *HTT* mRNA, which is believed to be the cause of Huntington's disease. It has the potential to delay or slow disease progression in people with Huntington's disease by binding specifically to *HTT* mRNA, after which synthesis of the HTT protein is inhibited. A global phase III study began in March 2019. RG6042 has received orphan drug designation as a treatment for Huntington's disease in Japan, the United States, and Europe, and was granted PRIME designation by the European Medicines Agency in 2018.

Schizophrenia

Schizophrenia, a psychiatric disorder characterized by hallucination and delusion, occurs with high frequency, affecting just under one in 100 people. The symptoms are associated with impairment of daily life, affecting the ability to interact with others and conduct a family and social life, and impaired awareness of the illness, so that patients tend to be unable to recognize in retrospect that their perceptions, thoughts, and actions are distorted by the disease. As with many psychiatric disorders, it frequently develops chronically, with acute phases marked by more intense hallucinations and delusions. The development of new drugs and advances in psychosocial care mean that almost half of initially diagnosed patients can now be expected to make a full recovery or experience long-term remission (WHO 2001). The condition was previously sometimes referred to as "split personality disorder," but in Japan the official medical term was changed in 2002 to "schizophrenia."

RG7906 Development project
Partial TAAR1 agonist
(Generic name: ralmitaront)
RG7906 has the novel pharmacological action of working as a partial agonist of trace amino-associated receptor Type 1 (TAAR1). In August 2019, it completed a phase I clinical study in Japan in which a good safety profile was confirmed. Global phase II studies for schizophrenia began in February 2020.

Parkinson's Disease
Parkinson's disease is a progressive neurodegenerative disease characterized by aggregation of α-synuclein in the central nervous system and peripheral nervous system. A wide range of motor symptoms (tremor, muscle rigidity, akinesia, impairment of postural reflexes, etc.) and non-motor symptoms (sleep disorders, autonomic dysfunction, cognitive and mental disorders, etc.) occur. The estimated number of patients in Japan is 200,000. A progressive disease seen mainly in people age 50 or older, it can lead to becoming bedridden as the condition worsens.

RG7935 Development project
Anti-α-synuclein monoclonal antibody
(Generic name: prasinezumab)
RG7935 is a monoclonal antibody that targets α-synuclein. It slows the expansion of nerve cell death by inhibiting the cell-to-cell propagation of aggregated forms of neurotoxic α-synuclein, and is expected to reduce and delay progression of the disease. In a phase I clinical trial that began in 2018, RG7935 demonstrated good tolerability, and there were no significant racial differences in pharmacokinetics.

Neuromuscular Disease

GYM329/RG6237 Development project (In-house development)
Anti-latent myostatin sweeping antibody
GYM329, created by Chugai, is a next-generation antibody that applies Chugai's proprietary antibody engineering technologies, including its recycling antibody and sweeping antibody technologies. Latent myostatin is an inactive form that is mainly secreted from muscle cells, and is activated by BMP-1 and other protein degrading enzymes. Activated myostatin inhibits muscle growth and hypertrophy, and by inhibiting myostatin, GYM329 is expected to improve the various conditions associated with muscle atrophy and loss of muscular strength. Currently under development for neuromuscular disease, this antibody began a phase I clinical trial in October 2018. Chugai out-licensed GYM329 to Roche at an early stage before the start of clinical trials in order to accelerate global development by taking advantage of Roche's experience and expertise.

Other Diseases

COVID-19
Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus SARS-CoV-2. The main symptoms of COVID-19 are fever, cough, fatigue, and breathing difficulties. Many of those infected recover after only mild symptoms, but some experience rapid deterioration and develop pneumonia. These patients may need to be hospitalized for oxygen administration and artificial ventilation and some experience a fatal outcome.

Actemra (MRA/RG1569) (In-house development)
Humanized anti-human IL-6 receptor monoclonal antibody
(Generic name: tocilizumab)
Actemra, created by Chugai and the first therapeutic antibody originating in Japan, acts to inhibit the inflammatory cytokine IL-6. Sales were launched in Japan in June 2005, with the intravenous infusion formulation approved for RA and five further indications (Castleman's disease, sJIA, pJIA, cytokine release syndrome induced by tumor-specific T-cell infusion therapy, and adult Still's disease) and the subcutaneous formulation for three indications (RA, Takayasu arteritis, and giant cell arteritis). Approval has currently been obtained in more than 110 countries worldwide.

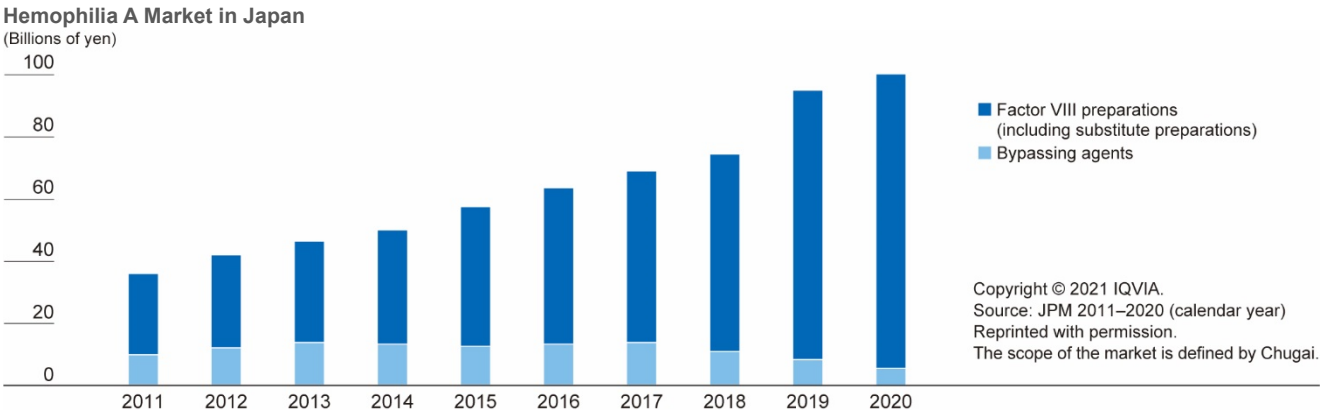
Outside of Japan, the phase III COVACTA clinical study in COVID-19-associated pneumonia led by Roche did not meet both the primary endpoint of improvement in clinical status and the key secondary endpoint of reduced mortality rate. The EMPACTA clinical study, which focused on minority patients with insufficient access to medical services, achieved its primary endpoint, with Actemra administration reducing the likelihood of mechanical ventilation being needed.

A single-arm phase III J-COVACTA clinical study was conducted in Japan. Of the 48 patients treated with Actemra, 35 (72.9 percent) had been discharged from the hospital or were ready to be discharged at 28 days after the start of Actemra administration, while 5 (10.4 percent) experienced fatal outcome.

For information on development for other indications and sales performance, including for COVID-19-associated pneumonia, please refer to the Bone and Joint Diseases/Autoimmune Diseases section above.

Hemophilia
Hemophilia is a disease that leads to bleeding in the joints, muscles, and other areas in the body due to a congenital deficiency or abnormal function of blood coagulation factors. A low level or absence of blood coagulation factor VIII is known as hemophilia A, while a low level or absence of blood coagulation factor IX is referred to as hemophilia B. Treatment of hemophilia A is centered on replacement therapy to supplement factor VIII. However, since it involves intravenous injections one to three times a week, treatment is a significant burden, particularly on children. Moreover, patients must be monitored for the development of autoantibodies, called inhibitors, to the supplemented factor. Patients with inhibitors are treated by means such as bypass therapy or immune tolerance therapy, but these therapies are limited in terms of convenience and the stability of their effects. A more useful treatment method is therefore needed.

Meanwhile, the autoimmune disease where patients develop autoantibodies to factor VIII is known as acquired hemophilia A. Acquired hemophilia A is associated with more frequent serious hemorrhage than the congenital form, and immunosuppressant therapy to eliminate the autoantibodies raises the risk of infectious diseases, making this a disease with poor prognosis.



Hemlibra (ACE910/RG6013) (In-house development)

Anti-coagulation factor IXa/X humanized bispecific monoclonal antibody
(Generic name: emicizumab)
Launched in Japan: May 2018

Hemlibra is a bispecific antibody that employs Chugai's innovative antibody engineering technologies. Like factor VIII, which is low or missing in hemophilia A, Hemlibra simultaneously binds to factor IXa and factor X, stimulating the activation of factor X by activated factor IX and promoting normal blood coagulation for hemostasis. Unaffected by inhibitors, Hemlibra can prevent bleeding with subcutaneous injections once a week, once every two weeks, or once every four weeks, and is promising as a drug that can change the existing system of treatment. Another key feature is that Chugai's proprietary technology ART-Ig is applied to Hemlibra, enabling industrial production of bispecific antibodies.

Chugai concluded an out-licensing agreement with Roche in July 2014 and in May 2017 entered into a license agreement with JW Pharmaceutical Corporation for the exclusive marketing rights in South Korea. The drug received breakthrough therapy designation from the U.S. FDA in September 2015 for its potential to prevent bleeding in hemophilia patients with inhibitors, and in April 2018 for its potential to prevent bleeding in patients without inhibitors. In the United States, Hemlibra received priority review designation in August 2017, and in November 2017 obtained approval for routine prophylaxis with once-weekly subcutaneous administration in adult and pediatric patients with hemophilia A with factor VIII inhibitors. Hemlibra was also granted accelerated assessment in Europe, and received regulatory approval from the European Commission in February 2018. In Japan, it obtained approval in March 2018 and was launched in May 2018. It also obtained approval in Taiwan in December 2018 and was launched there in November 2019.

Applications were filed in the United States, Europe, and Japan in April 2018, and in Taiwan in January 2019, for routine prophylaxis of bleeding episodes, as well as for additional dosage and administration as a biweekly or four-weekly treatment, for people with hemophilia A without inhibitors. In the United States, Hemlibra was granted priority review status in June 2018, and in October 2018, it obtained approval for prophylactic treatment by subcutaneous administration once weekly, every two weeks, or every four weeks in adults or children with hemophilia A without inhibitors, as well as additional dosing options of every two weeks or every four weeks in adults and children with hemophilia A with inhibitors. Hemlibra also obtained approval in Japan in December 2018, and in the EU in March 2019.

Chugai also began a phase III clinical study for the treatment of acquired hemophilia A in June 2020.

Review of 2020 Performance

Sales of Hemlibra increased ¥8.9 billion, or 35.3 percent, year on year to ¥34.1 billion. Due to repricing based on market expansion, the NHI drug price was reduced by 15 percent in April 2020. Hemlibra achieved good market penetration in non-inhibitor patients driven by its differentiated mode of action from factor VIII agents and longer half-life. However, as the impact of the COVID-19 pandemic slowed down the switch to Hemlibra, performance remained below expectations.

NXT007 Development project (In-house development)

Anti-coagulation factor IXa/X bispecific antibody

NXT007, created by Chugai, is a bispecific antibody that stimulates blood coagulation using the same mode of action as Hemlibra. One difference from Hemlibra is the application of Chugai's antibody engineering technologies FAST-Ig, which enhances large-scale production of the bispecific antibody and ACT-Fc, which is expected to improve antibody pharmacokinetics. NXT007 is expected to achieve the levels of hemostasis found in healthy adults and children, and is being developed to improve convenience, including the administration device. A phase I/II clinical trial for hemophilia A began in August 2019.

Influenza

Influenza is an acute infectious disease characterized by the rapid onset of high fever (38 degrees centigrade or higher) and severe systemic symptoms. It is highly infectious, and epidemics can develop quickly. In some cases, secondary infections can lead to very serious illness and death. Influenza is classified into types A, B, and C based on differences in the antigenicity of the underlying virus. Types A and B can infect humans and cause major outbreaks.

Tamiflu

Anti-influenza agent
(Generic name: oseltamivir)
Launch in Japan: February 2001

Tamiflu is an oral anti-influenza agent that is effective against both type A and type B infections. It inhibits viral replication by blocking the action of neuraminidase, an enzyme essential for the multiplication of the influenza virus. Launched in capsule form in February 2001 and dry syrup form in July 2002, dosages are available for patients one year of age and older. From March 2007, restrictions on the use of Tamiflu in teenage patients with seasonal influenza were in force in Japan. The measure was

introduced as a safety precaution following several reports of abnormal behavior in influenza patients who had taken Tamiflu. In May 2018, the Subcommittee on Drug Safety of the MHLW confirmed that abnormal behavior occurs regardless of whether anti-influenza drugs have been given, and in July 2018, the same subcommittee decided that the restrictions should be removed. Accordingly, the package insert was revised and restrictions on the use of Tamiflu in teenage patients were removed in August 2018.

The shelf life of Tamiflu capsules was extended to 10 years from seven years for capsules manufactured after July 2013, and the shelf life of Tamiflu dry syrup was extended to 10 years starting with the portion shipped in 2015. In March 2017, Chugai obtained approval for additional dosage and administration of Tamiflu dry syrup for neonates and infants younger than 12 months.

Review of 2020 Performance
Ordinary sales of Tamiflu decreased ¥6.6 billion, or 89.2 percent, to ¥0.8 billion, while sales for government stockpiles were ¥3.7 billion. Not only was the spread of influenza in the January to March period of the 2019-20 season very limited in scale, but the 2020-21 season had seen no outbreak at all as of the end of December 2020. Sales performance therefore remained far below expectations.

Others

CellCept
Immunosuppressant
(Generic name: mycophenolate mofetil)
Launch in Japan: November 1999
Sales of CellCept decreased ¥0.2 billion, or 2.2 percent, to ¥9.1 billion. CellCept is used to treat refractory rejection after kidney transplants and to prevent rejection after kidney, heart, liver, lung, and pancreas transplants. The need for transplantation medication has been rising in Japan, driven by advances in transplantation therapy. In May 2016, CellCept received approval for the indication of lupus nephritis, a refractory disease associated with the autoimmune disease systemic lupus erythematosus.

Atopic Dermatitis
A type of allergic disorder, atopic dermatitis is a chronic skin disease characterized by an itchy rash that alternately improves and worsens. Scratching the affected area exacerbates the skin symptoms and makes the itching worse, leading to an itch-scratch cycle. The basic treatment is drug therapy using topical steroid preparations and/or immunosuppressants to control the inflammation and a skin care regimen to prevent the inflammation from recurring.

Prurigo Nodularis
Prurigo nodularis is a chronic skin disorder that causes thick papules or nodules accompanied by intensive itching. Patients with prurigo nodularis worry that the severe itching will interfere with their daily lives. The cause of prurigo nodularis is not yet fully understood, and control of the symptoms is difficult, and thus an effective treatment is needed.

CIM331 Development project (In-house development)
Anti-IL-31 receptor A humanized monoclonal antibody
(Generic name: nemolizumab)
Nemolizumab (CIM331) is an anti-IL-31 receptor A humanized monoclonal antibody originating from Chugai. The drug is expected to improve itching and skin inflammation in atopic dermatitis by blocking IL-31, a proinflammatory cytokine, from binding to its receptor.

In July 2016, Chugai entered into a global license agreement granting Galderma S.A. of Switzerland exclusive rights for the development and marketing of nemolizumab worldwide, with the exception of Japan and Taiwan. In September 2016, Chugai entered into a license agreement granting Maruho Co., Ltd., the rights for the development and marketing of nemolizumab in the skin disease area for the Japanese market. In development for atopic dermatitis, Maruho, filed an approval application in Japan in the third quarter of fiscal 2020, while Galderma initiated global phase III studies in 2019. In addition, nemolizumab was granted breakthrough therapy designation by the U.S. FDA for pruritus associated with prurigo nodularis. Galderma launched a phase III clinical study for the treatment of prurigo nodularis in October 2020, while Maruho, started phase II/III clinical studies in Japan in December 2020.

Paroxysmal Nocturnal Hemoglobinuria
Paroxysmal nocturnal hemoglobinuria (PNH) is a disorder that leads to complications such as thrombosis and CKD, in addition to anemia and dark brown urine caused by hemolysis as well as infections and bleeding tendency associated with a decrease in white blood cells and platelets. It is an acquired genetic disorder that affects hematopoietic stem cells, causing the creation of red blood cells that have no complement resistance, and hemolysis occurs when complements are activated in vivo. Although the estimated number of people affected is small, with 764 in Japan (based on the number of holders of specific medical expense recipient certificates for designated intractable diseases as of the end of fiscal 2018), and around 5,000 worldwide, it is a progressive disease with a high mortality risk.

SKY59/RG6107 Development project (In-house development)
Anti-C5 recycling antibody
(Generic name: crovalimab)
SKY59 is a recycling antibody discovered by Chugai that inhibits the C5 complement component.

The onset of a number of diseases is reported to be caused by complement activation. SKY59 is expected to inhibit cleavage of C5 to C5a and C5b, thus suppressing complement activation and improving disease conditions. In PNH, SKY59 may have a suppressive effect on hemolysis by preventing the destruction of red blood cells. Application of multiple Chugai proprietary antibody engineering technologies resulted in a prolonged half-life, and the antibody is being developed as a subcutaneous self-injection. Due to the severity of the disease, regular administration is necessary, but making self-injection possible is expected to lessen the burden on patients by reducing the frequency of hospital visits. In September 2020, Chugai launched a global phase III study for the treatment of PNH in co-development with Roche. In September 2017, SKY59 received orphan drug designation in the United States for PNH.

wAMD/DME
Wet age-related macular degeneration (wAMD) is a disease in which abnormal blood vessel growth (choroidal neovascularization) caused by age-related accumulation of waste products extends into the space under the retinal pigment epithelium (RPE) or between the retina and the RPE, leading to retinal tissue damage. If the choroidal neovascularization and the associated effusion progress into the fovea centralis, which

governs vision, it may lead to deterioration of visual acuity along with the symptoms of image distortion, vision loss, and central scotoma. Left untreated, wAMD may lead to irreversible visual impairment.

Diabetic macular edema (DME) is a retinal disease associated with diabetic retinopathy. In diabetes, consistently high blood sugar causes blockage of retinal capillaries, ischemic change, and edema induced by vascular hyperpermeability. Blurred vision occurs when swelling extends to the central part of the macula, which governs vision. Left untreated, DME may lead to irreversible visual impairment.

RG7716 Development project

Anti-VEGF/Ang-2 bispecific antibody
(Generic name: faricimab)

RG7716, which Chugai in-licensed from Roche, is the first bispecific antibody for ophthalmology diseases. It selectively binds to vascular endothelial growth factor A (VEGF-A), a key mediator of angiogenesis and vascular permeability, and angiopoietin-2 (Ang-2, an antagonist of Ang-1, which contributes to the stability of mature vessels), a destabilizer of chorioretinal vessels and inducer of vascular permeability. By simultaneously neutralizing intraocular VEGF-A and Ang-2 in wAMD and DME patients, RG7716 is expected to demonstrate better treatment outcomes and a more sustained effect than the anti-VEGF drugs that are the current standard of care. Two global phase III studies for the treatment of DME achieved their primary endpoints in December 2020, as did two global phase III studies for the treatment of wAMD in January 2021.

Endometriosis

Affecting one out of 10 women in their twenties to forties, endometriosis is the repeated proliferation and shedding of endometrial tissue outside the uterus, accompanied by dysmenorrhea and chronic lower abdominal pain, and is a cause of infertility. The disease can interfere with daily life, including absences from work or school, as sufferers find it difficult to do more than lie still when symptoms are severe. The only existing medications are hormonal agents. Moreover, if the pain cannot be controlled by drugs, the only treatment is surgical removal, and many patients experience a recurrence several years after surgery, making this a disease with a high level of unmet medical needs.

AMY109 Development project (In-house development)

AMY109 is the third therapeutic antibody to apply the recycling antibody engineering technology created by Chugai. Its approach differs from hormone therapy, which is the standard treatment for endometriosis, and its anti-inflammatory action is expected to provide new value to patients. A phase I clinical trial started in February 2018.

Type 2 Diabetes

Type 2 diabetes is an illness in which genetic predisposition and lifestyle cause impaired insulin secretion and resistance to insulin action, resulting in high plasma glucose concentration. There are no symptoms in the early stages, but if the condition is left untreated, the risk of cardiovascular diseases such as stroke and myocardial infarction increases. The disease can also cause complications such as retinopathy, nephropathy, and neuropathy, which lead to blindness, dialysis, and leg amputation, respectively, significantly reducing QoL. According to the International Diabetes Federation, the number of people with diabetes worldwide, including prediabetes, is 463 million in 2019, and is projected to increase to 700 million in 2045. Treatment of this condition is thus a worldwide issue.

OWL833 Development project (In-house development)

OWL833 is an oral non-peptidic GLP-1 receptor agonist created by Chugai. GLP-1 agonists have potent hypoglycemic action and induce weight loss, but convenience for patients has been an issue because they are conventionally administered in a subcutaneous injection. Because OWL833 is orally bioavailable, it is easier for patients to take, and is thus expected to contribute to the treatment of diabetes, including through improvement of drug adherence. In September 2018, Chugai licensed the worldwide development and commercialization rights for OWL833 to Eli Lilly and Company. A phase I clinical study by Eli Lilly is under way.