



KAKEN PHARMACEUTICAL CO., LTD.

R&D Briefing Session

December 10, 2025

Event Summary

[Company Name]	KAKEN PHARMACEUTICAL CO., LTD.	
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[Event Name]	R&D Briefing Session	
[Fiscal Period]		
[Date]	December 10, 2025	
[Number of Pages]	42	
[Time]	13:30 – 14:49 (Total: 79 minutes, Presentation: 44 minutes, Q&A: 35 minutes)	
[Venue]	Kaken Pharmaceutical Head Office/Webcast	
[Number of Speakers]	6	
	Horiyuki Horiuchi	President and Representative Director
	Mitsuru Watanuki	Director, Chief Officer of R&D Division
	Tatsuhiko Harada	Corporate Officer, Deputy Chief Officer of R&D Division, Chief of Drug Research Center
	Yasutomi Kato	General Manager of Research and Development Planning & Project Management Department
	Hideki Kawabata	Head of Clinical Development department
	Gaku Kametsu	General Manager of Corporate Communications Department
[Analyst Names]*	Jaeheon Lee	Morgan Stanley MUFG Securities
	Kazuaki Hashiguchi	Daiwa Securities
	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Kota Maeda	Nomura Securities
	*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.	

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Presentation

Kametsu: Now that our time has come, we would like to open the KAKEN PHARMACEUTICAL CO., LTD. R&D Briefing Session. Thank you very much for taking time out of your busy schedule to attend our information session today. We hope that this briefing session will provide an opportunity for you to learn more about our R&D efforts and future prospects.

I am Kametsu from the Corporate Communications Department and will serve as today's moderator. Thank you very much for your cooperation.

This briefing session will be held in a hybrid format, with a live streaming via Zoom at the same time as it is conducted on-site. To prevent feedback, please turn off your microphone and speakers when watching the live streaming in the venue.

Here is a reminder to all participants from Zoom. If the delivery is interrupted or the video is frozen during viewing, please wait a few moments before accessing the site again. If you experienced any issues with the video or audio that prevented you from viewing it properly, we will post the video on our company website at a later date. We kindly ask that you view it there.

A script distribution will be scheduled at a later date for a more in-depth understanding of the contents of this briefing. We would appreciate your understanding and cooperation in this matter, as it will include statements and presentations made during the briefing.

I will now announce the Company's attendees. In attendance today are Hiroyuki Horiuchi, President and Representative Director; Mitsuru Watanuki, Director, Chief Officer of R&D Division; Tatsuhiro Harada, Corporate Officer, Deputy Chief Officer of R&D Division; Yasutomi Kato, General Manager of Research and Development Planning & Project Management Department; and Hideki Kawabata, Head of Clinical Development department.

Here is today's schedule. The entire session, including Q&A, is expected to last approximately one hour. There will be time for questions and answers after all presentations. First, we will take questions from the audience participants, followed by answers to questions from those attending via Zoom.

These are reminders for today's briefing. Today's presentation will follow the presentation materials posted on the Company's website. Please note that the information in the presentation materials is based on our reasonable judgment based on the information available at this time and may differ significantly from these future technologies. Although it contains information on pharmaceuticals, the content is not intended as advertising or medical advice.

Prior to the meeting, Horiuchi, President and Representative Director, would like to make a few words.

Horiuchi: I am Horiuchi, the President. We are very grateful that you are attending our R&D presentation today and that you are watching it online and through other means. Thank you very much.

In fact, this is the first time that we are holding an R&D presentation for our company. As an R&D-oriented company, I am truly delighted that we have finally reached a point where we can broadly share with you the status of our pipeline, a factor that will shape our future.

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Our company formulated the long-term business plan 2031 in 2022. With the goal of expanding our pipeline to achieve this plan, we have actively pursued research activities and introductions to date. At this point, we have reached the point where we have 10 in-licensed products and 12 in the pipeline.

We believe that we still need to expand our pipeline in order to further advance this original research and pharmaceutical product in the future. We believe that the pipeline we are presenting to you today is the first step in what we will increasingly need for the future of our company. We would greatly appreciate your continued opinions, support, and guidance today. We intend to use this as encouragement to advance our activities, so we kindly ask for your support.

Now, I know that time is limited, and I would like to thank you for your cooperation today. Thank you very much.

Kametsu: Now, Watanuki, Director and Chief Officer of R&D Division, will give an explanation.

Watanuki: I am Watanuki, Director and Chief Officer of R&D Division. Thank you for your cooperation today. I would like to present our growth strategy for 2031 from the perspective of R&D in this R&D briefing session. Thank you for your cooperation.

Today, I would like to provide an explanation based on the information presented here.

Vision and Strategy Toward FY2031

VISION

1. A company that contributes to longer healthy life expectancy by developing and supplying innovative new drugs in a speedy manner.
2. A research-based pharmaceutical company with a global presence, primarily in the areas of dermatology and orthopedics.

Strategy for achieving the VISION

"3Xs"

~Three Transformations~



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4

First, this shows our corporate vision and R&D strategy.

Our vision is to be a company that contributes to the extension of healthy life expectancy through the rapid creation of breakthrough new drugs, and a global drug discovery company with a focus on dermatology and orthopedics. To this end, we are drawing up a growth foundation for 2031 by combining the speed and quality of drug discovery, our overseas business development capabilities, and the strengthening of our management base.

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Vision and Overview of R&D Strategy

VISION

Continuously launch innovative, world-class drugs in our three priority fields of drug discovery

POLICY

- Utilize KAKEN's own research base
- Expand into new therapeutic areas
- Take on the challenge of new modalities
- Actively invest in research and development

PRIORITY MEASURES

- ① **Improve launch probability**
 - Utilize process innovation and achieve higher efficiency to shorten length of research and development
 - Diversify approaches to increase success rates
- ② **Expand pipeline**
 - Increase the number of licensed products
 - Use external resources in early-stage development
 - Seek new indications and drug repositioning
- ③ **Address new needs and overseas expansion**
 - Identify original targets that address unmet medical needs
 - Promote research and development aimed at overseas clinical development
- ④ **Take on challenge in new fields**
 - Select and work on modalities and take on the challenge of regenerative Medicine
 - Consider the introduction of digital therapeutics in orthopedics and dermatology

Allocate ¥260 billion for R&D investment over the 10 years of the plan

TARGET

- Secure a development pipeline capable of launching eight new products over the 10 years of the plan (maintain at least eight projects in Phase I or later phases at any given time)
- Secure at least one new licensed products or new marketing alliance every year expanding global products as target. (10 products over the 10 years of the plan, including five for overseas development)



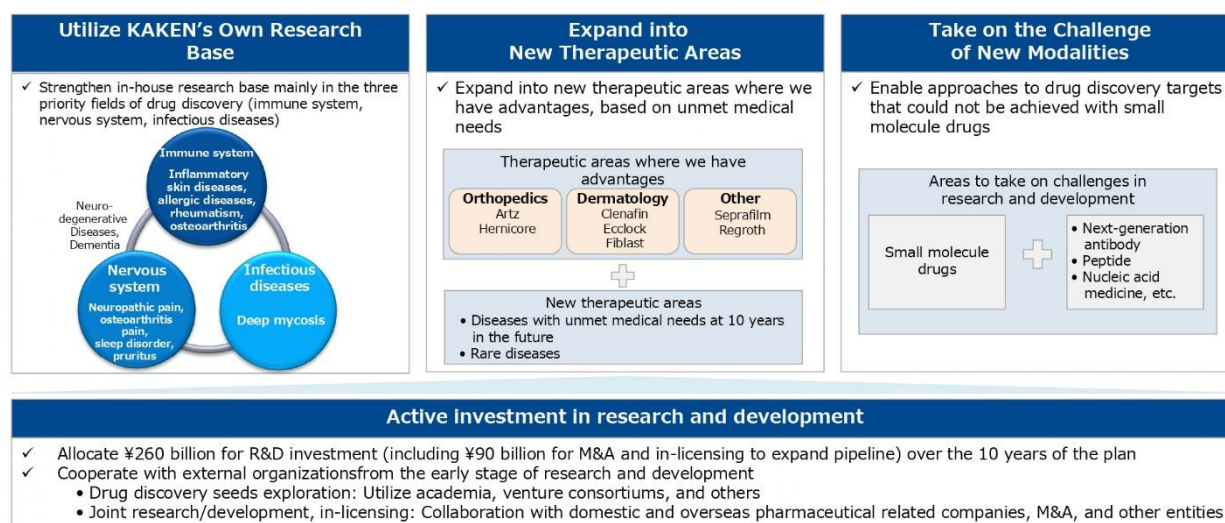
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In research and development, our goal is to continuously launch world-class, breakthrough new drugs to achieve our vision. To achieve this, we will maximize the value of our pipeline by balancing development, in-licensing, and in-house drug discovery, while improving launch certainty, expanding our pipeline, and responding to new needs and overseas expansion.

Basic R&D Policies

► For R&D, we will work on each measure based on the following four basic policies.



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Our R&D policy is to further strengthen and expand our core drug discovery areas where we are strong, and to actively collaborate with external parties from an early stage in joint research and development, licensing-in and out, and the challenge of developing new modalities for targets that cannot be addressed by small molecule compounds.

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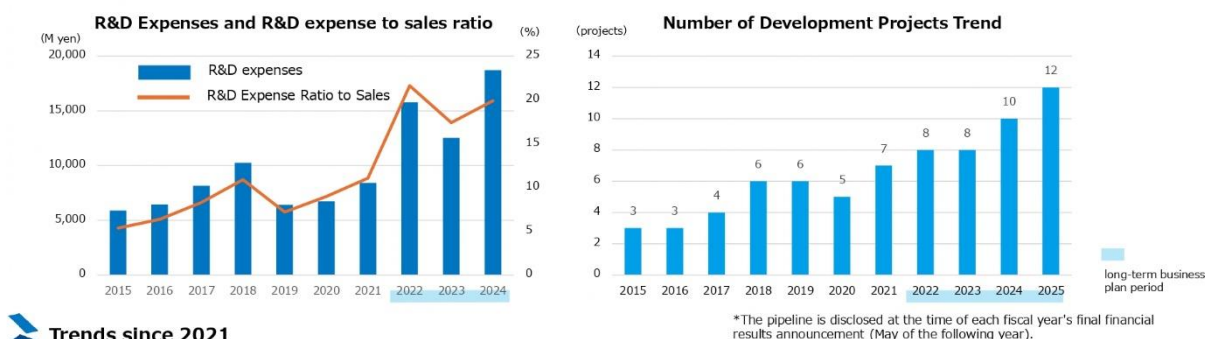
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Specifically, we have designed this approach to enhance the quality and quantity of our work from exploration to development by strengthening and expanding our in-house capabilities while actively leveraging external partnerships.

R&D Expenses Trend



Trends since 2021

Upgrading our in-house developed products	NM26, KP-483, KP-910, KP-723 (STAT6)
In- licensing	Teriparatide BS, KC-8025, Tildacerfont, Silk-elastin, ESK-001, Sebetralstat, Navenibart, gMSC1
Out- licensing	Clenafin (Chaina, EU), Ecclock(Korea), NM26 (J&J), STAT6 (J&J)
M&A	ARTham (KP-001, KP-648) , Aadi (Fyarro)
Joint research&development	NM26-2198 (Numab), ND081 (Numab), Exosome Drug Discovery (CellSource), Axcelead DDP
Other	AI Drug Discovery Platform (Elix), DTx (Cross MED)



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7

Here, we show on the left the trend of R&D expenses and on the right the transition of the number of development projects.

As shown in the 2021 and beyond transactions, after 2021, in-house drug discovery, then joint R&D, in-licensing, out-licensing, and M&A have been active. As a result, the number of development projects has increased significantly, and especially since 2022, when the long-term business plan was launched, R&D expenses have also increased significantly.

We are fully committed to advancing our diverse portfolio through various means, from in-house drug discovery to the introduction of late-stage development candidates, thereby laying the foundation for future KAKEN PHARMACEUTICAL and ultimately achieving the launch of new drugs.

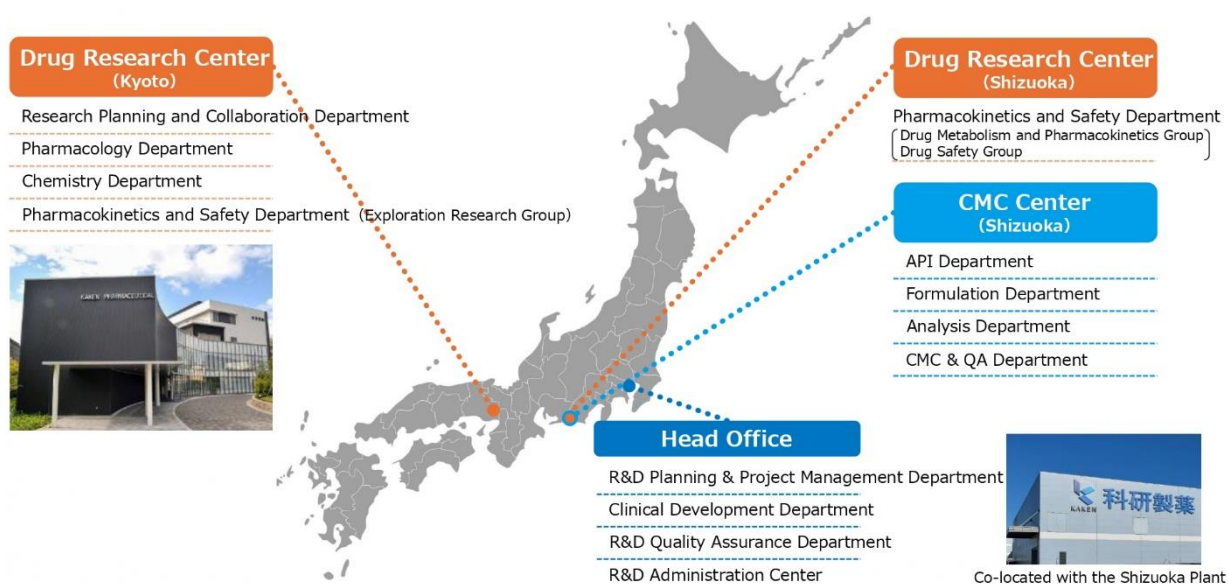
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Kaken's R&D Structure



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Next, I will show you our R&D structure.

The Drug Research Centers, which are responsible for drug discovery research, are located in Kyoto and Shizuoka. The CMC Center, which is in charge of API production and commercialization, is located in Shizuoka, together with the Shizuoka Plant. The head office has departments for R&D Planning & Project Management, Clinical Development, R&D Quality Assurance, and R&D Administration. In addition to a structure that enables implementation in the value chain from discovery to non-clinical, then CMC and clinical, we will actively utilize collaborative research and external sources.

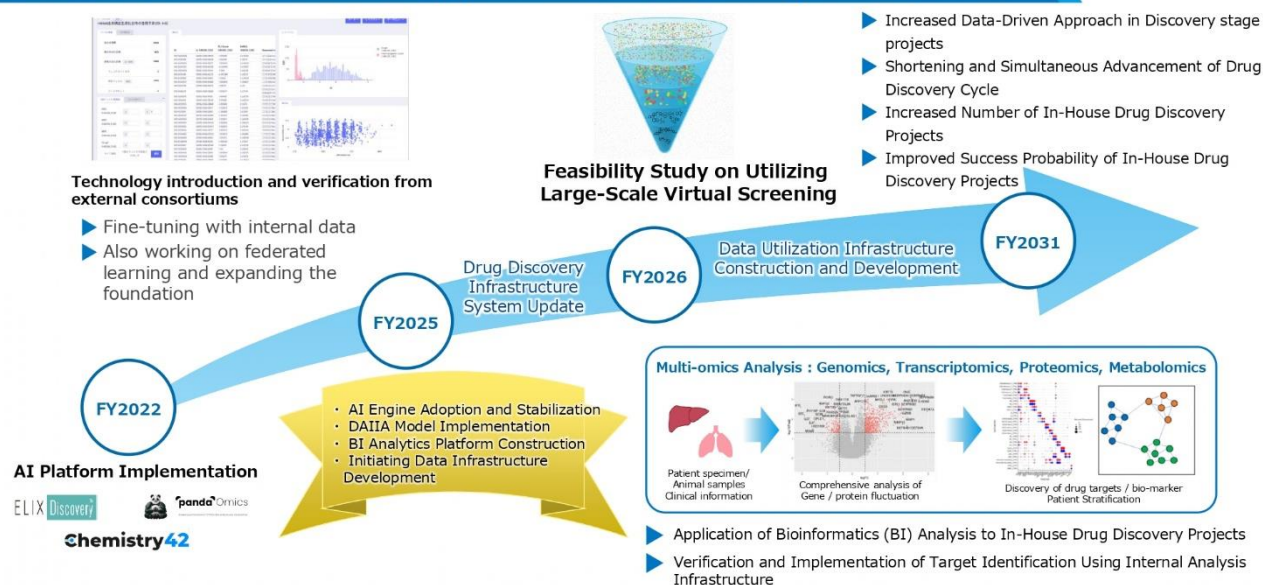
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AI-Based Drug Discovery: From Inception to Present and Future Initiatives Toward the application of Data-Driven Drug Discovery



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Next, I will explain a little about the reform of drug discovery, which is the key to new drug development.

This section provides a roadmap for the establishment of an AI drug discovery structure, showing where we have been from the start, where we are now, and where we want to go in the future. The AI platform was introduced in 2022, and to date, in cooperation with Elix, the use of the AI engine is now well established.

In addition, bioinformatics, language learning, and data infrastructure building are underway, and in the future we will extend data-driven drug discovery from target discovery to clinical candidates, aiming to shorten the drug discovery cycle and significantly improve the probability of success.

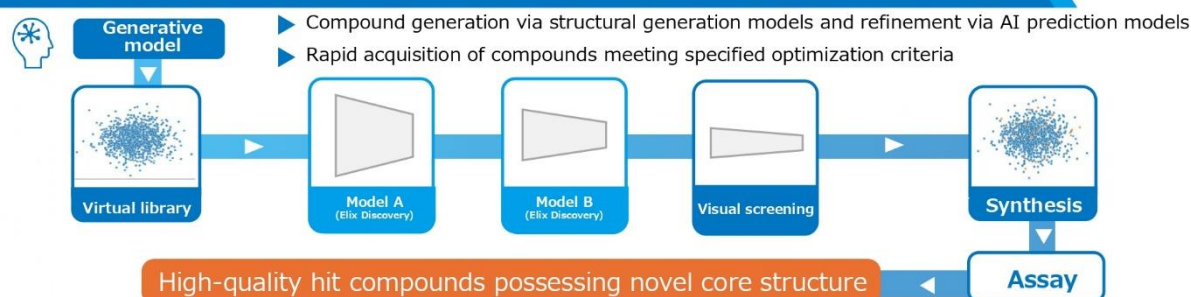
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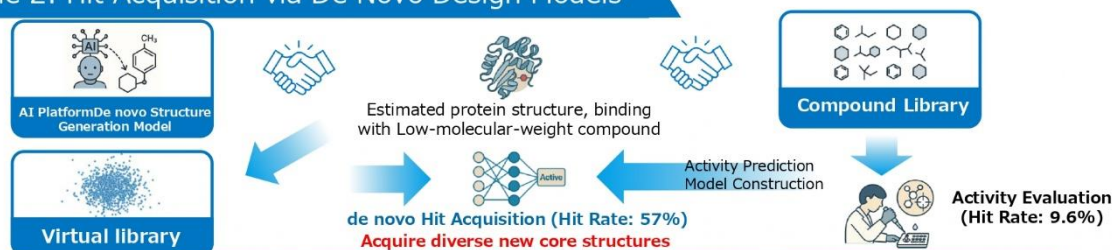
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Example 1: Acquiring High-Quality New Hits Using Generative Models



Example 2: Hit Acquisition via De Novo Design Models



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Next, we will introduce some specific examples of AI drug discovery applications.

First, I would like to show the acquisition of new hits using generation models. Conventional drug discovery involves selecting candidates from a vast compound library, which is time-consuming and costly. Currently, we are able to acquire new hit compounds that directly lead to lead compounds in a short period of time by presenting compounds through generation models and narrowing them down through AI prediction models.

Next, we will continue with Example 2. This is a structure that was established to quickly obtain compounds that meet the optimization criteria via De Novo design models. This approach has significantly increased the hit rate from 9.6% to 57%, and we are now in a position to acquire diverse new core structures in a short period of time. This is an important achievement that directly leads to shorter drug discovery cycles and higher success rates.

We believe that the integration of the AI-based generation models described above is the technological foundation that will dramatically increase our drug discovery competitiveness.

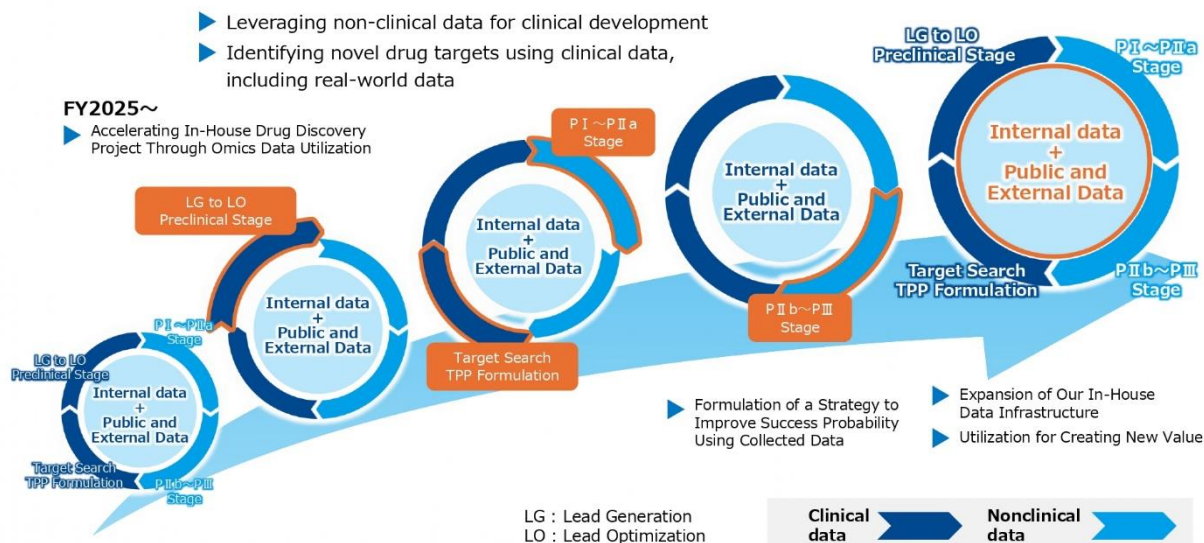
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Toward the Practice of Data-Driven Drug Discovery Utilizing Omics Information



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We are also working to accelerate our own drug discovery projects through the use of Omics data. Our plan is to make clinical real-world data and non-clinical data available to the Group, from target search to clinical practice.

In this way, we will continue to create new value by building a structure to make data-driven drug discovery an in-house standard.

Drug Discovery Research for Allergic Diseases (Type 2 Inflammatory Diseases) Such as Atopic Dermatitis

NM26... Bi-specific antibody-based therapeutics

- Simultaneous inhibition of IL-4/IL-13/IL-31
- Joint research & development with Numab Therapeutics AG
- ▶ Differentiation from current antibody drugs (UMN)
- ▶ Transfer of intellectual property to J&J
- ▶ Symbol of global expansion

KP-723... Small molecule STAT6 inhibitor

- Oral Small molecule Drugs for Type2 inflammatory Diseases ▶ **Dosing Convenience (UMN)**
- In-House Drug Discovery Product ▶ **Licensed to J&J** ▶ **Towards Global Expansion**
- **With maximum milestone payments of \$1.2 billion + royalty income**

From In-House Drug Discovery to Global Blockbusters



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Next, I will explain our drug discovery research in the field of immunology, one of our key drug discovery areas, as well as our global expansion efforts.

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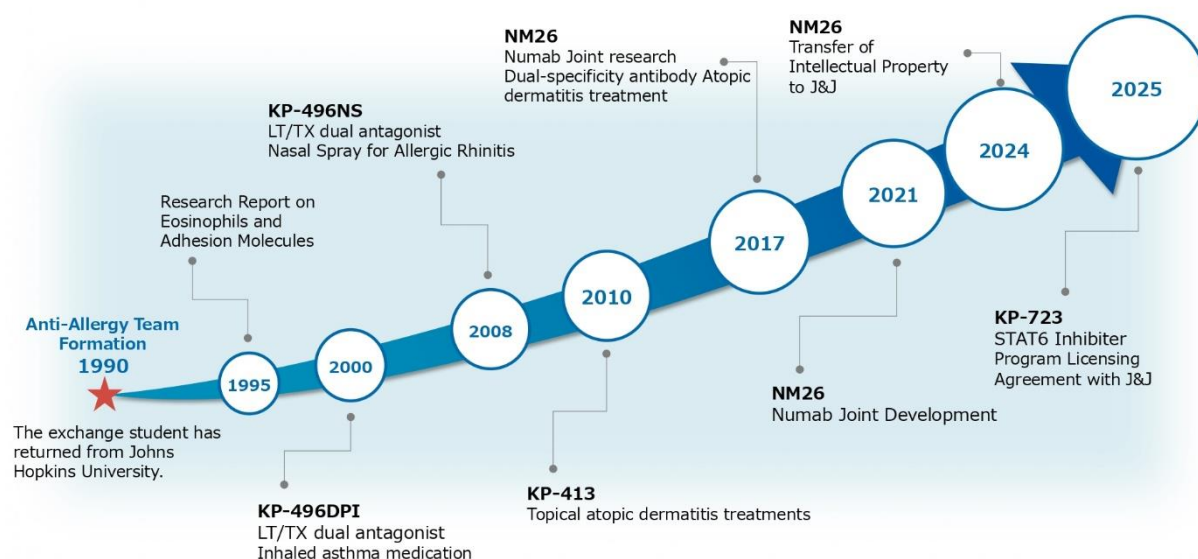
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In this area, the results of drug discovery research for type 2 inflammatory diseases such as atopic dermatitis led to the transfer of intellectual property and the conclusion of a license agreement last year. We have high expectations that these will be large global products.

Kaken's Drug Discovery Research for Allergic Disease Treatments



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Last year, we were able to provide a major topic of conversation in the area of type 2 inflammatory diseases, and we sometimes hear people ask why KAKEN PHARMACEUTICAL was involved. I would like to talk a little about our company's drug discovery research for the treatment of allergic diseases.

Our anti-allergy drug discovery research began when a researcher who had studied under Professor Kimishige Ishizaka and Professor Teruko at Johns Hopkins University, who discovered IgE, returned to Japan in 1990 and established our anti-allergy team.

In fact, as you can see from the fact that we reported our research on eosinophils and adhesion molecules early on, we have been conducting research targeting eosinophils dependent on type 2 helper T cells for type 2 inflammation from the beginning.

On the other hand, we have been conducting research targeting chemical mediators and keratinocytes, and have developed KP-496 targeting asthma and allergic rhinitis, and KP-413 targeting atopic dermatitis, both of which have advanced to the clinical stage.

Although not many people are aware of this, we have a track record of presenting research results at allergy conferences and submitting research papers. After this, we continued our drug discovery research in this area and in 2017 began a collaboration with Numab Therapeutics. At the same time, we began drug discovery research for STAT6 inhibitors. As a result, we believe that this led to the development of NM26 and KP-723.

KAKEN PHARMACEUTICAL did not suddenly start drug discovery research in this area, but rather has been conducting research in this area for more than 34 years.

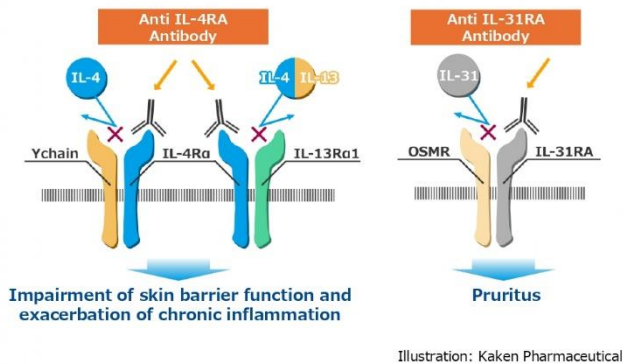
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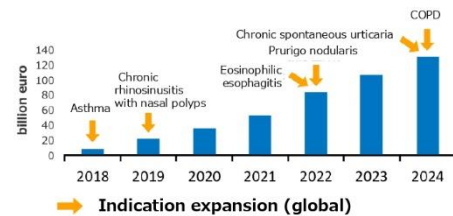
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Drug development for type 2 inflammatory diseases such as atopic dermatitis



Dupilumab's 2024 sales targeted at over ¥2 trillion with appropriate additional indications contributing to sales.



IL-4Ra and IL-31RA are promising targets for atopic dermatitis



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As you are all aware, many pharmaceutical companies are now embarking on research and development in the area of type 2 inflammatory diseases due to the success of dupilumab, an antibody preparation against the IL-4 receptor. In recent years, an antibody preparation, nemolizumab, against the IL-31 receptor, which is the main cause of itching, has been launched and is proving to be very successful.

Anti-IL-4 receptor antibodies against atopic dermatitis can strongly suppress inflammatory responses by blocking IL-4 and IL-13. However, it has not fully suppress successfully the strong itching mediated by IL-31. This led to the idea of NM26, which has been researched and then developed in collaboration with Numab Therapeutics.

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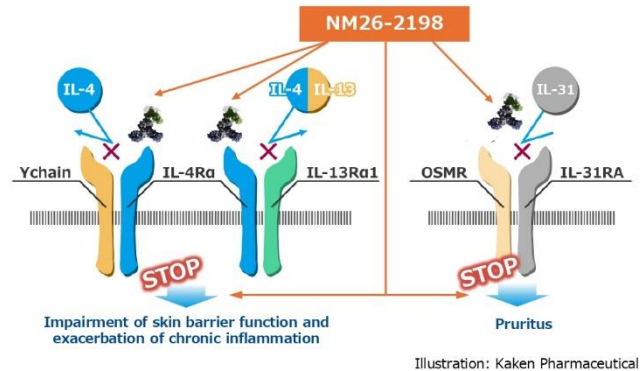
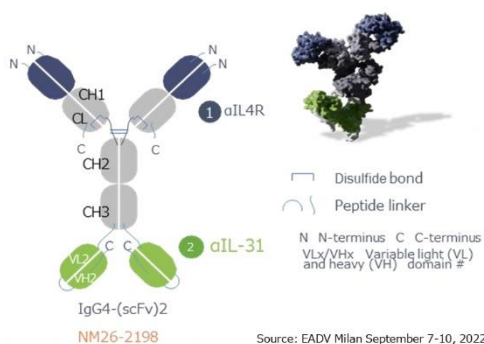
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NM26 : A Bi-specific Antibody for the Treatment of Atopic Dermatitis

- ▶ A **bi-specific antibody** targeting IL-4Ra and IL-31 simultaneously.
- ▶ Controls **both IL-4/IL-13 signaling inhibition and IL-31 neutralization** with a single agent.
- ▶ NM26-2198 blocks the primary symptoms of atopic dermatitis with **just one antibody**.



NM26-2198 blocks the primary symptoms of atopic dermatitis with a single antibody



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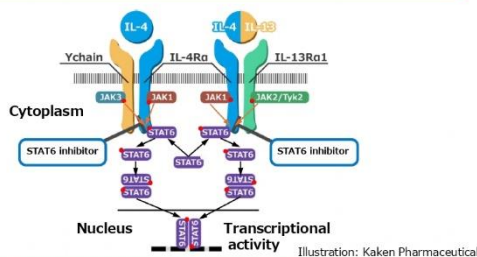
It is a bispecific antibody with a binding site for IL-4 receptor alpha and a binding site for IL-31. This has led to the development of an antibody drug that enables simultaneous inhibition of IL-4/IL-13-mediated inflammation and IL-31-mediated itching with a single agent.

We transferred the intellectual property rights for this drug to Johnson & Johnson in May of last year. We believe this drug has the potential to improve symptoms for patients with atopic dermatitis who do not achieve remission with current treatments.

STAT6 inhibitor targeting type 2 inflammation

Differences Between Dupilumab and STAT6 Inhibitors

- ▶ **Differences in Targets**
The antibody inhibits extracellular IL-4Ra.
STAT6 inhibitors directly inhibit intracellular signaling.
- ▶ **Differences in Scope of Effect**
Antibodies are inhibitors specific only to IL-4/IL-13.
STAT6 inhibitors broadly inhibit STAT6-related signaling.
- ▶ **Differences in administration routes**
Antibodies are administered by injection (subcutaneous administration).
STAT6 inhibitors are administered orally.



STAT6: Master transcription factor of IL-4/IL-13 signaling

STAT6 plays multiple roles

- ▶ Promotes Th2 cell differentiation (immune response)
- ▶ Stimulates IgE production (via B cells)
- ▶ Involved in airway hyperresponsiveness (asthma/allergy)

STAT6 inhibitors are expected to be therapeutic agents for a broad range of type 2 inflammatory diseases

News Release



December 26, 2024

KAKEN Entered into a License Agreement for STAT6 Inhibitor

Kaken Pharmaceutical Co., Ltd. ("Kaken"), head office: Bunkyo-ku, Tokyo; President and Representative Director, Hiroyuki Horiuchi, announced it has entered into a license agreement with Johnson & Johnson ("J&J") for the global development, manufacturing and commercialization of a STAT6 program that Kaken is developing on December 26, 2024.

Under the terms of the agreement, Kaken will grant Johnson & Johnson an exclusive license for the worldwide development, manufacturing and commercialization of STAT6 program including KP-723, an oral STAT6 inhibitor in preclinical development. Kaken will advance KP-723 to the completion of Phase I clinical trials, after which Johnson & Johnson will conduct the worldwide clinical development and commercialization. Kaken will retain the commercialization rights in Japan, while Johnson & Johnson will have an option to enter into a co-promotion agreement with Kaken.

Due to its high level of visibility and completeness, we have entered into a licensing agreement with Johnson & Johnson.



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I would also like to explain about STAT6 inhibitors.

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First, STAT6 is the master transcription factor for IL-4/IL-13 signaling. It has a role in the differentiation of type 2 helper T cells, the production of IgE that triggers allergic reactions, and hypersensitivity, and is a major contributor to the development of type 2 inflammation.

STAT6 inhibitors are currently attracting attention as targets for next-generation drug discovery research for type 2 inflammation, and many pharmaceutical companies are conducting research and development of STAT6 inhibitors, resulting in fierce competition.

We have been conducting drug discovery research on STAT6 inhibitors as orally-administrable type 2 anti-inflammatory drugs. Last year, we signed a licensing agreement with Johnson & Johnson. We believe that our drug discovery research has been recognized by a global mega-pharma company, and at the same time, this has paved the way for the fastest possible global deployment of our proprietary drugs and the maximization of their value.

NM26 and STAT6 inhibitors are both development candidates born from our internationally recognized research in immunology. They are expected to generate substantial future sales royalty income, in addition to upfront payments and milestone.

NM81 : From New Joint Research with Numab to Development



Drug Development Concept

November 2024: Start of joint research. November 2025: Transition to joint development

Unmet Medical Needs in Inflammatory Bowel Disease (IBD)

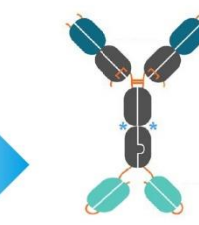
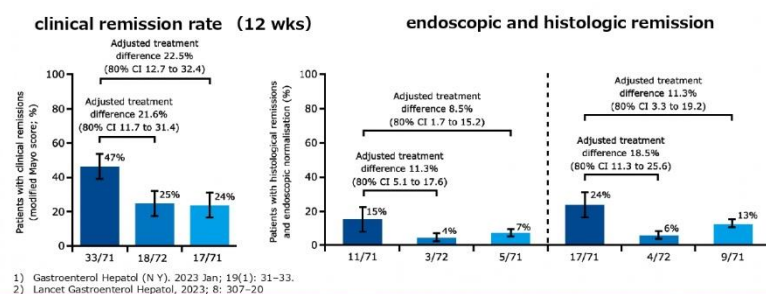
- ▶ **Clinical remission rates** in trials of biologics and JAK inhibitors are at most **around 30–40%**. ¹⁾
- ▶ Need for a drugs that demonstrate higher efficacy

New findings

Combination therapy with two antibodies targeting different pathways **significantly increases clinical remission rates as well as endoscopic and histologic remission**. ²⁾

Drug Development Concept

- ▶ Inhibit multiple targets with a single molecule
- ▶ **Expect a higher clinical remission rate than existing therapies**



Source: EADV Milan September 7–10, 2022



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20

In this process, I would like to explain about NM81, which we started joint research with Numab in November of last year and jointly developed in November of this year.

This is also in the field of immunology, and the target disease is inflammatory bowel disease. Which is known as IBD. The advent of biologic agents has significantly improved clinical remission rates in IBD treatment; however, even at their highest, these remission rates are said to remain limited to 30 to 40%. The emergence of such drugs that can further improve these clinical remission rates, as well as endoscopic and histological remission rates, is eagerly awaited. In fact, many formulators are also embarking on R&D in this disease area.

In recent years, clinical studies have reported that the combination of 2 antibody preparations has increased all remission rates. Therefore, we and Numab are conducting research and development of multispecific antibodies that can simultaneously block such multiple targets to maximize clinical efficacy.

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This drug has the potential to be a breakthrough drug that can show a high remission rate that cannot be achieved with existing therapies. We are very excited about the progress of this project.

Pipelines



In-house discovered and in-licensed projects

As of November 10, 2025

(*) The development stage includes the preparatory period for clinical trials.

Development code	Stage *	Therapeutic Area	Planned Indication	Remarks
KAR	P III	Dermatology, Pediatrics	Head lice	In-licensed from Arbor Pharmaceuticals, LLC (Currently, Azurity Pharmaceuticals) Product name in the U.S.: Sklice
KP-001	P III	Pediatrics, Plastic Surgery, Hematology/Oncology, Dermatology	Refractory vascular malformations	Product discovered in-house Announced the topline data from the confirmatory trial
KC-8025	P III	Gastroenterology, Hepatology, Internal Medicine	Primary biliary cholangitis	In-licensed from CymaBay Therapeutics, Inc. (Currently, Gilead Sciences, Inc.) Product name in US, UK, CA: Livdelzi Product name in EU: Lyvdelzi
ESK-001	P III	Dermatology	Plaque psoriasis	In-licensed from Alumis Inc. Under global P III (incl. Japan)
Navenibart	P III	Allergy, Dermatology, Internal Medicine, ENT	Hereditary angioedema	In-licensed from Astria Therapeutics, Inc. Under global P III (incl. Japan)
KP-483	P I	—	Solid tumors (Immuno-oncology)	Product discovered in-house
KP-910	P I	Orthopedics, Pain Clinic, Diabetology	Peripheral neuropathic pain	Product discovered in-house
Tildacerfont	P I	Pediatrics, Internal Medicine	Congenital adrenal hyperplasia	In-licensed from Spruce Biosciences, Inc. Strategy under Cconsideration
KP-001 (U.S.)	P III	Same as above	Refractory vascular malformations	In-house discovery Preparing for P III trial

Note: Kaken will advance KP-723, an oral STAT6 inhibitor in preclinical development, to the completion of Phase I clinical trials, which had entered into a licence agreement with J&J.



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22

I will continue with an explanation of our R&D pipeline.

This slide shows the overall picture of our development pipeline. We believe that we are now in a situation where we can support a step-by-step timeline for monetization through in-house drug discovery and in-licensing. Many are currently in the PIII stage, and the topline data in the PIII for KP-001 and KAR has just been reported. I will explain this pipelines in the P-III phase separately later today.

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Other Development Programs



Other

As of November 10, 2025

Development code	Planned Indication	Development Stage	Remark
Sebetralstat	Hereditary angioedema	Authorization application	- Applied by KalVista Pharmaceuticals, Inc. - Obtained approval in the US and Europe (Product name: Ektelyr) - Exclusive sales rights in Japan
gMSC1	Knee osteoarthritis with a focal defect	Preparing for PⅢ	- Allogenic synovial mesenchymal stem cell-derived three-dimensional artificial tissue - Development by the licensor, TWOCELLS Co., Ltd. - Joint development and exclusive sales rights in the area of orthopedics in Japan
NM26	Atopic dermatitis	PⅡ	- Clinical trial underway by J&J after IP transfer - Option rights to negotiate a sales partnership agreement in Japan



Status of Out-Licensed Products Overseas

Generic name (domestic sales name)	Planned indication	Development Stage	Developing country
Efinaconazole(Clenafin)	Onychomycosis	PⅢ	AIM(China)
Efinaconazole(Clenafin)	Onychomycosis	Approval	Almirall S.A. (Germany: Approved in August 2025) ※Italy: Approved in March 2025
SofpironiumBromide (Ecclock)	Primary axillary Hyperhidrosis	Approval	Dong-Wha Pharm Co.,Ltd (Korea: Approved in August2025)



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23

This is followed by a list of other development programs.

I will pick up and explain about Sebetralstat among them later today.

KAR : Head Lice Infestation Inadequately Controlled by Current Treatments

Ivermectin Lotion 0.5%

Kaken responded to the Ministry of Health, Labour and Welfare's public call under the "Review Committee on Unapproved Drugs and Off-Label Use with High Medical Need" and began domestic development in 2019.

- ▶ A drug capable of addressing unmet medical needs in dermatology
- ▶ Expansion of the development pipeline

Indication

Head lice infestation with inadequate response to existing treatments

Disease Overview

- ▶ Adult and nymph lice cling to hair and feed on blood from the scalp. The bite sites cause itching and, if scratched excessively, may lead to scalp inflammation.
- ▶ Transmission occurs through head-to-head contact, sharing towels, combs, pillows, or hats, and communal living environments such as schools and daycare centers.

Treatment

No approved prescription drugs are available in JP.

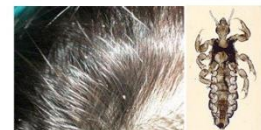
Over-the-counter treatments (e.g., phenothrin) in powder or shampoo form are commonly used.

Powder is applied to hair and left for 1–2 hours before rinsing, while shampoo is used on wet hair and rinsed after 5 minutes. Because efficacy against eggs (nits) is limited, repeated treatment every 3 days for 3–4 cycles is recommended.

Number of patients

Approximately 830,000 households per year

Naomi S, et al., *Med. Entomol. Zool.*, 60(3), 225-231, 2009.



Source: Japanese Dermatological Association
Diseases of the Skin – Head Lice Infestation



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24

Well, we issued a release the day before yesterday. I would like to first introduce KAR, a treatment for head lice infestation. This is a topical drug containing ivermectin, the active ingredient of which is well known as Dr. Omura of Kitasato University won the Nobel Prize.

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Although it was marketed in the US, it was not developed or marketed in Japan. The Ministry of Health, Labor and Welfare's Committee for Review of Unapproved Drugs and Off-Label Drugs, which evaluates drugs with high medical necessity, had publicly solicited development companies for this drug. Our company proposed development based on the fact that this drug has the potential to address unmet medical needs in the dermatology field and also contributes to expanding our development pipeline. Consequently, we commenced domestic development in 2019.

As for head lice, as shown here, it has been reported in various places that the number of phenothrin-resistant head lice has been increasing recently. Therefore, we have been working on the development of a drug that is effective against head lice, for which existing treatments are inadequately effective.

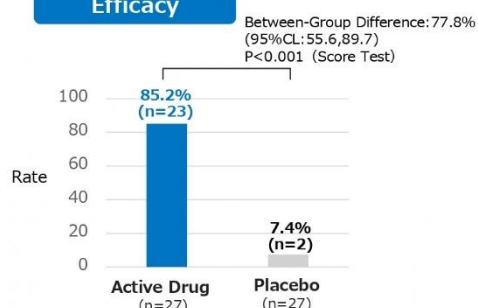
KAR : Results of JP Phase III Trial

Clinical Trial Summary

Indications	: Head lice infestation with inadequate response to existing treatments
Study design	: multicenter, randomized, double-blind, vehicle controlled, parallel-group
Sample size	: Primary subject: 54 (Target: 66) , total subject 117
Dose	: Apply the specified amount of KAR 0.5% or KAR 0%
Primary endpoint	: Treatment success rate in primary subjects (No live head lice observed 3 weeks after application)

Results

Efficacy



Safety

	Double-Blind Period		Open-Label Period	
	KAR 0.5% 56名	KAR 0% 61名	Active→Active 7名	placebo→active 55名
Adverse events n (%)	10 (17.9%)	8 (13.1%)	0	6 (10.9%)
Severity n (%)				
Mild	10 (100%)	4 (50%)	0	6 (10.9%)
Moderate	0	4 (50%)	0	0
Severe	0	0	0	0
Serious adverse events n (%)	0	0	0	0
Side effects n (%)	4 (7.1%)	1 (1.6%)	0	0

Mechanism of Ivermectin's Selective Action on Head Lice

- Selective toxicity: strong binding to parasites, weak binding to humans
- Humans lack GluCl channels
- Low affinity for mammalian GABA receptors
- Blood-brain barrier prevents CNS penetration



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25

We are pleased to present the results of this Phase III study of KAR.

The study is being conducted on patients who have had inadequate results with existing treatments, and who still have head lice.

As for the patients, the target patients to be evaluated are 54 individuals. In addition, there are family members of the patients, so a total of 117 people have participated in the program, including such patients.

The result is here. The primary endpoint, the treatment success rate, the proportion of patients who achieved a lice-free status, was 85.2% in the KAR group and 7.4% in the placebo group, representing a statistically significant difference. In addition, all patients who did not respond to the first application were successfully treated after the second application.

In terms of safety, adverse events were minor and no serious side effects were observed. We believe that this is a result of the selective properties of ivermectin based on its mechanism of action, which have also been confirmed clinically.

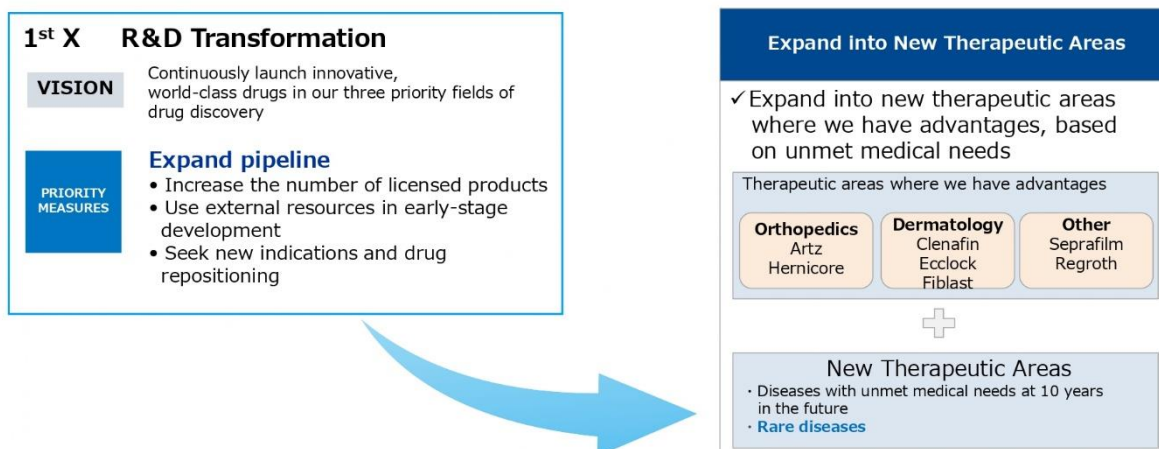
We were planning to submit an application for approval of this drug as the first ethical drug for head lice in Japan. We believe that this is the kind of product that will solve unmet needs in the field of dermatology.

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- ▶ Eliminating drug loss and drug lag to contribute to Japanese patients suffering from intractable diseases
- ▶ To ensure a stable supply of pharmaceuticals, we will secure revenue prior to the launch of promising in-house discovery drug product



Next, I would like to explain our initiatives in rare diseases.

Our mission is also to eliminate drug loss and drug lag, and to bring new drugs to Japanese patients suffering from intractable diseases. The long-term business plan 2031 also specifies the introduction of rare disease areas to ensure the pipeline.

In the area of rare diseases, there are products under development in which Japan does not participate in international joint clinical trials, and the risk of drug loss is high in this area. In order to solve these issues, we have been actively introducing drugs for rare diseases.

Another important strategy is to secure a revenue base until the launch of large in-house drugs and to realize a stable supply of pharmaceuticals by possessing a large number of drugs for the treatment of rare diseases.

In this way, we believe that our commitment to rare diseases is a pillar of our growth strategy, both in terms of contribution to patients and sustainable corporate growth. I will now outline the current status of our initiatives in drugs for the treatment of rare diseases.

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KP-001 : Refractory vascular malformations

Indication

Refractory vascular malformations

Some of vascular malformations are designated as **Intractable Diseases** and/or **Specific Pediatric Chronic Diseases**

Disease Overview

- Abnormal clusters of blood vessels that occur in children or young adults **causing disfigurement, bleeding, pain and infection**
- May become **fatal depending on the lesion site** such as respiratory tract

Treatment

- Surgical excision/Sclerotherapy**: Standard care
- Limited **surgical excision** due to bleeding/lesion site
- Rapamycin (Sirolimus) approved in Japan in Sep. 2021

Number of patients

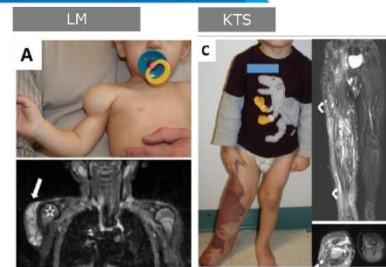
	Japan	U.S. (population: 330M)
• Venous Malformation (VM)	20,000 ^{*1}	33,000~66,000 ^{*2}
• Lymphatic Malformation (LM)	10,000 ^{*1}	20,000~55,000 ^{*3}
• Klippel-Trenaunay Syndrome (KTS)	3,000 ^{*1}	3,000~ 7,000 ^{*4}
• PIK3CA-related Overgrowth Spectrum (PROS)	—	4,760 ^{*5}

^{*1} : Epidemiological Survey by the MHLW Research Group (Mimura Team), 2014

^{*2} : Behraves S, et al., *Cardiovasc Diagn Ther*, 2016 Dec; 6(6): 557-569.

^{*3} : Churchill R, et al., *J. Pediatric Surgery*, 46(5), 912-922, 2011.; Acevedo, J.L, et al., *Otolaryngol Head Neck Surg*, 2008; 138: 418-424.

^{*4} : Lorda-Sanchez I, et al., *Ann Hum Genet*, 1998; 62(Pt 3): 235-239. ^{*5} : Orphanet



Source: Luks et al., *J Pediatr*. Author manuscript; available in PMC 2016 April 01.



Source: JOHNS HOPKINS MEDICINE HP



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28

First, KP-001.

The main target diseases are refractory vascular malformations, venous malformations, lymphatic malformations, and Klippel-Trenaunay syndrome. These diseases involve abnormalities in the formation of blood vessels and lymphatic vessels. They progress with growth and do not resolve spontaneously, necessitating lifelong treatment and disease management. The number of patients in Japan is reported to be 20,000 for venous malformations, 10,000 for lymphatic malformations, and 3,000 for Klippel-Trenaunay syndrome.

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KP-001 : Results of JP Phase III confirmatory Trial (KP-001-301)

Clinical Trial Summary

Purpose	The efficacy of KP-001 administered once daily for at least 24 weeks and up to 52 weeks in patients with venous malformations, lymphatic malformations, and KlippelTrenaunaysyndrome will be verified using response of the target lesion based on MRI imaging as an indicator. In addition, safety and pharmacokinetics will be investigated.
Study Design	Multicenter, Non-controlled, Open-label, Single-arm Study
Intervention	KP-001 is given orally once after breakfast
Sample size	32 subjects on active treatment
Primary Endpoint	Target lesion response based on MRI at the last evaluation after 24 weeks of treatment

Clinical Trial Results

- ▶ JP Phase III confirmatory trial (KP-001-301) :At Week 24, response rate (≥20% reduction in MRI target lesion volume) statistically exceeded the predefined threshold.
- ▶ No adverse events raising safety concerns were observed.
 - Focus on multiple outcomes: Lesion reduction, symptom improvement, QOL, safety, patient satisfaction.
 - Treatment goals: Lesion stabilization, symptom control, and maintaining/improving quality of life.
 - In chronic or adult cases, lesion reduction may be difficult due to fibrotic maturation.

A Long-term Study (JRCT)

Underway to evaluate safety and efficacy beyond 52 weeks.



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29

Results of the Phase III studies.

At the final assessment point after week 24 for the primary endpoint, the response rate, defined as a 20% or greater reduction in MRI target lesion volume, statistically significantly exceeded the pre-specified threshold. Therefore, the primary endpoint was achieved. In terms of safety, there have been no serious immune-related side effects.

We are currently in the process of further evaluating the efficacy and other aspects of this drug for vascular malformations, with a view to submitting applications in Japan and the US. We are planning to submit an application for approval in fiscal 2026. In addition, we are continuing to evaluate the long-term safety and efficacy of the product in a continuous dosing study.

KP-001 is a drug developed in-house for refractory vascular malformations such as venous malformations and lymphatic malformations. We would like to further accelerate development both domestically and internationally.

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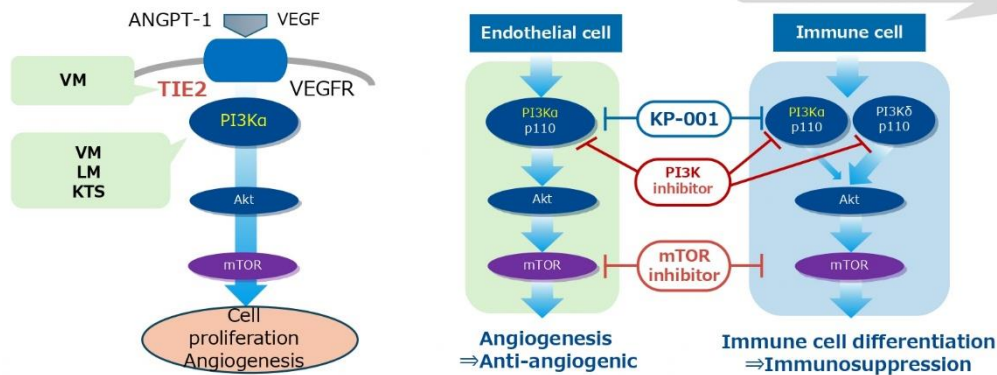
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KP-001 : Mechanism of Action

Genetic mutations in the pathways causing hemangiomas and vascular malformations
Target site of KP-001 : phosphatidylinositol 3-kinase(PI3Kα)



Vascular malformations need lifelong management from childhood.

- ▶ Targeting upstream PI3K selectively to achieve a reduced immunosuppressive profile.
- ▶ To date, no evidence of increased serious immune-related adverse events.

Illustration: Kaken Pharmaceutical



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30

This is the mechanism of action of KP-001.

Since this is more about safety than efficacy, I would like to explain a little more.

In the case of KP-001, it targets PI3Kα, the causative gene for vascular malformations. By inhibiting this pathway, it suppresses excessive vascular formation. In addition, its high specificity for PI3Kα means that it has little effect on immune cells. Therefore, it is expected to have fewer side effects resulting from immunosuppression.

In fact, the results of the Phase III study conducted this time did not show an increase in serious immune-related adverse events, which had been a concern. Based on these considerations, we believe that results supporting this theory have also been observed in clinical practice.

Vascular malformations are diseases that require treatment during childhood and throughout life. It is hoped that new therapeutic agents will be developed that can be safely taken over a long period of time, starting from really young children. We are committed to bringing this drug to patients as soon as possible.

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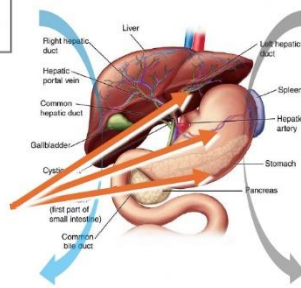
KC-8025 : Primary Biliary Cholangitis (PBC)

- ▶ Primary Biliary Cholangitis (PBC) **Designated Intractable Disease**
- ▶ More common in **women after middle age** (male/female ratio 1:4)
- ▶ Most cases are **asymptomatic** and are detected through health check.
Rapid progression of disease when it turns symptomatic
- ▶ **5-year survival rate** decreases with **increasing bilirubin levels**
- ▶ Number of patients in Japan: approximately **37,000**^{*1}
- ▶ Number of patients in US : approximately **130,000**
Livdelzi Q3 2025 \$ 105M^{*2}

antimitochondrial
antibodies
(used for diagnosis)

- Immune cell activation
- Destruction of bile ducts
- Stasis of bile acids
- Destruction of hepatocytes
- Increased ALP, γ-GTP and bilirubin levels
- pruritus, fatigue, jaundice

liver cirrhosis, liver cancer



Source: AMERICAN LIVER FOUNDATION

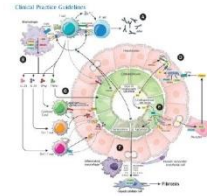
KC-8025

- Inhibition of Immune cell activation
- Inhibition of bile ducts destruction and stasis of bile acids
- Decreased ALP, γ-GTP and bilirubin levels
- Improvement of pruritus, fatigue, jaundice
- Inhibition of progression to liver cirrhosis, liver cancer**

Peroxisome proliferator-activated receptor δ (PPAR δ) agonist

Mode of Action

- Chronic inflammation mediated by JAK-STAT and NFκB signaling
- Cytotoxic T cells activation
- Elevated bile acids via CYP7A1&2
- Both senescent and apoptotic cells secrete mediators perpetuate inflammation, and promote fibrosis



Source: Journal of Hepatology 2017 vol. 67 | 145-172

*1 : Research on Intractable Liver and Biliary Tract Diseases (Ministry of Health, Labour and Welfare Research Project on Intractable Diseases)

*2 : Gilead Sciences, Inc. Public Information
https://s29.q4cdn.com/585078350/files/doc_financials/2025/q3/GILD-Q325-Earnings-Presentation-30-October-2025.pdf



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31

Next drug is KC-8025, Seladelpar.

Primary biliary cholangitis, the target disease, is also a designated intractable disease. The number of patients in Japan is reported to be 37,000. The disease results in chronic inflammation due to the activation of immune cells. As a result, the thin bile ducts in the liver are destroyed. That is the description of the disease.

The issue with current treatment is that for patients unresponsive to the first-line drug ursodeoxycholic acid, there are no treatment options available that can suppress disease progression and provide symptom improvement.

This agent is an agonist of the peroxisome proliferator-activated receptor. This drug is thought to act across multiple events involved in the pathogenesis of this disease. Consequently, it suppresses inflammation, inhibits destruction of bile ducts and hepatocytes, improves primary symptoms, and ultimately is expected to suppress progression to cirrhosis and hepatocellular carcinoma.

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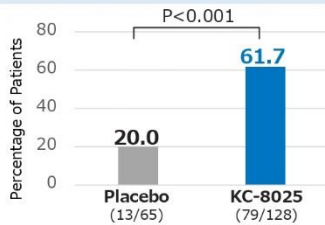


KC-8025 : Global Joint Phase III Trial

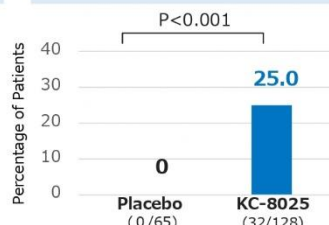
Result of Phase III Trial

The FDA granted accelerated approval for Seladelpar (Livdelzi) as a treatment for PBC on August 14, 2024.
- The first and only therapy to demonstrate normalization of ALP levels and a statistically significant reduction in pruritus scores compared to placebo-

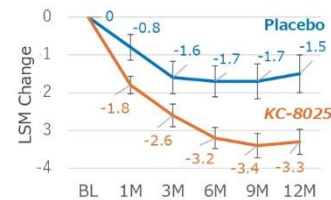
- ▶ Composite endpoint of ALP and total bilirubin [TimeFrame:12 months]
- ▶ ALP < 1.67× ULN, ≥ 15% decrease in ALP, and Total bilirubin ≤1.0× ULN



- ▶ Normalization of ALP [TimeFrame:12 months]



- ▶ Change in baseline numerical rating scale (NRS) [TimeFrame:6 months] pruritus NRS in subjects with baseline NRS ≥4



A Phase III Trial of Seladelpar in Primary Biliary Cholangitis. G.M. Hirschfield and Others. N Engl J Med 2024; 390: 783- 794

Status of Domestic Phase III Trial: Subject enrollment completed by the end of October 2025

Patient	: PBC patients with inadequate response to UDCA(ursodeoxycholic acid) or intolerance to it
Study design	: Uncontrolled, open-label, multicenter trial
Investment period	: 52 weeks
Primary Endpoint	: Composite endpoint ALP < 1.67 * ULN, ALP reduction of at least 15% from baseline, and total bilirubin <= ULN



Source: Gilead Sciences, Inc.
-news-detail-August 14, 2024
Gilead Sciences, Inc. - Gilead's Livdelzi (Seladelpar) Granted Accelerated Approval for Primary Biliary Cholangitis by U.S. FDA



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32

This shows the US situation and the results of the P III.

CymaBay Therapeutics, now Gilead, sells it in the US in 2024. The trade name is Livdelzi. As of Q3 of 2025, total sales have been disclosed as USD105 million. We have heard that the start of the program was successful.

Below are the results of the international Phase III trial, excluding Japan. Compared to placebo, it demonstrated normalization of alkaline phosphatase levels, a key biomarker, and a reduction in pruritus scores.

The Phase III study of this drug has completed enrollment of patients at the end of October this year. We will complete the validation study and proceed to make the product available to patients in Japan as soon as possible.

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Hereditary Angioedema (HAE): Disease Overview and Unmet Needs

HAE

- ▶ **Designated intractable disease** (primary immunodeficiency syndrome) 、 Estimated **2,500 patients** in Japan (approximately one in 50,000)
- ▶ HAE is a rare genetic disease caused by deficiency or dysfunction of the **C1 esterase inhibitor**.
- ▶ HAE attacks are characterized by **recurrent edema affecting** the skin, gastrointestinal tract, and airways, and may be life-threatening.
- ▶ Symptoms usually **peak within 24 hours** and resolve within a few days.

Unmet Medical Needs

- ▶ **Previously only available as an injectable**
- ▶ Preventive medication causes **injection-site pain and requires frequent dosing**
- ▶ Lack of reliable technologies for **early detection and monitoring** of attacks
- ▶ **Impact on the patient's QOL**

HAE Treatment

- ▶ **On-demand therapy**
pdC1-INH, Kallikrein inhibitors (ecallantide), Bradykinin B2 receptor antagonist (icatibant)
- ▶ **Prophylaxis of attacks**
C1-inhibitor replacement therapy, Kallikrein inhibitors (lanadelumab, berotralstat)

Hereditary Angioedema (HAE) Clinical Practice Guideline ~ 2023 Revision

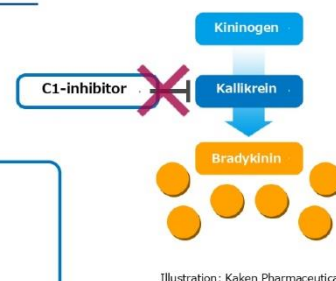


Illustration: Kaken Pharmaceutical



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33

Next is hereditary angioedema.

Hereafter referred to as HAE. Let me explain this. HAE is a rare disease, with a prevalence of 1 in 50,000. There are approximately 2,500 patients in Japan. This HAE is caused by a genetic mutation that reduces plasma levels of C1 inhibitor, which inhibits kallikrein. As a result, bradykinin is overproduced. This is the description of the disease.

The disease causes recurrent swelling called angioedema that lasts for two to three days in all parts of the body, and when the stomach or intestines swell, vomiting and severe pain may occur, as in intestinal obstruction. Swelling near the pharynx can also be life-threatening.

Due to its low recognition and the high level of expertise required to diagnose HAE, it takes an average of 15.6 years from the initial symptoms to the diagnosis of HAE in Japan. In the meantime, patients are suffering from these diseases, of which we do not know what they are, and which are sometimes potentially life-threatening.

Treatment options include medications used during seizures and preventive medications taken daily to prevent seizures; however, as shown here, there are unmet medical needs for each, making the development of new drugs highly anticipated.

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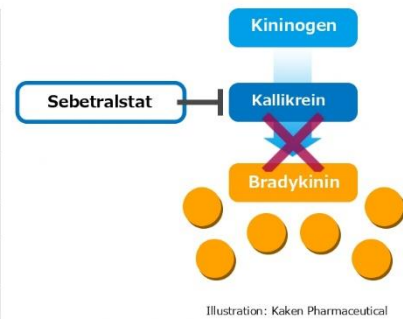
Sebetralstat : The world's first oral on-demand treatment for HAE

Mechanism of Action

- ▶ An oral drug that selectively inhibits plasma kallikrein.
- ▶ By inhibiting the activation of plasma kallikrein, it prevents excessive bradykinin production and suppresses the increased vascular permeability that causes HAE attacks.
- ▶ As an oral on-demand treatment alternative to injectable drugs, it is expected to improve patient convenience.

Phase III Trial : KONFIDENT Study Overview

Objective	Evaluating the efficacy and safety of sebetralstat
Study Design	randomized, double-blind, placebo-controlled
Dose	Single dose of 300 mg, 600 mg, or placebo during attacks
Patient	136(12 years and older)
Primary Endpoints	Time to Beginning of Symptom Relief Patient Global Impression of Change (PGI-C)
Secondary Endpoints	Severity of attacks, Time to Complete HAE Attack Resolution, safety
Indications	All HAE attacks, (including laryngeal attacks and breakthrough attacks during prophylaxis)



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Sebetralstat is the world's first oral on-demand treatment.

A small molecule compound that directly inhibits activated plasma kallikrein and suppresses the overproduction of bradykinin during seizures.

Sebetralstat : PhaseIII KONFIDENT trial - Results

efficacy

▶ Primary endpoint (Time to Relief PGI-C)

Median(95%CI) : 300mg : 1.61h (1.28-2.27)
600mg : 1.79h (1.33-2.27)
placebo : 6.72h (2.33->12)

▶ Secondary endpoint

Time to reduction in attack severity was significantly shorter compared to placebo.
Time to complete resolution of the attack was significantly shorter compared to placebo.

safety

- ▶ No discontinuations due to adverse events.
- ▶ No severe treatment-related adverse events reported.
- ▶ Adverse events : 300mg (2.3%) , 600mg (2.2%) , placebo (4.8%)

Ekterly®
(sebetralstat) tablets 300 mg

Source: KalVista Pharmaceuticals, Inc.Hp

Potential

- ▶ As the world's first oral on-demand treatment, it is expected to enable and **improve patient's QOL and access to care.**
- ▶ By providing rapid symptom relief, it also helps **alleviate anxiety during attacks**
- ▶ It has been **designated as an orphan drug** by both the FDA and EMA, and **is approved in the U.S., the E.U., the U.K., Switzerland, Singapore and Australia.**
- ▶ It has been designated as an orphan drug in Japan
The application for **manufacturing and marketing approval was submitted** in January 2025.



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Here is a summary of the Phase III study of Sebetralstat.

A total of 136 patients aged 12 years and older have participated in the study. The primary endpoint is time to symptom relief, and secondary endpoints include seizure severity and time to complete remission.

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Asia's Meetings, Globally

The result is here. For the primary endpoint, time to symptom relief was 1.6 and 1.8 hours for the 300 mg and 600 mg groups, respectively. This is significantly shorter than the 6.7 hours in the placebo group. In addition, the time to symptom reduction and the time to complete resolution of seizures were also reduced compared to placebo.

Regarding safety, there were no reports of discontinuation or serious adverse events, and the incidence of adverse reactions was low.

As the first oral on-demand treatment, this new drug is expected to make a significant contribution to patient convenience and quality of life, and has the potential to revolutionize the way HAE is treated. In Japan, KalVista submitted an application for approval in January of this year.

Navenibart : Long-Term Prophylaxis (LTP) Phase I / II ALPHA-STAR trial - Results

Mechanism of Action

- ▶ Plasma kallikrein inhibitory monoclonal antibody (Humanized IgG1 monoclonal antibody)
- ▶ YTE mutation in the Fc domain → Extended half-time
- ▶ Allosteric inhibition → strong inhibition of plasma kallikrein

Clinical Trial Summary

Objective	Assess the Safety, Tolerability, Clinical Activity, Pharmacokinetics, Pharmacodynamics, and Immunogenicity
Study Design	Non-Randomized, Open Label
Dose	Single or multiple subcutaneous administration of Navenibart
Patient	29 (years and older)
Primary Endpoints	Duration of HAE Attacks, Monthly HAE Attack Rate
Indications	HAE type I or II (Experienced at least 2 HAE attacks during the Run-In period)

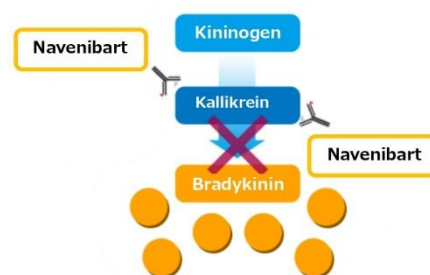


Illustration: Kaken Pharmaceutical



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36

Navenibart is a long-acting HAE prophylaxis.

It is a humanized monoclonal antibody against plasma kallikrein, and by introducing a mutation in the Fc domain, it is possible to extend the half-life and extend the administration interval from three months to six months. Furthermore, by allosteric inhibition, it exhibits potent inhibitory effects unattainable through direct inhibition.

Here is a summary of the Phase I and Phase II studies. Twenty-nine HAE patients aged 18 years and older participated in the study.

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Navenibart : Long-Term Prophylaxis (LTP) Phase I / II study (ALPHA-STAR) - Results

efficacy

(average six months)

Cohort 1

(450mg single dose, n=4)

Reduction Rate of Monthly Attack Frequency : 91% decrease
Reduction Rate of Moderate and Severe Attacks : 96% decrease
Frequency of Acute Rescue Medication Use : 94% decrease
Rate of no attacks : three months : 50%, six months : 25%

Cohort 2

(600mg→after three months 300mg, n=6)

Reduction Rate of Monthly Attack Frequency : 95% decrease
Reduction Rate of Moderate and Severe Attacks : 95% decrease
Frequency of Acute Rescue Medication Use : 94% decrease
Rate of no attacks : six months : 67%

Cohort 3

(600mg→ after one month 600mg, n=6)

Reduction Rate of Monthly Attack Frequency : 92% decrease
Reduction Rate of Moderate and Severe Attacks : 96% decrease
Frequency of Acute Rescue Medication Use : 91% decrease
Rate of no attacks : six months : 67%

safety

- ▶ No serious treatment-related adverse events
- ▶ Four non-serious treatment-related adverse events, dizziness, transient injection site reaction(rash), injection site erythema, injection site pruritus

Potential

- ▶ Injection site pain is **less frequent** with this drug.
- ▶ **The dosing interval is long.**



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37

The results are here.

Although the results were based on a very small number of patients, the overall cohort showed a reduction in monthly seizure frequency, moderate and severe seizures of more than 90%, and a maximum of 67% of patients were seizure-free for six months. In addition, the frequency of use of acute rescue medications has also decreased significantly.

The safety of the drug has also been shown to be well tolerated with no serious adverse events. Injection site reactions, which had been a concern, are very minor and the frequency of administration is low, which we believe will greatly contribute to reducing the burden on patients.

Phase III trials are currently underway, and we believe that this drug also has the potential to significantly change the way HAE is treated.

We aim to address the unmet needs of Japanese patients suffering from this HAE with both Sebetralstat and Navenibart.

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ESK-001: Innovative TYK2 Inhibitor for Psoriasis Treatment

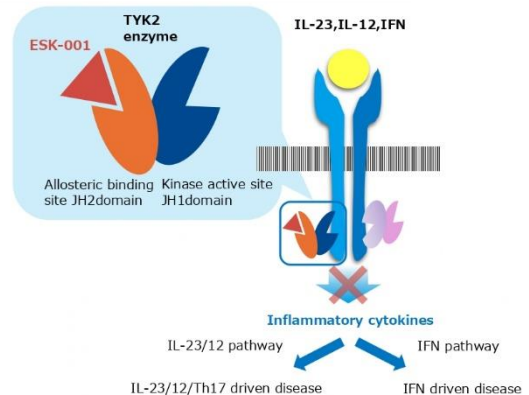
Developer : Alumis Inc. (U.S.)
Mechanism of Action : **Highly selective inhibition of TYK2** (Tyrosine Kinase 2)
Administration : **Oral** (twice daily; once-daily modified-release formulation also under development)

Development Status:

- ▶ **Moderate to Severe Plaque Psoriasis** (Phase III trial)
- ▶ **Systemic Lupus Erythematosus (SLE)** (Phase II trial)

ESK-001 is a highly selective, oral, allosteric small molecule TYK2 inhibitor

- ▶ ESK-001 is potent and intrinsically selective for **TYK2**.
- ▶ ESK-001 **allosterically** inhibits TYK2, with **maximal target inhibition maintained over 24 hours** with 40mg BID dose



Source: European Academy of Dermatology & Venerology Congress, September 25-28, 2024, P1004



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39

Next is other in-licensed development products.

Here, I would like to explain ESK-001, a breakthrough TYK2 inhibitor for the treatment of psoriasis. This drug is an orally administered medication that highly selectively inhibits TYK2. TYK2 is involved in the signaling of cytokines related to autoimmune diseases such as IL-23, IL-12, and interferon, and selectively inhibiting them improves the pathophysiology of inflammatory diseases.

This ESK-001 is characterized by a very high selectivity and safety profile that does not inhibit JAK1/2/3. Clinical studies have confirmed that the maximum dosage avoids the risk of side effects due to JAK inhibition.

A Phase III trial targeting moderate to severe plaque psoriasis is currently underway, with over 20 medical institutions participating in Japan. Phase II trials are underway for systemic lupus erythematosus, and the drug is also expected to be developed for autoimmune diseases other than psoriasis.

ESK-001 is a new treatment option that can be administered orally, and we believe it will make a significant contribution to improving patient convenience and resolving unmet needs.

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ESK-001 : Innovative TYK2 Inhibitor for Psoriasis Treatment

Mechanism of Action

- ▶ An oral inhibitor with intrinsic selectivity for TYK2 (Tyrosine Kinase 2)
- ▶ TYK2 is involved in the signaling of cytokines such as IL-23, IL-12, and Type I IFNs, which play key roles in autoimmune diseases

Phase II Trial (Moderate to Severe Plaque)

- Indications** : Patients with moderate to severe plaque psoriasis
- Dose** : Oral ESK-001 twice daily (multiple doses)
- Primary endpoint** : Dose-dependent increase in PASI-75 achievement rate at Week 12
→ PASI-75 achievement rate exceeded 70% in the highest dose group
Response rates increased from Week 12 to Week 24, with durability in PASI response rates observed in a 52-week OLE (Open-Label Extension) study
→ PASI-100 achievement rate was 39% in the OLE study
- Adverse Events** : Just state that to date a low rate of adverse events has been observed

Potential

- ▶ High selectivity and efficacy
- ▶ Favorable safety profile
- ▶ Ongoing Phase 3 trials in psoriasis; **potential for expansion into multiple autoimmune indications beyond psoriasis**



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40

In the phase II study, ESK-001 was administered orally twice daily to patients with moderate to severe or, as I mentioned, plaque psoriasis. The primary endpoint, the achievement rate of PASI-75 at 12 weeks, was dose-dependent and higher in all treatment groups than in the placebo group. In addition, the response rate increased from 12 to 24 weeks, and in a 52-week open-label extension study, the PASI-75 and PASI-100 achievement rates were 78% and 39%, respectively, confirming the long-lasting efficacy of the drug.

The safety profile of the drug was well tolerated, with mild to moderate adverse events.

Based on these results, we believe ESK-001 represents a novel therapeutic option for infection treatment and holds the potential to be a groundbreaking drug applicable to a wide range of autoimmune diseases.

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Market Size

Disease	Region	Estimated Number of Patients	Market Size
Vascular malformations	JP	VM : 20,000* ¹ LM : 10,000* ¹ KTS : 3,000* ¹	¥43.5 billion (290M \$) * ⁷
	U.S.	VM : 33,000~66,000* ² LM : 20,600~55,000人* ³ KTS : 3,300~17,000人* ⁴ (Estimated Using a U.S. Population of 330M)	¥180 billion (1,200M \$) * ⁷
Hereditary angioedema (HAE)	JP	2,500* ⁵	¥19.2 billion (128M \$) * ⁸
Primary biliary cholangitis (PBC)	JP	PBC : 37,000* ⁶ UDCA-refractory (30% of PBC) : 11,100* ⁶	¥22.5 billion (150M \$) * ⁹

(1 USD = 150 JPY)

*1 : Epidemiological Survey by the MHLW Research Group (Mimura Team), 2014

*2 : Behraves S, et al., *Cardiovasc Diagn Ther*, 2016 Dec; 6(6): 557-569.

*3 : Churchill P, et al., *J. Pediatric Surgery*, 46(5), 912-922, 2011.; Acovedo, J.L, et al., *Otolaryngol Head Neck Surg*, 2008; 138: 418-424.

*4 : Lorda-Sanchez I, et al., *Ann Hum Genet*, 1998; 62(Pt 3): 235-239.

*5 : HAE-info (Japan Hereditary Angioedema Diagnostic Consortium)

*6 : Research on Intractable Hepatobiliary Diseases (MHLW Policy Research Program for Intractable Diseases)

*7 : Healthcare Services, Arteriovenous Malformations Market Forecast Reaching \$4.1 Billion by 2029 at 7.2% CAGR.

*8 : Vascular Malformations Drugs 2025-2033 Trends and Competitor Dynamics: Unlocking Growth Opportunities

*9 : Global Hereditary Angioedema Therapeutics Market Size & Outlook, 2030.

*9 : Primary Biliary Cholangitis Market Report 2030, STRATEGIC MARKET RESEARCH, Challenges to Overcome in Primary Biliary Cholangitis Industry Market Growth: Analysis 2025-2033.



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42

Finally, I will explain the market size for the target diseases of our main development products and the schedule leading up to the application.

I will show you the estimated number of patients and the size of the market. First, I would like to discuss about rare diseases. As shown in the table here, it is estimated that there are approximately 33,000 patients with vascular malformations in Japan and up to 66,000 patients in the US. The market size is expected to be approximately JPY43.5 billion in Japan and JPY180 billion in the US.

Next is hereditary angioedema. In Japan, the number of patients with this disease is very small, estimated at 2,500, but it is a highly profitable area with a market size of JPY19.2 billion. The size of this market has increased significantly in recent years, largely due to the emergence of antibody drugs.

Finally, PBC, primary biliary cholangitis. It is estimated that there are approximately 37,000 patients in Japan, and the market size is currently estimated at JPY22.5 billion. For PBC, there has been no new drug with a new mechanism of action for a long time. Therefore, it is believed that the size of the market has not fluctuated significantly.

Although the number of patients with rare diseases is small, there is a high unmet medical need for drugs for rare diseases, and we believe that this is a highly profitable area if we can launch a breakthrough new drug.

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30

Market Size

Disease	Region	Estimated Number of Patients	Market Size
Psoriasis	JP	Psoriasis : 430,000 ^{*10} Plaque Psoriasis (90% of psoriasis) : 387,000 ^{*11}	¥76.65 billion (511M\$) ^{*17}
Head lice	JP	Head lice : 1,710,000 (affected households 830,000 ^{*12} × average household size 2.06 ^{*13}) Insufficient efficacy with existing treatments : 115,000 (1,710,000 × prevalence of treatment-resistant head lice infestation 6.7% ^{*14})	—
Systemic lupus erythematosus (SLE)	JP	about 60,000~100,000 ^{*15} Registered as intractable disease (SLE) : about 65,000 ^{*15}	¥19.05 billion (127M\$) ^{*17}
Atopic dermatitis	JP	1,609,000 ^{*16}	¥99.3 billion (662M\$) ^{*17}
Asthma	JP	1,857,000 ^{*16}	¥97.95 billion (653M\$) ^{*17}

(1 USD = 150 JPY)

^{*10} : Kubota K, et al. *BMJ Open*, 2015; 5(1): e006450.

^{*11} : Kamiya K, et al. *J Dermatol*, 2023; 50(1): 12-15.

^{*12} : Naomi S, et al. *Med. Entomol. Zool*, 60(3), 225-231, 2009.

^{*13} : Ministry of Internal Affairs and Communications, Population, Demographic Trends, and Number of Households Based on the Basic Resident Register (as of January 1, 2025).

^{*14} : Shinji K, et al., *J. Med. Entomol.*, 46(1), 2009: 77-82.

^{*15} : Japan Intractable Diseases Information Center website, Systemic Lupus Erythematosus (SLE) (Designated Intractable Disease No. 49).

^{*16} : Ministry of Health, Labour and Welfare, Patient Survey 2023.

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43

Next, we will explain the market size of major diseases.

The number of psoriasis patients in Japan is estimated to be approximately 430,000, with a market size of JPY76.6 billion.

As for systemic lupus erythematosus, the number of patients is estimated to be approximately 60,000 to 100,000 in Japan, with a market size of approximately JPY19 billion.

As for atopic dermatitis and asthma, there are 1.6 million and 1.85 million patients, respectively, and the market size is approximately JPY100 billion, as shown here. We believe that this is an important area for global expansion.

Then there is head lice. This is an area where no ethical drugs exist, and although we conducted various market surveys, no data were available. Based on past surveys and population per household, it is estimated that approximately 1.71 million people in Japan are affected by this disease. It is estimated that 115,000 of these patients have inadequate response to existing treatments. We believe that the KAR, which we are developing, will satisfy these unmet needs.

In this way, we plan to provide innovative therapeutic drugs not only for rare diseases but also for diseases with large patient numbers and market size, and to develop our own drugs on a global scale.

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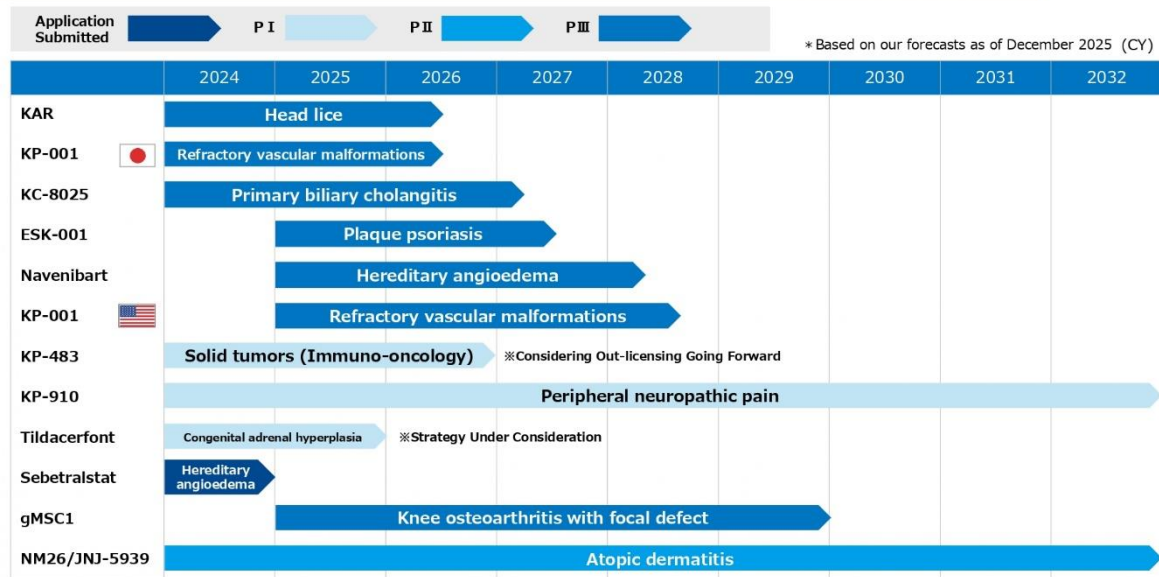
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Pipeline Progress Forecast



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44

This slide shows the progress of each development product, organized in calendar years.

We will continue to make solid progress on each of our development products in order to achieve important milestones in the future.

First, approval of new drugs sequentially, starting with the launch of Sebetralstat in 2025. 2026. Starting with the launch of Sebetralstat, we plan to gradually approve new drugs.

We will first establish a solid profit structure in the short term while delivering new drugs that are needed by patients in Japan, especially for rare and intractable diseases, and then we will work toward the launch of large global products in the future.

Furthermore, we plan to proceed with the introduction of new development funds in a planned manner while keeping an eye on the situation, as well as additional investments through M&A and the acquisition of technological foundations.

This timeline is the core of our growth strategy we are formulating. We plan to do so, ensuring that we achieve our milestones for the year 2031.

That is all from me. Thank you for your attention.

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Question & Answer

Kametsu [M]: We will now move on to the question-and-answer session. We will first take questions from the audience, followed by answers to questions from Zoom.

Here is how to ask a question from Zoom. If you have any questions, please press the “raise your hand” button at the bottom of the screen. I will call on those who have raised their hands. Please unmute yourself and state your company name and full name before asking your question. If you wish to cancel your question in the middle of the process, please press the “hand down” button.

Now, first of all, I would like to take questions from the audience. Please raise your hand if you have any questions. Well, Mr. Lee, thank you very much.

Lee [Q]: Thank you very much. I’m Lee from Morgan Stanley. Thank you very much for your time today. Two questions, please.

The first point is about KP-001 and the second about KP-723. About the development of KP-001 in the US. When I heard about Novartis' VIJOICE and the current market size, I felt the US market still looks quite promising. I understand that the US will now skip the Phase II and start the Phase III. Please tell me about this disease, vascular malformation, and whether there are any racial differences between Japanese and Americans.

Watanuki [A]: Thank you for your question. First of all, KP-001, I think that the development in the US is as you guessed, Mr. Lee. We are also aware of the very large size of the market. Looking at the actual launch of VIJOICE and the subsequent sales trends, we view it as highly promising.

As for the difference between patients in the US and Japan, the incidence rate does not seem to be very different, as the result shows. Probably the mechanism of action is exactly the same. We see no major difference between them, as the incidence of such cases is the same.

Lee [Q]: Thank you very much. Therefore, we can expect that the results of the domestic Phase III trial will be similar in the US.

Watanuki [A]: Thank you very much. That is correct. That is our expectation as well.

Lee [Q]: Thank you very much. One more point in follow-up. On page 31, I think you showed the number of patients with 001, or refractory vascular malformations. The US in particular has quite a large number. Is there such a thing as a treatment rate, such as in Japan, as well as in the US?

Watanuki [M]: Do you mean the treatment rate, the number of patients treated?

Lee [Q]: Perhaps it is the number of target patients you are showing us now. Of these, the treatment rate is 5%, 10%, or something like that, if you have such figures, I would like to know them.

Watanuki [A]: In the US, I believe statistics were released regarding the number of patients actually receiving treatment or management for venous malformations or similar conditions; however, since that number was quite large and we have not yet verified whether it is accurate, we have not included it here. We will look into the data to find out more about this and will introduce it to you in the future.

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Lee [Q]: Thank you very much. I'm looking forward to it. Finally, I would like to ask again about KP-723 and its potential. This Monday or Tuesday's data from Kymera in the US showed the effectiveness of Dupi equivalents, and I still felt that STAT6 would be interesting. On the other hand, it is my understanding that there is a lot of competition.

At this point, I'd like to know if Mr. Watanuki has identified any of the KP-723 differentiating factors in your mind. We can expect Phase I results next year, and if there are any hints or elements suggesting such differentiation is anticipated, I would appreciate your guidance on them. That's all from me.

Watanuki [A]: Thank you very much. Mr. Lee, I am also encouraged by the results, and we are thinking very positively about it. The concept we had envisioned has indeed yielded such results in clinical practice, which has strengthened our resolve to redouble our efforts in the research and development of KP-723.

Regarding Kymera specifically, since it is a disassembling agent, we intend to closely monitor how these differences will impact future developments. For example, since it's a proteolytic enzyme, overdoing it could potentially lead to loss of control. I'm wondering if that's where it differs from low-molecular-weight compounds. Going forward, we intend to carefully differentiate our approach based on the outcomes of their clinical trials.

Lee [Q]: Thank you very much. I know that Kymera highlighted the itching quite a bit. Am I correct in understanding that itching, NRS, etc. will be key points in this KP-723 as well?

Watanuki [A]: We also believe that that test targeted atopic dermatitis. There is of course such itching that is dependent on Th2, so it suppresses the itching to some extent. On the other hand, I think we need to look a little more into whether we can manage the non-dependent itching and whether it can be suppressed.

Lee [M]: Thank you very much. That's all from me.

Kametsu [M]: Next, Mr. Hashiguchi, please welcome.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. I also have two questions.

The first is that in your opening remarks, Mr. Horiuchi, I believe you mentioned that the pipeline still needs to be expanded. I'd like to understand more about what that means.

Do you mean more is better or are you talking about after what you have now is finished? Or does that mean as a field, that dermatology has already enough options but there's a shortage in orthopedic surgeons? If there are enough in the Phase III but few in the Phase I.

Or perhaps, given the success probability and expected sales, it means they're still far from satisfied. Does it mean that there is a surplus of people and gadgets? I can think of many possibilities, but what was your intention?

Horiuchi [A]: Thank you very much. To put it simply, though it may sound like a play on words, the fundamental idea is that there's no end point when it comes to sustaining a company's growth. For example, even with the pipeline, it's not like we can just wrap things up here and expect our company to keep going for 100 or 200 years from this point, right? The idea is that even if we launch it, we'll still need the next one.

Even though we're currently at 10 items, we must always maintain a pipeline of 10 items. So, whenever we launch 2 items, we need to add 2 more to the pipeline. I hope you understand it that way. The idea is not that we have a budget surplus and need to buy more. So, I also meant that we need to control the budget so that it can be continued in that way. Do I answer your question?

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Hashiguchi [Q]: In that sense, considering the current R&D budget, resources, personnel, and other factors, would it be accurate to understand that the pipeline is becoming quite robust?

Horiuchi [A]: Considering our current scale and various factors, when evaluating whether 20 items of pipeline is truly necessary, I believe the best approach is to consistently maintain and proceed around 10 items, the number outlined in our long-term business plan.

And if things improve a bit more after the initial launch, maybe next time we could increase it to 15 items. In that sense, we think it's acceptable to proceed in this manner for now. If you could take that as an implication that we still need to continue to do that way.

Hashiguchi [Q]: I understand. Then, AI utilization needs. I would like to ask where is your advantage over other companies and what differentiates you from them.

Are the analytical tools you're using the kind that other companies can also access, meaning, are you using fairly general-purpose tools that are available for a certain price, or do they include something custom-built?

Of course, even if it is a general-purpose product, you can differentiate yourself, if there is experience and know-how in how to use it, I suppose. Could you please explain in a little more detail where your company's characteristics come from?

Watanuki [M]: Harada is the Chief of Drug Research Center, and he will answer your question.

Harada [A]: I will answer. As you say, we use a platform that can be used anywhere as long as you pay for it. However, such AI systems grow and evolve based on the data used to train them. By leveraging our own unique, accumulated data, we can establish our distinctiveness. Although it is still a work in progress, we would like to create such a highly original form.

Hashiguchi [M]: Thank you very much. That is all.

Kametsu [M]: Well then, Mr. Muraoka, please go ahead.

Muraoka [Q]: I'm Muraoka, from Morgan Stanley. Thank you very much.

Regarding NM81, I thought I should review the clinical paper in the lower left section, which focuses on the combined administration of 2 antibodies. Looking back at the previous papers, this appears to be data on the combination of Tremfya and Simponi. In other words, a combination of IL-23 and TNF. Then, I realized, oh, I see, I see, IBD. I was wondering if it was following a pattern here that worked well with the IL-4, IN31 combination. Is it not a misunderstanding to consider IL-23 and TNF?

Watanuki [A]: Thank you, Mr. Muraoka. I, Watanuki, will respond to your question. As Mr. Muraoka can probably understand that, we cannot disclose the targets. I'm sorry.

Muraoka [Q]: Yes, but. Actually, if we think about the premise of IL-20, Tremfya and Simponi, they are all Johnson & Johnson again. When considering future BD strategies with Johnson & Johnson, there are parts that excite me and parts that make me think, "Is this it again?" What about that?

Watanuki [A]: Indeed, this is the paper that Janssen published. I think it might be getting too far ahead. We have not heard anything like that yet.

Muraoka [Q]: I understand. Thank you very much. Also, let me ask one more science question.

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About STAT6. Earlier, I thought, “Oh, I see,” when I realized that since the Kymera's medicine is a PROTAC, if it breaks down into a protein, that's scientifically acceptable.

My question is, this is a transcription factor, right? I do think it would be problematic if the transcription factors were to disappear. Is the human transcription factor STAT6 rapidly resynthesized within the body if it is degraded? Or, this protein does take quite a while to increase the volume, so scientifically speaking, it is a bit concerning, I mean, although Phase I showed really good safety results, is that how we should think about it? It would be helpful if you could tell us a little about it.

Watanuki [A]: I believe that what is currently being done clinically will be thoroughly evaluated. As for the non-clinical side, I would like Mr. Harada to answer, if he knows.

Harada [A]: I am not certain of the time, but I think it disappears for a very long time and does not recover. Degraded, I mean.

Muraoka [Q]: So, we need to take a hard look at the long-term safety data by Kymera, which is great at this stage, although it is great.

Harada [A]: Yes, that's right. As for me, the effect is very good and I am looking at it with high expectations regarding the PoC of STAT6 inhibition. However, regarding the safety aspect of the degraders, we believe we must view it as a key differentiator from our compounds and approach it with the perspective of what we hope to achieve.

Muraoka [M]: I understand. Thank you very much. That is all.

Kametsu [M]: Thank you. Well then, Mr. Maeda, please go ahead.

Maeda [Q]: Thank you for your presentation. I am Maeda of Nomura Securities. I would like to ask two points.

The first point is about alliances, and I think you summarized the transactions after 2021 on page seven. I think there have been both successes and failures, but I would like to know how your thoughts on the various deals have changed, from your thoughts in 2021 to your current thoughts. In other words, it's about whether you understood what was important amidst all that happened. Please tell me about this point first.

Watanuki[A]: Thank you for your question. What we have actually done since 2022 is actually to expand the scope of the in-licensing. We put the rare diseases there. Upon actual consideration, it became clear that there are still many such diseases where we can introduce treatments and ensure they reach Japanese patients effectively.

Furthermore, I feel that if we thoroughly negotiate regarding those TYK2 inhibitors, such as ESK-001, we are now in a position where such opportunities will properly come our way.

I feel that by consistently pursuing in-licensing, we've started to see a cycle where such opportunities naturally come our way.

Maeda [Q]: Thank you. Are there any changes in governance or internal systems?

Horiuchi[A]: Thank you. As for the rare disease issue, I believe the most significant turning point was the acquisition of ARTham. Here, we first introduced rare disease issues into our company, and from there, a certain opening was created in that area.

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Regarding the governance or framework for handling transactions thereafter, it is true that we expanded into areas such as in-licensing, including for rare diseases, and strengthened our business development and related efforts in that direction. So, it's a personnel part, and various [inaudible] part. It went on.

Ultimately, when considering last year's initiatives, such as overseas introductions and in-licensing efforts encompassing rare diseases, the term "rare diseases" itself becomes a key focus. I believe this also connects to the work being done at Aadi.

Therefore, rather than specializing solely in this area, we aim to broaden our scope and proactively address unmet needs across multiple domains. We hope you understand that this approach has led to our current structure.

Maeda [Q]: I understand very well. On the second point, I would like to ask about AI drug discovery. On page 11, there are three platforms, and I think you have included the logo for the introduction of the AI platform.

If you've carefully selected these three platforms among the many AI platforms available, could you tell me what factors were decisive in your choice? I wonder if it could be the difference in machine learning models, or the strength of the service, etc. What are they?

Harada [A]: Harada will answer. We have been working with Elix since its inception, and the most decisive factor for us was that they could help us with the implementation. As for Chemistry42, Elix did not initially have a model for generative AI, but we wanted to include generative AI as well, so Chemistry42 was added together with Elix.

In addition, PandaOmics was included because it is needed by Omics. There are many other things, but as to why we chose PandaOmics, I'm sorry, I don't remember exactly, so I can't answer that question right now. I'm sorry.

Maeda [M]: I understand very well. Thank you very much. That's all from me.

Kametsu [M]: Thank you very much. We will now conclude the question-and-answer session.

This concludes the KAKEN PHARMACEUTICAL R&D Briefing. Thank you very much for taking time out of your busy schedule to join us today.

[END]

Document Notes

1. Portions of the document where the audio is unclear are marked with [inaudible].
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