R&D Briefing

– Growth Strategy Toward 2031 –

December 10, 2025

Kaken Pharmaceutical Co., Ltd.

Cautionary Notes regarding Forward-looking Statement

- The performance forecasts described in this material are rational based on the information currently available and have been determined by the Company as reasonable.
- Considerable financial investment and a long development time are required before a new drug is launched. The Company carefully develop new drugs by confirming their efficacy and safety. There is a possibility that their development may be discontinued before completion, in such case where anticipated efficacy has not been proven or safety issues have been identified.
- The “Pipeline” is based on the current development plans. The status may change depending on their progress.
- The information about pharmaceutical products (including those under development) included in this material is not intended as an advertisement or medical advice.

Agenda

1

Corporate Vision and R&D Strategy

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～

- 1st X **R&D** Transformation
- 2nd X **Overseas Expansion** Transformation
- 3rd X **Management Base** Transformation

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

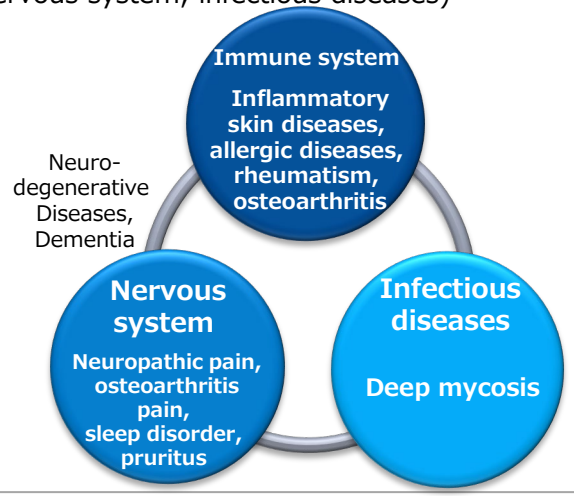
- Secure a development pipeline capable of launching eight new products over the 10 years of the plan (maintain at least eight projects in Phase I or later phases at any given time)
- Secure at least one new licensed products or new marketing alliance every year expanding global products as target.(10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

Basic R&D Policies

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

Utilize KAKEN's Own Research Base

✓ Strengthen in-house research base mainly in the three priority fields of drug discovery (immune system, nervous system, infectious diseases)



Expand into New Therapeutic Areas

✓ Expand into new therapeutic areas where we have advantages, based on unmet medical needs

Therapeutic areas where we have advantages

Orthopedics	Dermatology	Other
Artz Hernicore	Clenafin Ecclock Fiblast	Seprafilm Regroth

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New therapeutic areas
- Diseases with unmet medical needs at 10 years in the future
- Rare diseases

Take on the Challenge of New Modalities

✓ Enable approaches to drug discovery targets that could not be achieved with small molecule drugs

Areas to take on challenges in research and development

Small molecule drugs ＋
- Next-generation antibody
- Peptide
- Nucleic acid medicine, etc.

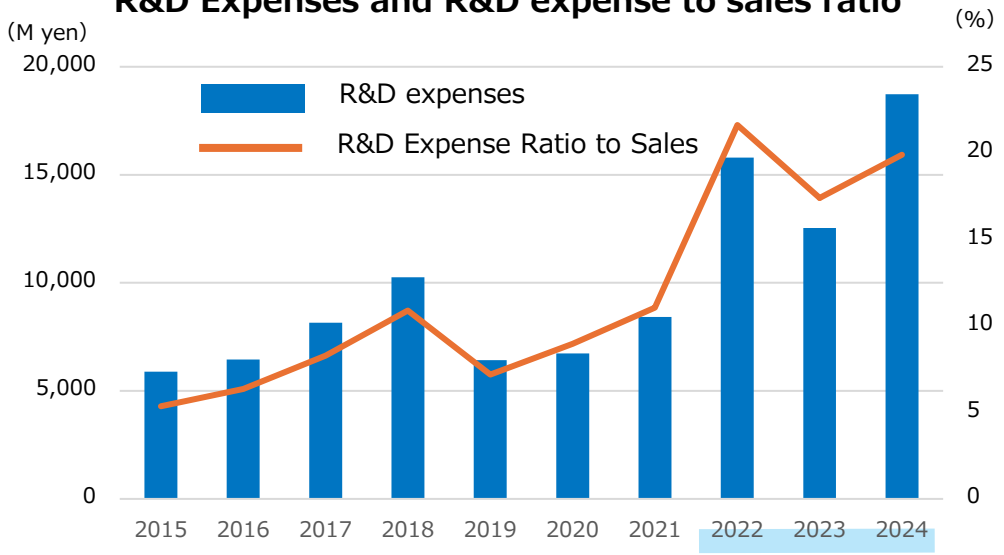
Active investment in research and development

✓ Allocate ¥260 billion for R&D investment (including ¥90 billion for M&A and in-licensing to expand pipeline) over the 10 years of the plan

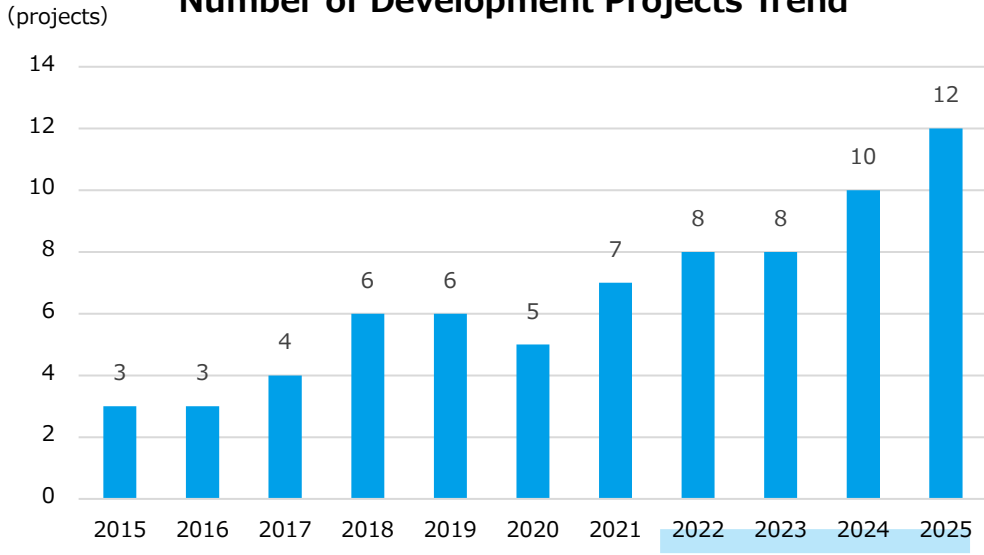
✓ Cooperate with external organizationsfrom the early stage of research and development
- Drug discovery seeds exploration: Utilize academia, venture consortiums, and others
- Joint research/development, in-licensing: Collaboration with domestic and overseas pharmaceutical related companies, M&A, and other entities

R&D Expenses Trend

R&D Expenses and R&D expense to sales ratio



Number of Development Projects Trend



long-term business plan period

*The pipeline is disclosed at the time of each fiscal year's final financial results announcement (May of the following year).

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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R&D Structure

Kaken's R&D Structure

Drug Research Center (Kyoto)

- Research Planning and Collaboration Department
- Pharmacology Department
- Chemistry Department
- Pharmacokinetics and Safety Department（Exploration Research Group）

Drug Research Center (Shizuoka)

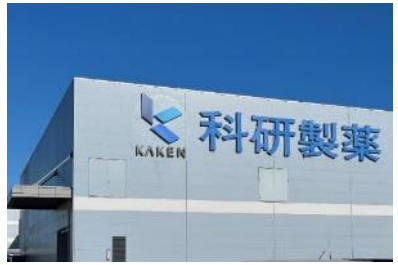
- Pharmacokinetics and Safety Department
  - Drug Metabolism and Pharmacokinetics Group
  - Drug Safety Group

CMC Center (Shizuoka)

- API Department
- Formulation Department
- Analysis Department
- CMC & QA Department

Head Office

- R&D Planning & Project Management Department
- Clinical Development Department
- R&D Quality Assurance Department
- R&D Administration Center



Co-located with the Shizuoka Plant

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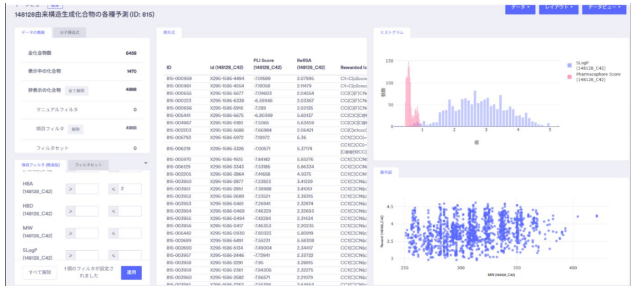
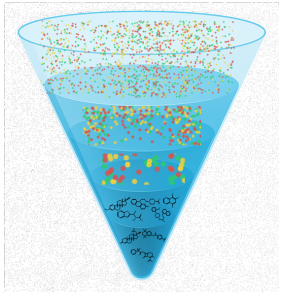
Transforming Drug Discovery

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



Technology introduction and verification from external consortiums

- Fine-tuning with internal data
- Also working on federated learning and expanding the foundation



Feasibility Study on Utilizing Large-Scale Virtual Screening

- Increased Data-Driven Approach in Discovery stage projects
- Shortening and Simultaneous Advancement of Drug Discovery Cycle
- Increased Number of In-House Drug Discovery Projects
- Improved Success Probability of In-House Drug Discovery Projects

FY2022

AI Platform Implementation

ELIX Discovery™ pandaOmics Chemistry42

FY2025

Drug Discovery Infrastructure System Update

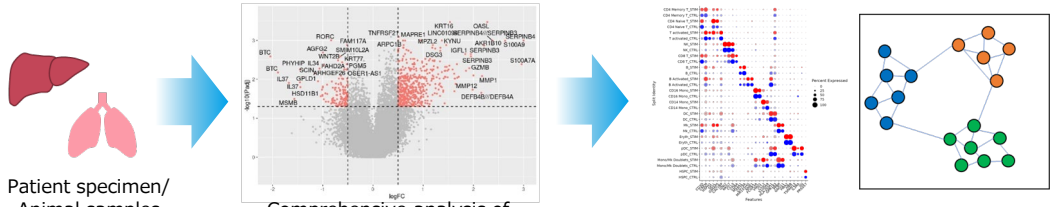
- AI Engine Adoption and Stabilization
- DAIIA Model Implementation
- BI Analytics Platform Construction
- Initiating Data Infrastructure Development

FY2026

Data Utilization Infrastructure Construction and Development

FY2031

Multi-omics Analysis : Genomics, Transcriptomics, Proteomics, Metabolomics



Patient specimen/ Animal samples Clinical information

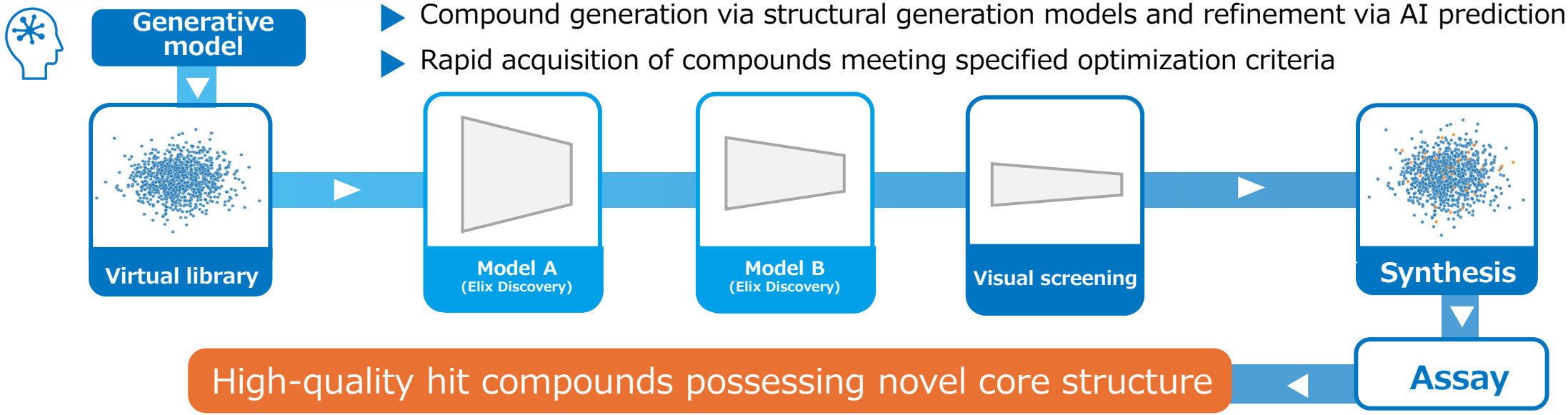
Comprehensive analysis of Gene / protein fluctuation

Discovery of drug targets / bio-marker Patient Stratification

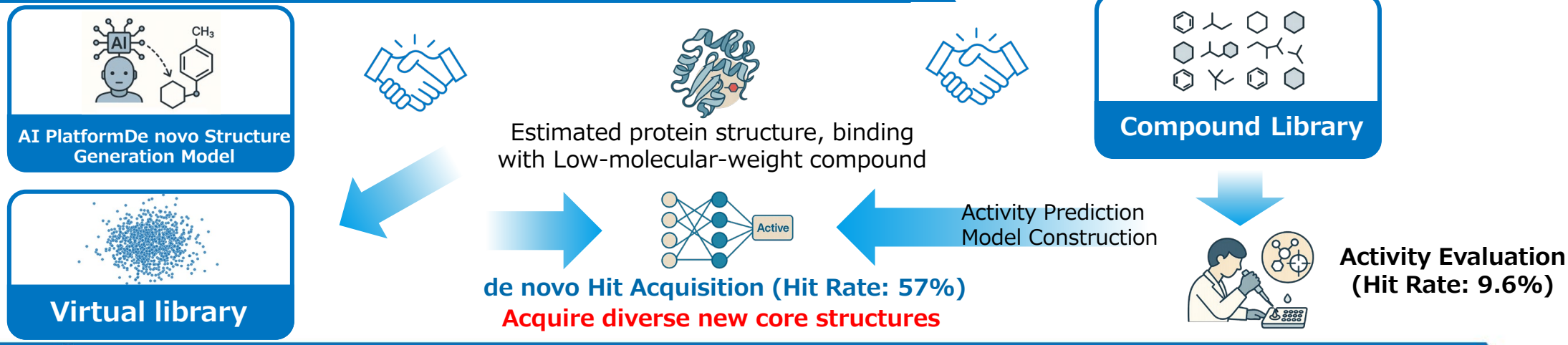
- Application of Bioinformatics (BI) Analysis to In-House Drug Discovery Projects
- Verification and Implementation of Target Identification Using Internal Analysis Infrastructure

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

- Compound generation via structural generation models and refinement via AI prediction models
- Rapid acquisition of compounds meeting specified optimization criteria



Example 2: Hit Acquisition via De Novo Design Models

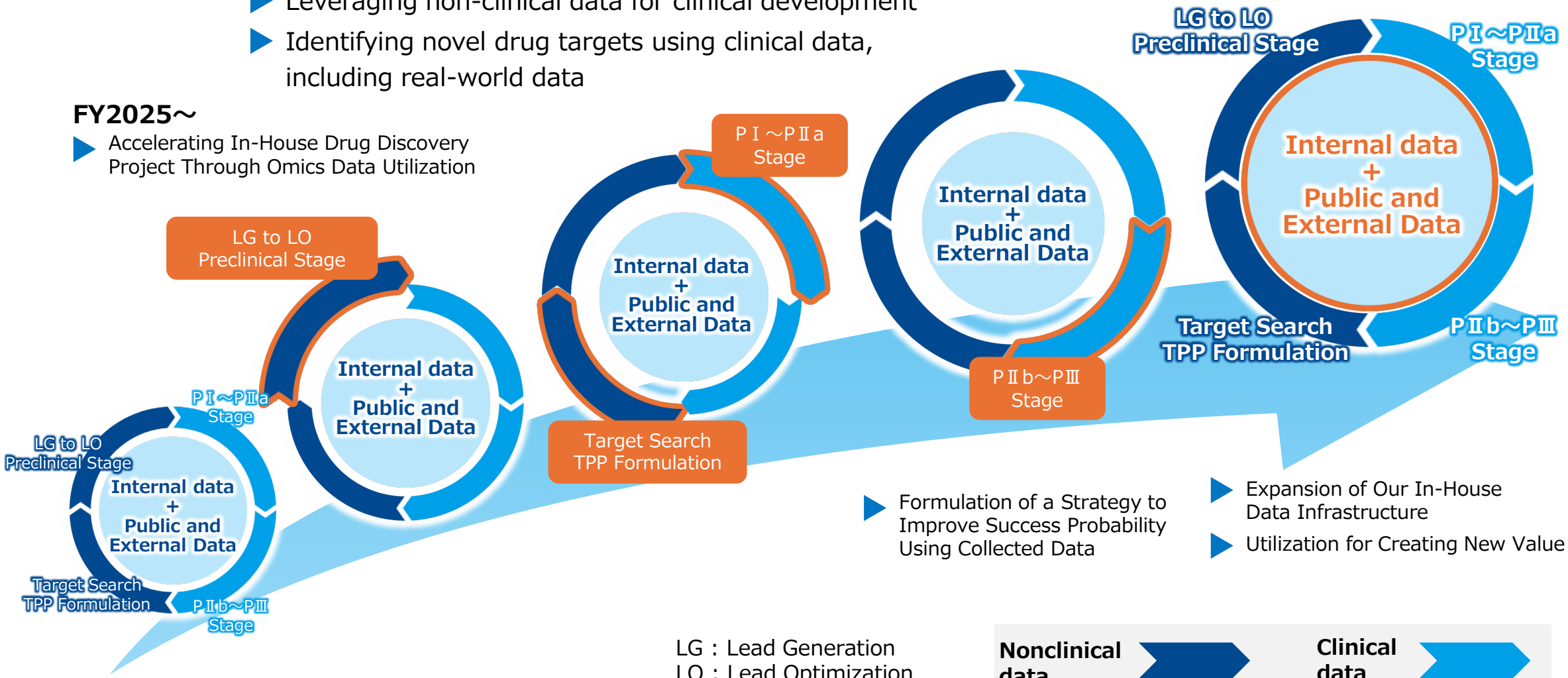


Toward the Practice of Data-Driven Drug Discovery Utilizing Omics Information

- Leveraging non-clinical data for clinical development
- Identifying novel drug targets using clinical data, including real-world data

FY2025～

- Accelerating In-House Drug Discovery Project Through Omics Data Utilization



- Formulation of a Strategy to Improve Success Probability Using Collected Data
- Expansion of Our In-House Data Infrastructure
- Utilization for Creating New Value

LG : Lead Generation
LO : Lead Optimization

Nonclinical data → **Clinical data**

4

Drug Discovery in Immunology: Towards Global Expansion

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

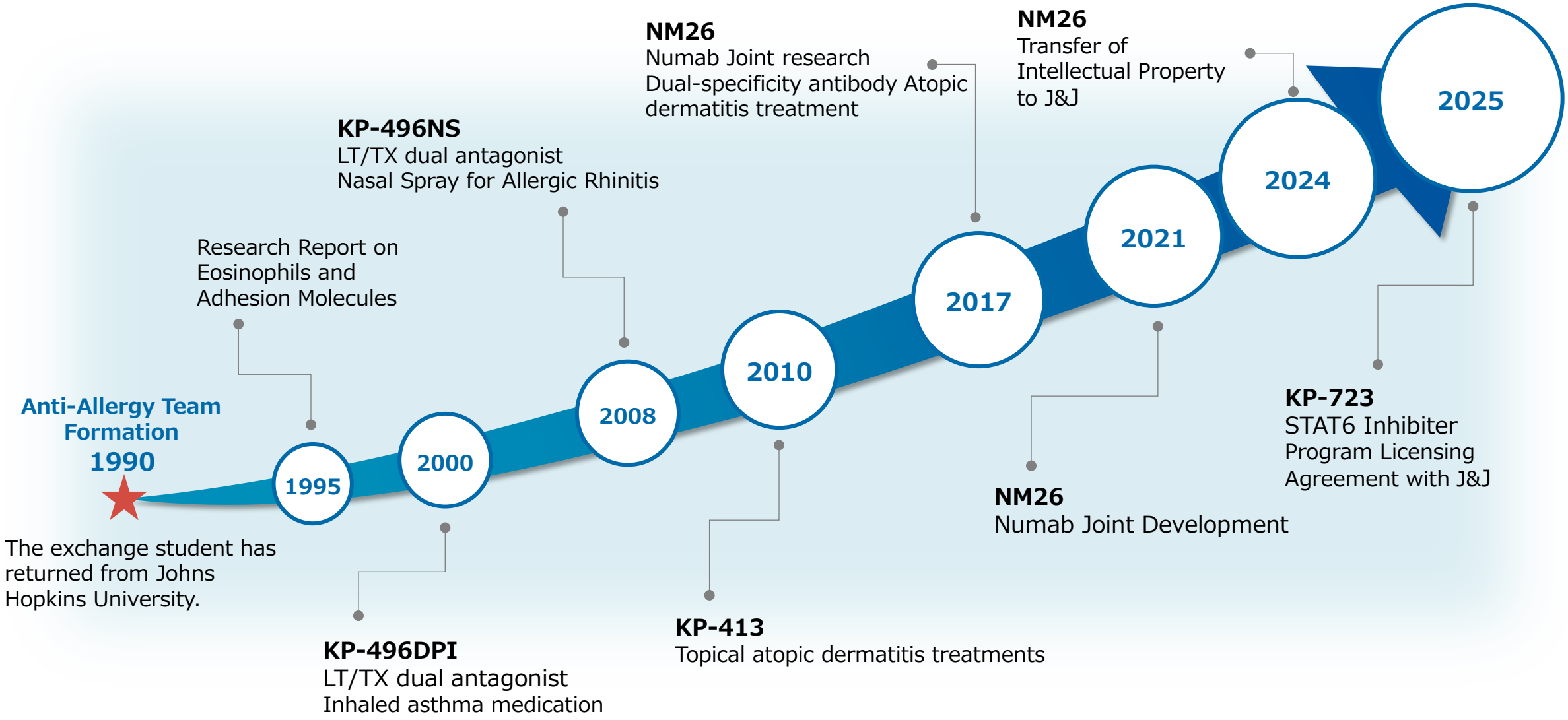
► Differentiation from current antibody drugs (UMN)
► Transfer of intellectual property to J&J
► Symbol of global expansion

KP-723…Small molecule STAT6 inhibitor

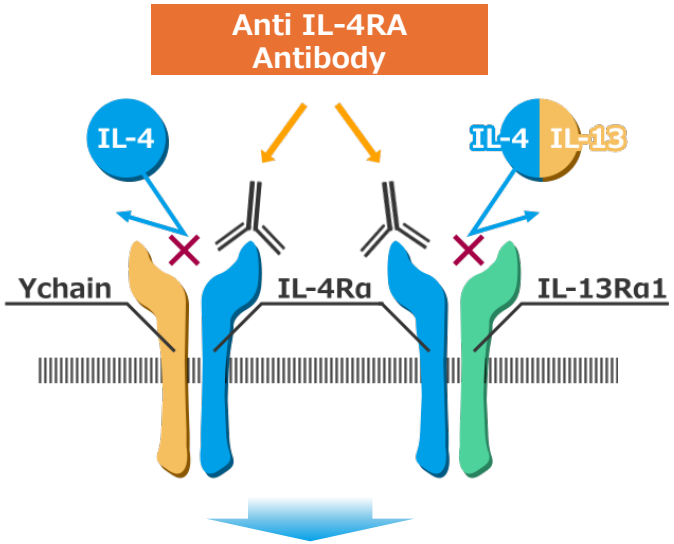
- Oral Small molecule Drugs for Type2 inflammatory Diseases ► **Dosing Convenience (UMN)**
- In-House Drug Discovery Product ► **Licensed to J&J** ► **Towards Global Expansion**
- **With maximum milestone payments of $1.2 billion + royalty income**

From In-House Drug Discovery to Global Blockbusters

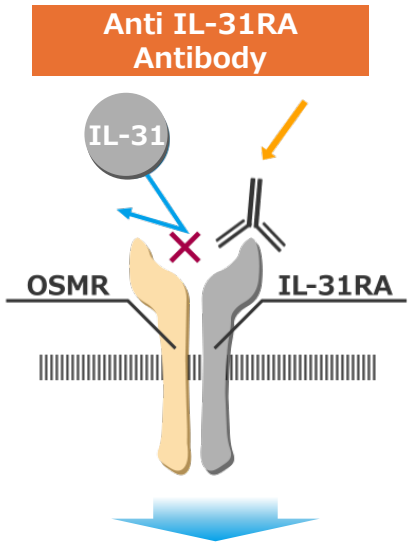
Kaken's Drug Discovery Research for Allergic Disease Treatments



Drug development for type 2 inflammatory diseases such as atopic dermatitis



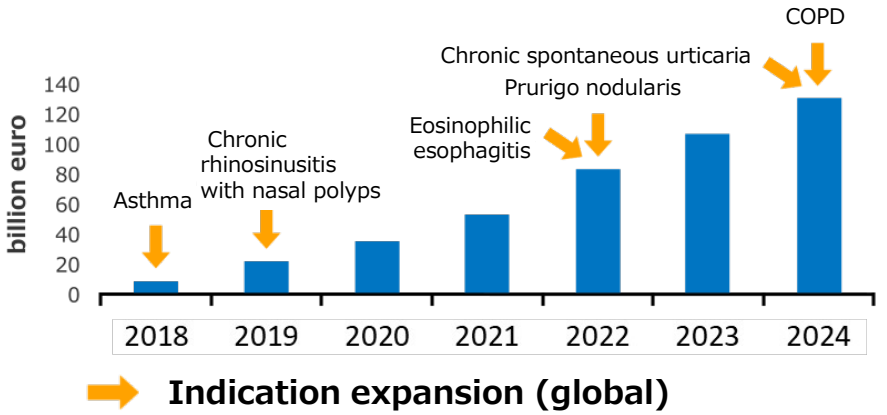
Impairment of skin barrier function and exacerbation of chronic inflammation



Pruritus

Illustration: Kaken Pharmaceutical

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



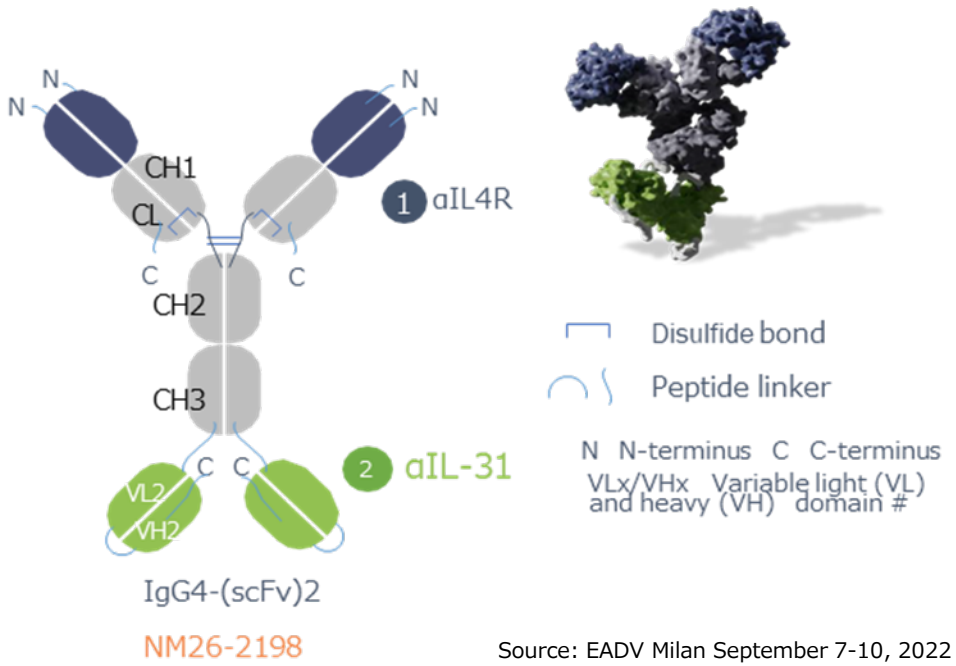
Indication expansion (global)

Source: Created based on materials disclosed on Sanofi's official website

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

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

- **A bi-specific antibody** targeting IL-4Rα 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**.



Source: EADV Milan September 7-10, 2022

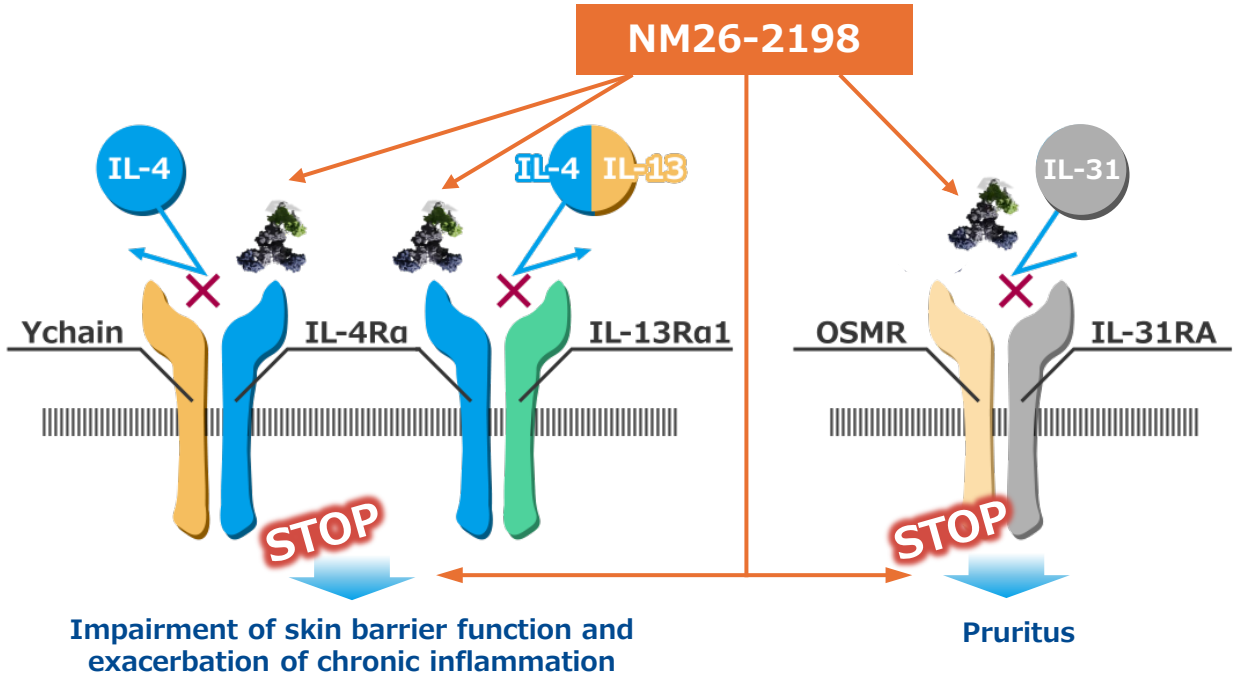


Illustration: Kaken Pharmaceutical

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

STAT6 inhibitor targeting type 2 inflammation

Differences Between Dupilumab and STAT6 Inhibitors

Differences in Targets
The antibody inhibits extracellular IL-4Rα.
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.

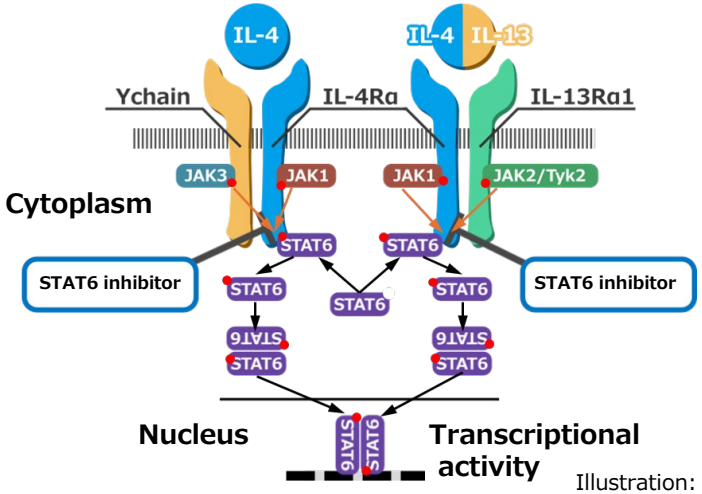


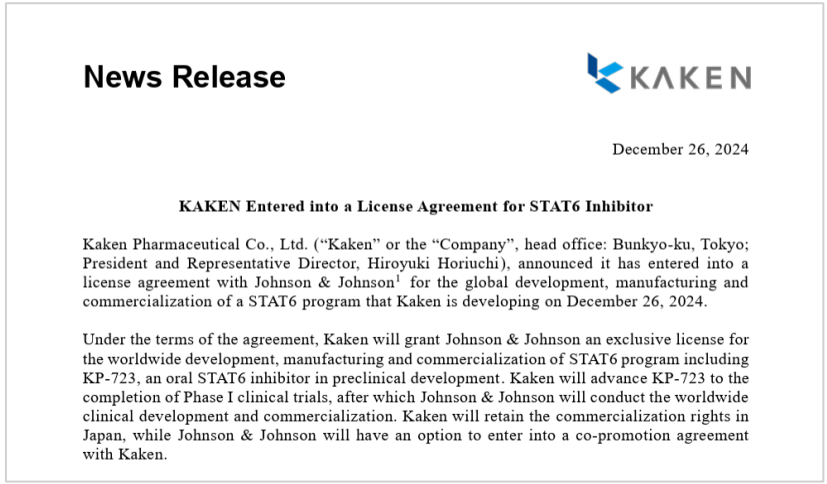
Illustration: Kaken Pharmaceutical

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

KAKEN

December 26, 2024

KAKEN Entered into a License Agreement for STAT6 Inhibitor

Kaken Pharmaceutical Co., Ltd. ("Kaken" or the "Company", head office: Bunkyo-ku, Tokyo; President and Representative Director, Hiroyuki Horiuchi), announced it has entered into a license agreement with Johnson & Johnson[1] 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.

NM81 : From New Joint Research with Numab to Development

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

Drug Development Concept

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

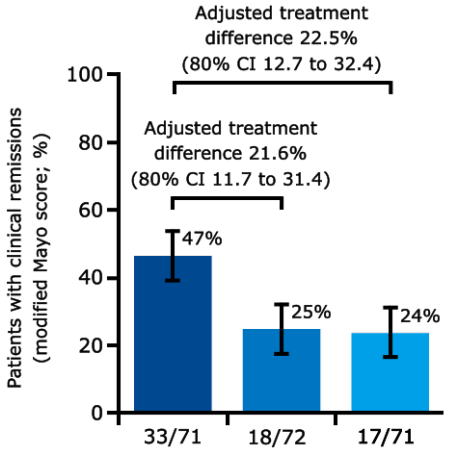
New findings

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

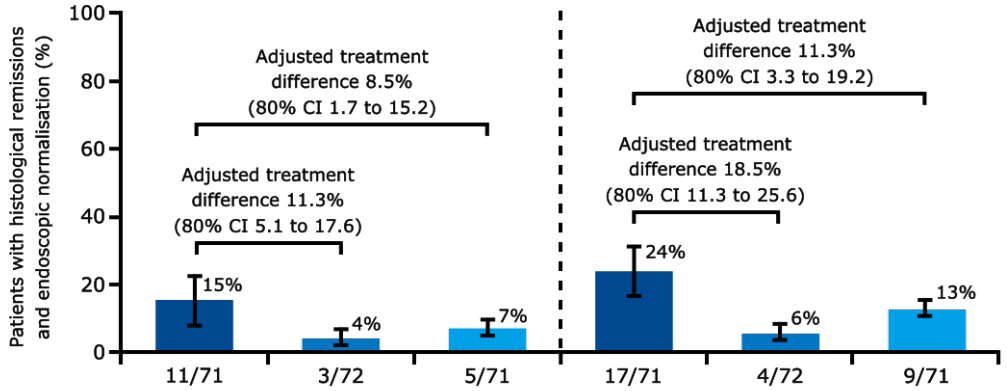
Drug Development Concept

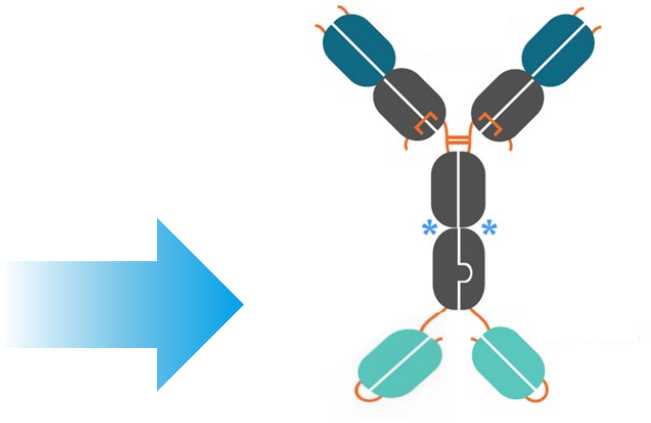
- Inhibit multiple targets with a single molecule
  - ➡ **Expect a higher clinical remission rate than existing therapies**

clinical remission rate （12 wks)



endoscopic and histologic remission





Source: EADV Milan September 7-10, 2022

1) Gastroenterol Hepatol (N Y). 2023 Jan; 19(1): 31–33.
2) Lancet Gastroenterol Hepatol, 2023; 8: 307–20

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Pipeline

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	PⅢ	Dermatology, Pediatrics	Head lice	In-licensed from Arbor Pharmaceuticals, LLC (Currently, Azurity Pharmaceuticals) Product name in the U.S.: Sklice
KP-001	PⅢ	Pediatrics, Plastic Surgery, Hematology/Oncology, Dermatology	Refractoryvascular malformations	Product discovered in-house Announced the topline data from the confirmatory trial
KC-8025	PⅢ	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	PⅢ	Dermatology	Plaque psoriasis	In-licensed from Alumis Inc. Under global PⅢ (incl. Japan)
Navenibart	PⅢ	Allergy, Dermatology, Internal Medicine, ENT	Hereditary angioedema	In-licensed from Astria Therapeutics, Inc. Under global PⅢ (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.）	PⅢ	Same asabove	Refractory vascular malformations	In-house discovery Preparing for PⅢ 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.

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: Ekterly） ・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 Hyper hidrosis	Approval	Dong-Wha Pharm Co.,Ltd（Korea: Approved in August2025）

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

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

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.

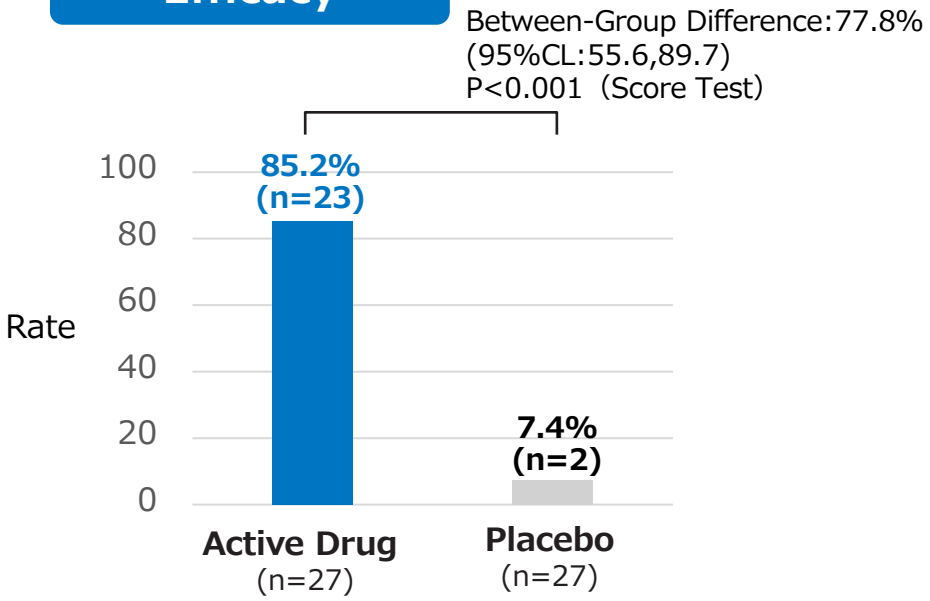
KAR： Results of JP PhaseⅢ Trial

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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Initiatives in Rare Diseases

Expansion into New Therapeutic Areas ～Initiatives in Rare Diseases～

1st X R&D Transformation

VISION

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

PRIORITY MEASURES

Expand pipeline

- Increase the number of licensed products
- Use external resources in early-stage development
- Seek new indications and drug repositioning

Expand into New Therapeutic Areas

✓Expand into new therapeutic areas where we have advantages, based on unmet medical needs

Therapeutic areas where we have advantages

Orthopedics	**Dermatology**	**Other**
Artz Hernicore	Clenafin Ecclock Fiblast	Seprafilm Regroth

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New Therapeutic Areas

- Diseases with unmet medical needs at 10 years in the future
- **Rare diseases**

- 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

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

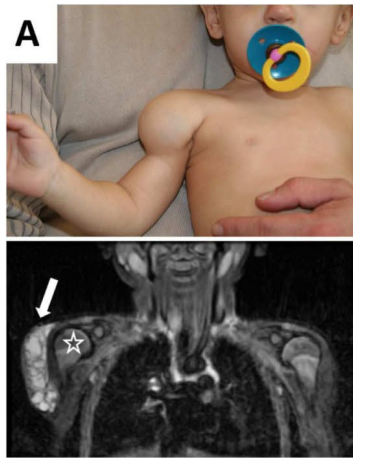
- **Surgical excision/Sclerotherapy**: Standard care
- Limited **surgical excision** due to bleeding/lesion site
- Rapamycin (Sirolimus) approved in Japan in Sep. 2021

Number of patients

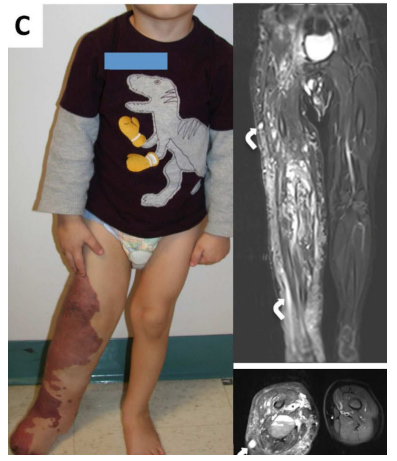
	Japan	U.S. (population: 330M)
• Venous Malformation (VM)	**20,000**[*1]	**33,000～66,000**[*2]
• Lymphatic Malformation (LM)	**10,000**[*1]	**20,000～55,000**[*3]
• Klippel-Trenaunay Syndrome (KTS)	**3,000**[*1]	**3,000～ 7,000**[*4]
• PIK3CA-related Overgrowth Spectrum (PROS)	—	**4,760**[*5]

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

LM



KTS



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

VM

Source: JOHNS HOPKINS MEDICINE HP

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.

KP-001 : Mechanism of Action

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

Immunosuppression caused by mTOR inhibition
Immunosuppression caused by PI3Kδ inhibition
→ Observed events: interstitial pneumonia, infections, stomatitis, skin disorders.

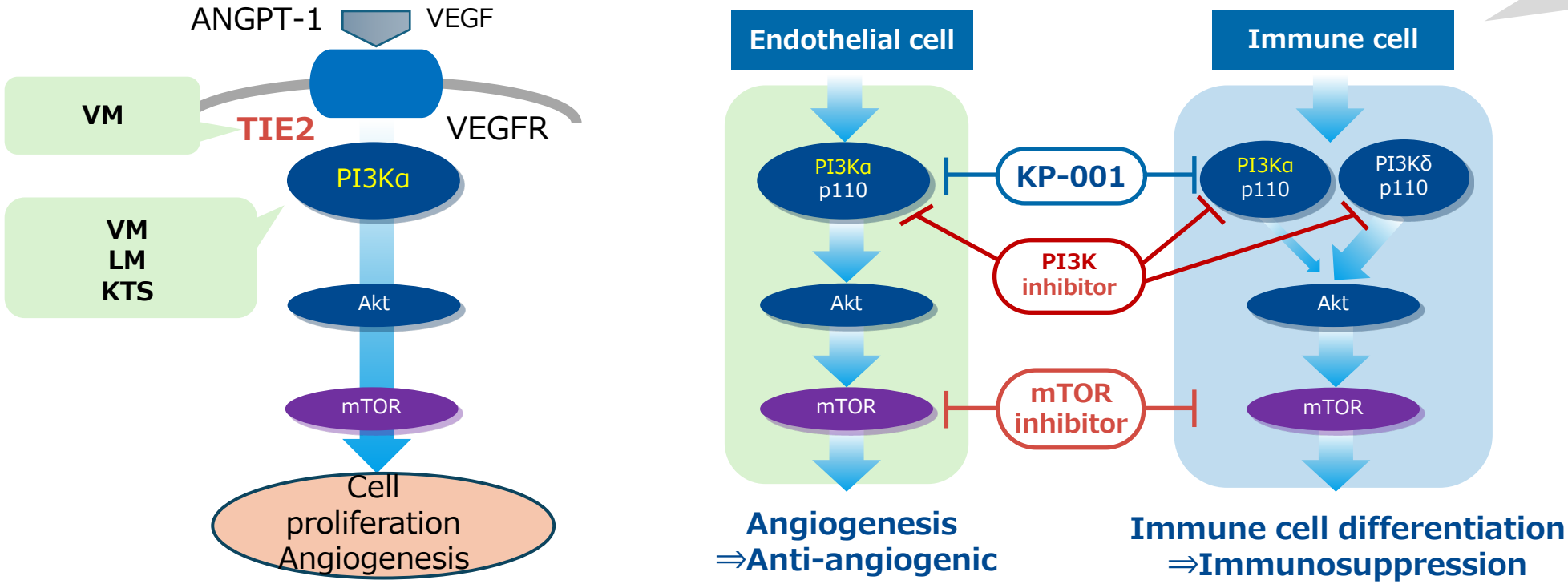


Illustration: Kaken Pharmaceutical

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.**

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)

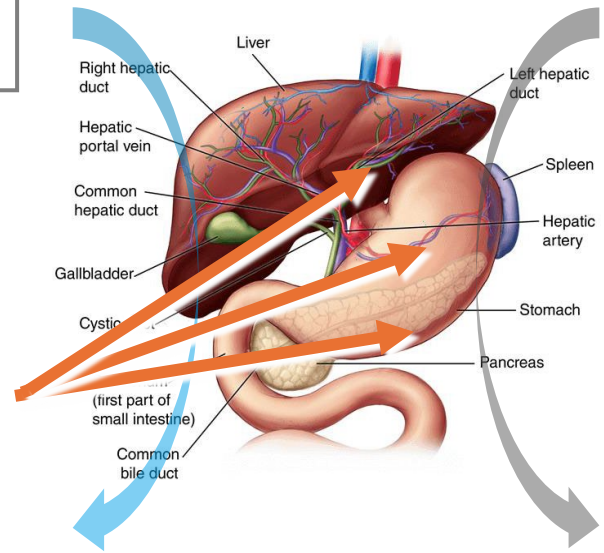
Immune cell activation

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

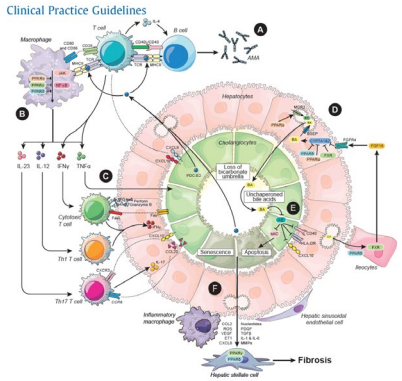
Improvement of pruritus, fatigue, jaundice

Inhibition of progression to liver cirrhosis, liver cancer

Peroxisome proliferator-activated receptor δ (PPAR δ) agonist

Mode of Action

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



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

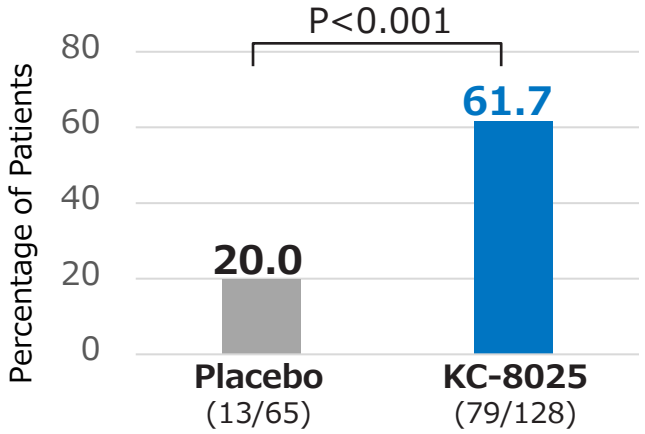
*1 : Research on Intractable Liver and Biliary Tract Diseases (Ministry of Health, Labour and Welfare Research Project on Intractable Diseases)
*2 : Gilead Sciences, Inc. Public Information
https://s29.q4cdn.com/585078350/files/doc_financials/2025/q3/GILD-Q325-Earnings-Presentation-30-October-2025.pdf

KC-8025 : Global Joint Phase Ⅲ Trial

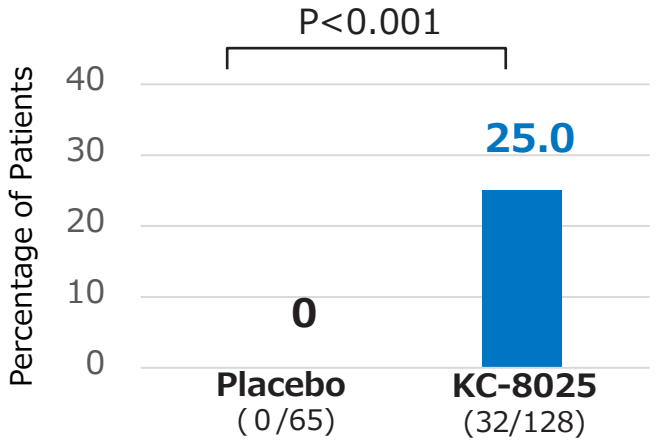
Result of Phase Ⅲ Trial

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-

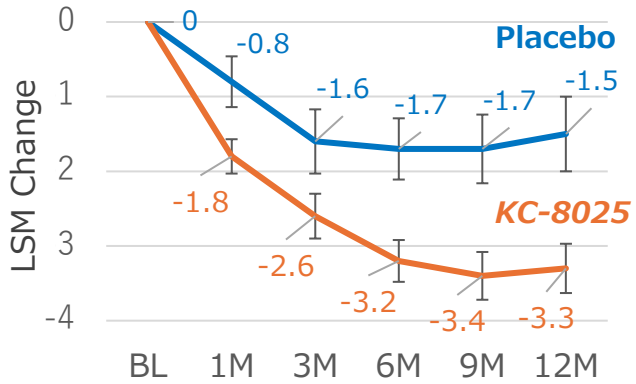
- Composite endpoint of ALP and total bilirubin [TimeFrame:12 months]
- ALP < 1.67× ULN,≥ 15% decrease in ALP, and Total bilirubin ≤1.0× ULN



- 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 Trail 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 wih 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-details-August 14, 2024
Gilead Sciences, Inc. - Gilead's Livdelzi (Seladelpar) Granted Accelerated Approval for Primary Biliary Cholangitis by U.S. FDA

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**

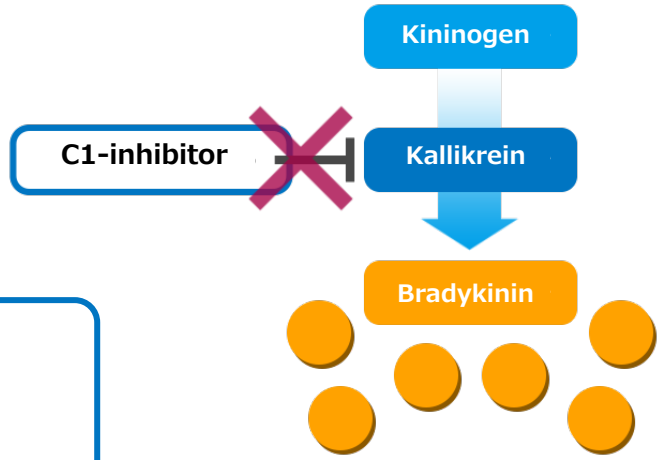


Illustration: Kaken Pharmaceutical

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

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.

PhaseⅢ 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 attaks, (including laryngeal attacks and breakthrough attacks during prophylaxis

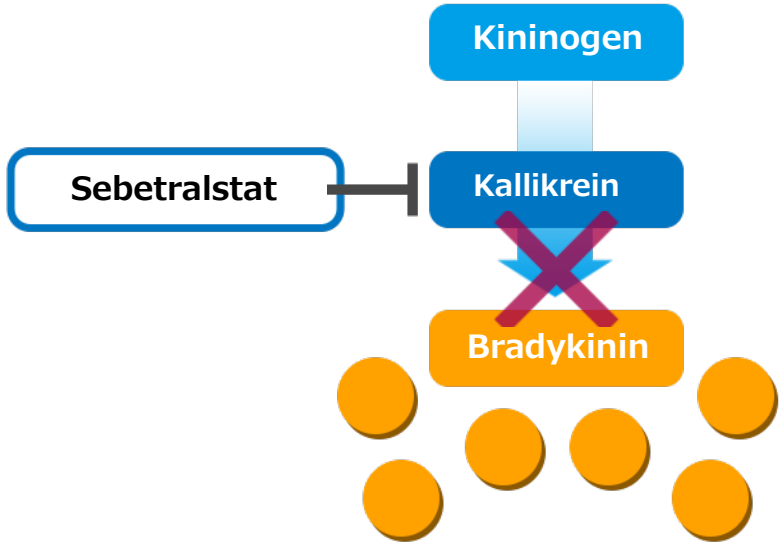


Illustration: Kaken Pharmaceutical

Sebetralstat : PhaseIII KONFIDENT trial - Results

Ekterly® (sebetralstat) tablets 300 mg

efficacy

▶ **Primary endpoint**（Time to Relief PGI-C ）

Median(95%Cl) : 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%）

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 beed designated as an orphan drug in Japan
  The application for **manufacturing and marketing approval was submitted** in January 2025.

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 Ⅰor Ⅱ（Experienced at least 2 HAE attacks during the Run-In period）

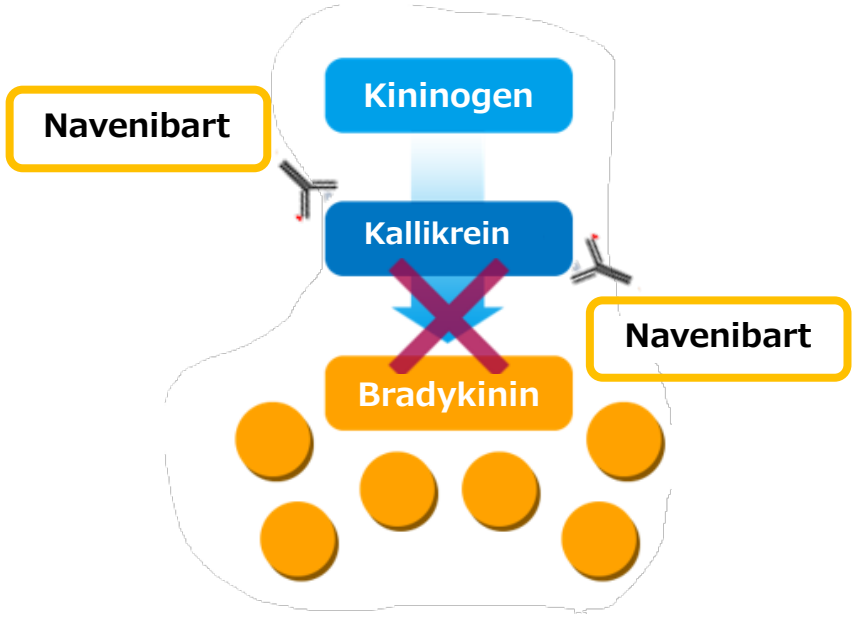


Illustration: Kaken Pharmaceutical

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

efficacy

(average six months)

Cohort 1
(450㎎ 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
（600㎎→after three months 300㎎、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
（600㎎→ after one month 600㎎、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.**

7

Other In-lisenced Development Products

ESK-001: Innovative TYK2 Inhibitor for Psoriasis Treatment

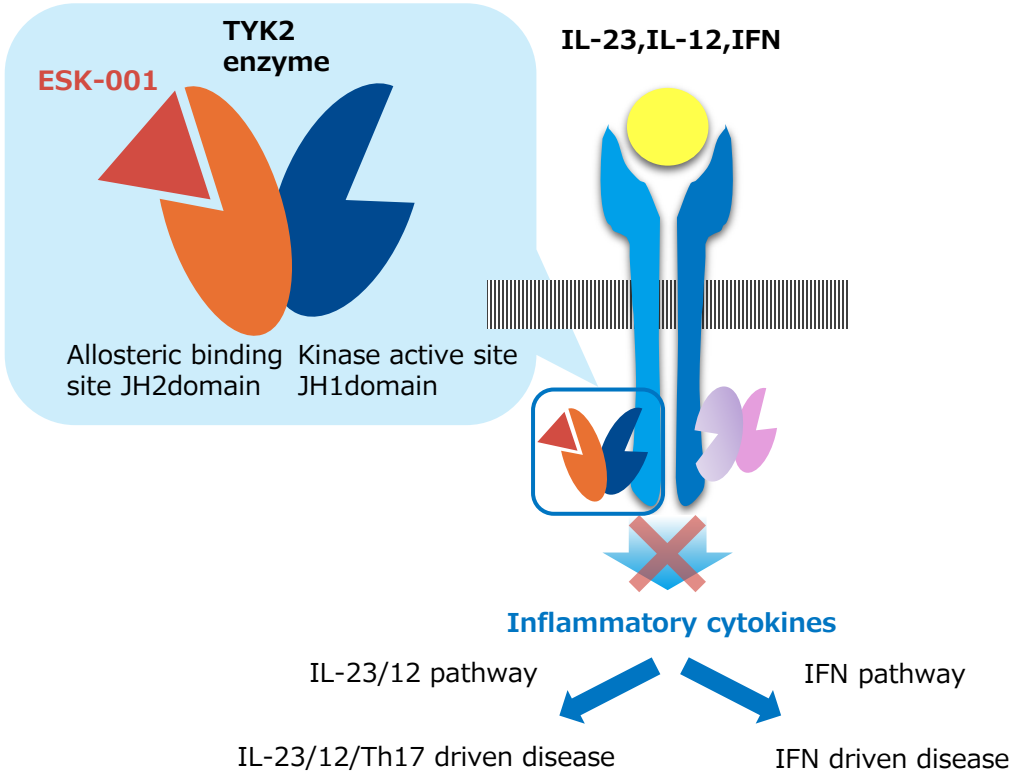
Developer : **Alumis Inc.** (U.S.)
Mechanism of Action : **Highly selective inhibition of TYK2** (Tyrosine Kinase 2)
Administration : **Oral** (twice daily; once-daily modified-release formulation also under development)

Development Status:

- **Moderate to Severe Plaque Psoriasis** (PhaseⅢ trial)
- **Systemic Lupus Erythematosus (SLE)** (PhaseⅡ 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 & Venereology Congress, September 25-28, 2024, P1004

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**

8

Market Size and Project Development Timeline

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

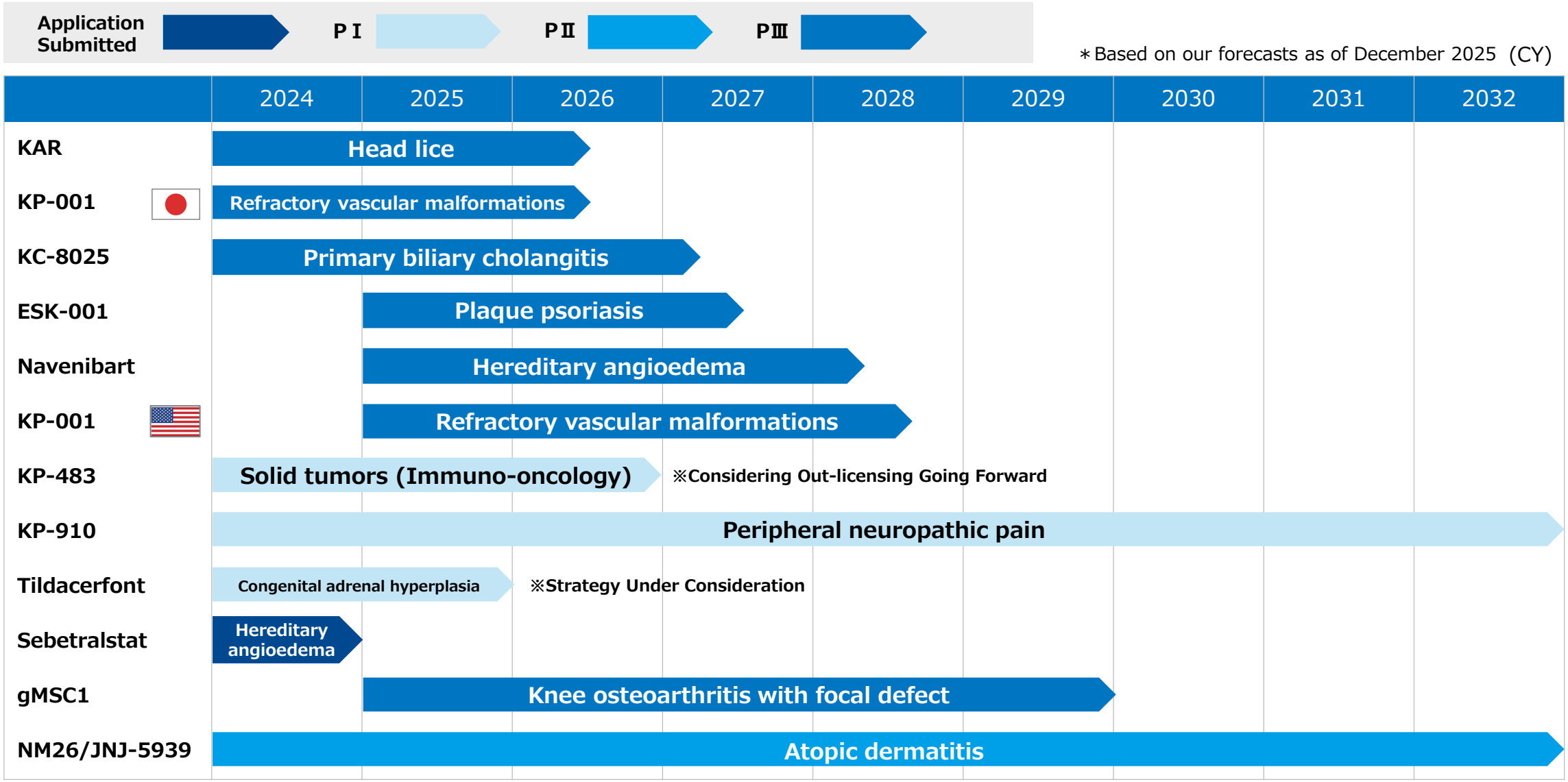
Market Size

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.
*17 : ©DRG [2021] DR/Decision Resources, LLC. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.

Pipeline Progress Forecast



Appendix

Pipeline Status (In-house Discovered & In-licensed Projects)

Development Phase	PⅠ	PⅡ	PⅢ	Application Submitted
In-house discovered	**KP-483** (Solid tumors) **KP-910** (Peripheral neuropathic pain) KP-723 is in pre-Phase I.	**Announced the topline data from the confirmatory trial**	**KP-001** (Refractory vascular malformations) **KP-001** (Refractory vascular malformations)	**Preparing for PⅢ**
In-licensed products	**Tildacerfont** (Congenital adrenal hyperplasia)		**KAR** (Head lice) **KC-8025** (Primary biliary cholangitis) **ESK-001** (Plaque psoriasis) **Navenibart** (Hereditary angioedema)	**In-licensed in August**

Pipeline Status (Other Development Products)

Development Phase	PⅠ	PⅡ	PⅢ	Application Submitted

Partner-developed Products

- KalVista Pharmaceuticals — **Sebetralstat** (Hereditary angioedema)
- 株式会社ツーセル TWOCELLS COMPANY, LIMITED — **gMSC1** (Knee osteoarthritis with focal defect) — Preparing for PⅢ
- Johnson&Johnson — **NM26** (Atopic dermatitis) — Approved in Italy and Germany in 2025

Out-licensed Products (Overseas)

- almirall feel the science — EU — **Efinaconazole** (Clenafin) Onychomycosis
- **AIM** China — **Efinaconazole** (Clenafin) Onychomycosis — Approved In August 2025
- SINCE 1897 — **Dong-Wha** Korea — **Sofpironium bromide** (Ecclock) Primary axillary hyperhidrosis

Pipeline Progress Forecast – Planned Disclosure of Upcoming Milestones

＊Based on our forecasts as of December 2025

Development code	Indication	2025 H1	2025 H2	2026 H1	2026 H2	2027 H1	2027 H2
KAR	Head lice		**Phase Ⅲ Topline Data Disclosure**				
KP-001	Refractory vascular malformations		**Phase Ⅲ Topline Data Disclosure**				
KC-8025	Primary biliary cholangitis				**Phase Ⅲ Completion**		
ESK-001	Plaque psoriasis		**Phase Ⅲ Topline Data Disclosure (PsO)**	**Phase Ⅱb Topline Data Disclosure (SLE)**			
Navenibart	Hereditary angioedema					**Phase Ⅲ Topline Data Disclosure**	
KP-483	Solid tumors (Immuno-oncology)		**Phase I Completion**	※Considering Out-licensing Going Forward			
KP-910	Peripheral neuropathic pain	**Phase I Completion**	※Data Analysis Underway for the Next Phase				
Tildacerfont	Congenital adrenal hyperplasia	**Phase I Completion**	※Strategy Under Consideration				
KP-001	Refractory vascular malformation	**Preparingfor Phase Ⅱ**	※Preparing for P Ⅲ trial				
KP-723	Type 2 Inflammatory Diseases	**Preparing for Phase I**					

Status of Other Development Products (Upcoming Milestones)

＊Based on our forecasts as of December 2025

Development code	Indication	2025		2026		2027	
		H1	H2	H1	H2	H1	H2
Sebetralstat	Hereditary angioedema		Marketing Approval Granted				
gMSC1	Knee osteoarthritis with focal defect		Preparing for PⅢ				
NM26	Atopicdermatitis			Phase Ⅱ Completion (Projection)			

Status of Overseas Out-licensed Products (Upcoming Milestones)

Generic name	Indication	Out-licensed	2025		2026		2027	
			H1	H2	H1	H2	H1	H2
Efinaconazole (Clenafin)	Onychomycosis	Almirall S.A. (EU)	Marketing Approval Granted					
Efinaconazole (Clenafin)	Onychomycosis	AIM (China)	※Phase Ⅲ trial Currently Ongoing. Detailed Completion Timeline Not Disclosed.					
Sofpironium Bromide (Ecclock)	Primary axillary hyperhidrosis	Dong-Wha (Korea)	Marketing Approval Granted					

gMSC1 –Joint Development Initiated with Two Cells Co., Ltd.

- Three-dimensional artificial tissue derived from allogeneic (donor) synovial mesenchymal stem cells, created by Two Cells
- Being developed as a regenerative medicine product for cell therapy to **repair damaged cartilage**

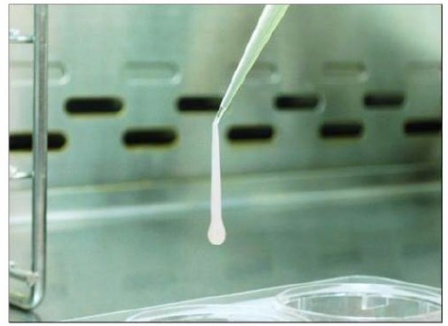


Image of gMSC1

Key Features

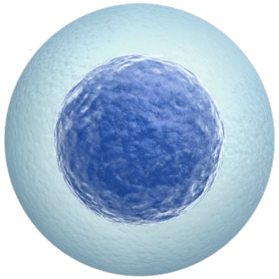
- Allogeneic cell-based product expected to enable stable supply
- Easy to handle during surgery, allowing simple and efficient procedures
  - Two Cells has conducted a Phase Ⅲ trial targeting “traumatic cartilage injury and osteochondritis dissecans”
  - gMSC judged to have high potential

⇒ **Plan to conduct a Phase Ⅲ trial targeting “knee osteoarthritis with focal defect”**

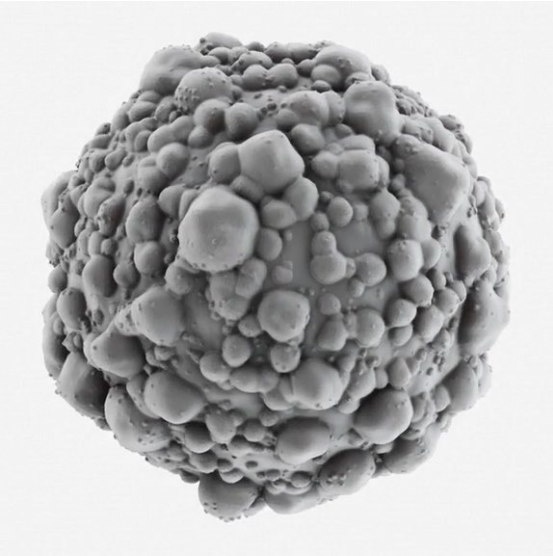
PEComa Treatment – FYARRO®

Primary Perivascular Epithelioid Cell Tumor (PEComa)

- Malignant PEComa: A rare cancer classified as a **soft tissue sarcoma**.
- "PEC" refers to the **perivascular epithelioid cells** that compose the tumor.
  Sarcomas: Rare cancers that arise in bones and soft tissues such as **fat, blood vessels, muscles, and nerves**.
- Malignant PEComa is **highly aggressive** and can metastasize.
- Early-stage tumors **may be surgically removed**.
- Locally advanced or metastatic PEComas **cannot be surgically removed** or have spread to other parts of the body.



Normal cells

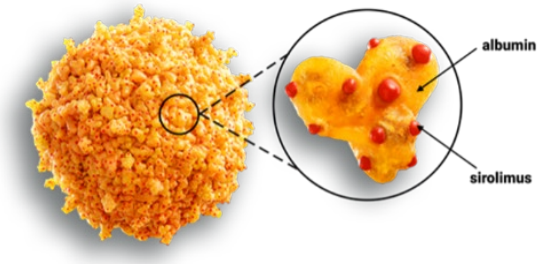


PEComa cells

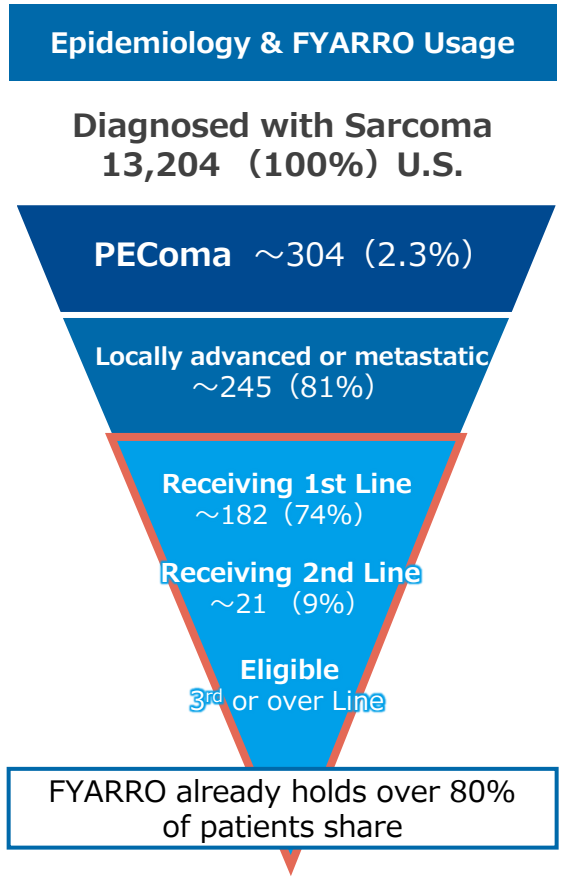
Source : FYARRO® web page https://www.fyarro.com/

FDA-approved in November 2021, launched in the U.S. in February 2022

- 100 mg/m² intravenous injection on Day 1 and Day 8 of a 3-week cycle.
- Active ingredient: Sirolimus, an mTOR inhibitor, suppresses genes involved in excessive cell proliferation.
- Utilizes nanoparticle technology to enhance sirolimus delivery to tumors and boost mTOR inhibition.
- Commands over 80% U.S. patient share, with a stable market outlook.



Source ： FYARRO® web page https://www.fyarro.com/



Source ： FYARRO® tracking Pulse- Wave 6（March 2024）

Genetic Mutations and FYARRO Mechanism of Action in PEComa

Cause of PEComa

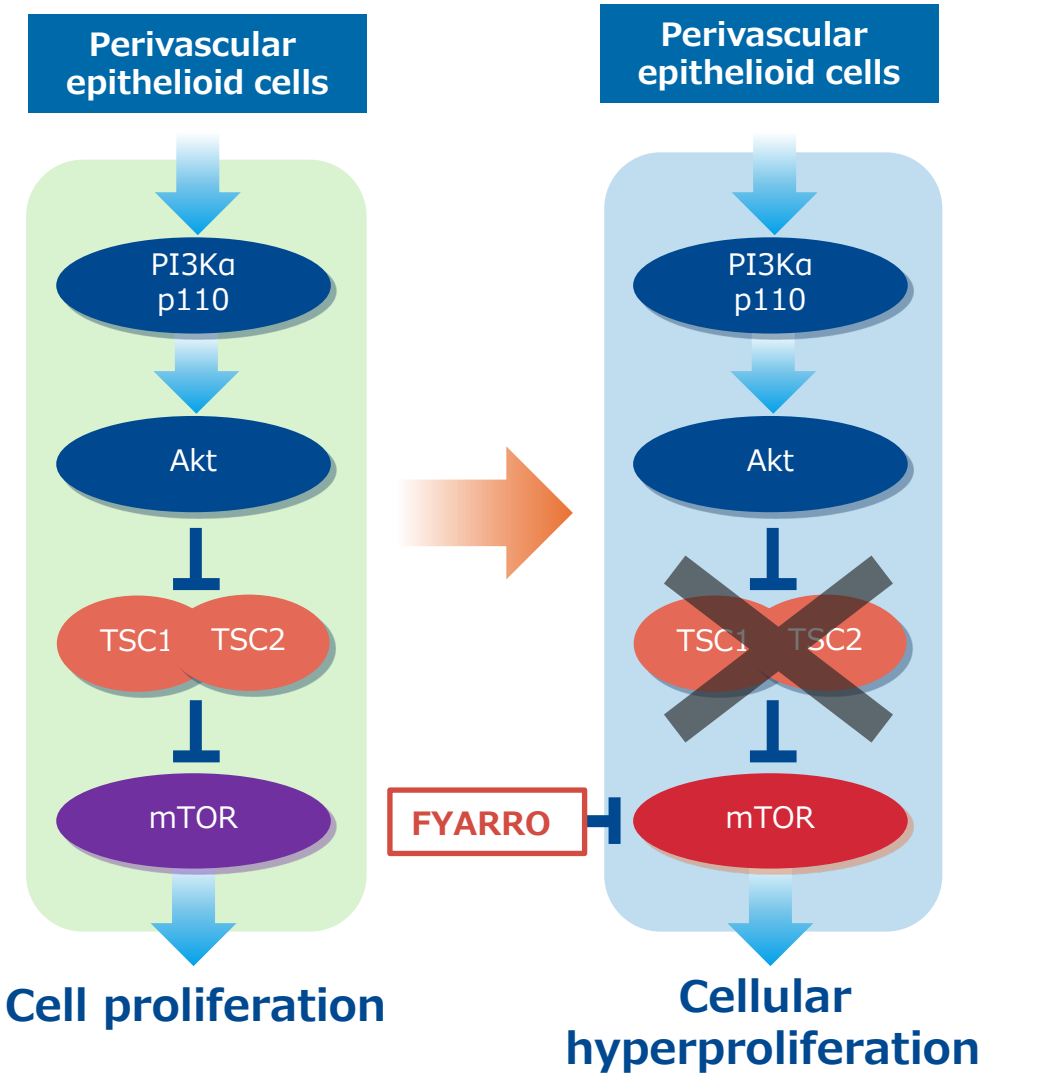
Often **involves mutations in TSC1 or TSC2** genes, leading to overactivation of the mTOR pathway, promoting tumor growth and angiogenesis.

Mechanism of FYARRO

Inhibits mTOR, **thereby suppressing PEComa cell proliferation and angiogenesis**.
Particularly effective in cases involving TSC1/TSC2 mutations.

Synergy with KP-001

mTOR, the target of FYARRO, is downstream of PI3Kα, the target of KP-001.
As PEComa is a rare disease, FYARRO's distribution network and marketing strategy can be leveraged for KP-001's U.S. market expansion.



(Illustration: Kaken Pharmaceutical)

Bringing Smiles to Everyone

KAKEN helps improve the quality of life of patients by serving as many people as possible to return smiles of happiness to their faces, through supplying superior pharmaceuticals.
In this endeavor, we always strive to be “the best,” rather than pursuing the scale of business.
We aspire to be, and to remain, a company that can create “Joys” for patients, society and our employees.
We also hope to contribute to society by demonstrating KAKEN’s distinctive and vigorous presence.

KAKEN

KAKEN PHARMACEUTICAL CO., LTD.