# SHIONOGI R&D Day 2024

June 7, 2024

Shionogi & Co., Ltd.

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# Agenda

## 1. Toward Realization of 2030 Vision

Isao Teshirogi, PhD / Chief Executive Officer

## 2. SHIONOGI R&D

- R&D Strategy — John Keller, PhD / Senior Executive Officer,
  Senior Vice President, R&D Supervisory Unit
- Actions in Focus Areas — Takeki Uehara, D.V.M., PhD / Corporate Officer,
  Senior Vice President, Drug Development and Regulatory Science Division
  - QOL Diseases with High Social Impact
  - High-impact Infectious Diseases that Threaten Society

## 3. Closing

Isao Teshirogi, PhD / Chief Executive Officer

# Toward Realization of 2030 Vision

Isao Teshirogi, PhD
Chief Executive Officer



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# SHIONOGI Group Heritage

SHIONOGI Group Heritage

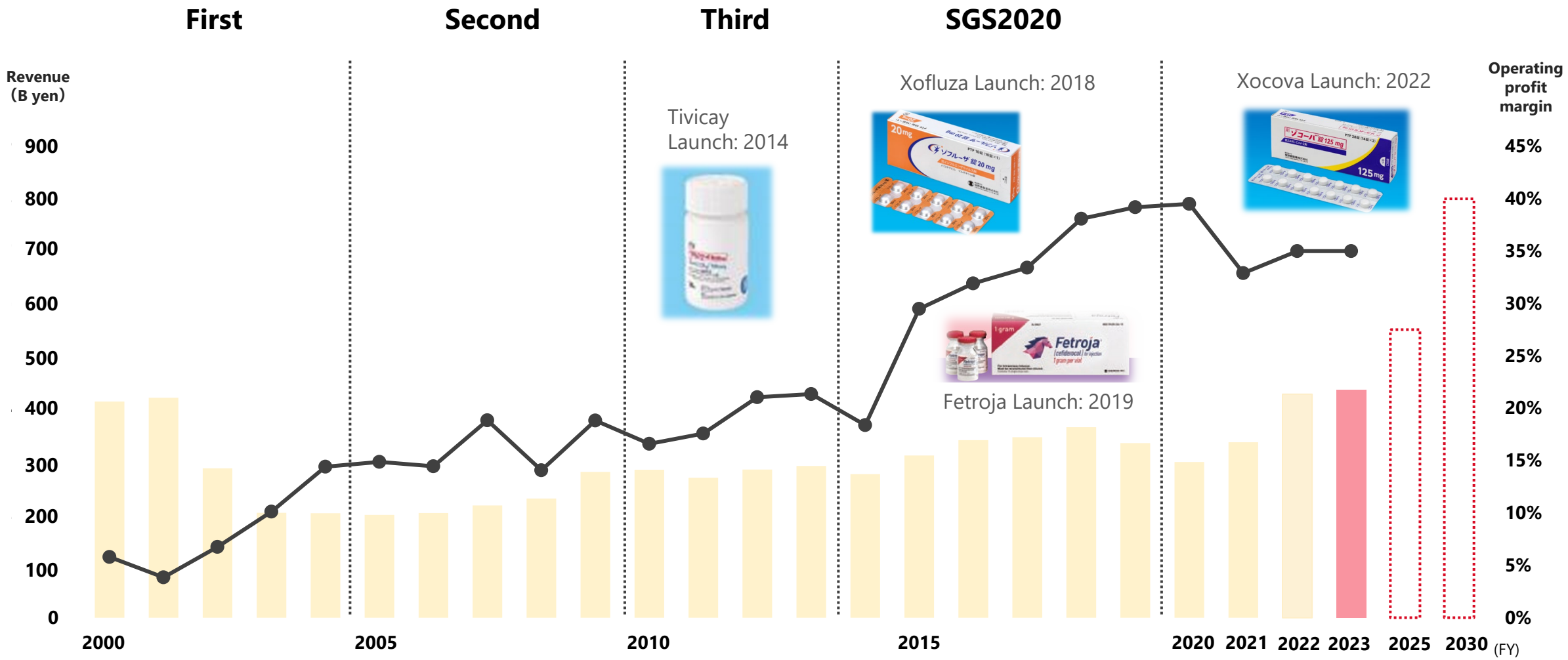
## SHIONOGI strives constantly to supply the best possible medicine to protect the health and wellbeing of the patients we serve.

The unwavering purpose of the SHIONOGI Group's corporate activities is expressed in the opening of "The Company Policy of SHIONOGI (SHIONOGI Group Heritage)" as the image of what SHIONOGI should be and the Company's social existence values. With the changes taking place in our environment, we are broadening our interpretation of "medicine" to encompass healthcare solutions.

*SHIONOGI: A general term for the SHIONOGI Group

# SHIONOGI's Growth Goes Hand in Hand with In-house Discovered Compounds

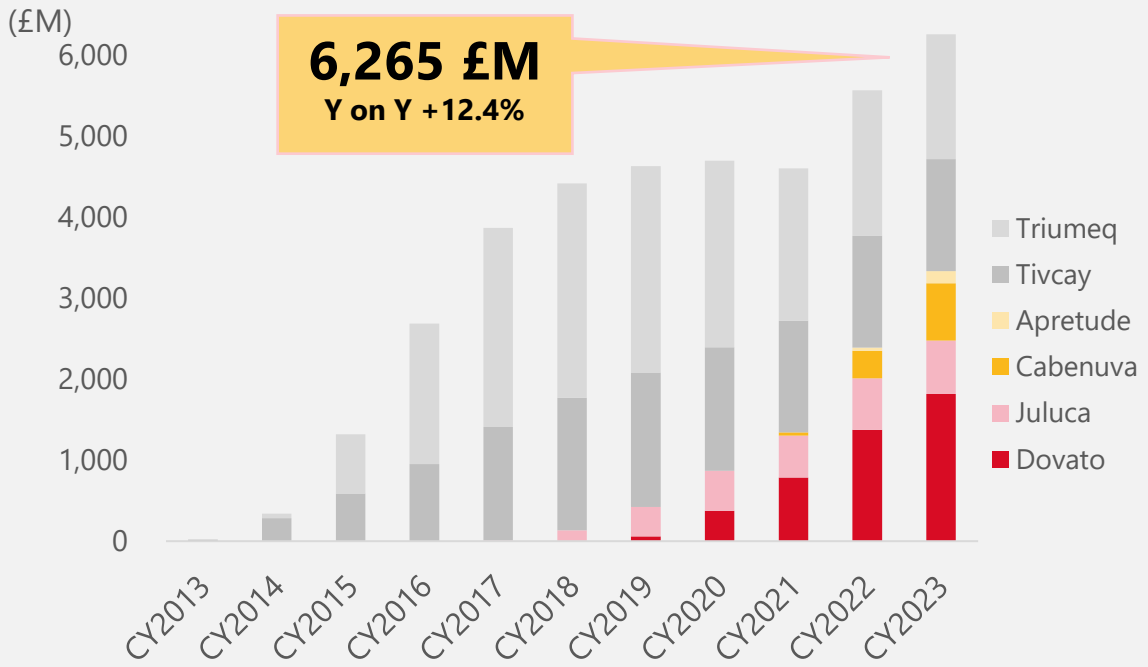
## Consistently stable financial performance



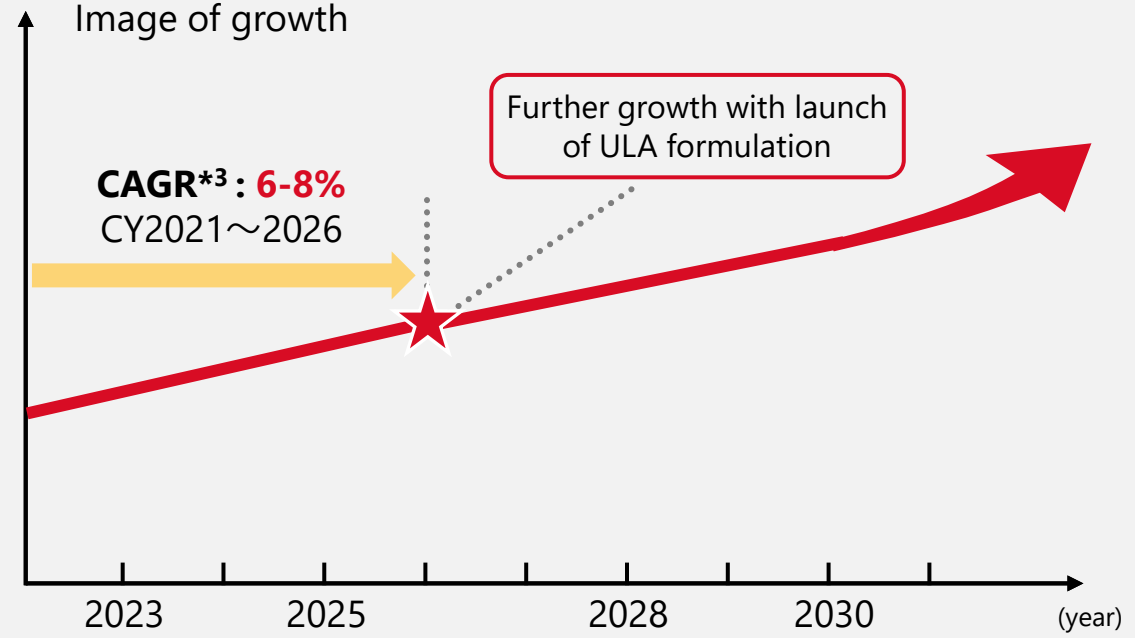
# Growth Factors ①: HIV Business

## HIV business continues to grow strongly and steadily

### HIV business is growing rapidly




### HIV business is expected to expand due to the growth of LA* and ULA*2 formulations






* Long acting *2 Ultra long acting *3 CAGR (Compound Annual Growth Rate)

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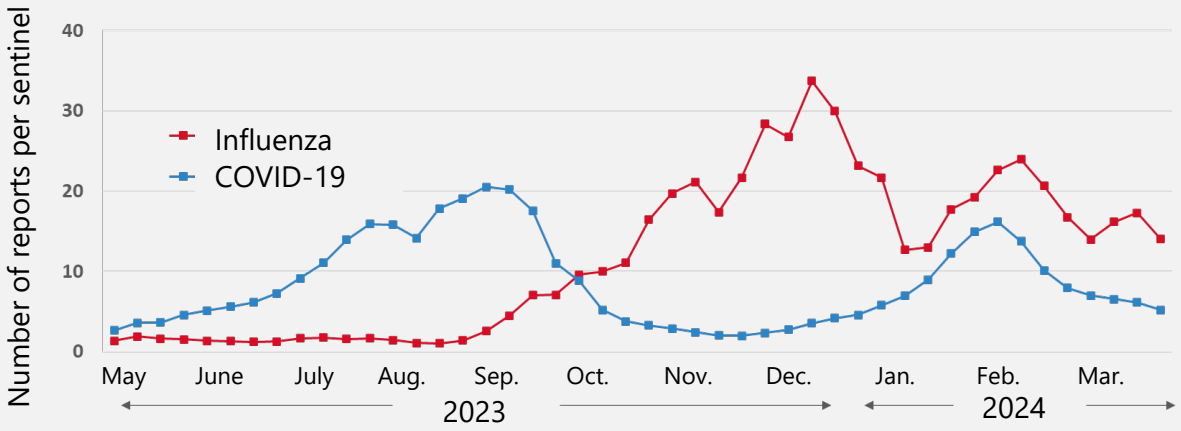
# Growth Factors ②
# : Embracing the challenge of evolving our business model

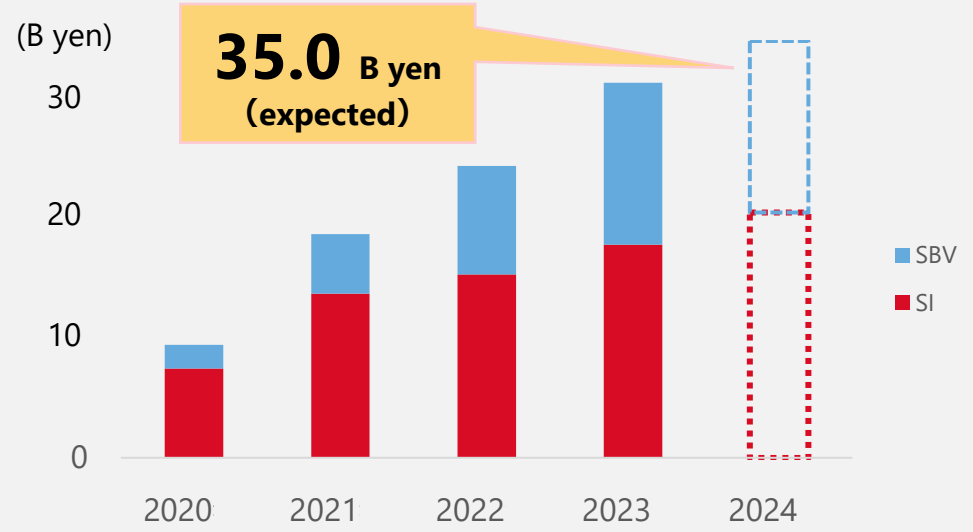
**Japan's acute respiratory infection business and overseas business are growing steadily**

## Stabilization of acute respiratory infection treatments




Stable revenue structure achieved through sales of both influenza and COVID-19 treatments

## Stable growth of overseas business




Steady progress of Cefiderocol



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# From Stability to Further Growth in Infectious Disease Business

**The domestic sales growth and global expansion of Xocova are of utmost importance**

**Value enhancement in Japan** → **Global expansion**

- Awareness of the importance of rapidly reducing the viral load in the body

- Importance of the “Test to Treat” initiative

**The key focus is to improve the diagnosis and treatment rates**

# SHIONOGI is Working to Implement Test toTreat Globally

## Pursuing “Test to Treat” towards the realization of STS2030

**Further evolution of the infectious disease business through diagnosis**

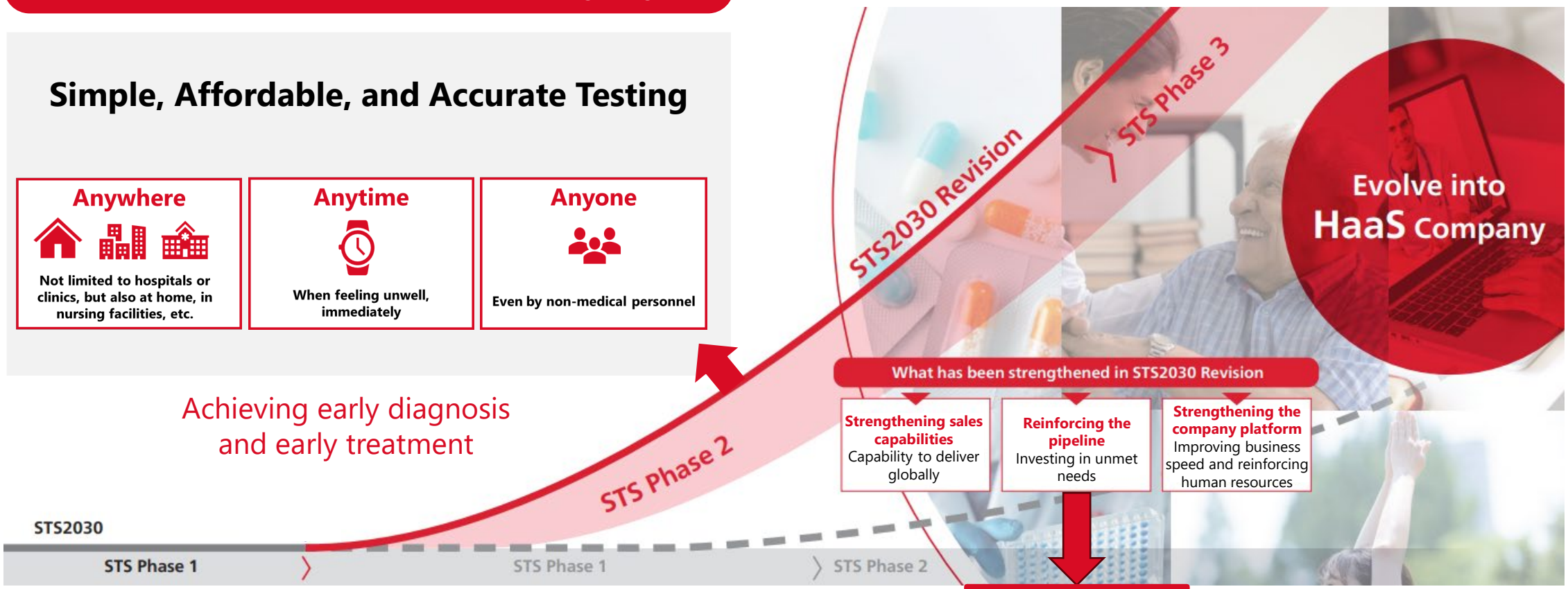
### Simple, Affordable, and Accurate Testing

**Anywhere**
Not limited to hospitals or clinics, but also at home, in nursing facilities, etc.

**Anytime**
When feeling unwell, immediately

**Anyone**
Even by non-medical personnel

Achieving early diagnosis and early treatment



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# SHIONOGI R&D

## R&D Strategy

John Keller, PhD
Senior Executive Officer, Senior Vice President,
R&D Supervisory Unit



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# 2030 Vision and Medium-Term Business Plan STS2030 Revision

## 2030 Vision

# Building Innovation Platforms to Shape the Future of Healthcare

Formulated a new strategy, **STS2030 Revision**, that clarifies the road to achieving the 2030 Vision without changing the direction we are aiming for

## Points to strengthen in STS2030 Revision

**Global top-line growth**

**Establishment of growth drivers**
**Investing in unmet needs**

**Strengthen the management base**
Improving business speed and strengthen human resources

# R&D Vision and R&D Strategy

## R&D Vision

**Create innovations within and beyond the borders of medical/pharmaceutical fields, unbound from existing concepts, addressing the critical healthcare needs of society**

## R&D Strategy

**Define critical unmet needs and commit to address them using all of our capabilities**

| | |
|---|---|
| **Unmet Need Selection** | • Healthcare issues and diseases that **are expected to remain unsolved and increase over the next 10–20 years**<br>• Issues and diseases for which **the best solutions can be realized by building on SHIONOGI's strengths, coupling with external expertise as needed** |
| **Finding Solutions** | • The needs to be pursued are confirmed by management and addressed by R&D's high execution capability<br>• **Extending the reach and range of SHIONOGI R&D, physically and collaboratively, to find the best solutions with urgency** |
| **Focus and Speed** | • Implement bold resource allocations learned from COVID-19 |

# R&D Disease Strategy: Focus Areas

**Focus on areas where unmet needs exist and where SHIONOGI's strengths can be maximized**

Protect people from the threat of infectious diseases

## High-impact infectious diseases that threaten society

**Acute respiratory viral infections**
COVID-19
Influenza
RSV, etc.

**Antimicrobial resistance (AMR)**

**Infectious diseases requiring a long period of treatment**
HIV, Malaria, tuberculosis, etc.

**Total care, including vaccines**

Contribute to a healthy and prosperous life

## QOL diseases with high social impact

**Cognitive Disorders**

**Obesity**

**Pediatric/Rare diseases**

**Sleeping disorders**

**Hearing impairment**

**Immunology/ Allergy**

# SHIONOGI's Strength in Small Molecule Drug Discovery at the Core

**In the areas of infectious diseases and QOL diseases, the advantages of small molecules can be maximized**

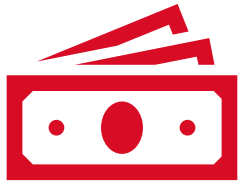
## Strengths of small molecule drugs

### High efficacy and safety

Target the cause of disease by entering cells and directly blocking specific enzymes or receptors

### Oral route

Highly convenient as patients can easily take medication themselves



### Affordable price

Easy to manufacture through chemical synthesis, reducing the economic burden

# Modalities at the Ready when Small Molecules Cannot Meet the Need

Aiming to discover drugs to meet the most difficult unmet needs, strengthen and expand our capability in modalities, expanding our armamentarium

**Capable of addressing unmet needs that are challenging to address with small molecules, e.g.**
Restoring lost function (nucleic acids)
Building specific immune response (vaccines)
Multifunctional capabilities in a single molecule (antibodies, peptides)

**Vaccines**
**(recombinant proteins)**
COVID-19, etc.

**Antibodies**
S-531011, etc.

**Peptides**
S-005151, etc.

**Nucleic Acids**
S-540956, etc.

# Actions to Realize the R&D Strategy: Strengths of the New Organization

## Drug Discovery Research Division

Specialize in research to integrate all modalities and create healthcare solutions to meet unmet needs

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## Pharmaceutical Technology Research Division

Pursue pharmaceutical technology from the perspectives of quality, speed, high functionality, and cost, and maximize the value of our products

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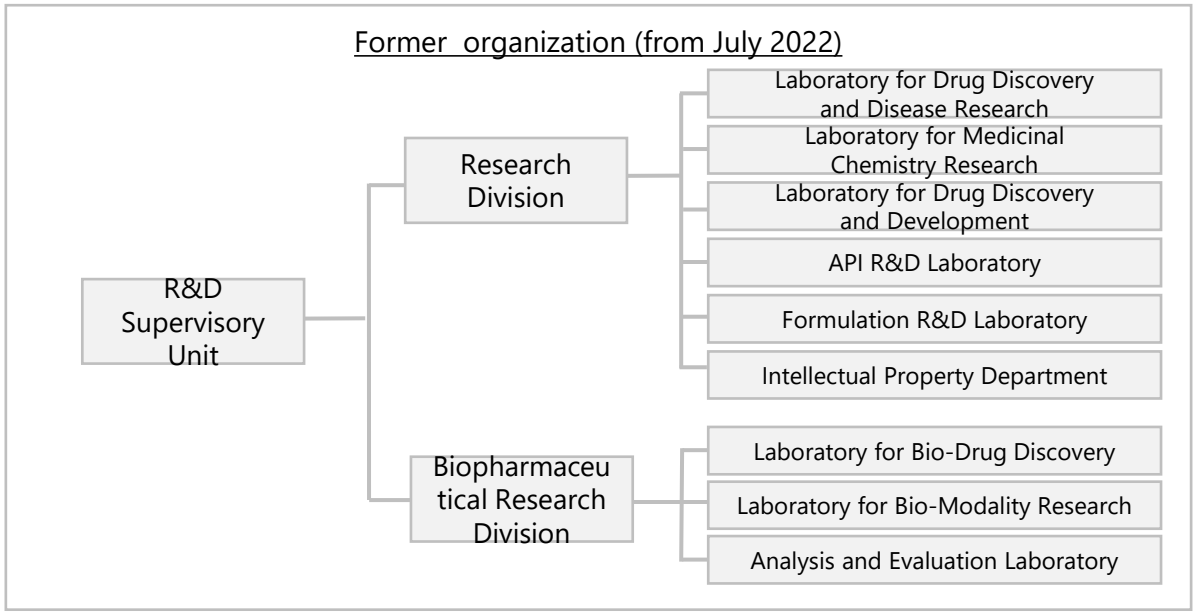
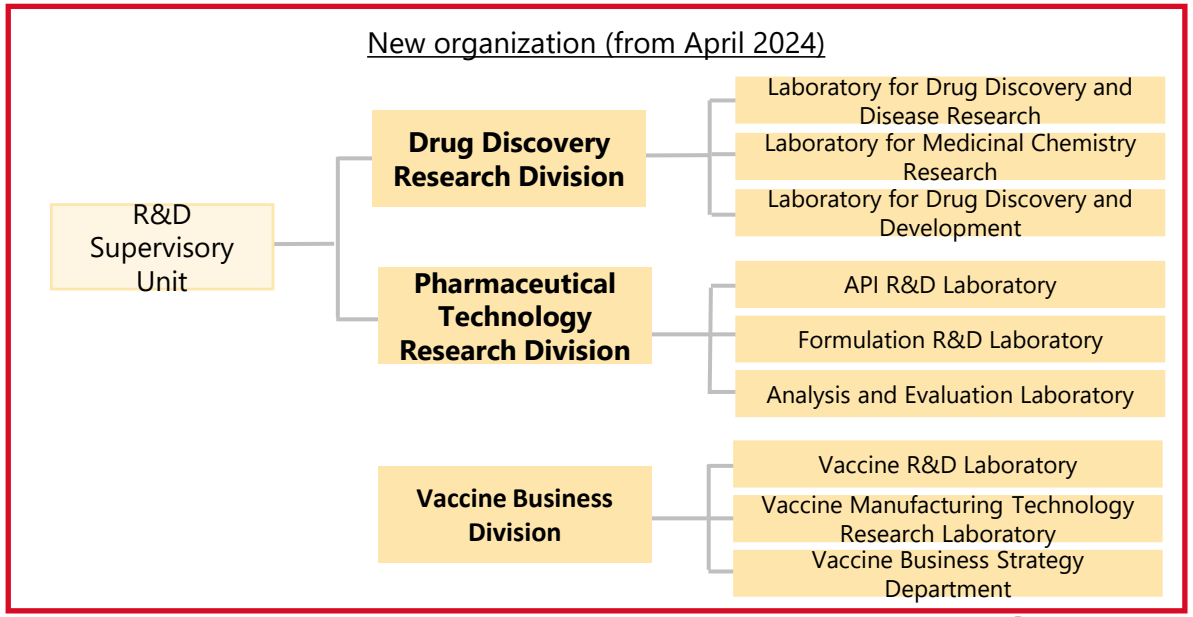
## Vaccine Business Division

Build a system integrating everything from research to supply (accelerate the establishment of a foundational business)



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# Current Status and Future Strengthening Points for Realizing the R&D Strategy

**Further improve the quality and speed of R&D by maximizing our own strengths augmented through external collaboration**

## Current R&D status

While creating a highly profitable earnings structure through the creation of in-house growth drivers, build upon what we have achieved and the lessons we have learned

- The need to understand clinical patient needs ⇒ Products that are best-in-class as compounds but do not provide the best solution for patients
- Changing R&D processes and mindsets through competition with global megapharma companies amid COVID-19
- Rapid response to changes in global (especially US) regulations and the competitive environment

## Future Strengthening Points

**Thorough pursuit of unmet needs**

**Speed to win global competition**

# Actions to Realize the R&D Strategy: Strengthening Collaboration with External Partners


## Highly selective and purpose-driven geographical presence

- QPEX
  ⇒ Establishing US antimicrobial research base, connecting us directly to directly to US infectious disease for preparations pandemic response
- Apnimed, Cilcare
  ⇒ JVs and Collaborations with direct relationships and physical proximity to the top clinical research centers in these new fields

## Government Institutions

- NIH (National Institutes of Health), NIAID
  ⇒Leadership and financial support for the global Phase 3 trial of ensitrelvir
- BARDA, EU HERA, WHO

## Venture capital relationships – an extended network of top experts at the ready

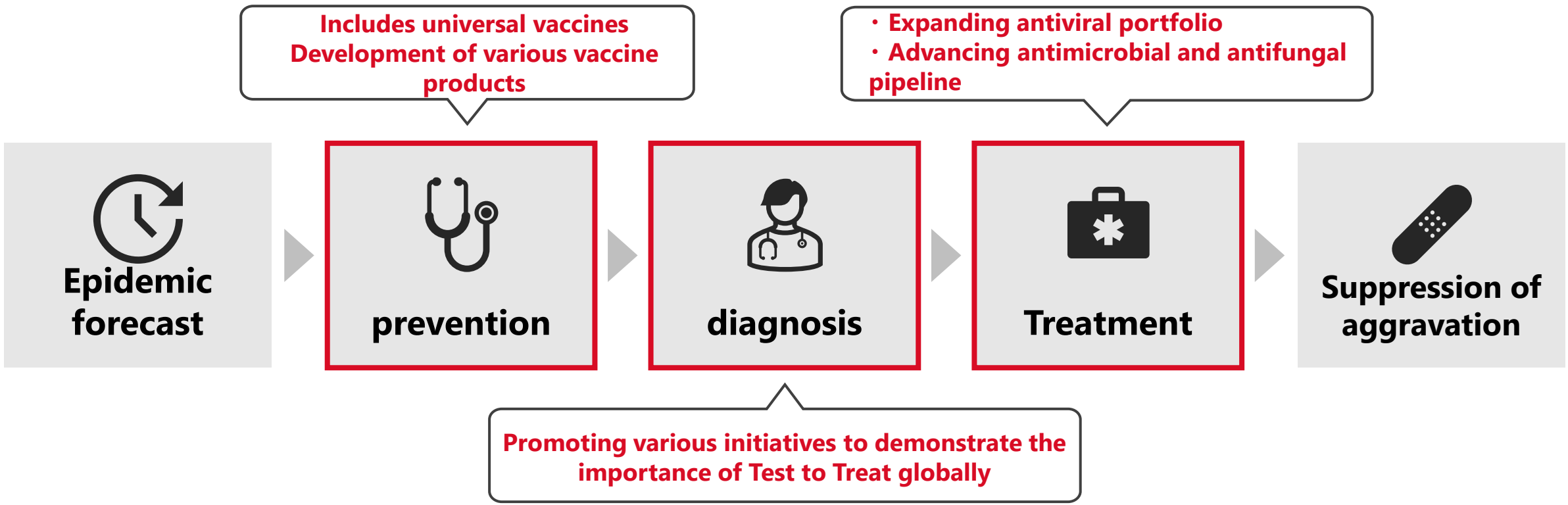
- LSP-Dementia Fund
  ⇒ Real-time project and portfolio guidance from the world's top central nervous system KOLs
- J.P. Morgan Life Sciences Private Capital, AN Ventures, Niremia Collective

## Academia

- Chiba University Hospital
  ⇒Established a joint research department to promote research and development of mucosal vaccines
- University of Texas, University of California, University of Cambridge

# Actions toward Total Infectious Disease Care

**Examining the importance of total care as a whole, concentrating personnel on prevention, diagnosis, and treatment, and accelerating efforts**



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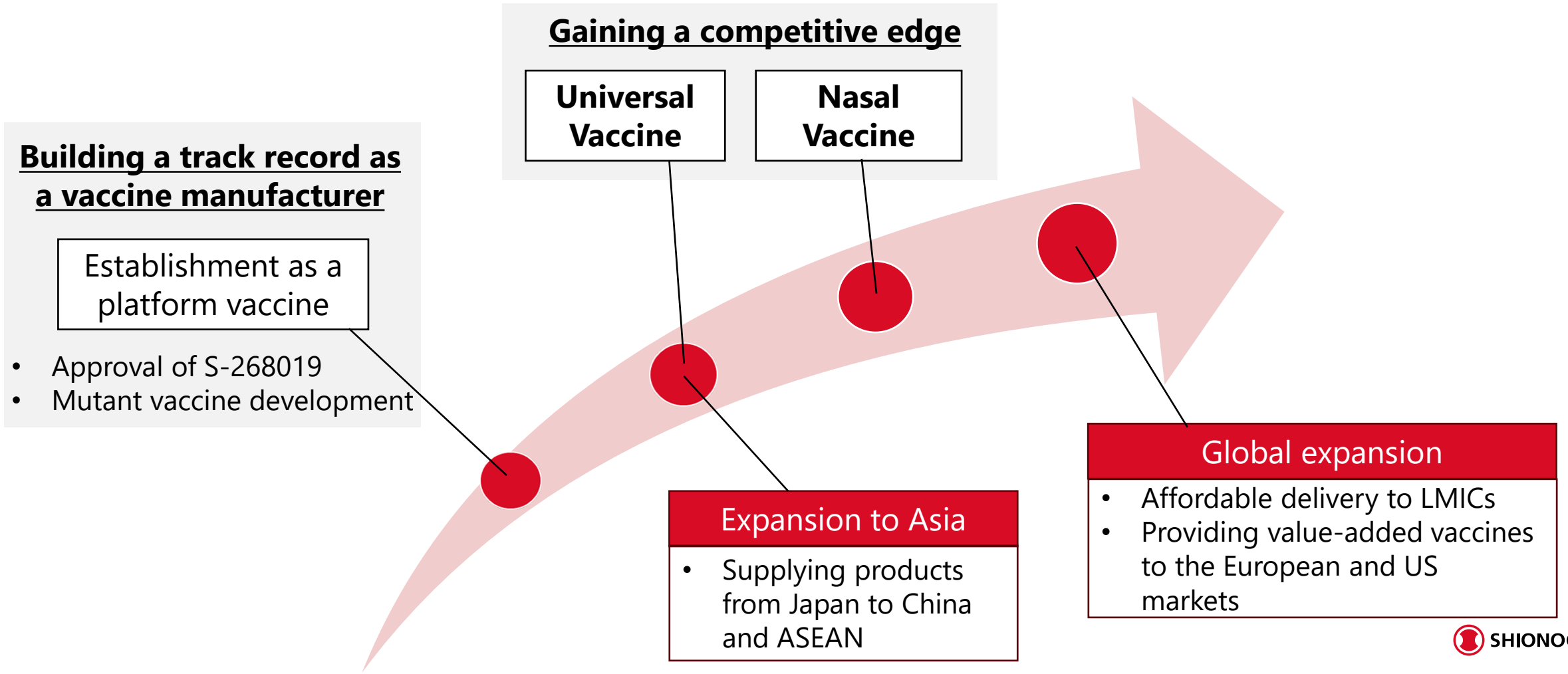
# Prevention: Vaccine Vision/Strategy

**Continue research and development of vaccines against respiratory infections and expand vaccine supply globally**



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# Diagnosis: SHIONOGI's Vision for Test to Treat

**Realize an environment where patients can receive prompt diagnosis and treatment whenever they need it, anywhere, globally**

## Anywhere

**Not only in hospitals and clinics,but also at home, nursing homes, etc.**

## Anytime

**Take action immediately when you feel unwell**

## Anyone

**Not limited to healthcare workers**

# Diagnosis: Challenge to Achieve the Vision

**There exist several needs to satisfy in the diagnosis process for achieving 'Test to Treat.'**

## Existing technological challenges

### PCR

- High testing cost
- Long time to obtain results
- Requires expensive equipment and expertise

### Antigen test

- Nasal swab causes discomfort in patients.
- Results assessed visually with considerable variability

## Needs in diagnosis to satisfy for achieving the vision

| | | |
|---|---|---|
| **Prompt**<br>A test can be completed within several minutes | **Simple**<br>No expertise is required | **Simultaneous**<br>Can address diversified pathogens |
| **Non-invasive**<br>Less discomfort for patients | **Lower price**<br>Reasonable price | **Highly selective**<br>Have confidence in the results |

- **Seeking to access new technologies such as image diagnosis and saliva testing**
- **Including the acquisition of assets and collaborative research, accelerating our diagnostic R&D**

# Treatment: Focus areas in Infectious Diseases

**While honing our strengths in infectious disease drug discovery, utilize external collaborations to satisfy global unmet medical needs**

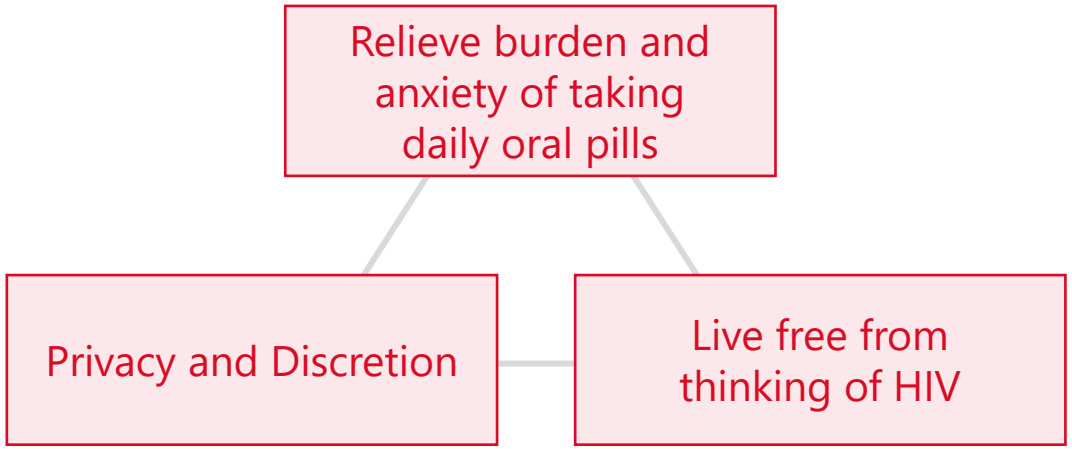
| | **Acute respiratory viral infections**<br>COVID-19<br>Influenza<br>RSV, etc. | **Antimicrobial resistance (AMR)**<br>antibiotic-resistant bacteria<br>antifungal-resistant fungi | **Infectious diseases requiring a long period of treatment**<br>HIV, Malaria, tuberculosis, etc. |
|---|---|---|---|
| Examples of targeted pathogens | Influenza<br>SARS-CoV2<br>RS virus<br>Dengue fever<br>Lassa fever (Arena)<br>Epidemic viruses in general | Resistant Gram-negative bacteria (Pseudomonas, Acinetobacter, Enterobacteriaceae, etc.)<br>Resistant fungi<br>Nontuberculous mycobacterial infections (*M. avium, M. abscessus)*<br>Tuberculosis | HIV<br>Malaria |
| Launched and development pipeline products (excluding vaccines) | Xofluza・Rapiacta<br>Xocova ・S-892216<br>S-337395 | Cefiderocol<br>S-649228<br>S-743229<br>Olorofim | Dolutegravir<br>Cabotegravir<br>S-365598 |

# HIV Franchise: ULAs Taking the Lead

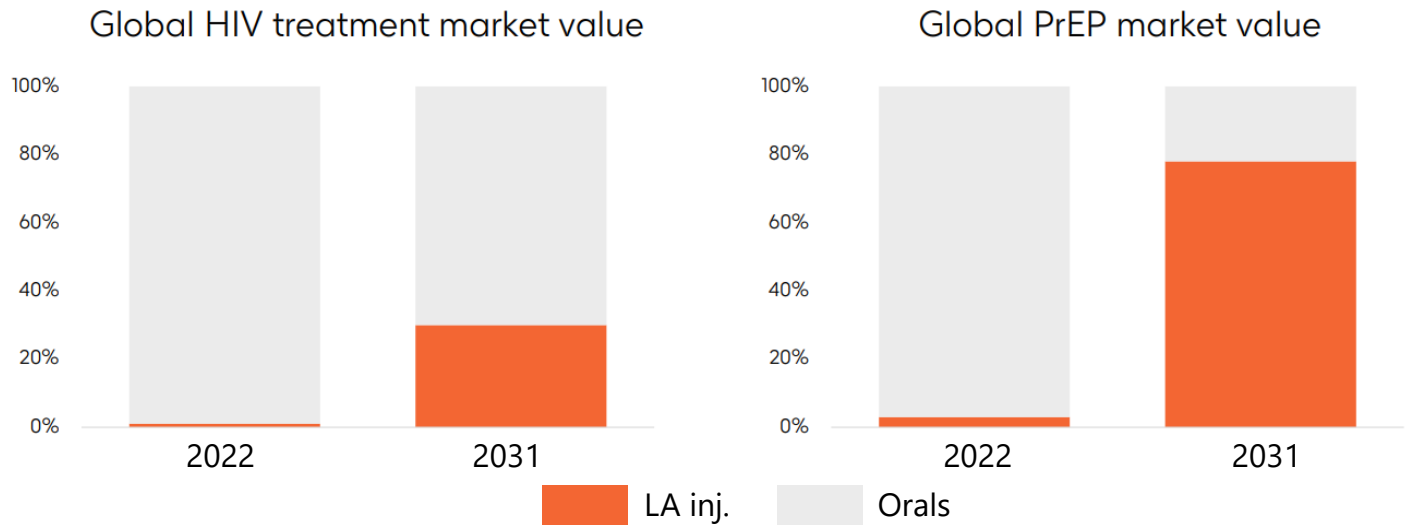
**The spread of ULA formulations will further accelerate the paradigm shift in HIV treatment and prevention**

**In parallel with ViiV's actions, SHIONOGI is committed to researching novel ULA candidates**

Unmet needs that cannot be fulfilled by oral pills




ViiV's market forecast for LA (including ULA) formulations*




* ViiV Healthcare Meet the Management (September 2023)



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# HIV Franchise: Creating the “Last in Class” ULA Therapy

**To meet remaining unmet needs, ULA R&D competition among companies has intensified**

## Anti-HIV drug R&D trends among major pharmaceutical companies

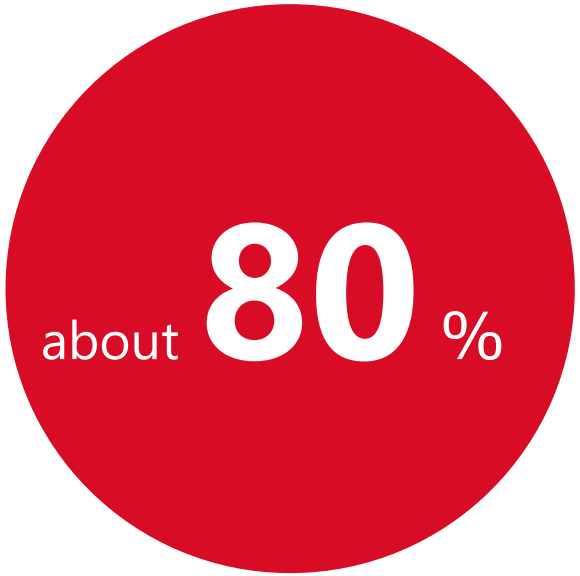
**Shift from once-daily oral to LA (oral and injectable)**

- Competitors enter market led by ViiV and SHIONOGI

**Focus on LA formulation of existing mechanisms**

- Integrase inhibitors and NRTTI* with established long-term efficacy and safety, etc.

Percentage of LA preparations in major pharmaceutical companies' pipelines*2




* Calculation based on the pipelines of ViiV, Gilead, Merck, and J&J (based on each company's 1Q 2024 financial results) *2 Nucleoside reverse transcriptase translocation inhibitors



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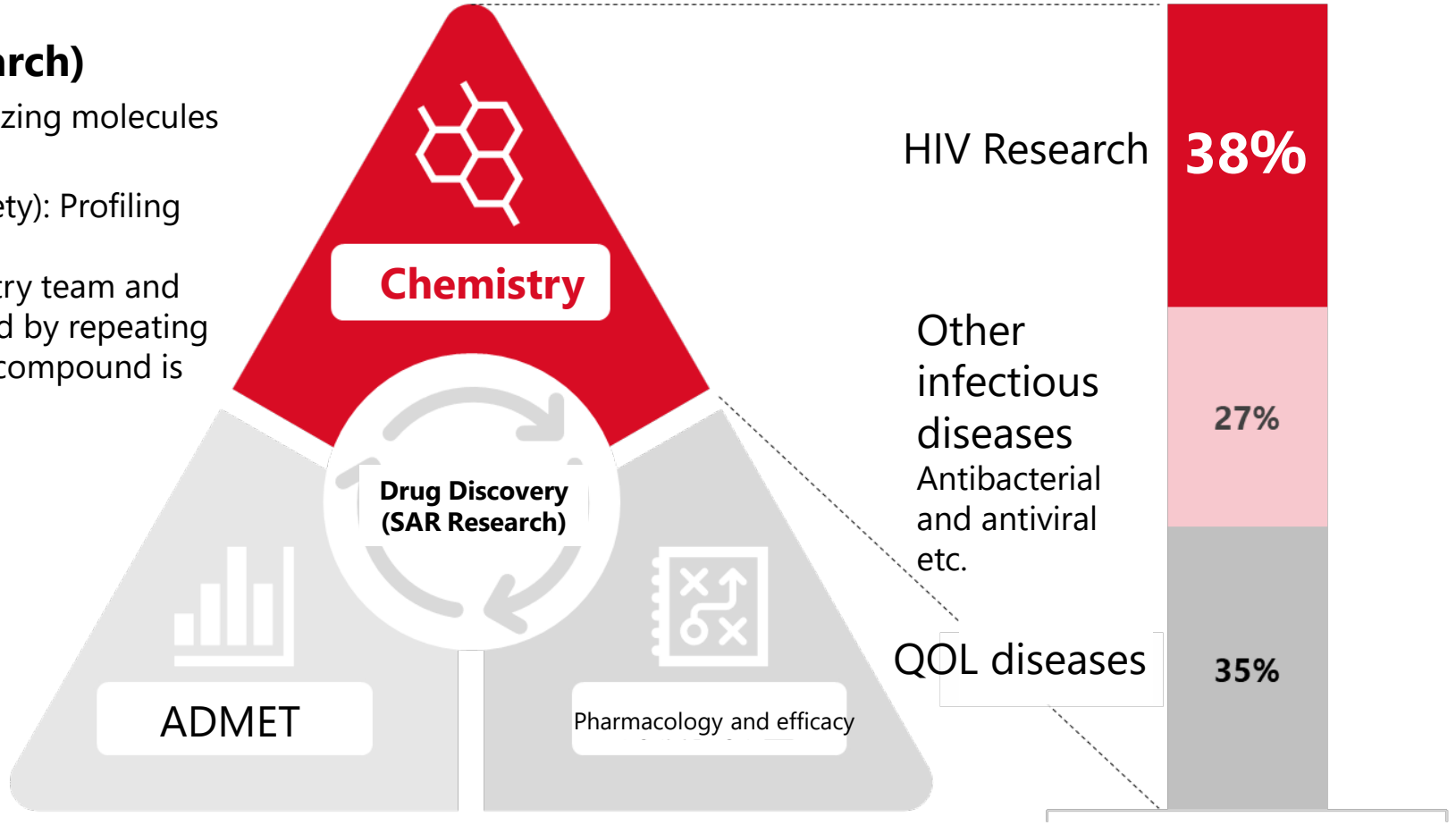
# Allocation of Human Resources in the Research Institute

**Appropriate resource allocation: 38% of chemical resources, the starting point for manufacturing, are allocated to HIV research**

## Drug Discovery (SAR Research)

- Chemistry: Designing and synthesizing molecules
- Pharmacology and efficacy, ADMET(pharmacokinetics and safety): Profiling and evaluation of compounds
  Based on this information, chemistry team and synthesizes better compounds, and by repeating this cycle multiple times, the lead compound is turned into a drug



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# Research and Development Policy for Bacterial Infections (Antibiotics)

**Established a new antimicrobial discovery laboratory in the US to utilize the experience base of Qpex and further build our US collaborative network**


## Opening of Qpex US Lab., a new drug discovery hub

- Activities taking advantage of the strengths of Qpex US Lab.
  - Based in San Diego, a significant biotech hub, build even stronger connections with US government, academia, and biotech
  - Maximize agility in research and development for AMR

**In cooperation with public institutions such as NIH and BARDA,**
**proactively work on research and development for difficult bacterial infections to prepare for future threats**



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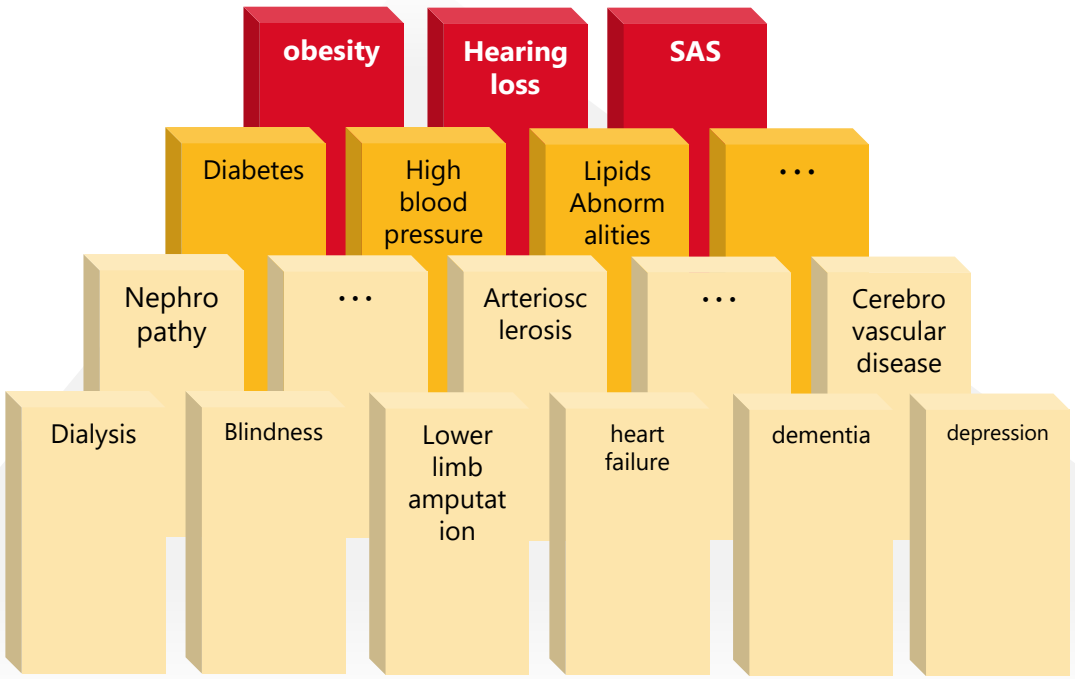
# Significance of Addressing QOL Diseases that have a Significant Social Impact

**Identify the root causes of diseases with cascading impact that shortens functional lifespan**

## Sequential chain of disease (image)




Before the onset of serious disease,there are multiple risk factors, which trigger further consequences like dominoes

**Seeking to address the underlying diseases before their irreversible consequences take hold**



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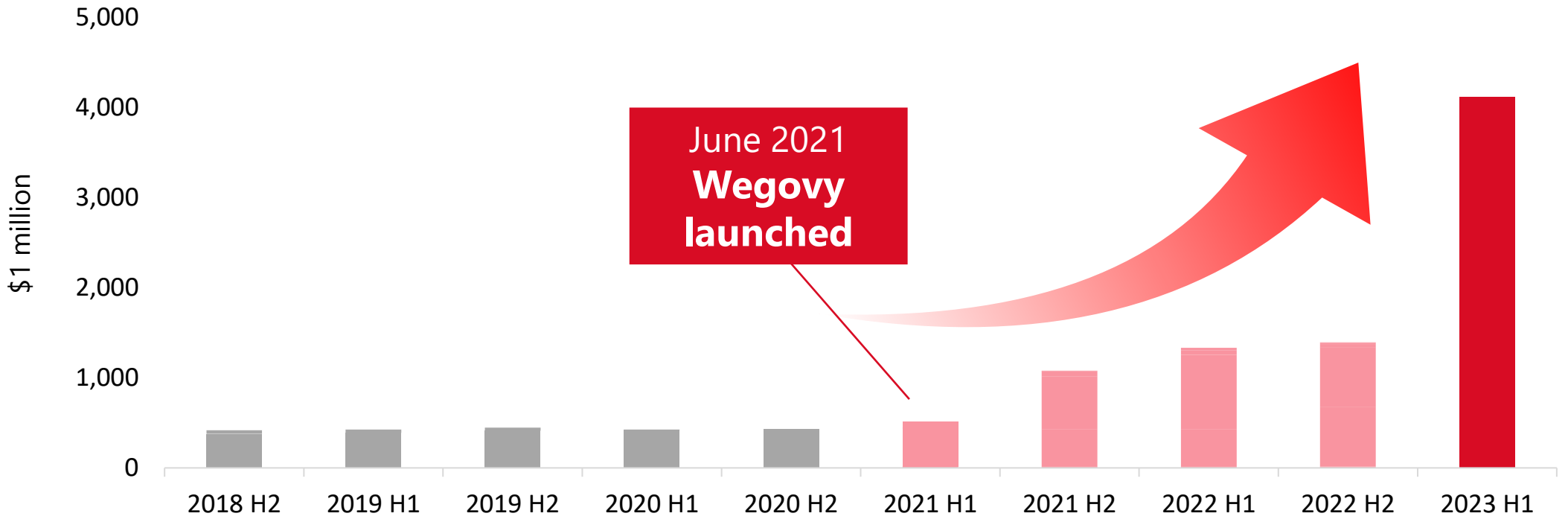
# InnovationInnovation in Consequential QOL Diseases Drive Major Market Opportunities

**The anti-obesity drug market has expanded dramatically with the emergence of GLP-1 agonists**

## US Anti-obesity drug market





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# Unmet Needs of QOL Diseases with a High Social Impact that SHIONOGI is Addressing

**Bringing new innovation to address unsatisfied needs, entering these fields with the intention to become the leader**

## Sleep Apnea Syndrome

**Estimated prevalence***

**900** million people

**Impact on lifespan*2**

8-year survival rate compared to healthy individuals **63** %

## Hearing Loss

**The issue of hearing loss due to earphones*3**

Patients exposed to potential risks **1.1** B people

**symptomatic therapy is common**

Effective treatment for hearing loss **0**

## Allergic diseases (hay fever)

**Japan's national disease*4**

**42.5** %

**Patient satisfaction with existing treatments*5**

**35** %

## Pompe disease

**Existing market*6**

**200** B yen

**Patients wanting new options*7**

Not satisfied with existing treatments **72** %

* https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30198-5/abstract

*2 Am Rev Respir Dis (1988) 138(2):337-40, PharmacoEconomics (2021) 39:653–665, J Abnorm Child Psychol (2019)47(8):1327-1338. Eur Respir J (2016) 47(4):1162-1169, Chest (1988) 94(1):9-14

*3 World Health Organization, , 2015. Available: https://www.who.int/news-room/events/detail/2015/03/03/default-calendar/world-hearing-day-2015-make-listening-safe

*4 花粉症に関する関係閣僚会議 花粉症対策（厚生労働省） *5「免疫アレルギー疾患研究10か年戦略」について *6 Amicus Therapeutics (amicusrx.com) *7 Can genes influencing muscle function affect the therapeutic response to enzyme replacement therapy （ERT) in late-onset Type II Glycogenosis?



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# QOL Diseases with High Social Impact: Develop New Focus Areas - SAS -

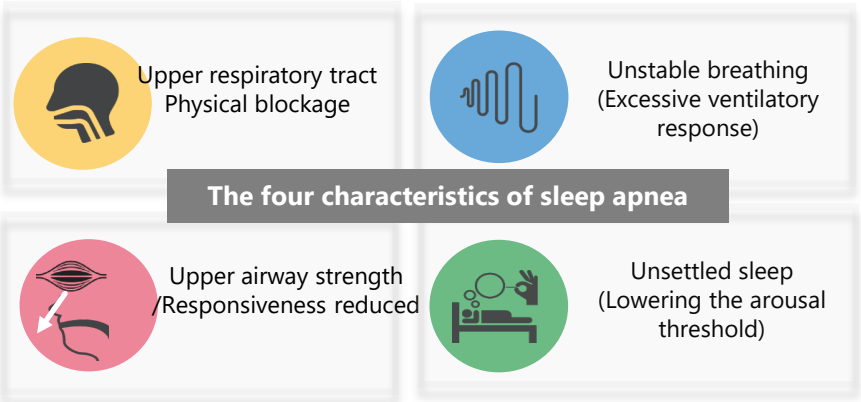
**Addressing the complex pathology and causes of OSA and providing the right therapies to the right patients**

## Global market for hearing loss*2

| | |
|---|---|
| CAGR from 2024 to 2030 | **6.5** % |
| Market forecast for 2030 | About **1,200** B yen |

## Unmet medical needs

- Highly effective and safe therapeutic drugs other than devices and surgical treatments
- Treatment options for patients with nasal continuous positive airway pressure (CPAP) resistance or intolerance
- The pathophysiology of SAS is mainly formed by the complex interplay of the following four factors, making treatment difficult (only 40% of SAS patients with obesity)





* Sleep Apnea Syndrome
*2 Sleep Apnea Devices Market by Type, Therapeutic (PAP Facial Interfaces, Oral Appliances, Accessories), Diagnostic, End User & Region - Global Forecast to 2028

# QOL Diseases with High Social Impact: Develop New Focus Areas - SAS -

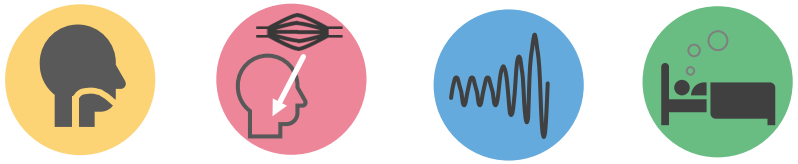
**Promoting innovation through joint venture activities that combine the strengths of both companies**

## Established *Shionogi-Apnimed Sleep Science, LLC*

Apnimed

### Expertise in OSA

- Robust R&D networks in clinical sites
- Experienced R&D team, especially strength in translational research, expertise in OSA
- Create new treatment combination approaches
  - Possesses multiple new drug candidates (assets) based on pathophysiology



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### Strengths in small molecule drugs

- Innovation skills
  - Highly efficient small molecule drug discovery engine
  - High ability to create best-in-class compounds

CRESTOR® rosuvastatin calcium

Tivicay® dolutegravir

xofluza® (baloxavir marboxil) tablets

Fetroja® (cefiderocol) for injection

XOCOVA

**Phase 2 trials scheduled to start in Q3 FY2024**

S-600918 [Sivopixant] + Partner drug X (For details, please refer to P. 93-95)

# QOL Diseases with High Social Impact: Development of New Focus Areas
## - Hearing Loss -

**Plans to introduce early treatment drugs providing new breakthrough options in the expanding hearing loss market**

## Global market for hearing loss*

| | |
|---|---|
| CAGR from 2024 to 2030 | **5.3** % |
| Market forecast for 2030 | About **1,800** B yen |

## Unmet medical needs

- There are no effective treatments, and **symptomatic therapy is common**
- Hearing loss occurs gradually, making it difficult to self-diagnose, leading to **a low diagnosis rate**
  - For example, the prevalence of hearing loss in diabetic patients is about 30%, but the diagnosis rate is only about 10%
- Hearing impairment is the biggest issue in communication with others, and it has a negative impact on both work and private life



* Hearing Loss Disease Treatment Market Size, Share & Trends Analysis Report By Product (Devices, Drugs), By Disease Type (Conductive, Sensorineural), By End-user (Hospitals, Otology Clinics), By Region, And Segment Forecasts, 2024 - 2030

# QOL Diseases with High Social Impact: Development of New Focus Areas
## - Hearing Loss -

**Acquired the option rights to a very promising low molecular compound (CIL001) from Cilcar**

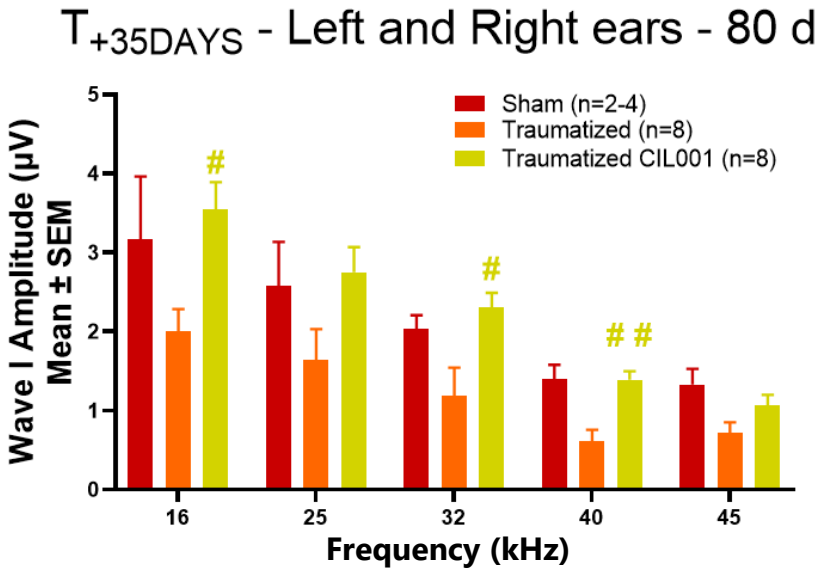
### Obtained the option rights for a candidate hearing loss treatment drug

- Exclusive license for the development, manufacturing, and commercial science of CIL001 and CIL003 compounds worldwide
- CIL001 confirmed auditory nerve protective effects in preclinical trials
  - Enhanced gene expression necessary for synaptic recovery
  - Confirmed an increase in the number of synapses
  - Improved the first wave of ABR* correlated with hearing loss

cilcare
MAKING HEARING A PRIORITY

### The effects of CIL001

(in preclinical trials with a mouse noise trauma model)




Improved the ABR Wave I amplitude across a wide range of frequencies

**Phase 2a clinical trial will start in FY2025*2**

*2 Auditory brainstem response (ABR) Wave I:
The first electrical signal generated by cochlear nerve cells in response to an auditory stimulus, believed to reflect the function of the cochlear synapse"

*2 Cilcare will conduct



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# QOL Diseases with High Social Impact: Development of New Focus Areas
## - Immunology and Allergies -

**Aiming to provide innovative solutions for hay fever, a condition referred to as the national affliction in Japan and a global social issue**

### Global market for allergic rhinitis*

CAGR from 2024 to 2030 | **4.8** %

Market forecast for 2030 | About **1,000** B yen

### Allergic rhinitis (including hay fever) market in Japan

Market in 2019 | **170** B yen*2

### Unmet needs

- Patient satisfaction with antihistamines for cedar pollen allergy is only 35%
  - Dissatisfied with the effectiveness and drowsiness



* Allergic Rhinitis Drugs Market by Route of Administration (Intranasal, Intraocular, Oral), Class of Drugs (Antihistamines, Immunotherapies, Intranasal Corticosteroids), Application - Global Forecast 2024-2030

*2 花粉症に関する関係閣僚会議 花粉症対策（厚生労働省）より

# QOL Diseases with High Social Impact: Development of New Focus Areas
## - Immunology and Allergies -

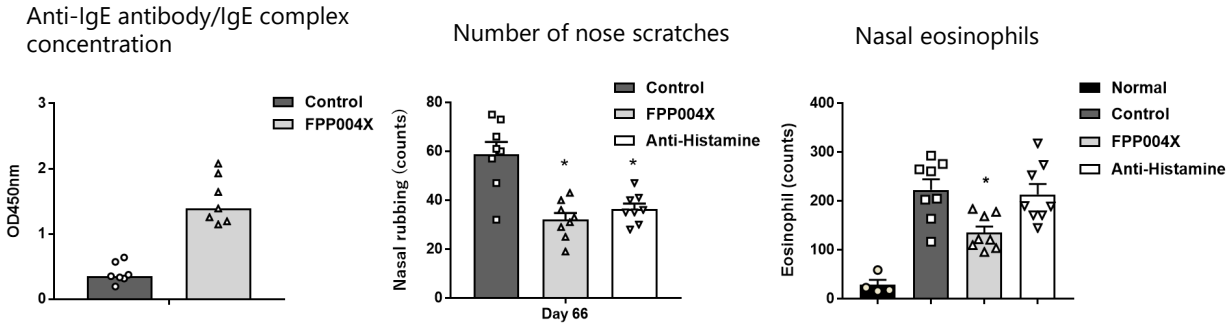
**Acquired the option rights for a promising hay fever vaccine candidate (FPP004X) from Funpep**

### Obtained the option rights for an anti-IgE antibody induction vaccine

- Exclusive research, development, and commercialization rights for FPP004X worldwide
- Expect to have sustained effects against allergies
  - Stimulate IgE antibody production in immune cells for a specific period
  - The anti-allergic effects resulting from the reduction of IgE are also attracting attention from other companies

### Efficacy of FPP004X (Preclinical trials in an allergic rhinitis model*)

- FPP004X demonstrated efficient induction of anti-IgE antibody
- Confirmed suppression of allergic reactions
  - A reduction in the frequency of nasal scratching and eosinophils




**Phase 1 clinical trial will start in 4Q FY2024*2**

* Nonclinical trial conducted using humanized mice with IgE/FcεR1

*2 Funpep will conduct

# QOL Diseases with High Social Impact: Development of New Focus Areas
## - Pompe Disease -

**Aiming for early introduction of therapeutic drugs that can break through the current situation in the high unmet needs Pompe disease market**

## Global Market for Pompe Disease*

**The market is expected to expand further with the launch of S-606001**

| | |
|---|---|
| CAGR of 2024-2030 | **4.3** % |
| Estimated market of 2030 | **300** B yen |

## Unmet needs

- The only existing treatment is intravenous enzyme replacement therapy (ERT)
  - Over **72%** of patients currently undergoing treatment want to further slow the progression of their disease
  - Over **82%** of people want to reduce the burden of visiting hospitals and avoid injections

## Features of S-606001

- Further improvement effects when used in combination with ERT
- The only oral small molecule drug in development

**Phase 2 clinical trial will start in FY2024**

* Global Pompe Disease Therapeutics Market - 2023-2030

S-606001 (For details, please refer to P. 84-86)



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# R&D Strategy: Today's Highlights

**Leveraging our strengths and external collaborations, provide innovative solutions that meet unmet needs**

Protect people from the threat of infectious diseases

## High-impact infectious diseases that threaten society

**Acute respiratory viral infections**
COVID-19
Influenza
RSV, etc.

**Antimicrobial resistance (AMR)**

**Infectious diseases requiring a long period of treatment**
HIV, Malaria, tuberculosis, etc.

**Total care, including vaccines**

Contribute to a healthy and prosperous life

## QOL diseases with high social impact

**Cognitive Disorders**

**Obesity**

**Pediatric/Rare diseases**

**Sleeping disorders**

**Hearing impairment**

**Immunology/ Allergy**

# SHIONOGI R&D

## Actions in Focus Areas

Takeki Uehara, D.V.M., PhD
Corporate Officer, Senior Vice President, Drug Development and Regulatory Science Division



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# High-impact infectious diseases that threaten society





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# High-impact infectious diseases that threaten society

## Acute infection

- Respiratory viral infections
- Pandemic Drug Discovery

# Threat of acute viral infections (respiratory)

## As a leading company in infectious diseases, Creating diagnostic technologies and therapeutic drugs to address society's needs

### A pandemic caused by a new viral infection

### Responding to the ever-changing mutations of the virus

- Ensitrelvir: Development and approval of a drug for treating COVID-19
- S-892216: Development of the next generation of COVID-19 treatments
- S-337395: Development of treatment for respiratory syncytial virus
- Pandemic drug discovery: Creating broad-spectrum antiviral drugs

### Borderless society leads to rapid spread of infection

- Ensitrelvir: Clinical trials to obtain post-exposure prophylaxis
- Baloxavir: Verification study to confirm its effect in suppressing transmission

# Ensitrelvir
## Indications: Treatment of SARS-CoV-2 infection and post-exposure prophylaxis

### Unmet needs:

【Treatment】

- Oral treatment that is easy to use for a wide range of patients

【prevention】

- Easy-to-use oral prophylactic drug

### Product Features:

- The first oral treatment to improve clinical symptoms in patients infected with the Omicron strain, regardless of the presence or absence of risk factors for severe disease
- Strong antiviral effect without booster
- Well tolerated

### Mechanism of action:

- SARS-CoV-2 3CL protease inhibitor

### Current status and future plans:

【Indication for treatment for ages 12 and over】

- Japan: Regular approval obtained (March 5, 2024)
- Global: Application in preparation
  - US: Application package currently under discussion with authorities
  - Scheduling application consultations in Europe and Asia

[Treatment for children aged 5 to 11 years old]

- Phase 3 study (Japan) enrollment scheduled to be completed in the first half of FY2024

[Post-exposure prophylaxis indications]

- Global Phase 3 study enrollment scheduled to be completed in the first half of FY2024

# Ensitrelvir: Summary of Results of the SCORPIO-HR trial

**Obtained the results of the SCORPIO-HR trial and proceeding with preparations for regulatory approval in the United States and globally**

| | | |
|---|---|---|
| **Primary endpoint** | **Symptom improvement effect** | • Although ensitrelvir demonstrated a numerical reduction in the time to symptom resolution compared to placebo among participants treated within 3 days of symptom onset, the difference was not statistically significant.<br>→ A pre-defined supportive analysis of resolution of six symptoms for one day using a statistical method similar to that used in the SCORPIO-SR Study (Phase 3 part of the Phase 2/3 study of ensitrelvir conducted in Asia) yielded a significant difference ($p<0.05$) in the time to resolution of symptoms |
| **Secondary endpoints** | **Effect for Long COVID** | • Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post COVID-19 symptoms (Long COVID) at three months, but there was a tendency for a higher proportion of participants to report "having returned to pre-COVID health" and "felt no fatigue" compared to placebo.<br>→ Further detailed analysis is planned, including additional follow-up at six months. |
| | **Antiviral effects** | • Ensitrelvir demonstrated a potent antiviral effect for both viral RNA and culture, compared to placebo.<br>• Symptomatic viral rebound was not observed in this study, supporting previous findings from SCORPIO-SR. |
| | **Hospitalization and death prevention** | • No deaths were observed in either group up to Day 29 of follow up, and very few cases of COVID-19 related hospitalization were observed in either arm. |
| **Safety** | | • No new safety concerns were identified.<br>• Ensitrelvir had similar tolerability to placebo and there were no reports of taste disturbance. |

# Ensitrelvir

**Conducting multiple clinical trials in parallel to resolve remaining issues related to COVID-19**

| | | | |
|---|---|---|---|
| **High Risk Outpatient** | **SCORPIO-HR trial** | Verification of efficacy in outpatients, including those with risk factors for severe illness | **Preparing for application**<br>• US Pre-NDA meeting<br>• Proceeding with regulatory applications in Europe and Asia, including China |
| **Children** | **Japan Pediatric Phase 3 trial** | Safety and pharmacokinetics verification in children | **Enrollment is scheduled to be completed in the first half of FY2024** |
| **Prevention** | **SCORPIO-PEP trial** | Verification of preventive effect of symptomatic SARS-CoV-2 infection in close contacts | **Enrollment is scheduled to be completed in the first half of FY2024** |
| **High Risk hospitalization** | **STRIVE trial** | Verification of efficacy, including mortality prevention effect in hospitalized patients (conducted by NIH) | **Enrollment is scheduled to be completed in the first half of FY2025** |

**Long COVID**

- Multiple investigator-initiated trials are underway
- Clinical research: Verification of efficacy and safety for Long COVID (Joint research with Osaka University)



HR: NCT05305547, Pediatric JRCT2031230140, Prevention: NCT05897541, STRIVE: NCT05605093, Investigator-led: NCT06161688, Osaka University Clinical Research: CRB5180007,

# S-892216

## Indications: Treatment and prophylaxis of infections caused by SARS-CoV-2

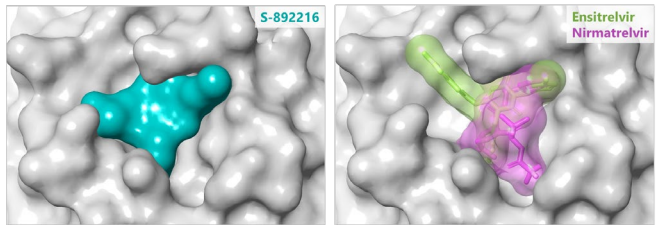
**Global Phase 2 trials will begin in the first half of FY2024, with the aim of conducting Global Phase 3 trials in the first half of FY2025**

### Mechanism of action:

- SARS-CoV-2 3CL protease inhibition

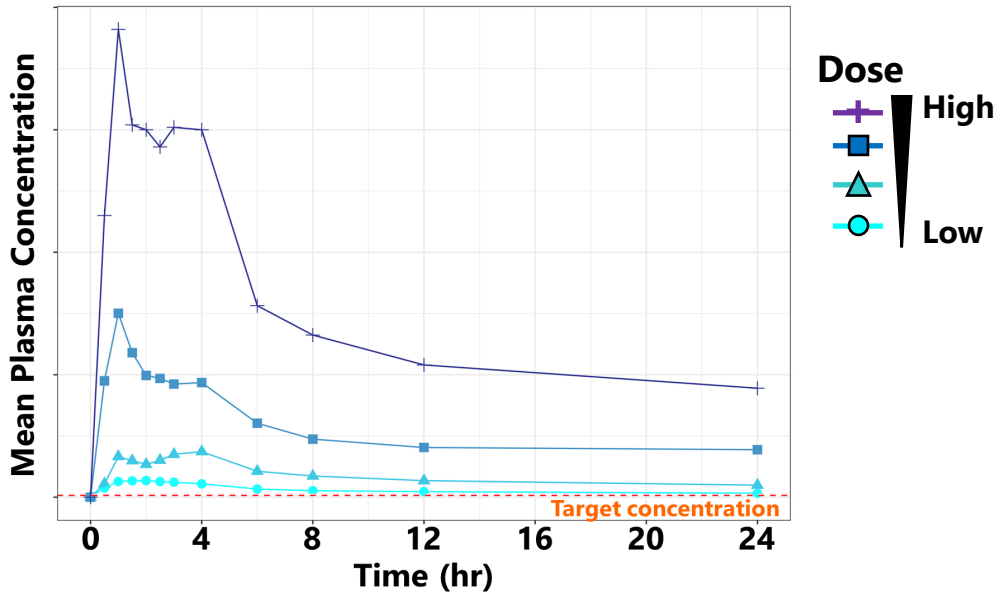
### Product Features:

- Fewer drug interactions
- Strong antiviral effects
- No contraindications for pregnant women (no teratogenic effects observed in non-clinical studies)
- Different binding mode from other 3CL protease inhibitors, resulting in a distinct drug resistance profile




### Result of Phase 1 trial

- Favorable pharmacokinetics, safety and tolerability
- No risk of CYP3A inhibition






This research and development is supported by AMED under Grant Number 22fk0108522

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# RSV Infection

**Even with widespread use of preventive vaccines, treatments for RSV infection is needed as a new option**

## Market :

- Pediatric* (Under 5 years old, Global) : 33.1 million people
- Elderly people*2 (Over 60 years old, in developed counties) : 5.2 million people

### Current situation

Multiple drugs have been approved and launched for pediatric and elderly populations

**However, all of them are preventive drugs**

### Patients who are expected to require treatment

**High risk patients**

- Pediatric with high risk factors, elderly, breakthrough infections

**Not vaccinated**

- US: Vaccination for elderly is not uniformly administered; it involves shared clinical decision making*3



* *Lancet*. 2022;399（10340):2047-2064. *2 Influenza Other Respir Viruses. 2023;17(1):e13031
*3 Not universally recommended for administration to all individuals in a group; proposals are made based on physician judgment, and agreement is reached between the physician and the patient

# S-337395
# Indications: RSV Infection

## Mechanism of action:

- By inhibiting the RNA-dependent RNA polymerase activity of the L protein, which is essential for viral replication, it inhibits the replication and transcription of the viral genome, thereby suppressing viral proliferation.

## Product Features:

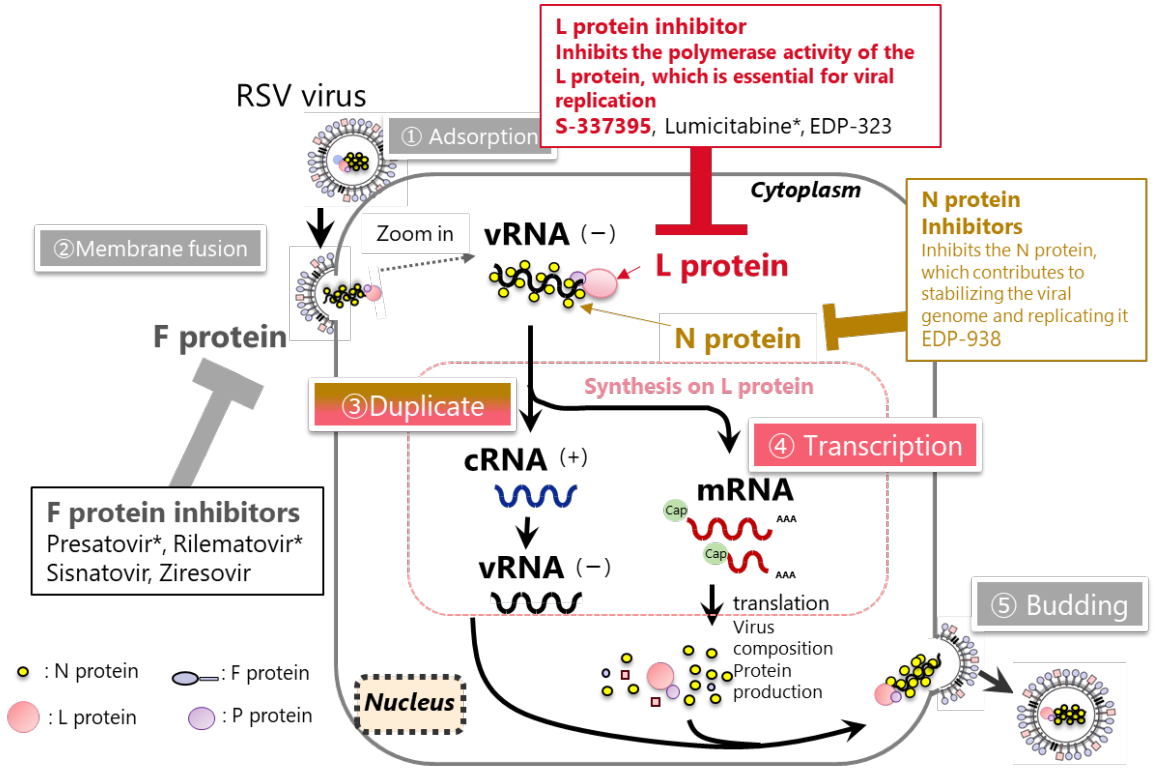
- Antiviral drug with a new mechanism of action (L protein inhibitor)
  - Compound discovered through joint research with UBE
- Easy to use oral medication
- Potent antiviral effect

## Current status and future plans:

- RSV human challenge study (UK) ongoing
- Patient trials to begin in FY2025

## RS virus replication process and site of action:

- Competitor products (small molecule drugs)
  Features of each mechanism of action:




*No ongoing clinical trials at this time



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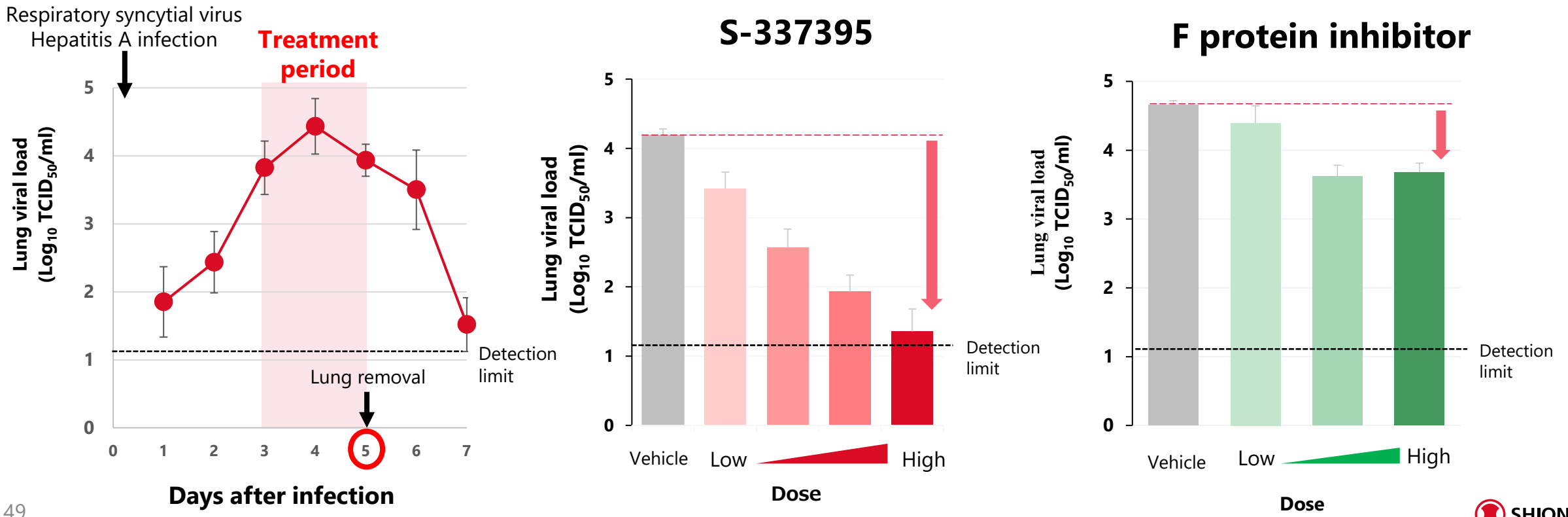
# S-337395: Non-clinical data

**Compared to F protein inhibitors, this drug shows a clear virus reduction effect even when administered near the peak of viral replication**

## RSV-infected mouse treatment model



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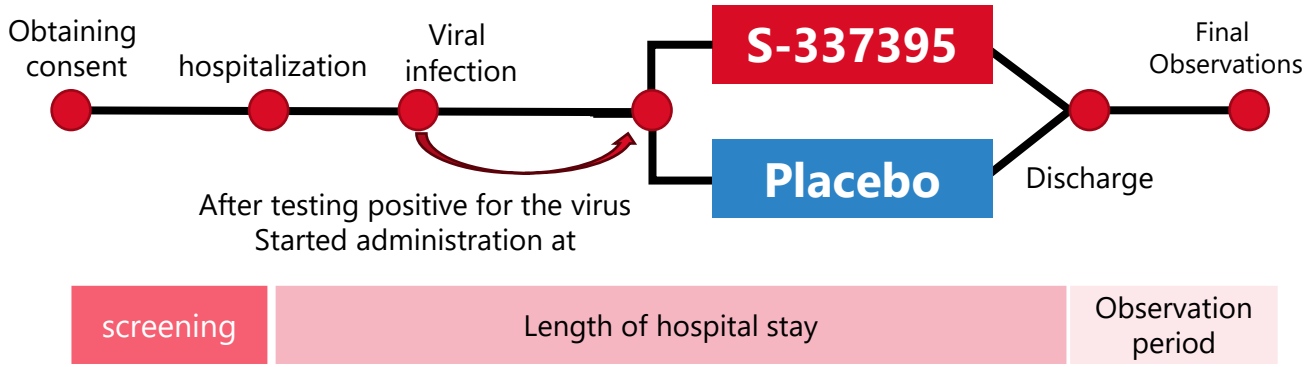
# S-337395: Clinical Development Plan

**Confirm drug potential in RS virus human challenge study, accelerate development globally**

## Human challenge trial (UK, ongoing)

- Healthy adults are inoculated with the virus, and after confirming viral infection, they are administered S-337395 or placebo
  - Confirm efficacy against RSV
- So far, no adverse events have occurred




## Adult development

- Dose setting in human challenge trial
- Verification trial will start in FY2025

## Pediatric development

- Observational trials (Japan, USA):
  - Understanding the pathology in children (viruses, symptom progression)
- Based on the findings from the observational trial, a trial plan will be drawn up and a patient trial will be conducted in FY2025



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# Xofluza

## Indications: Treatment and prophylaxis of Influenza A or B viral infection

**This single medicine can be used to treat and prevent the disease in adult and pediatric patients and to suppress transmission with its high antiviral benefits**

### Product Features:

- **High antiviral benefits, and high therapeutic and prophylactic effects with a single dose**
- **Approved in more than 75 countries in the world**
- **Surveillance has not shown an obvious increase of treatment-emergent amino acid substituted viruses**

### Treatment and prophylaxis

Obtained recommendation for adults and patients over 12 years old in Japan through continuous accumulation of evidences.*, *2

Aiming to enhance global presence by partnership with Roche

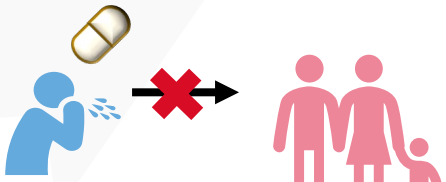
### Pediatric indication

The pediatric indication is growing globally.

US: Aug 2022　EU: Jan 2023
China: Mar 2023　Taiwan: Apr 2024

**Aiming to further accumulate evidences and enable early supply of granular formulation in Japan**

### Suppression of transmission



Taken by infected patients to suppress transmission

- Enrollment for transmission study (Centerstone study*3) has been completed.
- **Top-line results will be available in the first half of FY2024.**

**Emphasizing the effectiveness of antiviral drug treatment in suppressing transmission with resulting public health benefits**



* キャップ依存性エンドヌクレアーゼ阻害薬バロキサビル マルボキシル（ゾフルーザ）の使用についての新たな提言（日本感染症学会）
*2 2023/24 シーズンのインフルエンザ治療・予防指針（日本小児科学会）
* MV40618 - CENTERSTONE - Baloxavir marboxil in influenza transmission

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# SHIONOGI's Drug Discovery Strategy for Furure Pandemics ("Disease X")

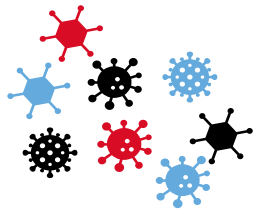
## Discover broad-spectrum antiviral drugs to respond quickly for future pandemic

**Broad-spectrum Antiviral Drug Discovery**
RNA viruses
DNA viruses

**Select the core viral disease**
Verify safety and efficacy in clinical studies

**Launch (normal)**
Contributing to the treatment of patients suffering from viral diseases

**Pandemic response**
Taking advantage of the broad-spectrum, Immediate response in case of a pandemic.



| | | |
|---|---|---|
| Ebola | Lassa | SARS |
| Drug-resistant influenza | Drug-resistant coronavirus | MARS |
| Zika | SFTS | West Nile |
| Monkeypox | Dengue | others |

- Confirm the drug has a certain degree of broad spectrum activity in non-clinical trials
- Confirm a certain level of efficacy and safety in humans by developing the drug for a core viral disease
- In case of a pandemic, our goal is to promptly verify the antiviral effectiveness and efficacy of drugs and provide them with society as quickly as possible

**Discussions have begun with relevant agencies on biodefense and national defense for broad-spectrum antivirals.**



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# Drug Discovery Research aimed at Creating Broad-spectrum Antiviral Drugs

**In anticipation of mobilizing in times of emergency,**
**we are advancing drug discovery for broad-spectrum antivirals**

| | RNA Viruses** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Compounds** | **Influenza virus A (H5N1)*** | **SARS-CoV-2** | **Entero virus (A71)** | **Dengue virus-2*** | **Zika virus*** | **Yellow Fever virus*** | **JEV** | **CHIKV*** | **La Crosse virus** | **RVF*** | **SFTSV** | **TMPV** | **Tula virus** | **RS virus** | **Rabies virus** |
| **Compound X** | W | M | M | S | S | S | S | S | S | S | S | S | S | NT | W |
| **Remdesivir** | W | S | S | M | M | W | S | W | W | W | W | NT | NT | S | W |
| **Ribavirin** | W | W | W | W | W | W | M | W | S | M | M | NT | NT | M | M |
| **Favipiravir** | W | W | NT | W | W | W | W | W | M | S | M | NT | NT | NT | W |

| | DNA Viruses | | | | | |
|---|---|---|---|---|---|---|
| **Compounds** | **HSV-2** | **VZV** | **HCMV** | **HHV-6** | **EBV** | **AdV3** |
| **Compound Y** | S | S | S | S | S | S |
| **Compound Z** | S | S | S | S | S | S |

*In vitro* antiviral activity: **S** M W S: strong, M: moderate, W: weak

NT = Not tested

*Designated high pandemic potential viruses (Economic Incentives and Strategies for Pandemic Preparedness from U.S. Government Accountability Office)
** Collaborative research with Hokkaido University

Japanese encephalitis virus (JEV), chikungunya virus (CHIKV), rift valley fever virus (RVF), severe fever with thrombocytopenia syndrome virus (SFTSV), thottopalayam thottimvirus (TMPV), Herpes simplex virus type-2 (HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (HCMV), human Herpesvirus 6 (HHV-6), epstein-barr virus (EBV), adenovirus serotype 3 (Adv3)



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# High-impact infectious diseases that threaten society

## Antimicrobial Resistance (AMR)

# Efforts towards Antimicrobial Resistance (AMR)

Bacterial infections due to AMR are steadily increasing and are threatening humanity as a "silent pandemic" that is expanding unnoticed

**Cefiderocol:**

**A new option for AMR infections caused by gram-negative bacteria**

- Launched in Japan, the U.S., Europe, etc.
- In partnership with GARDP and CHAI to expand access to 135 countries (about 70% of the world)

**S-649228 (Cefiderocol+Xeruborbactam):**

**A preparation for more advanced drug-resistant bacteria**

Preparing treatment options for highly drug-resistant bacteria that may emerge in the future

**S-743229 (Ceftibuten+Xeruborbactam):**

**Providing a new AMR treatment option of oral medication**

Achieving improved patient QOL and reducing the burden on healthcare workers

# Cefiderocol
## Indication：Gram-negative bacterial infections

**Obtaining approval in over 35 countries worldwide, further expanding into areas such as Australia and China**

**APEKS*-cUTI*2 Trial**
**（Complex urinary tract infections）**

US: Approved for complicated urinary tract infections in November 2019

Europe: Approved in April 2020

**CREDIBLE-CR*3 Trial**
**（Carbapenem-resistant bacterial infections）**

**APEKS*-NP*4 Trial**
**（Patients with hospital-acquired pneumonia）**

US: Approved for hospital-acquired pneumonia in September 2020

Japan: Approved in November 2023
China International Medical Tourism Pilot Zone: Use approved in January 2024
Macau: Approved in January 2024
Taiwan: Approved in February 202

Australia: Planning to apply in the first half of 2024

**cUTI*2Trial in China**
**（Complex urinary tract infections）**

**Bridging trial with APEKS-cUTI trial**
(Targeting a point estimate of the difference between the two groups of at least -15% in the composite endpoint*5)
**Achieved primary endpoints, preparing for application in June 2024**



* Acinetobacter、Pseudomonas、E. coli、Klebsiella、Stenotrophomonas、*2 Complicated Urinary Tract Infections、*3 Carbapenem Resistant 、*4 Nosocomial Pneumonia、*5 Composite assessment based on clinical efficacy and bacteriological efficacy

# S-649228 (Cefiderocol+Xeruborbactam Injection)
## Indication：Gram-negative bacterial infection

### Market：
- Market size of drug-resistant gram-negative bacteria (2023)*: $819.1 million

### Unmet needs：
- New treatment for expanding carbapenem-resistant gram-negative bacteria
- Future treatment options for the emergence of further resistant bacteria

### Product Characteristics：
- Injectable drug useful for treating various infections caused by multi-drug resistant gram-negative bacteria

### Current Status：
- Start of Phase 1 trial in 2Q 2024

### Mechanism of Action：
- Cell wall synthesis inhibition
- Improved power of cefiderocol with concomitant use of novel beta-lactamase inhibitor Xeruborbactam

Confirmed good antibacterial activity against a special collection of strains consisting only of cefiderocol low-susceptibility strains*2

| | | | Cefiderocol | Cefiderocol + XER (4 μg/ml) |
|---|---|---|---|---|
| Enterobacterales | Cefiderocol MIC>2 (N=52) | $MIC_{50}$ | 4 | 0.25 |
| | | $MIC_{90}$ | 64 | 1 |
| *Acinetobacter* spp. | Cefiderocol MIC>1 (N=124) | $MIC_{50}$ | >64 | 0.25 |
| | | $MIC_{90}$ | >64 | 1 |
| *Pseudomonas aeruginosa* | Cefiderocol MIC>1 (N=31) | $MIC_{50}$ | 2 | 2 |
| | | $MIC_{90}$ | 8 | 4 |

XER: xeruborbactam
All MIC units are in μg/mL

* Total sales of the following products in the major seven countries (USA, UK, Italy, Germany, Spain, France, Japan)：CEFIDEROCOL, AVIBACTAM-CEFTAZIDIME, CEFTOLOZANE-TAZOBACTAM, CILASTATIN-IMIPENEM-RELEBACTAM, COLISTIN, DURLOBACTAM-SULBACTAM, ERAVACYCLINE, MEROPENEM-VABORBACTAM, POLYMYXIN B, TIGECYCLINE



*2 Reference: Olga Lomovskaya, IDWeek2023



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# S-743229 (Ceftibuten+Xeruborbactam Oral)
## Indication：Complex urinary tract infections

### Market ：

- Complex urinary tract infections Annual incidence: 2.8 million people (US)*1
  - Many of the causative bacteria of complex urinary tract infections are Enterobacteriaceae*2
  - Annual medical expenses total: more than $6 billion (US) *1

### Unmet needs ：

- A new oral treatment for complex urinary tract infections that do not respond to existing oral antibiotics

### Product Characteristics ：

- Oral antibiotics that can be used to treat complex urinary tract infections caused by resistant bacteria

### Current Status ：

- Currently conducting Phase 1 clinical trials
- Aiming to enter Phase 3 trials by 2026

### Mechanism of Action ：

- Cell wall synthesis inhibition by ceftibuten, a cephalosporin antibiotic
- Improved efficacy of cefdibuten by concomitant use with novel β-lactamase inhibitor Xeruborbactam

Confirmed good activity against various β-lactamase-producing Enterobacteriales*3

| Phenotype | Number of isolates | | Ceftibuten | Ceftibuten + XER (4 μg/mL) |
|---|---|---|---|---|
| ESBL | (N=154) | $MIC_{50}$ | 8 | ≤0.03 |
| | | $MIC_{90}$ | >64 | 0.125 |
| KPC | (N=76) | $MIC_{50}$ | 16 | 0.125 |
| | | $MIC_{90}$ | 64 | 0.25 |
| OXA-48-like | (N=91) | $MIC_{50}$ | 32 | 0.25 |
| | | $MIC_{90}$ | >64 | 0.5 |
| Metallo | (N=79) | $MIC_{50}$ | >64 | 2 |
| | | $MIC_{90}$ | >64 | 64 |

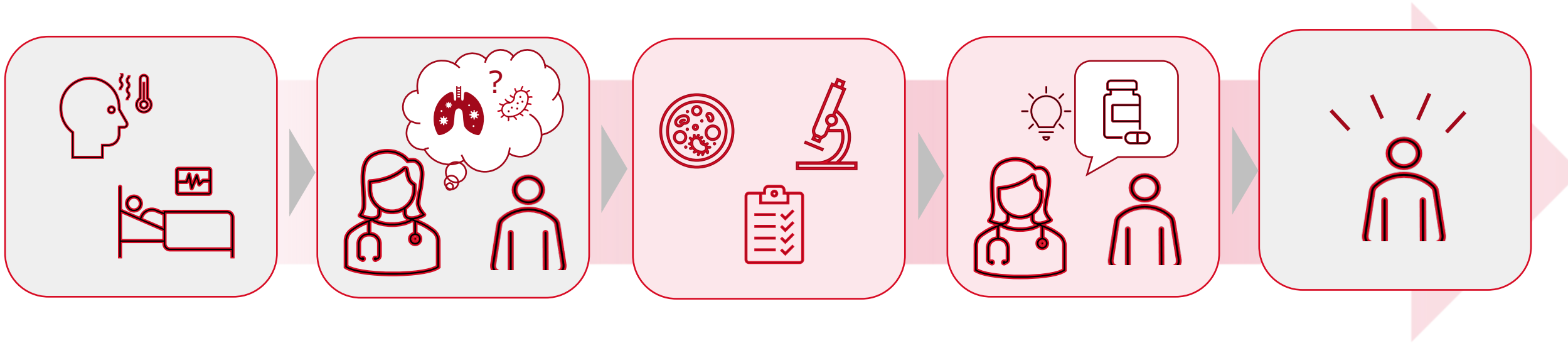
XER: xeruborbactam, ESBL　KPC: Klebsiella pneumoniae Carbapenemase,
OXA: OXA β-lactamase，Metallo: All units of metallo-β-lactamase MIC are in μg/mL.



*1 Carreno, Joseph J., et al. Open Forum Infectious Diseases. Vol. 6. No. 11. US: Oxford University Press, 2019.
*2 Nicolle LE. Urinary tract infection. Crit Care Clin. 29:699–715, 2013.　*3 Reference: Olga Lomovskaya, ESCMID Global (2024)

# Concurrent efforts for the development of antibiotics and corresponding antimicrobial susceptibility testing (AST)

**Establishing a diagnostic system to ensure appropriate treatment**



Patient develops infectious disease

Conducting examinations, collecting lesion samples, implementing empirical treatment

- Identifying pathogens within lesion samples
- **Performing Antimicrobial Susceptibility Testing (AST)**

**Switching to appropriate antibiotic treatment based on the results of the AST**

Treatment is effective and patient recovers

Promoting collaboration with AST device manufacturers around the world to ensure the availability of diagnostic devices by the time the antibiotic is launched



AST: antimicrobial susceptibility testing

# High-impact infectious diseases that threaten society

## Infections that require long-term treatment

- HIV
- malaria

# HIV Drug Discovery: Aiming for the Development of Last-in-Class ULA Formulation

**Significant investment in chemistry resources and a focus on the development of novel INSTI* and combination drugs with different mechanisms of action**

## Profile required for Last-in-Class ULA formulation

- **Ultra long lasting (once every six months)**
- **Low dose and low volume**
- **Good tolerance profile and barrier**

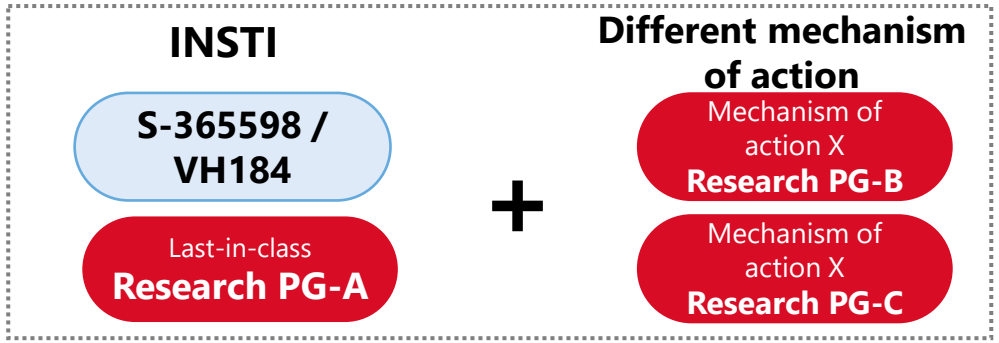
## ULA Discovery (INSTI) - Research PG-A -

**Striving for novel INSTI exceeding the profile of S-365598**

▶ Promoting research aiming for early clinical entry

## ULA Discovery (Different mechanism of action*2) - Research PG-B, C -

**Promoting two programs aiming for ULA formulations that can be used in combination with INSTI**




* Integrase inhibitor *2 6 Non-nucleic acid reverse transcriptase inhibitor etc.



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# Research on Concomitant Drug Candidates for HIV ULA Treatment

**Currently identifying lead series expected to have ultra long acting sustainability and conducting structural optimization**

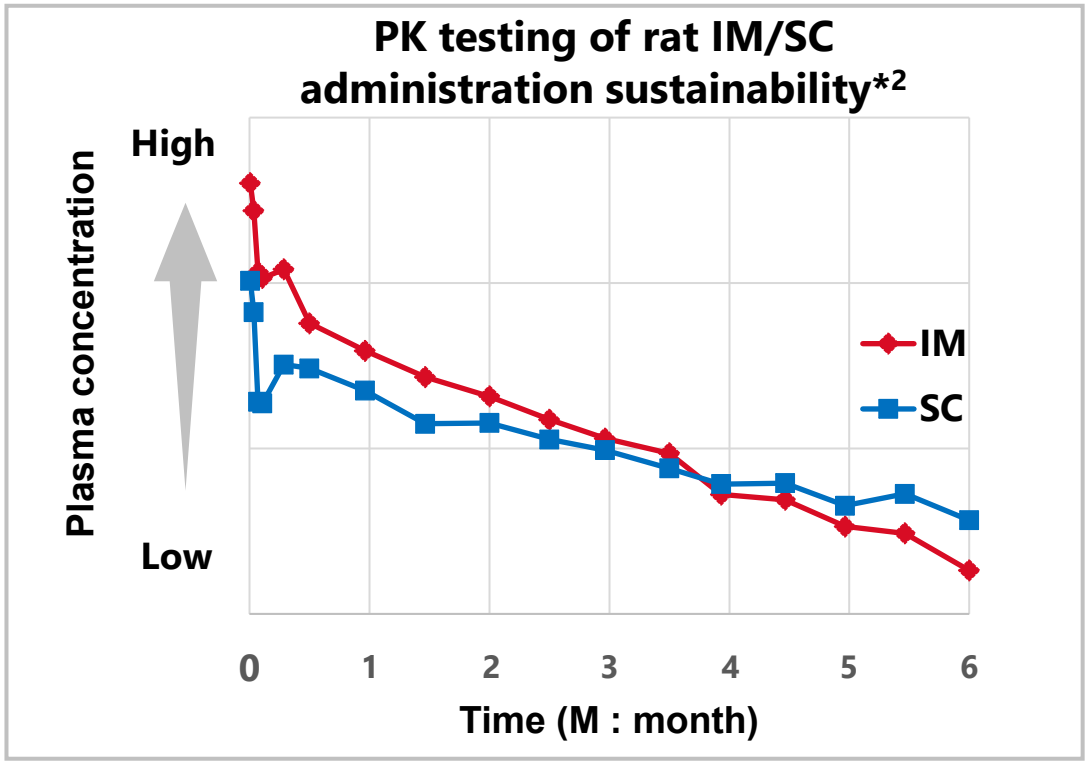
## Search for concomitant drug partners for integrase inhibitor

**ULA* regimen**

**INSTI** + **Concomitant medication**

- To develop concomitant ULA drug with integrase inhibitor, we are conducting research programs with multiple mechanisms of action
- In the top runner program, we obtained a lead compound with a potential to last six months in rats administered with IM/SC.
- We identified promising lead series and are currently conducting higher-order selection evaluation to progress into nonclinical studies

## Evaluation of ULA potential of lead compounds



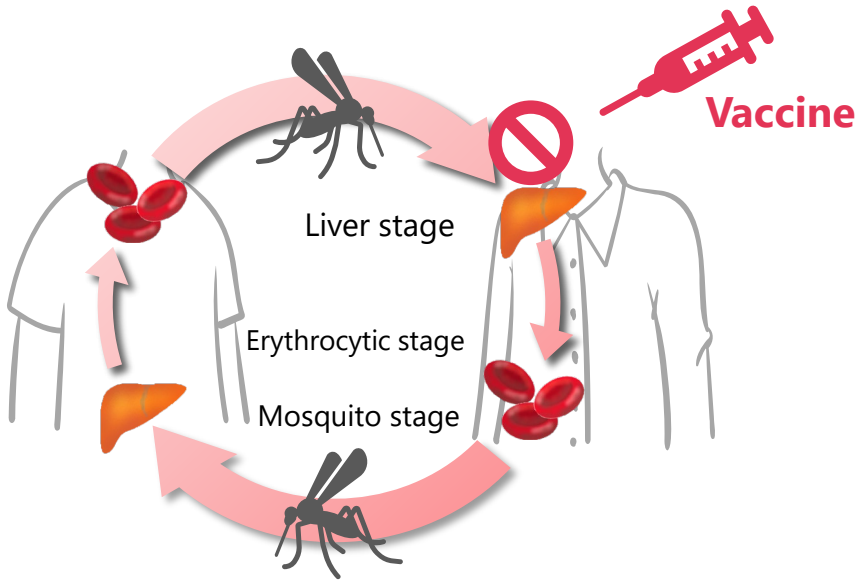



*ULA: Ultra long acting *2 Exploratory study with QA (Audit according to the reliability standards by the Reliability Assurance Department) not implemented yet, dose: 30 mg/head; SC: Subcutaneous, IM: Intramuscular

# SHIONOGI's drug discovery strategy for prevention of malaria

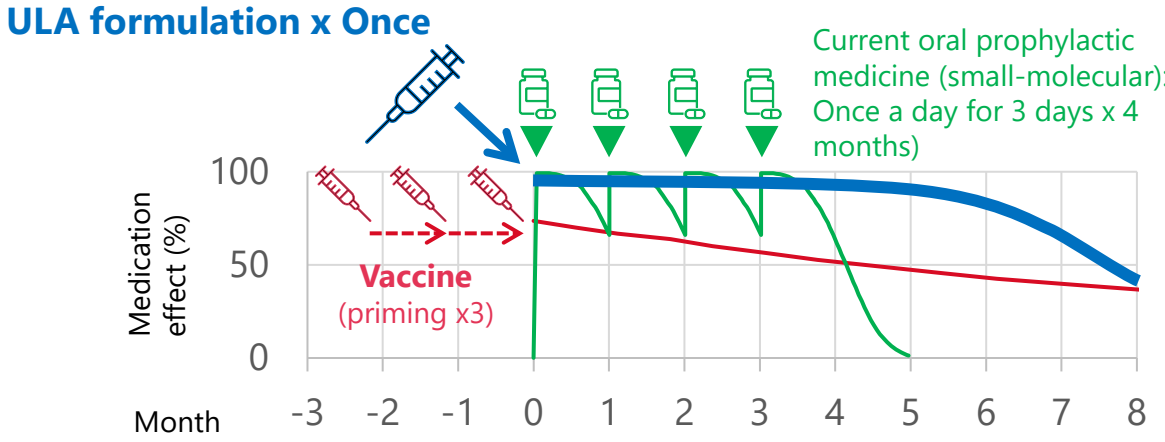
## Unmet needs in malarial prophylaxis

- Even efficacious vaccines* are only effective before malaria parasites enter the liver, possibly leading to breakthrough infections and risk of severe malaria
- Oral prophylactic medicines** adopted by public prophylaxis programs are highly effective but require patients to take them for three days every month, posing issues of compliance, sustainability and antimicrobial resistance




## Drug discovery concept

- Offering both therapeutic effects for asymptomatic patients who transmit the disease and transmission prevention effects to suppress mosquito season proliferation
- Sustainability and convenience to cover the entire epidemic season with a single shot
- Having a mechanism of action different from medicines currently used in Africa and showing no cross resistance

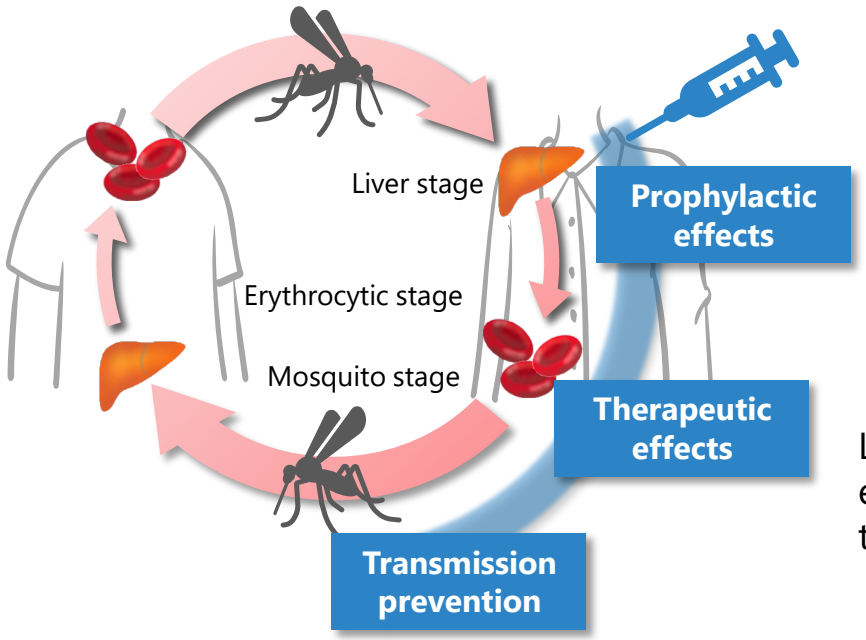





* RTS,S; R21 ** SPAQ

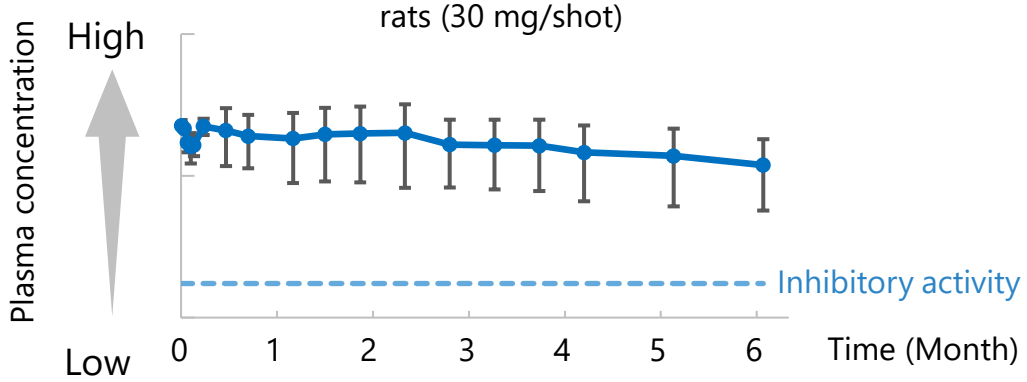
# Discovery of ULA medicines effective against malaria parasites in multiple stages

**We are promoting drug discovery studies for ULA formulations with superior prophylactic, therapeutic, and transmission prevention effects**




| Stage | $EC_{50}$ (nM) |
|---|---|
| Liver stage | 1.5 |
| Erythrocytic stage | 8.3 |
| Mosquito stage | 6.3 |

Plasma concentration after single shot administration to rats (30 mg/shot)




Lead compound A shows equivalent inhibitory activity in all the stages.*

Lead compound B shows ultra long acting sustainability in rats.*

Currently identifying compound groups expected to attain the both and conducting research on structural optimization

国立大学法人 長崎大学 NAGASAKI UNIVERSITY

NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES

MMV Medicines for Malaria Venture



This study has been supported by the GHIT Fund since April 2024.

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# High-impact infectious diseases that threaten society

## Total care including vaccinations



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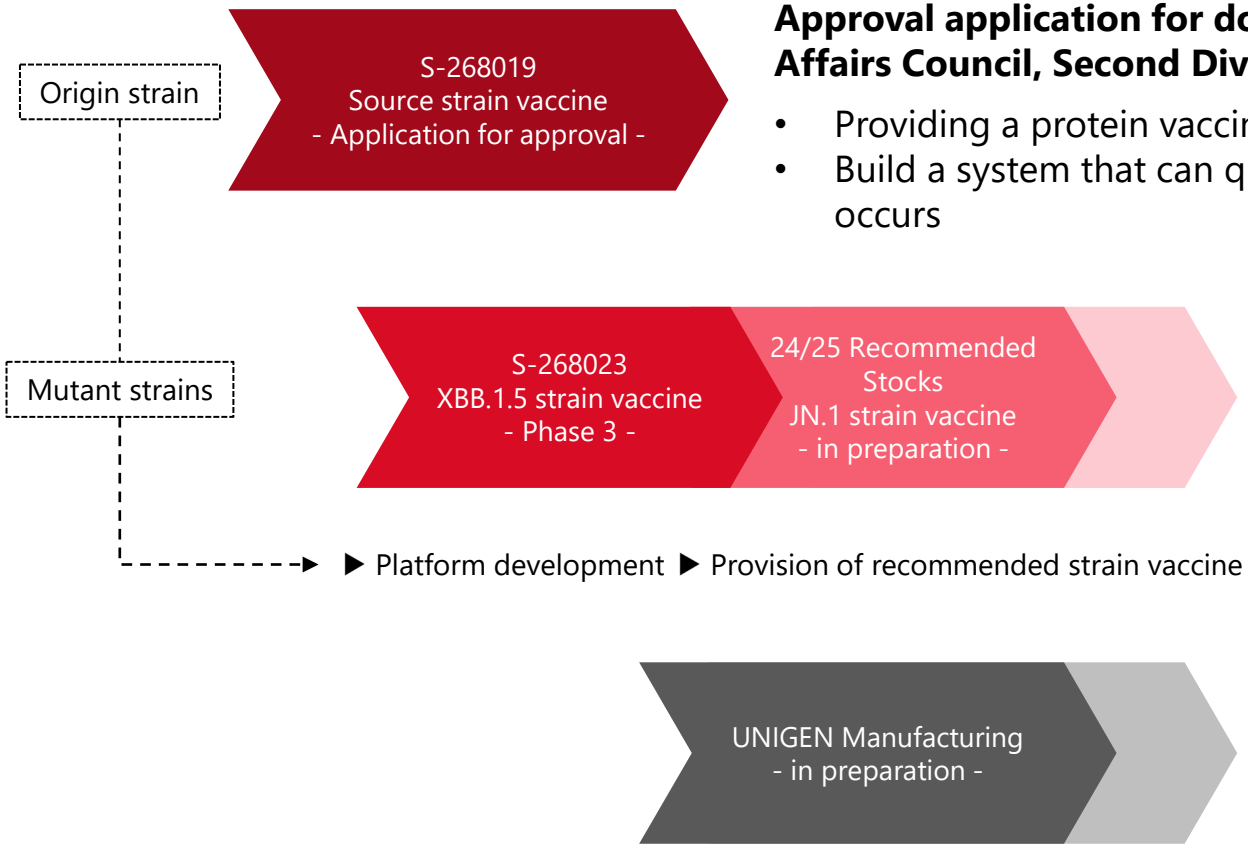
# COVID-19 Vaccine Platform

**Establishing a vaccine platform and aiming for timely market supply of vaccine formulations containing recommended strains**




**Approval application for domestic protein vaccine approved (May 24, 2024, Pharmaceutical Affairs Council, Second Division on Drugs)**

- Providing a protein vaccine option that has a long history of use and can be used with confidence
- Build a system that can quickly provide vaccines to the Japanese people when the next pandemic occurs

**Building a vaccine platform**

- By obtaining approval for mutant strains in addition to the original strain, we will advance the establishment of a platform vaccine.
- Establish a year-round vaccine development system and provide vaccine preparations containing the latest recommended strains to the market in a timely manner.

**Establishment of a commercial manufacturing system**

- Launching UNIGEN as a commercial manufacturing site to ensure a stable supply



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# S-567123: Universal vaccine

## The World we enbision with universal vaccines

- Vaccination in the early stages of a pandemic will save many human lives.
  - Life-saving measures that were not possible in the recent COVID-19 pandemic
- A seasonal vaccine in ordinary times will induce strong immunity and contribute to prevention of severe disease.
  - Preventing new pandemics

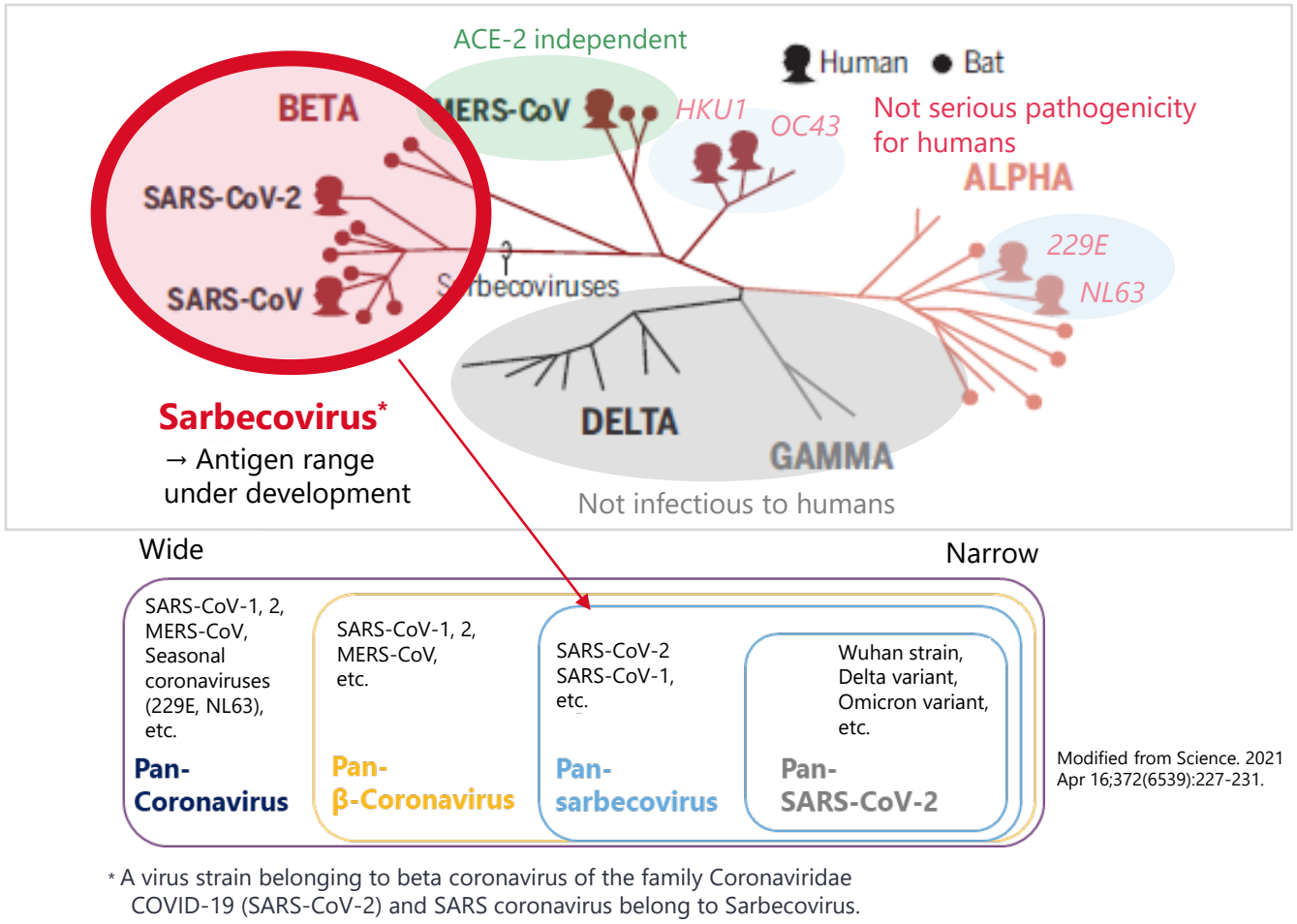
## Targeted vaccine concept

- Can be used as a prophylactic SARS-CoV-2 vaccine in ordinary times
- Can be used for outbreak of SARS-CoV-1 or other sarbecovirus infections
- Better safety than existing vaccines

KOTAI

NIID 国立感染症研究所
NATIONAL INSTITUTE OF INFECTIOUS DISEASES

**Phylogenetic tree of coronaviruses**




Modified from Science. 2021 Apr 16;372(6539):227-231.

* A virus strain belonging to beta coronavirus of the family Coronaviridae COVID-19 (SARS-CoV-2) and SARS coronavirus belong to Sarbecovirus.



This research and development is supported by AMED JP233fa827002

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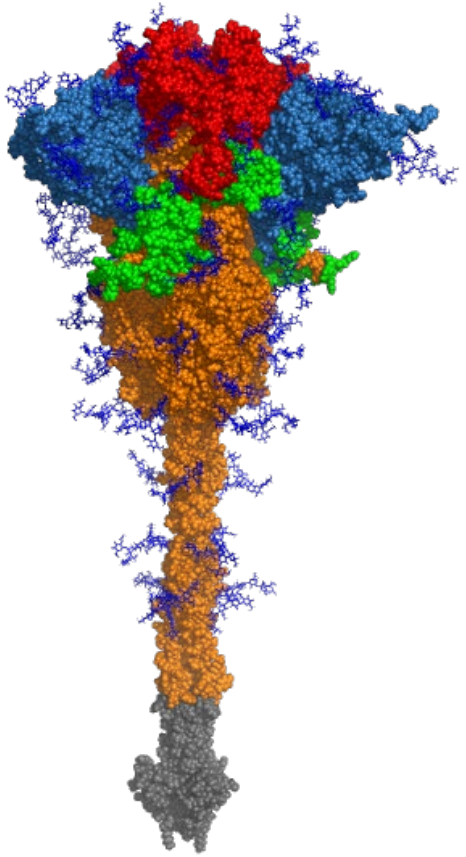
# S-567123: Advantages of S-567123

**Antibody induction to conserved regions of Sarbecovirus with coverage that competitors' vaccines cannot provide**

## Characteristics of antigen design technology and antigens

- Building an antigen design technology that induces antibodies against preserved regions, not in regions where mutations can easily occur
- Collaborating with KOTAI Co., Ltd. to  on this antigen design technology
  - Overview of antigen design technology
  - ① Induction of antibody production to conserved regions by glycan control
  - ② Introduction of epitopes preserved between different viruses and strains
  - ③ Increased immunogenicity by control of protein structure and dynamics

Schematic diagram of spike protein



**Creating a universal antigen that selectively induces antibodies across the entire family of Sarbecoviruses**



This research and development is supported by AMED JP233fa827002

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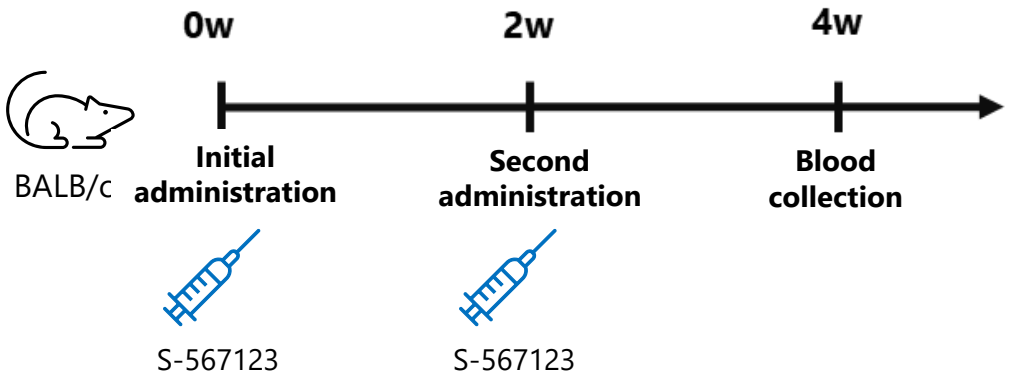
# S-567123: Progress and Data

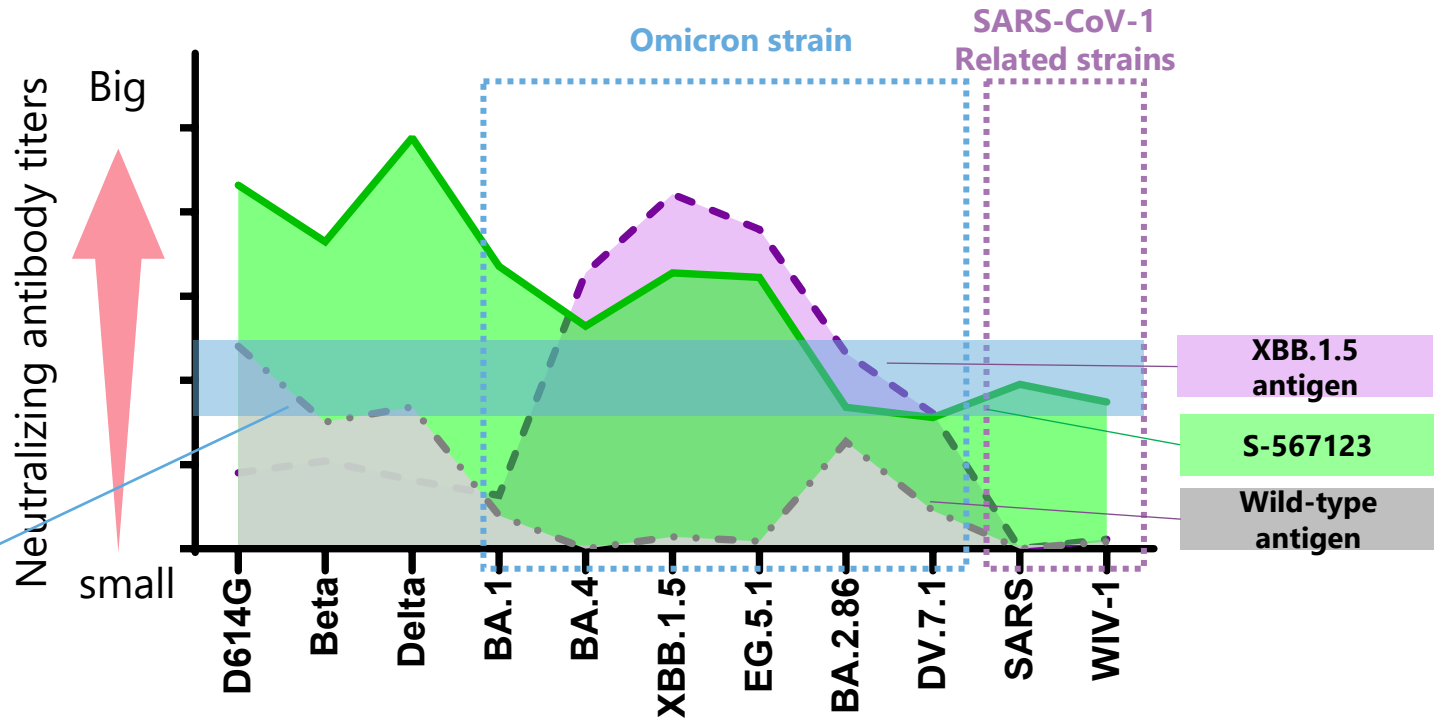
**Development antigen selection completed, Preparing for clinical trial entry within FY2024**

## Immunogenicity data in mouse priming model




Antibody titers that can be expected to prevent onset

**Neutralizing antibody titers after primary immunization of mice (pseudovirus)**






This research and development is supported by AMED JP233fa827002

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# QOL diseases with a high social impact

# QOL diseases with a high social impact

## Obesity



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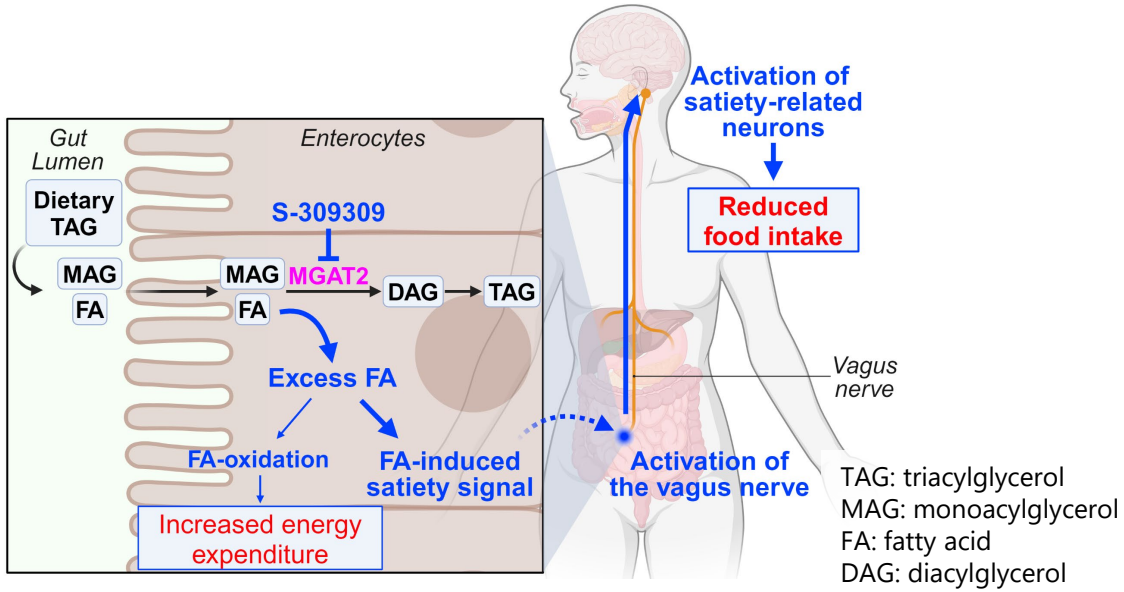
# S-309309
# Indication: Obesity

## Phase 1* trials confirm mechanism of action in humans

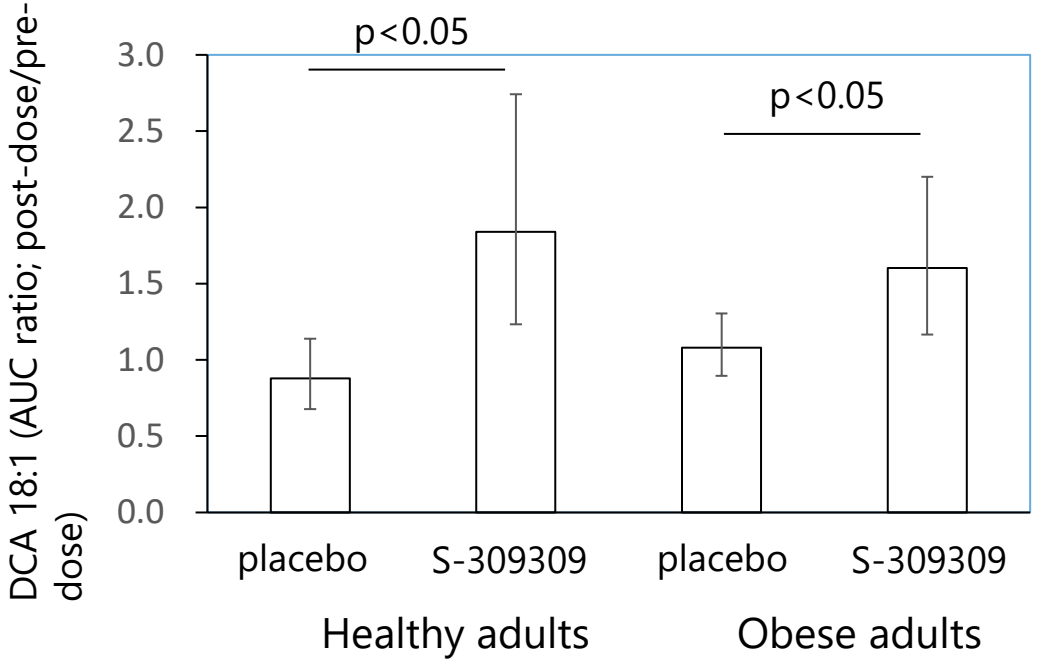
### Monoacylglycerol acyltransferase 2 (MGAT2) Inhibitors

- Inhibits the resynthesis of triglycerides, inhibits the absorption process of triglycerides (TAG) from the small intestine, and causes accumulation of dietary fatty acids in the small intestinal epithelium
- Food intake is suppressed via the vagus nerve




### Plasma DCA 18:1 measurement results

- DCA18:1 (oleic acid oxide): produced by oxidation of dietary fatty acids accumulated in the small intestinal epithelium, etc.






* US program: NCT05247970

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# S-309309: Topline Result of Phase 2 Clinical Trial

**Favorable safety profile confirmed, suggesting potential as a new option for obesity treatment**

## Overview*

| | |
|---|---|
| **Country** | US |
| **subject** | Adults with a BMI of 30 or more |
| **Study design** | Multicenter, randomized, double-blind, dose-finding, Placebo-controlled |
| **Dietary restrictions** | Daily calorie intake is calculated by subtracting 500 kcal from the total energy expenditure calculated based on age and sex.<br>(Complies with the Anti-Obesity Drug Development Guidelines) |
| **Dosage and Administration Number of cases** | • Once daily orally for 24 weeks<br>• No dose escalation, no food restrictions when taking medication<br>• S-309309: 3 doses, placebo, 80 cases per group (total 320 cases) |
| **Primary endpoint** | Weight change from baseline (24 weeks after administration) |

## Preliminary results (under analysis)

- Good tolerability was confirmed. The incidence of gastrointestinal symptoms, known to occur with GLP-1*2 preparations, was similar to that in the placebo group, and there were no concerns about tolerability.
- The rate of weight loss from baseline (group average), which was set as the standard for determining whether or not to develop a single agent, did not exceed 5%.
- A tendency towards weight loss in humans with this mechanism of action was confirmed

Consider a new development strategy based on the "unmet needs of existing treatments" rather than a development strategy based on S-309309 alone

*1 ClinicalTrials.gov: NCT05925114 *2 Glucagon-like peptide-1

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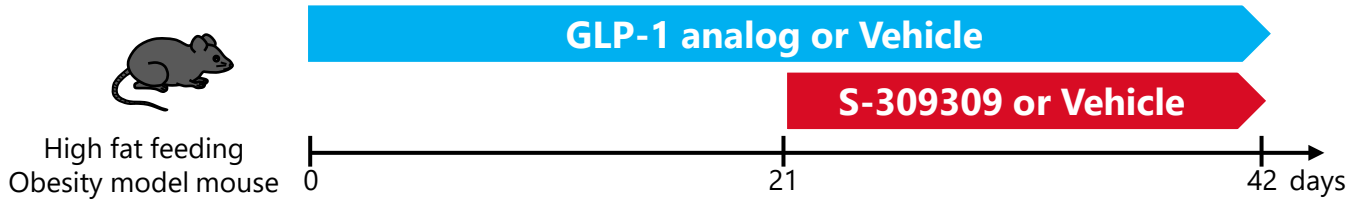
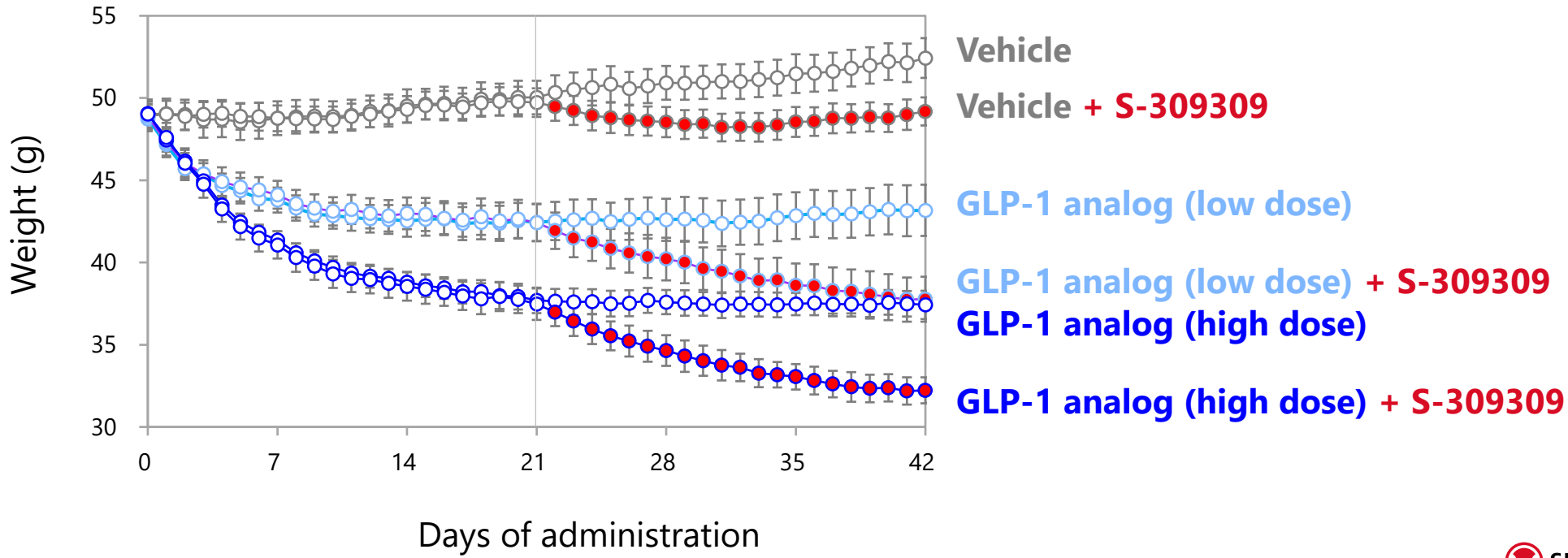
# S-309309: Non-clinical Trial Results - Add-on Effect

**S-309309, as an add-on, exerts an additive or greater effect on the weight-reducing effect of GLP-1 analog**



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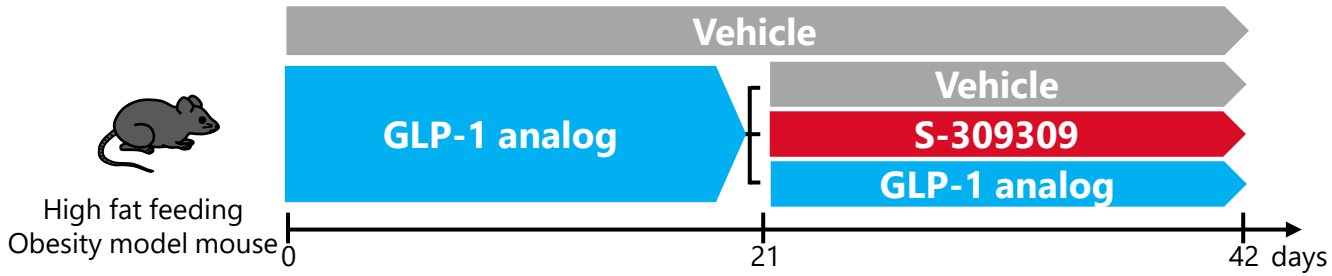
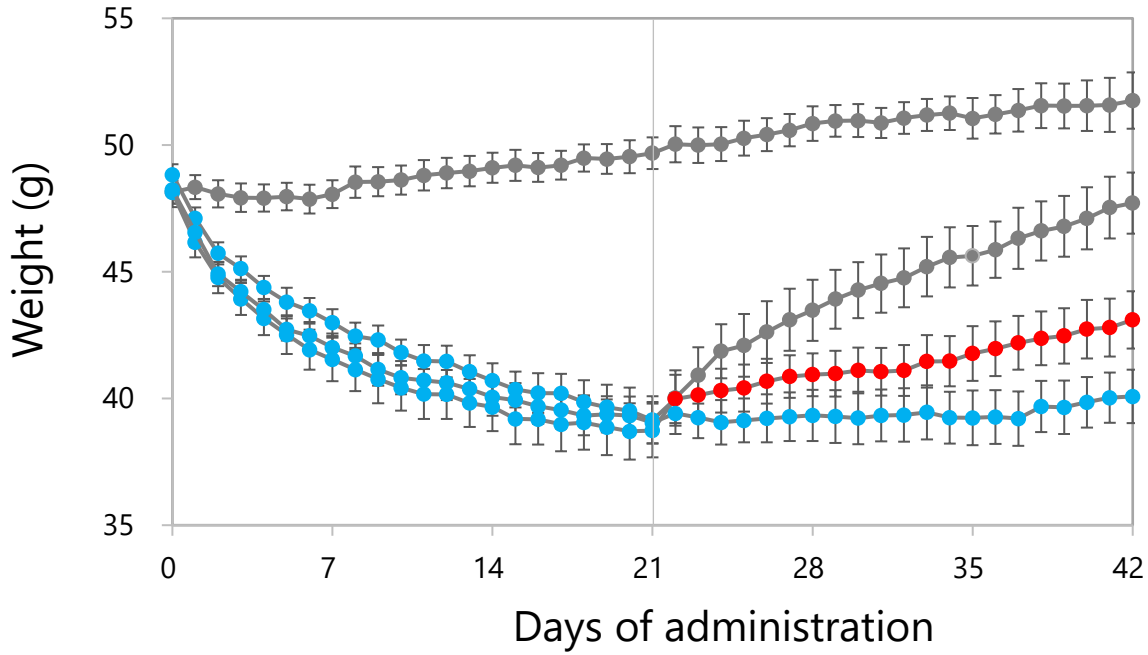
# S-309309: Non-clinical Trial Results - Efficacy Maintenance effect

**Switching to S-309309 after GLP-1 analog treatment reduced weight rebound compared to the vehicle group**




Vehicle

GLP-1 analog ⇒ Vehicle

GLP-1 analog ⇒ S-309309

GLP-1 analog ⇒ GLP-1 analog



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# SHIONOGI's View on Unmet Needs in the Anti-obesity Drug Market and Development Strategy for S-309309

**Resuming licensing activities to utilize the potential of S-309309 to address unmet needs**

## Unmet needs after launch of GLP-1

**Long-term medication with peace of mind (Price, side effects)**

**No rebound**

**Don't lose muscle mass**

## Future development strategy (under consideration)

**Potential to alleviate unmet needs by combining or switching between GLP-1 and S-309309**

- Reduction in the dosage of GLP-1 preparations by combination therapy
- Weight management and maintenance after weight loss using GLP-1

- Continuing treatment by reducing side effects of GLP-1
- Affordable out-of-pocket expenses



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# QOL diseases with a high social impact

## Solid tumors



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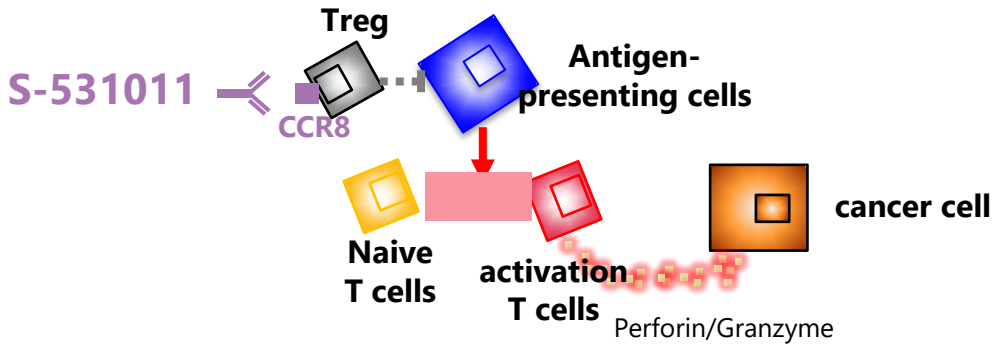
# S-531011
# Indications: Solid Cancer

## Product Features :

- Anti-CCR8* humanized monoclonal antibody
- Excellent safety and strong efficacy expected by activating tumor immunity
- Potential for use in a variety of cancer types
  - ➢ CCR8 is expressed in tumor-infiltrating Tregs in various cancer types and stages.

## Mechanism:

1. The antibody binds to CCR8, which is selectively highly expressed on regulatory T cells (Treg) in tumors, and removes the cells to relieve immune suppression.
2. Tumor immunity is restored and antitumor effects are achieved




## Development history

**2014**

Joint research course established with Osaka University*2

- Search for molecules other than PD-1 involved in tumor immune evasion

**2018**

**Discovery of CCR8**

- Patent application (Granted)

**2022**

Started Phase1b/2 in Japan and the US

- Phase 2 part in preparation

**Delivering new cancer treatments from Japan to the world**



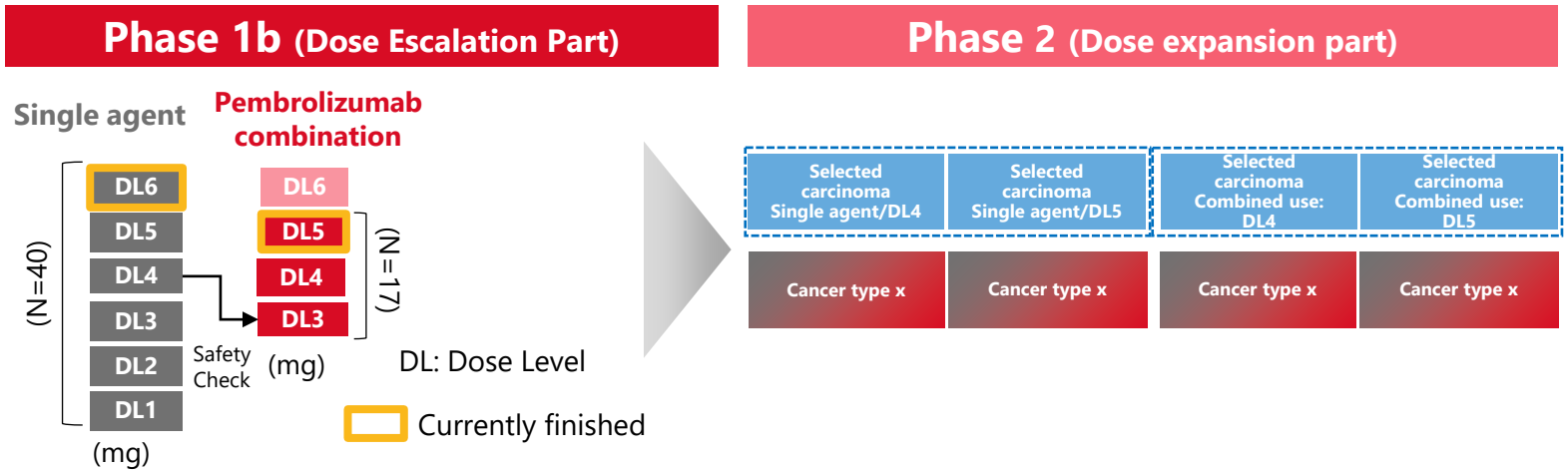
* CCR8: Chemokine (C-C motif) receptor 8

*2Department of Clinical and Basic Tumor Immunology, Center for Innovative Medical Innovation (CoMIT), Osaka University

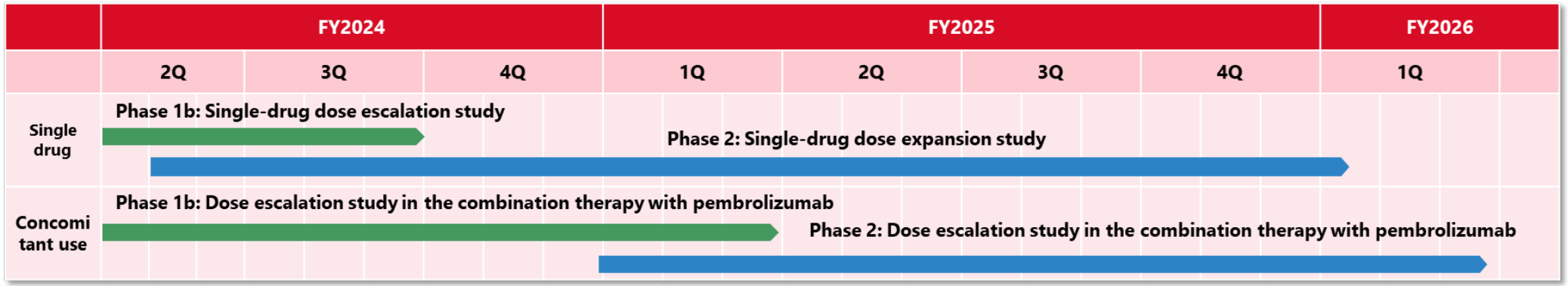
# S-531011: Progress of Phase 1b/2 Study in Japan and the US

**At present, there are no safety concerns regarding either the single agent or the combination**

## Development Plan




- Single-agent Phase 2 dose expansion part
  - Administration to start in Q2 of FY2024
- Combination Phase 2 dose expansion part*
  - Administration to start in Q1 of FY2025




* This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.



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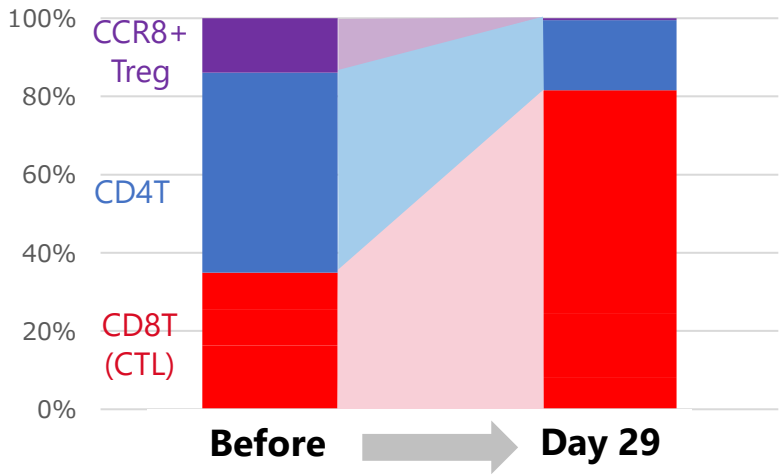
# S-531011: Pharmacodynamic Analysis (Single-Agent Dose Escalation Part)

**It has been confirmed that the administration of CCR8 leads to a reduction in suppressive Tregs and an increase in CD8 T cells within the tumor**

## Decreased CCR8+ Tregs and increased CD8 T cells in tumor tissue (percentage of T cells)

(Flow cytometry analysis)

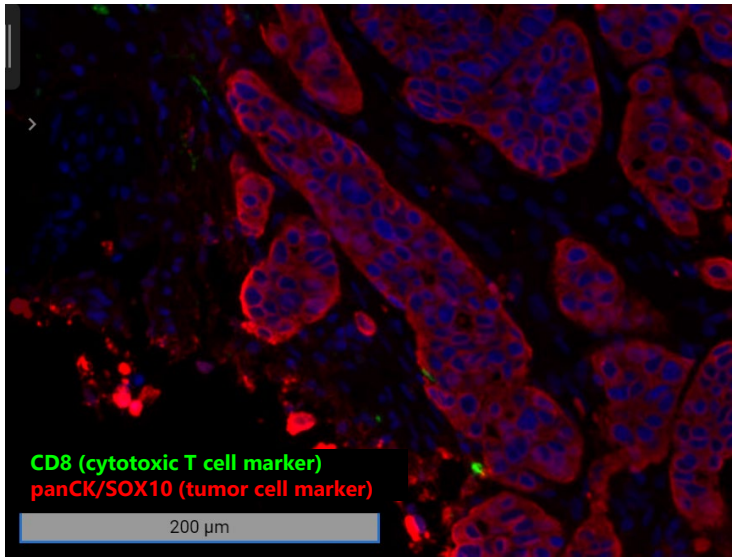



**CCR8+Treg: Decreased from 14% to 0%**
**CD8 T cells: increased from 34% to 81%**

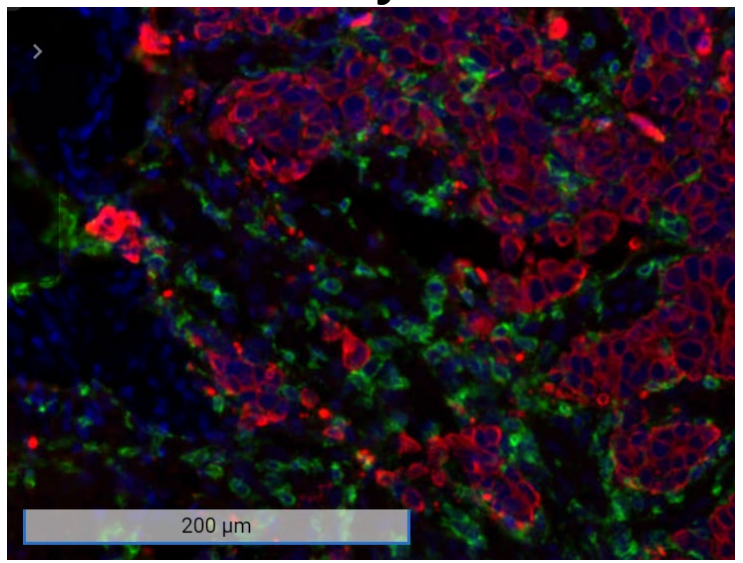
## CD8 T cells in tumor tissues are observed

(multiplex immunohistochemical staining)

**Before administration**




**Day 29**




**The administration of S-531011 results in an increase in CD8 T cells**



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# S-531011: Collaboration with Osaka University CoMIT* Joint Research

**Immune profiling within the tumors of patients responsive to S-531011 has been conducted to identify those with immune states where superior efficacy can be expected**

**CoMIT**

Cutting-edge Treg biology research using fresh clinical samples from multiple medical departments

**Data collation and analysis**

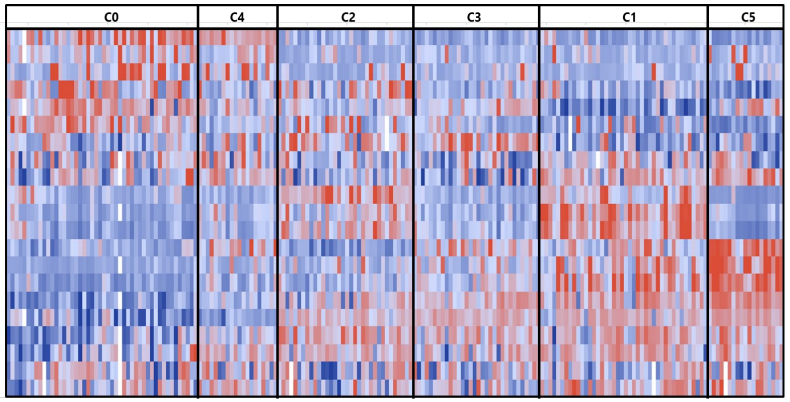
**Clinical trials**

Japan-US Phase 1b/2 study

Surgical specimens

Osaka University Hospital

**Flow cytometry analysis**




**Flow cytometry analysis**

Biopsy specimen

Clinical trial site

**Conducting detailed analysis of immune cells in tumors and blood of clusters of cases where treatment was effective, and searching for markers for patient stratification**

*SHIONOGI-Osaka University Joint Research Department: Clinical and Basic Tumor Immunology, Center for Innovative Medical Innovation, Osaka University (CoMIT)



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# S-531011: Strategies That Can Be Implemented Given Safety Profile

**Simple and low-burden treatment with potential application to childhood cancer**

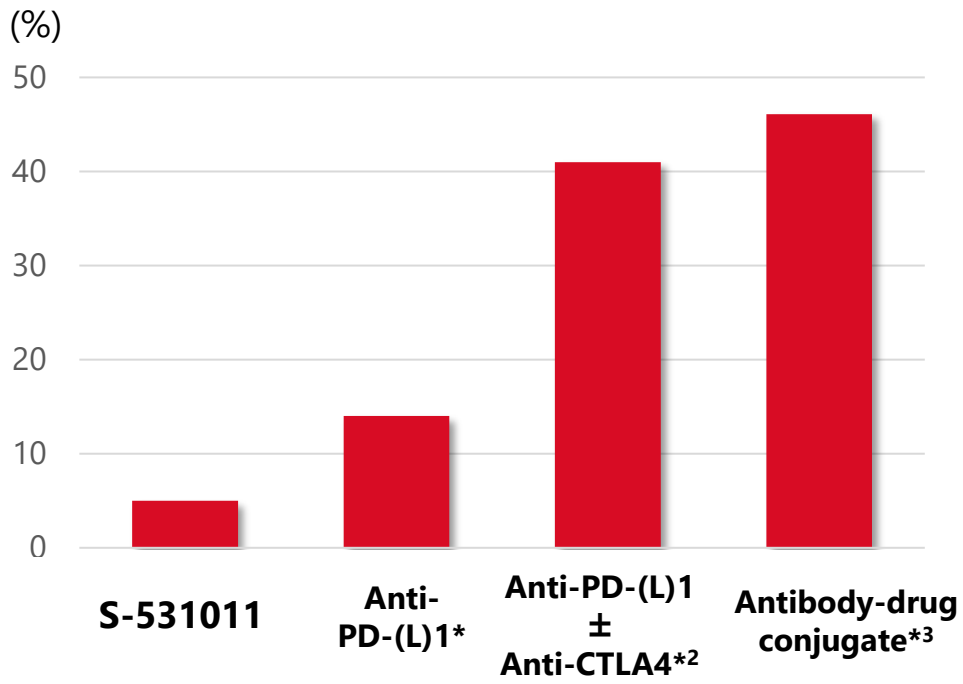
## Anticancer drug options free from side effects

- **Safe to use**
  - Minimize the impact on your daily life (grade 3 or higher)
- **Anyone can use it**
  - Even if you are physically weak

## High level of safety allows for various indications and approaches

- Combination therapy with various anticancer drugs
- Pediatric cancer drugs
- Subcutaneous formulation

## Adverse events causally related to the study drug






* Wang et al., 2019, JAMA, 5(7):1008, *2 Gu, et al., 2019, BMC Cancer, 19:559 *3 Zhu et al., 2023, Cancer, 129 (2):283

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# QOL diseases with a high social impact

## Pediatric and rare diseases

- Pompe disease
- Fragile X syndrome

## Dementia

# Introduction of S-606001【MZE001】, a New Therapeutic Drug Candidate for Pompe Disease

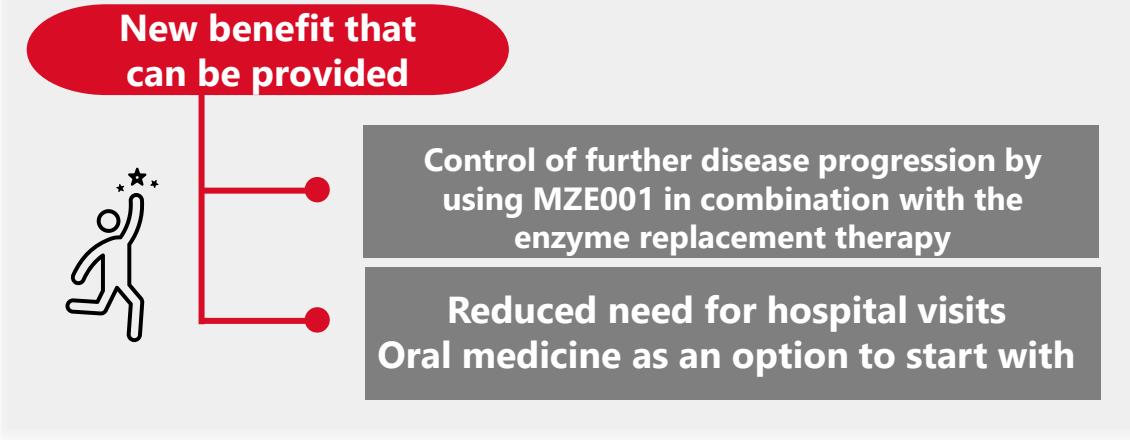
**Aiming for a paradigm shift in Pompe disease treatment with a new oral treatment with a novel mechanism of action**

## What is Pompe disease?

- A genetic disorder characterized by dysfunction of acid α-glucosidase
  - It causes an accumulation of glycogen in cells due to a deficiency in glycolysis
  - Symptoms include motor dysfunctions, respiratory disorders, and cardiac dysfunctions
- Enzyme replacement therapy (intravenous drip) is the only existing therapy
  - Disease progression occurs in many patients even under ERT (transition to artificial respiration, wheelchair)

## Characteristics of MZE001

- Introduced from Maze Therapeutics in May 2024
- Novel oral GYS1* inhibitor
  - It inhibits the synthesis of glycogen, which is the cause of accumulation in cells
- The only small molecular drug in the clinical development stage




* Glycogen synthase1 *2 Can genes influencing muscle function affect the therapeutic response to enzyme replacement therapy (ERT) in late-onset Type II Glycogenosis?
*3 Questionnaire survey on home enzyme replace therapy for lysosomal storage disease patients (N = 23, 2020)

# S-606001
## Indication: Pompe disease

### Market:

- Prevalence: About 50,000 people (Globally, estimate)
- Market size: US$160 million

### Unmet Needs:

- **Oral medicine that can reduce burden on the body due to injections and reduce burden caused by outpatient visits** (ERT requires intravenous injection once per 2 weeks.)
- **Disease progression can be stopped.**

### Product Property:

- Easy-to-use oral drug
- Since it has a mechanism of action different from ERT, enhanced effects can be expected when used in combination.

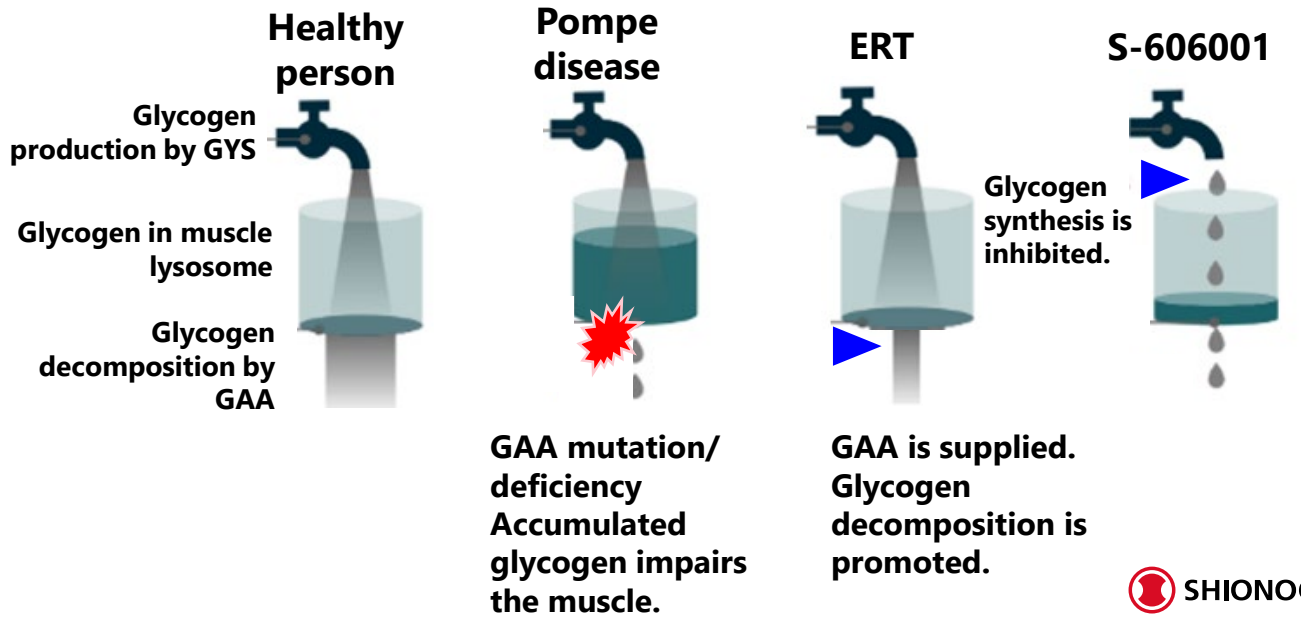
### Current Status :

- Q2 FY2024: Additional domestic Phase 1 study (BA/FE study for new formulation)
- Within FY2024: Phase 2 study will be started.

### Mechanism of Action:

- Pompe disease is a condition that glycogen abnormally accumulates in muscle lysosome due to mutation (decreased activity) of glycogenolytic enzyme (GAA) in muscle lysosome and muscular tissues are destroyed.
- S-606001 reduces accumulation of glycogen in muscle lysosome by inhibiting muscle-specific glycogen synthase (GYS1), thus suppressing destruction of muscles.

**Treatment concept using this drug**



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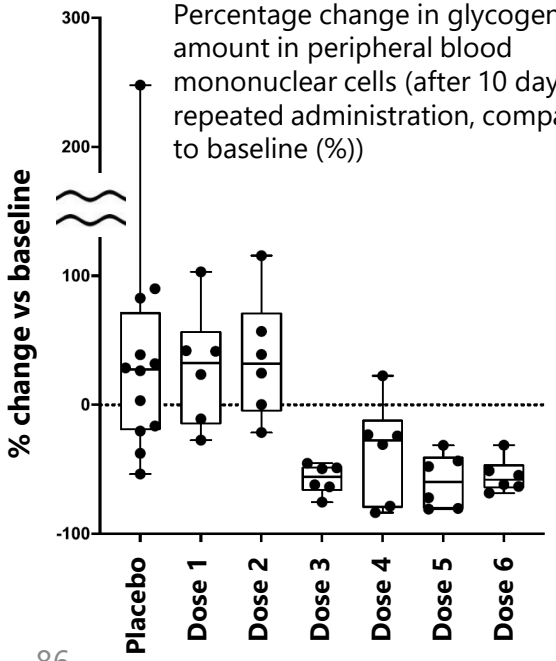
# S-606001 : Clinical Data

## Confirmation of good safety and Proof of Mechanism

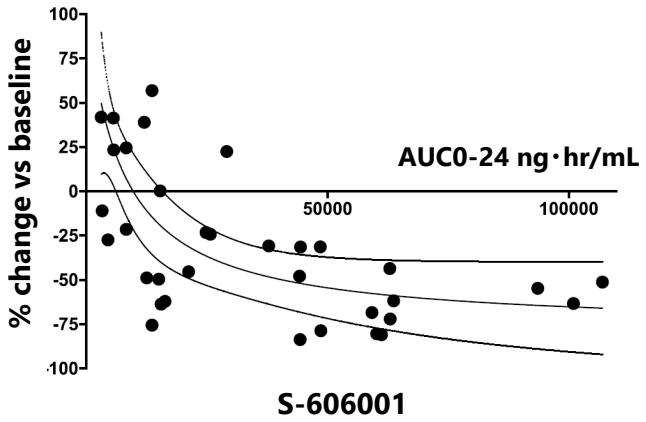
### Healthy human Ph1 trial in the US

- Good safety and tolerance
- Peripheral blood monocyte glycogen levels suppressed in an exposure-dependent manner

Percentage change in glycogen amount in peripheral blood mononuclear cells (after 10 days of repeated administration, compared to baseline (%))



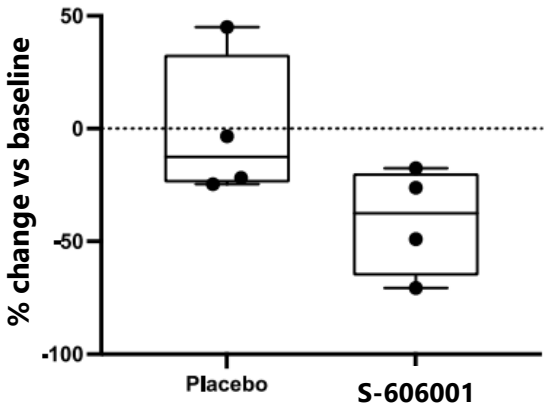

Percentage change in glycogen amount and drug exposure in blood




- Significant suppression of glycogen amount and glycogen production in muscle

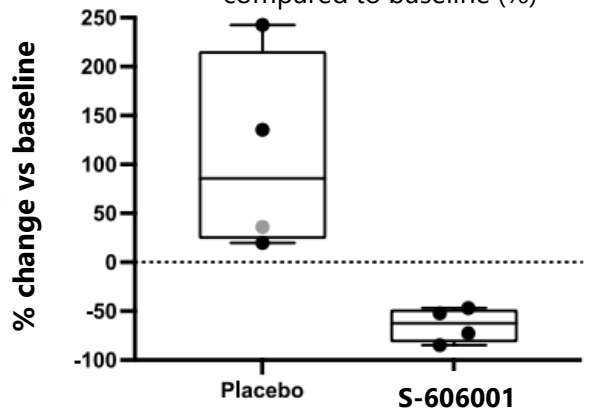
Glycogen amount in muscle

Change rate after 10 days of repeated administration, compared to baseline (%)




Glycogen production in muscle

Percentage change after 10 days of repeated administration, compared to baseline (%)



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# Zatolmilast [BPN14770]
## Indication: Fragile X syndrome (FXS)

### Fragile X Syndrome (FXS) :

- rare disease caused by the extension of a 3-base (CGG) sequence of the X chromosome FMR1 gene
- Main symptoms : Developmental delays and intellectual disabilities, behavioral abnormalities (autism, ADHD), and physical abnormalities

### Market:

- Prevalence: About 1 in 10,000 people
- Market size: 20 billion JPY or more
  (on male at 18 years old or over in the US)

### Unmet needs:

- No medicines have been approved for fragile X syndrome.
- High needs exist for relief from anxiety and improvement of cognitive functions, and medicines to improve communications between patients and caregivers (family) are needed.

### Designated as an Orphan/Fast track by FDA and EMA:

FDA

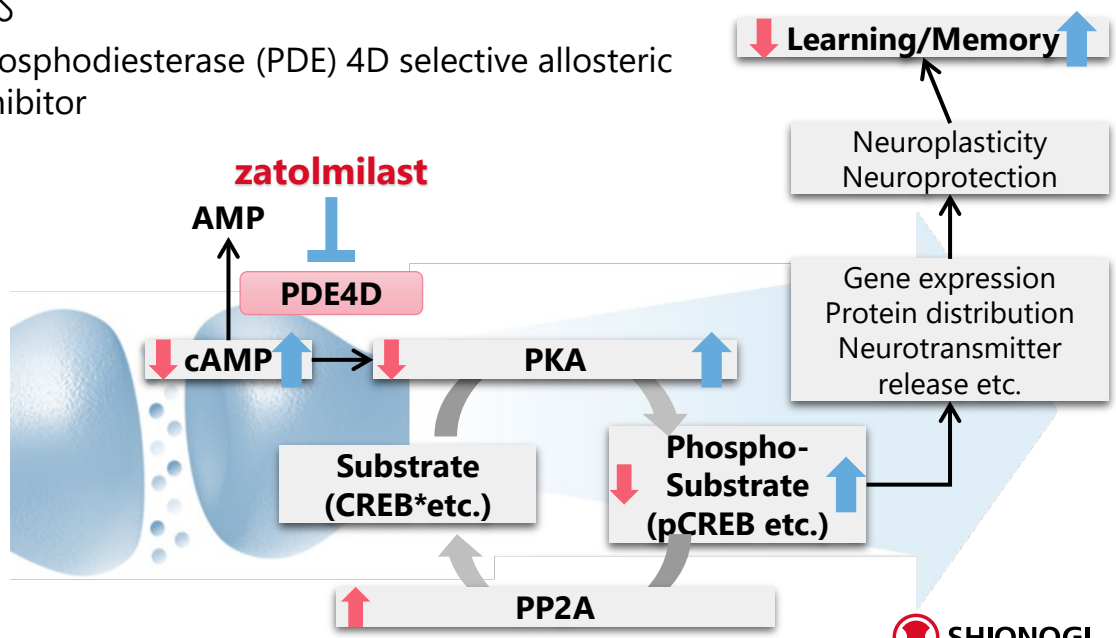
- Orphan Designation (April 2018)
- Designated for Rare Pediatric Diseases (September 2023)
- Fast Track Designation (March 2024)

EMA

- Orphan Designation (March 2024)

### Mechanism of action:

Phosphodiesterase (PDE) 4D selective allosteric inhibitor



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# Zatolmilast: Progress in development for fragile X syndrome

**Currently conducting clinical trials in the US with the cooperation of FXS support groups*, aiming to submit for approval by 3Q FY2025**

## US PoC Testing*2

- Conducting a Phase 2 study with support from FRAXA*
- Significant improvement in language function and daily life function

## US late-stage clinical trials

- Ph2/3 study for young males (ages 9-17)
- Phase 2/3 study for adult males (18-45 years old)
- Open-label extension study

tetra THERAPEUTICS
SHIONOGI Group Company

SHIONOGI

FRAXA Research Foundation

NATIONAL FRAGILE X FOUNDATION

**Global development including Europe, and expansion of indications to pediatric males (under 9 years old) and females under consideration**



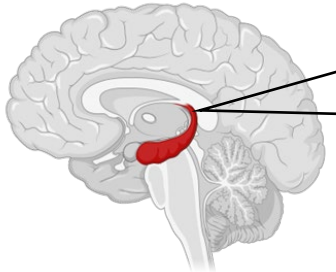
* FRAXA: FRAXA Research Foundation, NFXF: National Fragile X Foundation *2 Berry-Kravis EM. et al., Nat Med. 2021 May;27 (5) : 862-870

# Drug Discovery Aimed at Improving Symptoms of Dementia

## Drug discovery concept

**A compound that selectively inhibits PDE4D* within neuronal cells**

- Enhancing and maintaining the expression of genes related to neural function through the augmentation of the cAMP-CREB pathway*2
- Boosting neural and synaptic function, thereby improving cognitive functions including learning and memory

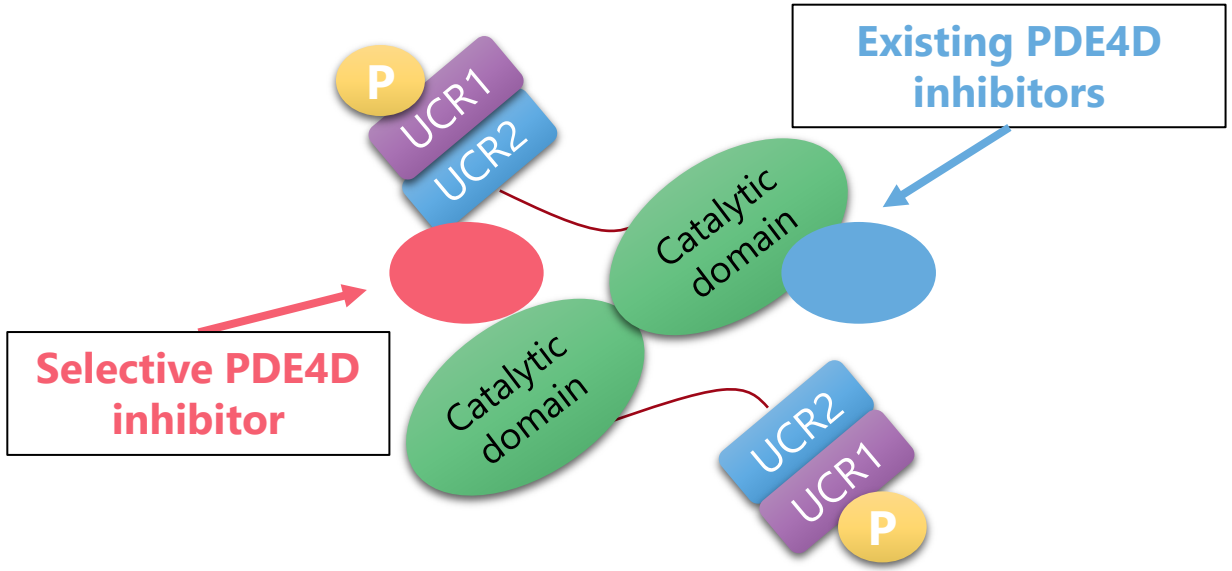


**cAMP↑** ▶ **pCREB↑** ▶ **Enhancement and consolidation of memory**

Creating an effective and user-friendly PDE4D inhibitor by selectively and appropriately regulating activity through the allosteric effect of PDE4D inhibition at low doses over a long period, tailored to the phenotype of symptom improvement in a wide range of age-related cognitive disorders, including Alzheimer's disease

## Mechanism

- Unlike existing PDE4 inhibitors, the UCR2*3 site is involved in binding
- The involvement of the UCR2 site in binding allows for the selective inhibition of PDE4D
- As a result, it is expected to avoid side effects such as vomiting and improve cognitive functions, including learning and memory




* PDE4D: Phosphodiesterase 4D *3 UCR2: Upstream Conserved Region 2
*2 cAMP: cyclic adenosine 3,5-monophosphate, CREB: cAMP response element binding protein



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# S-898270 : Preclinical study

**Aiming for Phase 1 entry by the first half of 2025**
**for a wide range of patients suffering from cognitive decline, including memory loss**

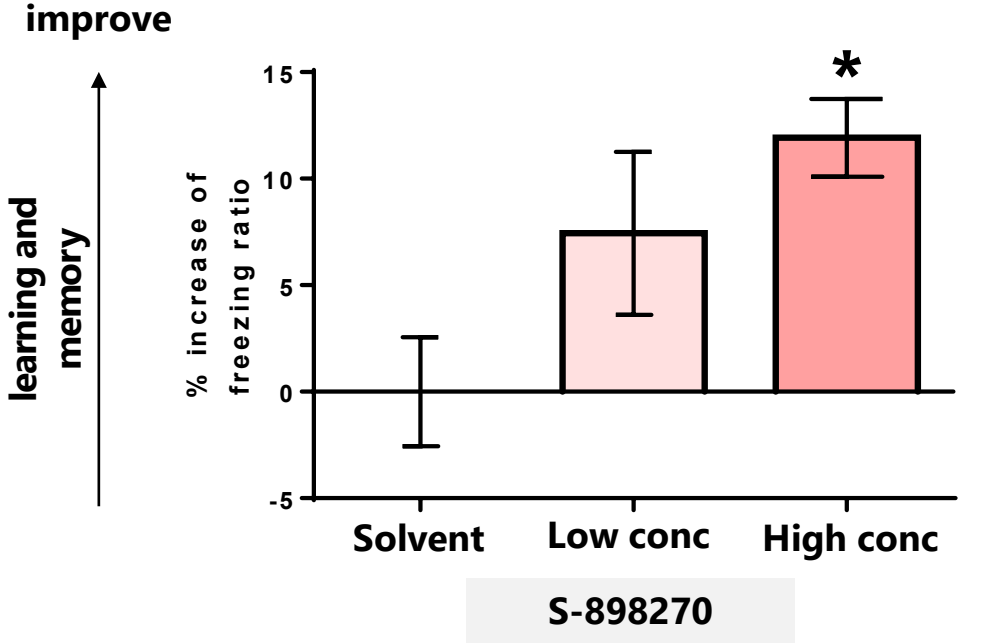
## In vivo efficacy (improving learning and memory)

Train mice to associate a specific stimulus with a testing environment

After a set period, present the testing environment without the stimulus

Verify if the mice remember the association between the testing environment and the stimulus

mean ± SEM, *$P$ < 0.05 vs. solvent




Administration of S-898270 improves learning and memory

Exploratory testing not yet conducted (QC already implemented)



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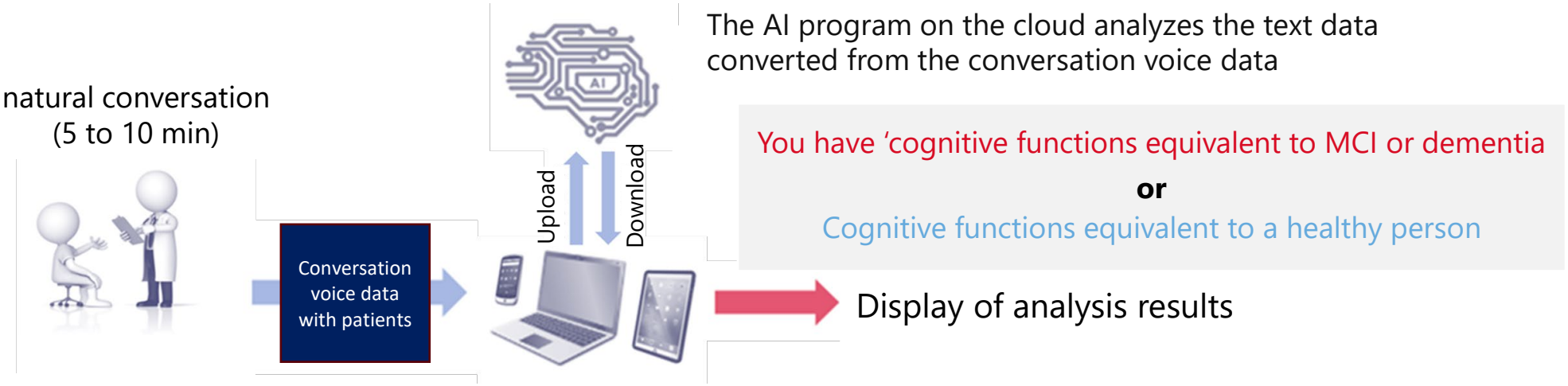
# SDS-881 (SaMD diagnostic support)
# Conversational Dementia Diagnosis Support AI Program (Collaboration with FRONTEO)

**Aiming to start by the third quarter of fiscal year 2024, preparations are underway for domestic validation trials**




- **Diagnosis based on natural conversation between patient and medical staff of about 5 to 10 minutes**
- Differences from existing neuropsychological tests (MMSE, etc.)
  - No specialist knowledge or experience required
  - Reduces the time and psychological burden on patients and examiners
  - No accustomization effect, so repeated (regular) tests are possible

**Promoting referrals and collaboration from non-specialists to specialists to achieve early treatment**

MMSE (Mini-Mental State Examination): A test to evaluate cognitive function including orientation, memory, calculation, language, and graphic ability, with a maximum score of 30 [11 questions in total]
Hasegawa-style assessment: Cognitive functions such as orientation, memory, and calculation are evaluated on a scale of 30 [9 questions in total]
Announcement of the Strategic Business Partnership Agreement for Diagnosis Support AI Program in Dementia and Depression between FRONTEO and Shionogi | SHIONOGI

# QOL diseases with a high social impact

## Sleep disorders



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# Expertise in Sleep DisordersEstablished a joint venture * with Apnimed, a company with outstanding expertise in sleep disorders

**Multiple programs are underway to address sleep disorders by addressing multiple mechanisms**

## Apnimed's Strengths

- High scientific expertise and development track record in the treatment of sleep apnea and other sleep disorders, as well as a global network for clinical research
- Multiple pipelines assets for sleep apnea syndrome

## Drug discovery based on hypotheses and drug target setting based on clinical evidence


**Set hypothesis for treatment approachand drug discovery targets** based on clinical experience and preclinical research reports on the mechanism of action

Testing hypotheses through **clinical research using existing drugs**

Synthesis of novel compounds using in vivo PoM*2 model (SAR)

Identifying appropriate patient demographics, selection of therapy based on pathophysiological classification - Conducting clinical trials



* Shionogi-Apnimed Sleep Science, LLC (SASS) *2 Proof of Mechanism

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# Market and Unmet Needs of Sleep Apnea Syndrome

## Market:

- Number of affected people: Approximately 900 M people

  Among the above, the target group is patients with increasingly unstable breathing


## Unmet needs:

- Highly effective and safe therapeutic drugs as alternatives to devices and surgical treatments
- Treatment options for patients with nasal continuous positive airway pressure (CPAP) resistance or intolerance



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# SASS (S-600918 [Sivopixant] + Concomitant drug X)
# Indications: Sleep Apnea Syndrome

## Mechanism

- S-600918's respiratory control:
  By inhibiting the P2X3 receptors of the carotid bodies (blood O2 sensors), it suppresses excessive hypoxic responses and stabilizes the rhythm of breathing
- In addition to S-600918, the combination with drugs of different mechanisms may bring clinically significant therapeutic effects for sleep apnea and hypoventilation

## Product Features:

- Oral once daily before bedtime

## Current status and future plans:

- SHIONOGI's Phase 2 trial of S-600918
  - In a subgroup of patients with unstable respiration (12 cases), **an improvement in the number of apneas and hypopneas suggesting efficacy was observed** compared to the placebo group (p=0.0161)
- Proof of Concept trial using S-600918 and combination drug X
  - to start in the 3rd quarter of fiscal year 2024
  - with interim results expected by 3Q of FY2025

# QOL diseases with a high social impact

**Neuropsychiatric disorders (domestic development)**

- Depression
- ADHD

# Zuranolone ($GABA_A$ receptor positive allosteric modulator)
# Indications: Major Depressive Disorder (Depression)

**Aim to become "the main drug for the acute treatment* of depression"**

## Strengths: Rapid effect (an important unmet need for depression treatment)

- **Achieved efficacy in just two weeks that would require six to eight weeks of treatment with existing drugs**
- Rapid improvement of symptoms after starting treatment leads to a favorable treatment course*[2] and is of great clinical significance

## Ease of use: Convenient, with administration for 2 weeks only when treatment is required

- No dose adjustment required, efficacy assessed in 2 weeks, **high adherence** expected

## Treatment concept: To improve depression symptoms in a short period of time for patients who require treatment

- The immediate efficacy of this medication shortens the difficult periods of depression
- It smoothly guides efforts towards depression treatment and social reintegration

** Acute phase of depression: From the start of treatment after diagnosis to remission (disappearance of depressive symptoms) (Source: Depression Treatment Guidelines, Key Points of Depression Treatment-10)*

*[2] J Clin Psychiatry 2009; 70(3):344-353



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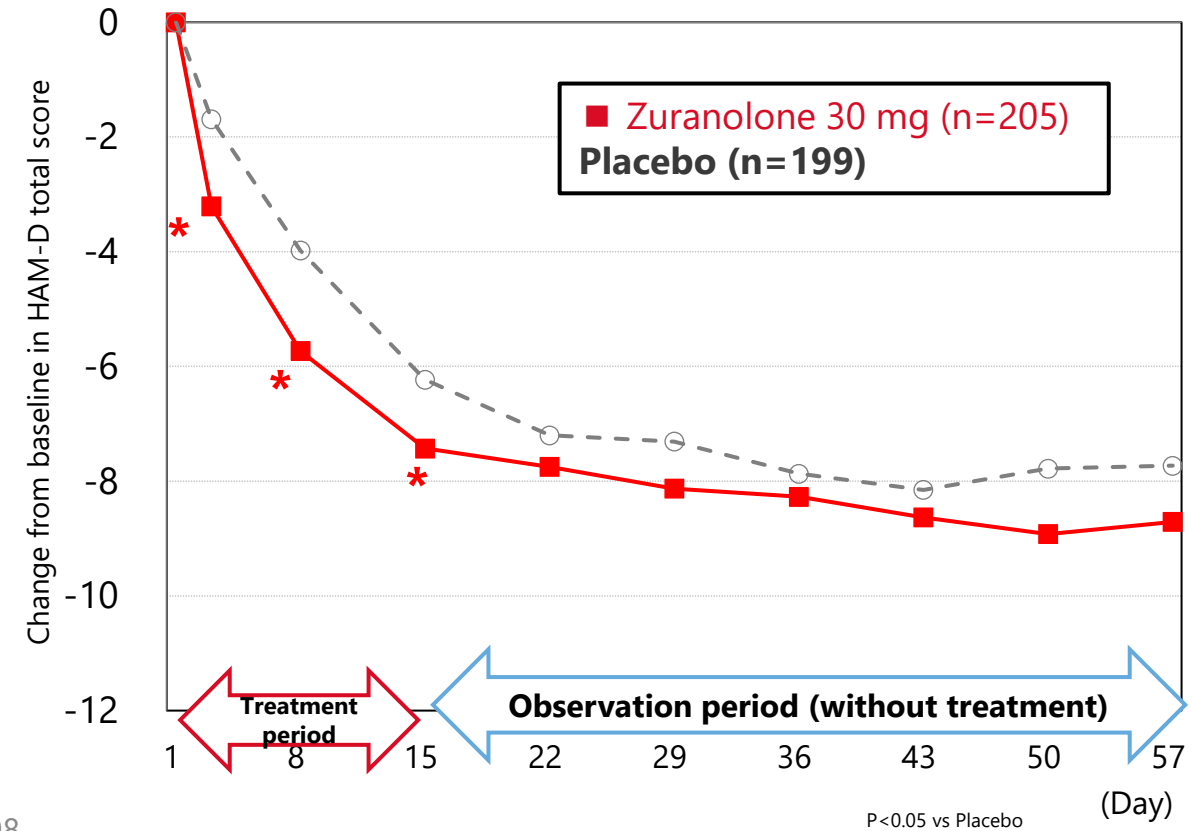
# Zuranolone: Phase 3 Study Results in Japan

**Demonstrated rapid improvements in depression symptoms, application for approval scheduled for 1Q FY2024**

## Change from baseline in HAM-D total score




## Efficacy

- **Domestic Phase 3 verification study: Primary endpoint achieved**
  - Significant improvement in the 30 mg group compared to placebo in the change from baseline in HAM-D total score from Day 3 to Day 15
  - During the observation period from Day 15 to Day 57, the treatment effect was confirmed to be sustained
- **Phase 3 Add-on Study**
  - The added effect of zuranolone on other antidepressants could not be confirmed (possibly due to the small number of subjects)

## Safety

- Consistent tolerability profile across studies; adverse events mild to moderate in severity
- No subjects reported dependence on the drug

* HAM-D: Hamilton Depression Rating Scale



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# SDT-001
# Indications: Attention Deficit Hyperactivity Disorder (ADHD) in Childhood

## Market :

- Approximately 260,000 pediatric ADHD patients diagnosed (domestic)

## Unmet needs :

- Convenient treatment options other than medication

(Due to a shortage of human resources in medical institutions, few can provide psychosocial treatments).

## Product Features :

- Digital therapeutic application
- Daily training for about 25 minutes using the application

## Current status and future plans :

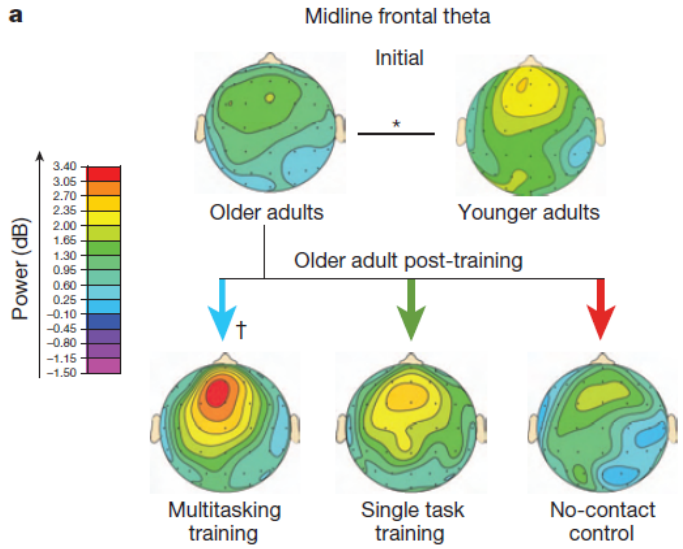
- Approval application in progress (domestic, February 2024)
- Approval obtained, insurance coverage (within 2025)

## Mechanism :

- By performing dual tasks adjusted for difficulty for each patient, the application activates the prefrontal cortex functions (which are diminished in ADHD patients) and improves symptoms of inattention and hyperactivity/impulsivity

Activation of brain function through difficulty-adjusted dual tasks*

**Dual task execution (Steering tapping)**




Dual task > Single task > Control
Training increases brainwaves (theta waves)

*Nature. 2013 Sep 5;501(7465):97-101



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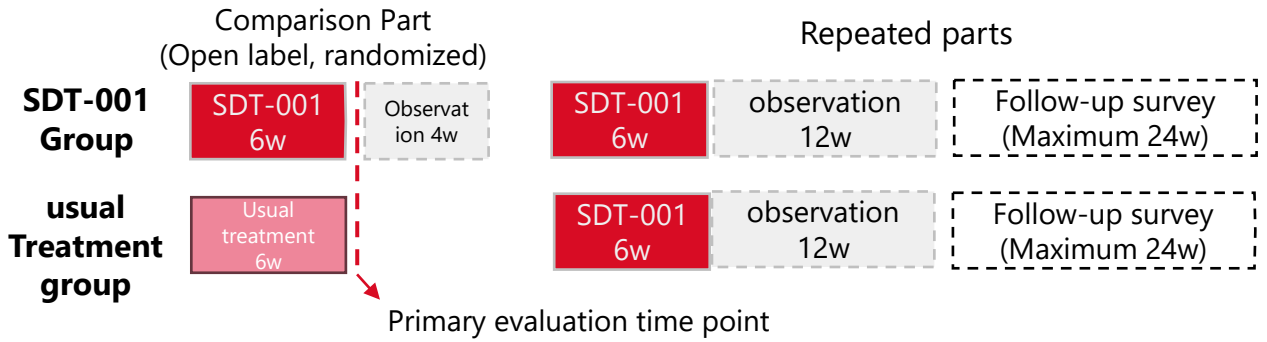
# SDT-001: Phase 3 Study in Japan for Pediatric ADHD Patients

## Primary and key secondary endpoints achieved

| | |
|---|---|
| **Subject** | Children with ADHD (ADHD-RS inattention score of 15 or more*) |
| **Primary endpoints** | Change from baseline in ADHD-RS-IV (clinician-rated) inattention score |
| **Secondary endpoints** | Efficacy, safety and tolerability of SDT-001 when used repeatedly |

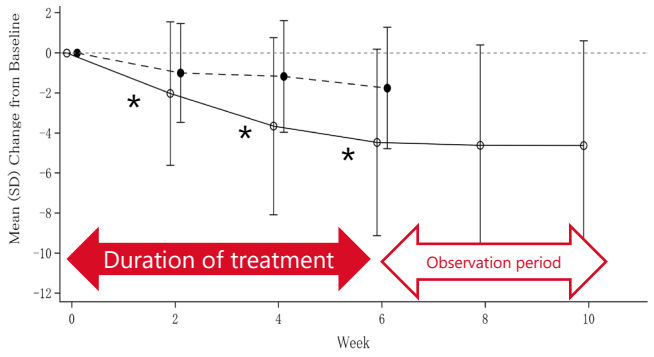



**Study results (comparison part): Change from baseline in ADHD-RS-IV (physician-assessed) scores**

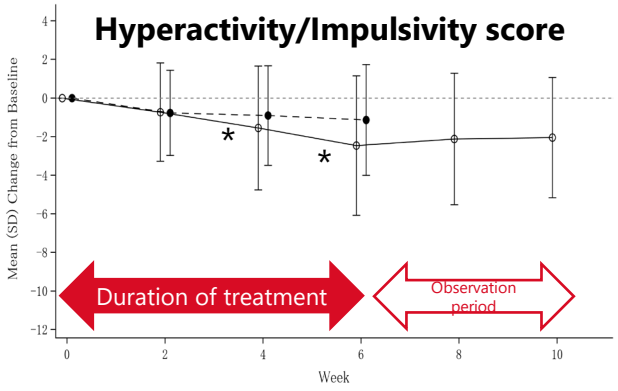
SDT-001 / TAU

TAU = treatment as usual *: p < 0.05 (MMRM analysis)

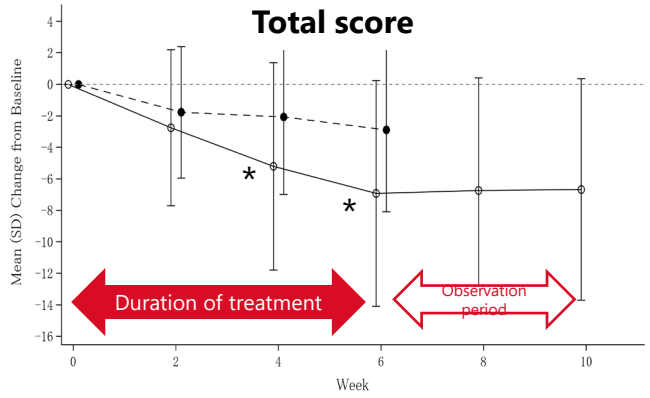
**Inattention score (primary outcome measure)**




**Hyperactivity/Impulsivity score**




**Total score**




- Comparison part: ADHD-RS-IV (physician-rated) inattention score, hyperactivity/impulsivity score, and total score were significantly improved compared to the usual care group
- Repeated Part: ADHD-RS-IV scores were reduced even after two cycles of SDT-001 use. Improved ADHD-RS-IV scores were maintained for at least 12 weeks after discontinuation of use



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# Actions in Focus Areas: Today's Highlights

- **SHIONOGI R&D's core strength and synergy through external collaboration have led to the enrichment of a robust pipeline**
- **Agile development of next-generation growth drivers will be accelerated through flexible resource allocation**

**The global expansion of ensitrelvir and the development of its preventive applications**

**Creation of a universal vaccine, with smooth preparations underway for clinical trials within fiscal year 2024**

**Efforts towards the realization of Test to Treat**
**(antimicrobial susceptibility testing, dementia diagnosis support)**

**Research on ultra-long-acting drug discovery for HIV**
**(novel INSTI, partner drugs)**

**Progress and expansion of the early-stage development pipeline**
**(S-892217, 337395, 649228, 743229, 531011, 606001)**

**Exploration of new focus areas and preparation for clinical trials**
**Sleep Apnea Syndrome** **(Shionogi-Apnimed-Sleep Science, LLC, S-600918 + combination drug X)**

# Summary of today

Isao Teshirogi, PhD

Chief Executive Officer



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# Progress of Major Development Products - Infection diseases -

※The bar starts from FPI and ends at CSR,　Topline results: It is the timing of acquisition, and the timing of disclosure will be considered separately

| | Pipeline | Indication | Current stage | FY2024 | FY2025 |
|---|---|---|---|---|---|
| COVID-19 Family | S-268019 | COVID-19 (Vaccine) | Consent for Approval* | | |
| | Ensitrelvir | COVID-19 | Submission・Phase 3 Phase 3（Pediatric） | Phase 3 topline results（FY24 4Q） | |
| | Ensitrelvir | COVID-19 (prevention) | Phase 3 † Data analysis in progress | Phase 3 topline results （FY24 3Q） | |
| | S-268023 | COVID-19 （XBB1.5,Vaccine） | Phase 3 | | |
| | S-892216 | COVID-19 | Phase 1 | Phase 2 start（FY24 2Q） topline results （FY24 4Q） | |
| | S-567123 | COVID-19 (Universal Vaccine ) | Preclinical | Phase 1/2 start （FY24 4Q） | topline results （FY25 2Q） |
| Infection diseases | Olorofim | Invasive aspergillosis | Phase 3 | | |
| | S-337395 | RSV infections | Phase 2 | | |
| | S-743229 | AMR (Complex urinary tract infection) | Phase 1 | Phase1 (combined use) topline （FY24 3Q） | |
| | S-649228 | AMR (Gram-negative bacteria infection) | Preclinical | Phase1 (combined use) start（FY24 2Q） | topline results （FY24 3Q） |

* Consent for approval was given at the Second Committee on Drugs held on May 24, 2024

# Progress of Major Development Products - QOL Diseases with High Social Impact -

※The bar starts from FPI and ends at CSR, Topline results: It is the timing of acquisition, and the timing of disclosure will be considered separately

| Disease area | Pipeline | Indication | Current stage | FY2024 | FY2025 |
|---|---|---|---|---|---|
| QOL Diseases with High Social Impact | SDT-001 | ADHD | Submission | Approval（FY24 4Q） | |
| | Zuranolone | Depression | Preparation for application | Submission （FY24 1Q） | Approval（FY25 1Q） |
| | Resiniferatoxin | Pain associated with knee osteoarthritis | Phase 3 | | Submission （FY25 3Q） |
| | Zatolmilast | Fragile X Syndrome | Phase 2/3 | | Phase 2/3 topline（FY25 1Q） Submission （FY25 3Q） |
| | Redasemtide | Acute ischemic stroke | Phase 2b | | |
| | | Dystrophic epidermolysis bullosa | Phase 2 | | |
| | S-309309 | Obesity | Phase 2 | Phase 2 topline（FY24 1Q） | Considering future development strategies |
| | S-531011 | Solid tumor | Phase 1b/2 | Phase 2 part start（FY24 2Q） | |
| | S-600918＋Drug X | Sleep apnea syndrome | Phase 2 | | Phase 2 start（FY24 3Q） Phase 2 topline（FY25 3Q） |
| | S-606001 | Pompe | Phase1 | | Phase 2 start（FY25 1Q） |
| | S-151128 | Chronic pain | Phase 1 | Phase 1b topline（FY24 2Q） | |



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# Appendix



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# Olorofim [F901318]

## Indication: Invasive fungal infections with limited treatment options

### Market：

- Number of cases: The number of diagnoses of invasive aspergillosis is over 200,000 combined in Europe, Japan, and China
- The number of deaths from invasive aspergillosis is increasing worldwide.

### Unmet Needs：

- Oral drug with a new MoA for invasive aspergillosis, where treatment options are limited due to resistance and tolerability issues
- A new treatment option for patients with rare fungal infections

### Product Characteristics：

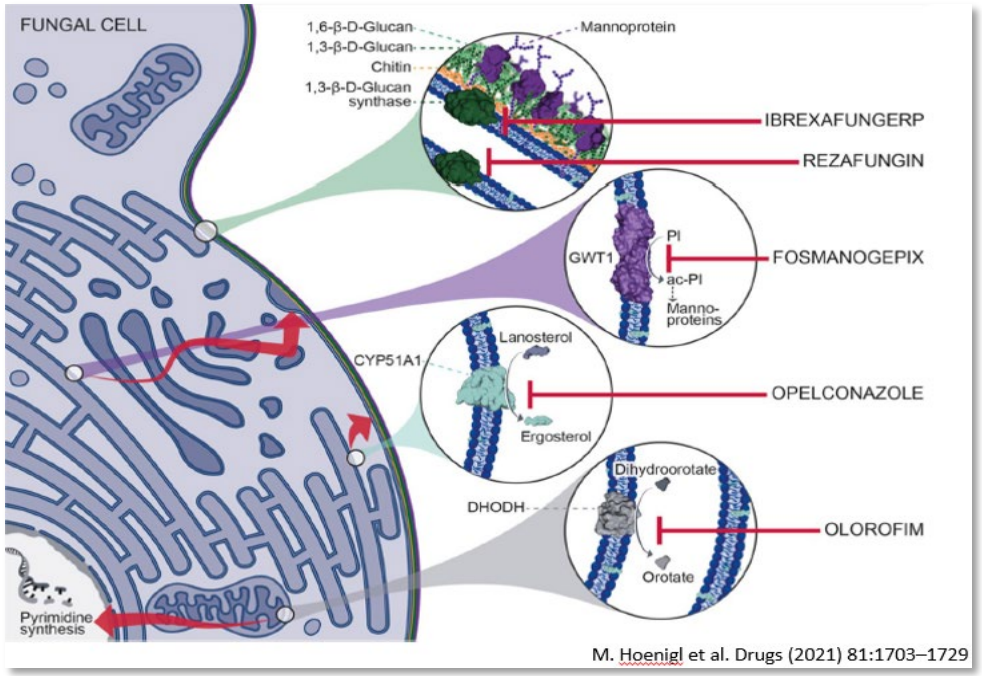
- Oral antifungal drug with novel mechanism of action different from existing drugs

### Current Status：

- Global Phase 2b trial：Completed
- Global Phase 3 trial：Being implemented in more than 20 countries around the world, including Japan and China

### Mechanism of Action (MoA)：

1. Fungal dihydroorotate dehydrogenase inhibitor
2. Fungicidal activity by inhibiting the pyrimidine synthesis pathway essential for fungal growth



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# Olorofim [F901318]: Global Phase 2b Trial

**Announcement of favorable Global Phase 2b trial results from F2G (co-development partner)***

## Trial Summary

- A multi-center, open-label Phase 2b trial to evaluate F901318 for the treatment of invasive fungal infections in patients lacking suitable alternative treatment options
- Target sample size: 200 cases
- Implementation countries: United States, Europe, APAC

## Trial Results

- Efficacy determination based on EORTC-MSG criteria*3 :
  Overall response rate at 42/84 days was 28.7% / 27.2%
  The rate including stable has increased to 75.2% / 63.4% respectively
- 114 out of 202 cases continued into extended treatment phase
- Generally good safety and tolerability confirmed

| | Number of valid cases*3 n (%) | | Total number of deaths due to all causes n (%) | |
|---|---|---|---|---|
| **Fungal species** | **Day 42** | **Day 84** | **Day 42** | **Day 84** |
| **Overall (n: 202)** | 58 (**28.7**) | 55 (**27.2**) | 23 (**11.4**) | 32 (**15.8**) |
| ***Aspergillus* spp. (n: 101)** | 35 (34.7) | 34 (33.7) | 18 (17.8) | 26 (25.7) |
| ***Lomentospora prolificans* (n: 26)** | 11 (42.3) | 11 (42.3) | 3 (11.5) | 3 (11.5) |
| ***Scedosporium* spp. (n: 22)** | 8 (36.4) | 5 (22.7) | 2 (9.1) | 2 (9.1) |
| ***Scopulariopsis* spp. (n: 6)** | 5 (83.3) | 5 (83.3) | 0 | 0 |
| **Other Olorofim-sensitive fungi(n: 8)** | 1 (12.5) | 2 (25.0) | 0 | 1 (12.5) |
| ***Coccidioides* spp. (n: 41)** | 0 | 0 | 0 | 0 |

* 11th Trends in Medical Mycology Congress *2 NCT03583164
*3 Efficacy determination by Data Review Committee based on EORTC-MSG criteria per Segal 2008 CID

# S-151128
## Indications: Chronic Pain

### Market:

- Number of symptomatic people : 44 million (US)*1
- Market size: $11.4B (US)*2

### Unmet needs:

- It has an analgesic effect even for pain for which existing drugs are ineffective.
- Long-lasting effect provides long-term pain control
- A treatment that is safe to use and has low risk of side effects

### Product features:

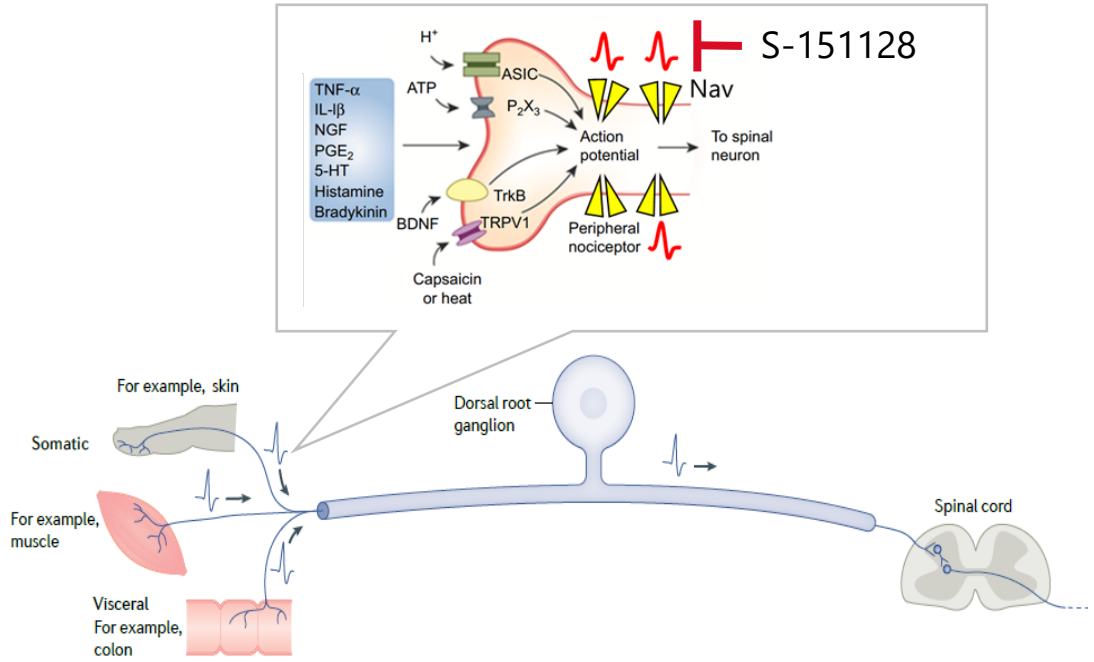
- Long-lasting effect (intravenous infusion once every four weeks is expected)
- High safety and tolerability

### Current status and future plans:

- Phase 1 single-dose study in healthy adults completed
- Currently conducting a Phase 1b repeated administration study targeting patients with knee osteoarthritis
- Currently selecting target pain disorders

### Mechanism of action:

1. Selective inhibition of voltage-gated sodium channel (Nav) 1.7
2. Suppresses the generation and conduction of action potentials that are the source of pain






*1Epi Database®, Oracle Life Sciences / Synix Corporation

*2Clarivate, Chronic Pain Disease Landscape & Forecast 2021

*J Pain Res. 2017 Mar 29;10:709-736.*
*Nat Rev Neurosci. 2021 May;22(5):263-274.*

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# S-151128: Development Status

**Confirmed tolerability and favorable pharmacokinetics Phase 1 trial with healthy adults, Phase 1b trial with multiple doses is currently underway**

## Phase 1 single dose trial

| | |
|---|---|
| **Country** | Japan |
| **Subjects** | Healthy adults |
| **Study design** | Single-center, randomized, placebo-controlled, double-blind |
| **Dosage and administration Target number of subjects** | Single intravenous dose (60 min)<br>1 cohort: 8 cases × 7 cohorts: 56 cases in total |
| **Endpoints** | Safety, pharmacokinetics, QT/QTc prolongation risk assessment |

- Safety: no side effects have been reported in S-151128 group.
- Anti-drug antibodies: negative in all cases
- Pharmacokinetics: Dose-dependent increase in exposure was observed
- Risk of QT prolongation: Not recognized

## Phase 1b repeated dose trial

| | |
|---|---|
| **Country** | Japan |
| **Subjects** | Knee osteoarthritis patients |
| **Study design** | Multicenter, randomized, placebo-controlled, observer-blind |
| **Dosage and administration target number of subjects** | Treatment group: Active drug, placebo, total 74 cases<br>28-day interval, 2 doses intravenously (30 minutes) |
| **Endpoints** | Safety, Pharmacokinetics, and Efficacy |

- June 2024: Last Patient Out
- Safety: No significant adverse events were reported

# Resiniferatoxin
## Indications: Knee Osteoarthritis

### Market:

- Number of symptomatic people : 25 million* (Japan)
- Market size: Over 70 billion yen (Japan)

### Unmet needs:

- Insufficient efficacy or short duration of effect is a problem with existing drugs, and there is a need for drugs that can control pain for a long time
- Drugs with strong analgesic effects are required as adjuvants for exercise therapy

### Product features:

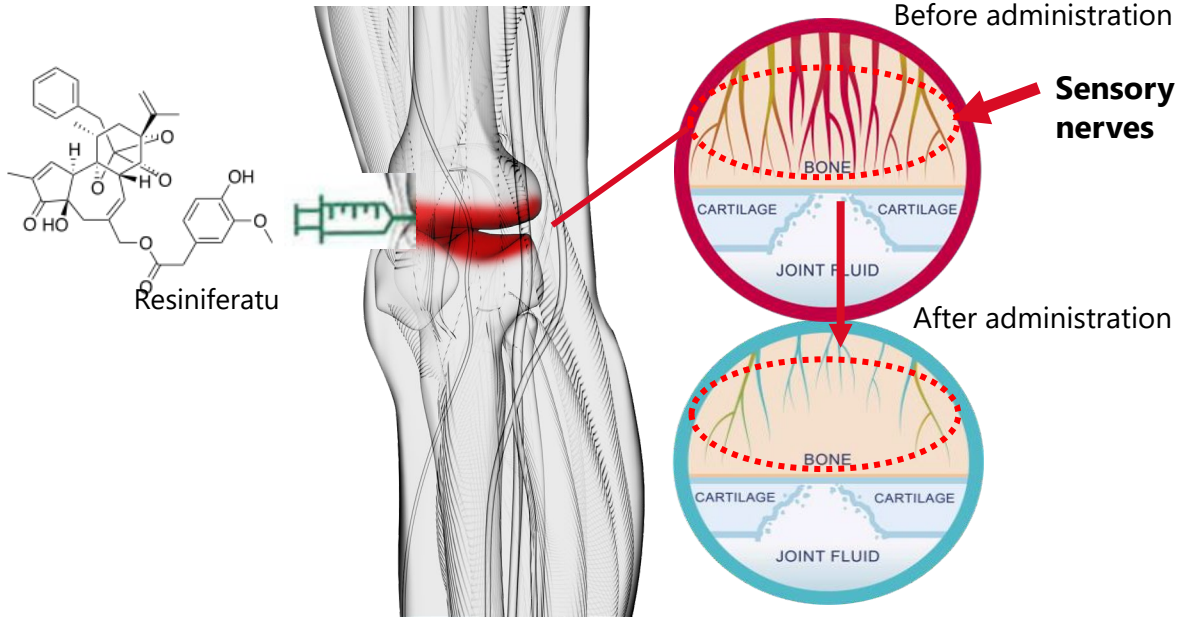
- An injection that can be administered into the knee joint once every six months on average, and is expected to reduce pain and improve function.

### Current status and future plans:

- Patient enrollment for Global Phase 3 study in Japan, the US and Europe has been completed and evaluation is ongoing

### Mechanism of action:

1. Resiniferatoxin acts on TRPV1* on sensory nerves projecting into the knee surface
2. Causes strong desensitization and retraction of sensory nerves from the knee (pain is suppressed)




*Number of people aged 40 or older with some kind of deformity on imaging



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# S-005151
## Indications: Acute cerebral infarction

### market:

- Number of affected people: 1.75 million (Incidence in 7MM)
- Market Size: 1200 Million Dollars (Market Size in 7MM)

### Unmet needs:

- A drug that can provide social independence to patients with acute cerebral infarction who have no other treatment options and are left with no after-effects
- Drugs with greater flexibility in the time allowed between onset and administration

### Product Features:

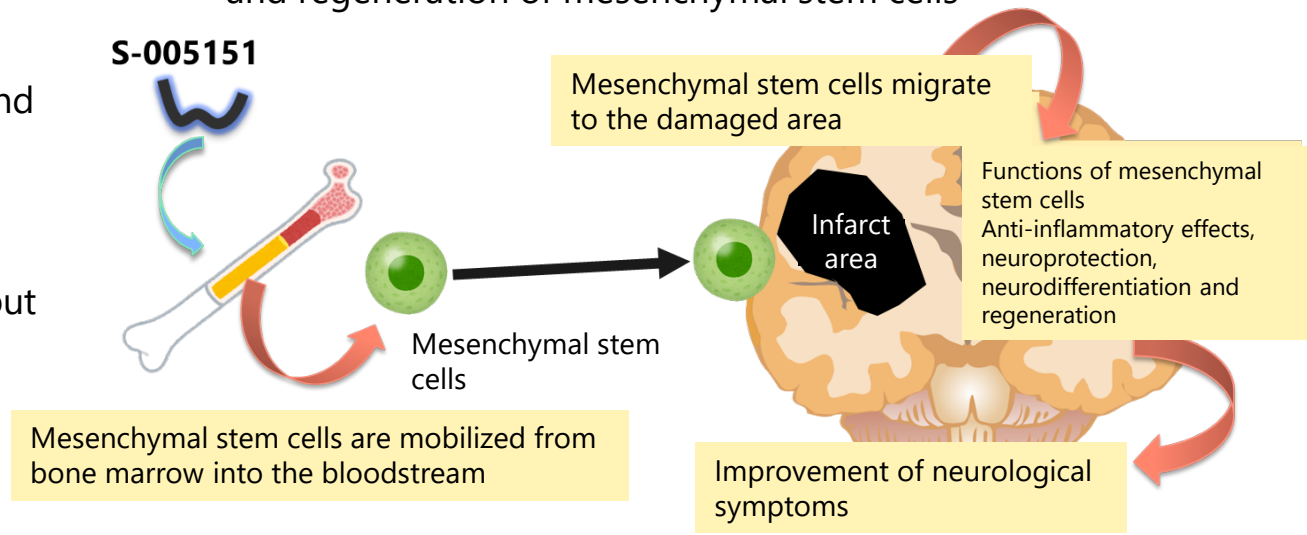
- Drug administration can induce regenerative ability stably, without relying on facilities.
- Can be administered up to 25 hours after onset of symptoms

### Current status and future plans:

- Global Phase 2b trials are underway in 19 countries, including Japan, the US, Europe and China.

### Expected mechanism of action:

1. S-005151 mobilizes mesenchymal stem cells from bone marrow into the blood
2. Mobilized mesenchymal stem cells accumulate at the site of injury
3. Improve neurological symptoms through the anti-inflammatory effects, neuroprotection, neurodifferentiation and regeneration of mesenchymal stem cells



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# S-005151 (Acute Cerebral Infarction): Global Phase 2b study

**A global Phase 2b study is currently underway for patients with acute cerebral infarction.**

## Overview

| | |
|---|---|
| **Country** | 19 countries including Japan, the US, Europe and China |
| **Subject** | Acute cerebral infarction patients<br>• Age 18 or older and within 25 hours of onset<br>• NIHSS: 8 to 22 |
| **Study design** | Multicenter, randomized, double-blind, dose-ranging, placebo-controlled |
| **Dosage and administration Target number of subjects** | • Intravenous administration over 90 minutes once daily for 5 days<br>• S-005151: 2 doses, placebo, 209 cases in each group (total 627 cases) |
| **Primary endpoint** | General prognostic assessment scale after 90 days of treatment Modified Rankin Scale (mRS) Day 90 |
| **Secondary endpoints** | • BI score after 90 days of treatment<br>• NIHSS score, SF-36, SAQoL-39g, PGI-C, etc. |

- Clinical trial applications have been completed in Japan, the US, Europe and China, and patient enrollment has already started at 130 sites in 18 countries.
- Further countries and sites will be considered for addition, with the aim of completing the trial in 2025
- After determining the optimal dose in a global Phase 2b study, a global Phase 3 study will be conducted to prepare for the application for manufacturing and marketing approval.

BI: Barthel Index (a scale for assessing activities of daily living)
NIHSS: National Institute of Health Stroke Scale (a scale for assessing the neurological severity of stroke)
SF-36: general QoL assessment, SAQoL-39g: stroke and aphasia-specific QoL assessment
PGI-C: Patient Global Assessment of Improvement

# S-005151
## Indications: Dystrophic Epidermolysis Bullosa

### Disease overview:

- A genetic disease in which there is a mutation in the protein gene that is a structural component of the skin, causing blisters and ulcers to form on the skin and mucous membranes even with slight stimuli in daily life.
- Skin symptoms persist from birth and often lead to complications, causing significant disruption to daily life.

### Market:

- Number of symptomatic people : Approximately 300 (Japan)

### Unmet needs:

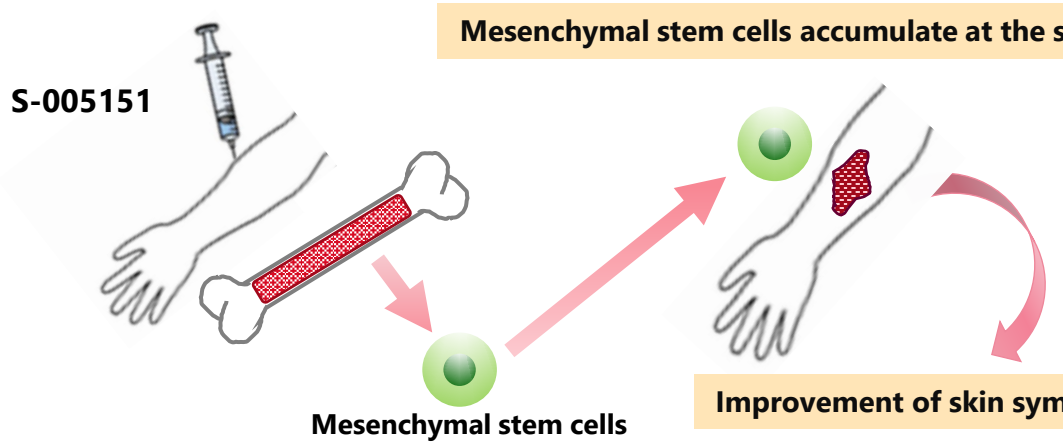
- Currently, there is no cure, and symptomatic treatment is the norm, so new, inexpensive treatments that act systemically are needed.

### Current status and future plans:

- Additional Phase 2 trial in progress
  - Implementing various measures to promote case entry
- Aiming to apply during fiscal year 2026

### Mechanism of action:

1. S-005151 mobilizes mesenchymal stem cells from bone marrow into the blood
2. Mobilized mesenchymal stem cells accumulate at the site of injury
3. Improves skin symptoms through the anti-inflammatory and anti-fibrotic effects of mesenchymal stem cells



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