

# SHIONOGI R&D Day 2022

October 12, 2022  
Shionogi & Co., Ltd.



SHIONOGI

# Agenda

## 1. Shionogi's R&D

- Opening
- Progress of COVID-19-related R&D
- Progress of Shionogi R&D
  - ✓ Development area
  - ✓ Research area
  - ✓ Vaccine Business
  - ✓ Summary of R&D

## 2. Summary

## 3. Q&A

### **John Keller, Ph.D.,**

Senior Vice President, R&D Supervisory Unit

### **Takeki Uehara, Ph.D.,**

Senior Vice President, Drug Development and Regulatory Science Division

### **Takeki Uehara, Ph.D.,**

### **Yasuyoshi Iso, Ph.D.,**

Senior Vice President, Research Division

### **Yasunori Aoyama, Ph.D.,**

Senior Vice President, Biopharmaceutical Research Division

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Chief Executive Officer

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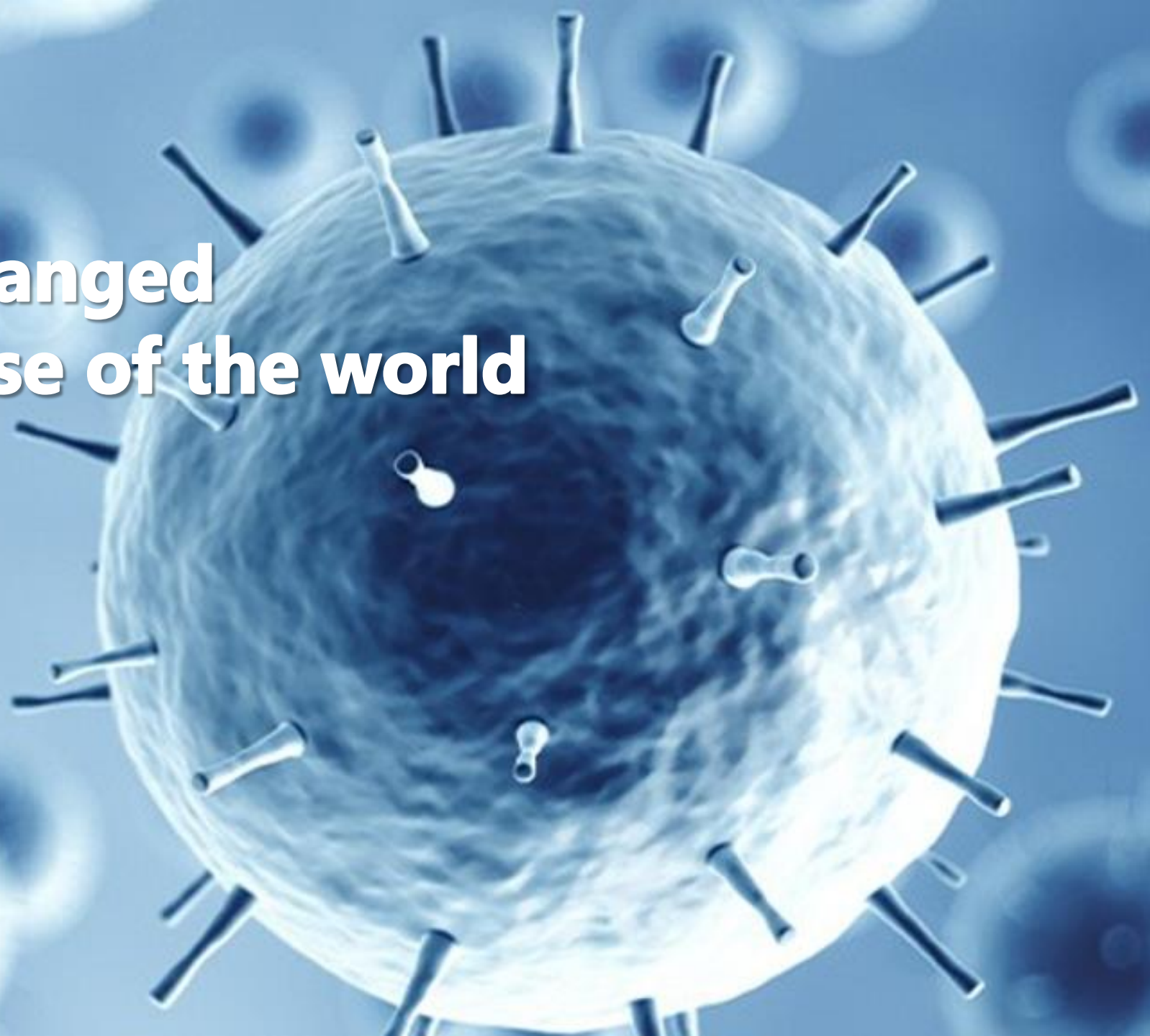
# Opening

- R&D transformation
- Environmental changes surrounding HIV business



**John Keller, Ph.D.,**  
Senior Vice President, R&D Supervisory Unit

**COVID-19 has changed  
the common sense of the world**



# Changes in the environment and in Shionogi's direction

## Changes in the external environment

- Changes in society's awareness of pandemics
- Changes in society's expectations from the pharmaceutical industry
- Changes in the pace and nimbleness of competitors

## Changes in the internal environment

- R&D transformation through significant resource shifts and process changes
- Rapid advancement in our ability to implement certain modalities (e.g. vaccines)

Although there were major changes in the external/internal environment due to COVID-19, these were likely inevitable changes that were merely realized ahead of schedule.

**Although our direction has not changed from the SHIONOGI Group Vision, the path has become clearer and urgency is increased**

# SHIONOGI Group Vision - What Shionogi wants to achieve in 2030 -

## SHIONOGI Group Vision

# Building Innovation Platforms to Shape the Future of Healthcare

### As SHIONOGI family we promise to:

- Imagine new ways to deliver innovation, and catalyze the formation of new healthcare platforms
- Create innovative products and deliver them worldwide compliantly with high quality at a fair price
- Embrace social responsibility and contribute to longer, healthier lives everywhere

# 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**
  - Flexible application of existing experience and new technologies and modalities
  - Utilize external collaboration to further strengthen and expand the tools and knowledge available
  - Rapid and flexible resource allocation and clear prioritization

strategy realization  
approach

**Organizational  
transformation**

- Flexible and responsive to environmental and competitive change
- Able to devote maximal resources on short notice

**R&D personnel**

- Skilled in key technologies
- Capable and flexible collaborators



# R&D disease strategy

R&D  
Disease  
strategy

**While focusing on infectious and psycho neurological diseases as our core fields, we will pursue other therapeutic areas as society's needs demand, while establishing a research management system that enables flexible and clear prioritization**

- Disease areas where unmet medical needs are increasing due to COVID-19
- Building on our R&D strengths (small molecule drug discovery, infectious disease, know-how in the psychiatric, neurological, and pain fields) with new modalities, tools and skills

<b>Infection</b>	<b>Realization of total infectious disease care at pandemic speed</b>
<b>Psychiatry/ Nervous/Pain</b>	<b>Realization of total care by integrating pharmaceutical therapy with new approaches (e.g. DX-driven) of treatment and support</b>
<b>New Growth area</b>	<b>Taking on unmet needs where our expertise can be combined with the strengths of academic experts, alliance partners, and the application of new modalities</b>

# R&D disease strategy - Total care for infectious diseases that meets needs -

## From epidemic prediction to the control of severe disease

Epidemiological  
forecast



prevention



diagnose



treatment



Suppression of  
aggravation



## From bacteria and viruses to protozoa and fungi

bacteria



virus



parasite  
(protozoa)



fungus



# R&D disease strategy - Three pillars to build a sustainable infectious disease business -

**chronic infection**  
(Three major infectious diseases: HIV, malaria, tuberculosis/non-tuberculous mycobacteria, etc.)

**vaccines**  
(COVID-19, influenza, etc.)

**acute infection**  
(COVID-19, influenza, respiratory syncytial virus, etc.)



Build a model for stable earnings over the medium to long term



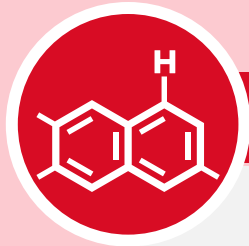
By utilizing push-type/pull-type incentives, etc.,  
Building a business model that can recover investment



**Establish business models for each to achieve sustainable growth while contributing to global health**

# Strengthen and expand modalities

## Current strength areas



### Small molecule

Xofluza®  
ensitrelvir  
HIV franchise



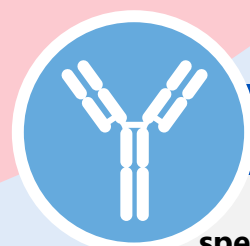
### Vaccines

Effective vaccines,  
rapidly created,  
administered through a  
variety of routes



### Peptide

Peptides allowing  
new mechanisms to  
be approached  
S-005151



### antibody

Harness the  
specificity and power  
of the immune system  
S-531011



### nucleic acid

Creating new  
vaccines and  
therapeutics  
S-540956



### DTx

New modalities to  
help patients, in CNS  
and other diseases  
SDT-001  
insomnia app



### Drug Delivery

Bringing new and  
existing modality  
therapeutics to the sites  
and for the durations  
they are needed



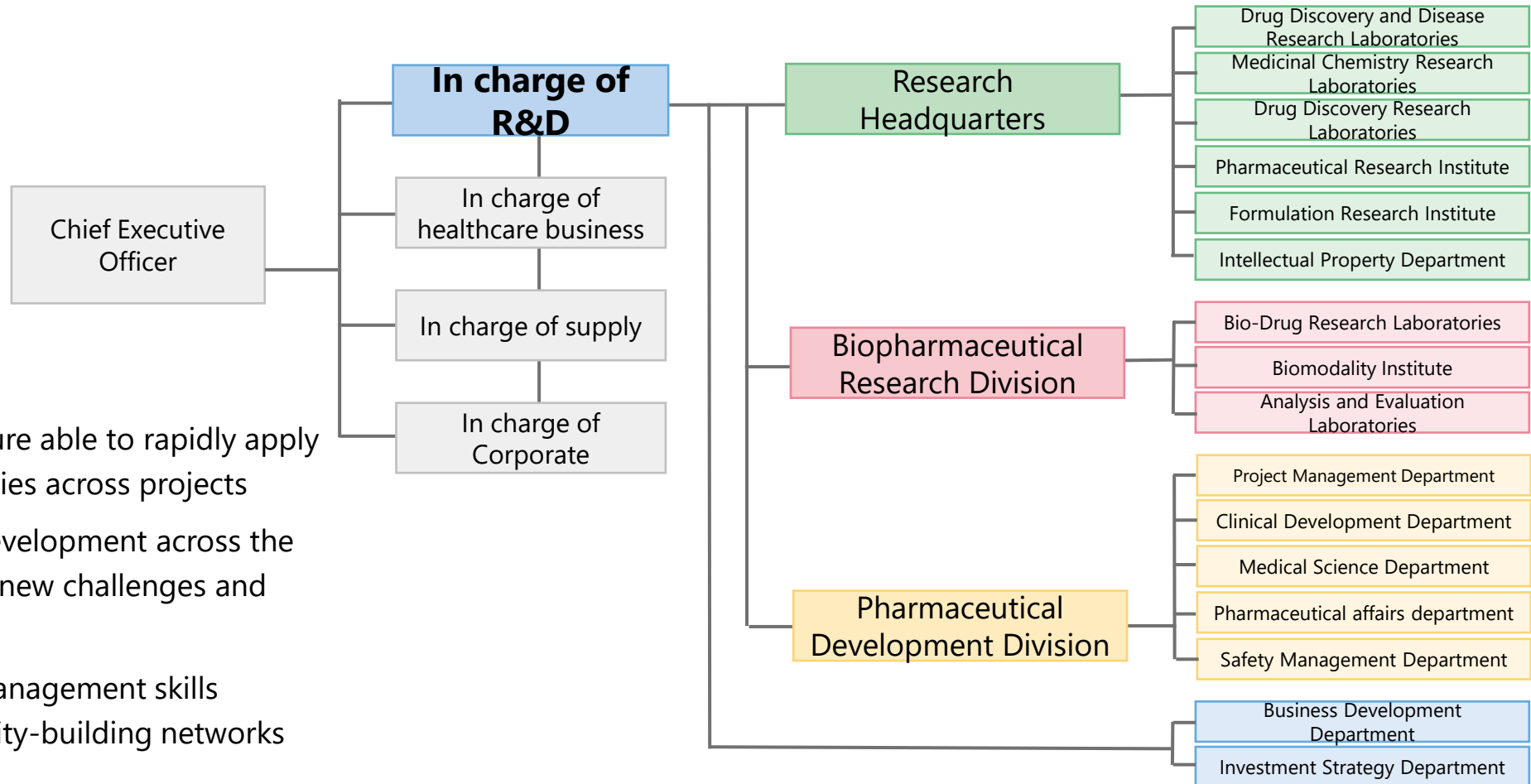
### Comprehensive care

Combining tools  
and modalities to  
provide more effective,  
comprehensive  
solutions for patients

**Acquiring diverse modalities to discover new treatments addressing that meets diverse unmet medical needs**

# Approach to Realizing R&D Strategy - Organizational reform -

## **New R&D system (from July 2022)**

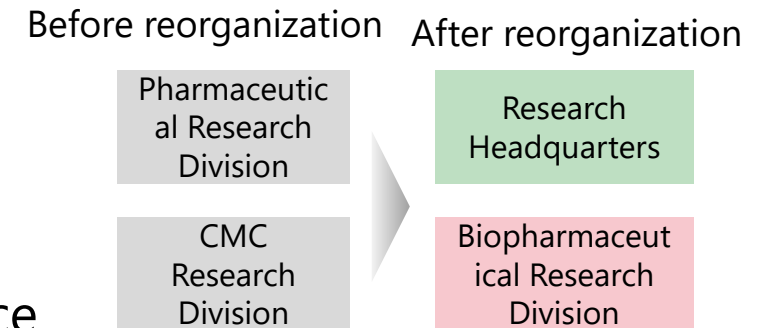


- Function-driven structure able to rapidly apply resources and capabilities across projects
- Knowledge and skill development across the organization, to tackle new challenges and new modalities
- Alliance and project management skills needed for the capability-building networks we require

# Approach to realizing R&D strategy - Organizational reform -

## Outline of reorganization

- **Establishment of management**
  - Focus on decision-making quality and speed
  - Responsive resource deployment and prioritization
  - Seamless collaborations across divisions and functions
- **Pharmaceutical Research Division and CMC Research Division integrated for the two primary modalities, low-molecular-weight drugs and biopharmaceuticals (including vaccines)**
  - Integrating all steps from exploratory research to product and process development Building functional expertise and experience
- **Established the Investment Strategy Department and incorporated the Business Development Department, both within R&D**
  - All the capabilities to establish and nurture the technological development required to realize these healthcare solutions are under one organization



# Approach to realizing R&D strategy - Strengthening R&D human resources -

## **Capabilities to be strengthened in the future**

**Strengthen human resources with capabilities to meet unmet needs**



- **World-class knowledge of new modalities including vaccines**
- **Ability to deeply understand unmet needs and focus on using every tool possible to address them**
- **Creation and maintenance of an expanded external network, including academic, SME, VC/investor, and mega-pharma, to rapidly access needed technologies, expertise, and infrastructure**

# Opening

- R&D transformation
- Environmental changes surrounding HIV business



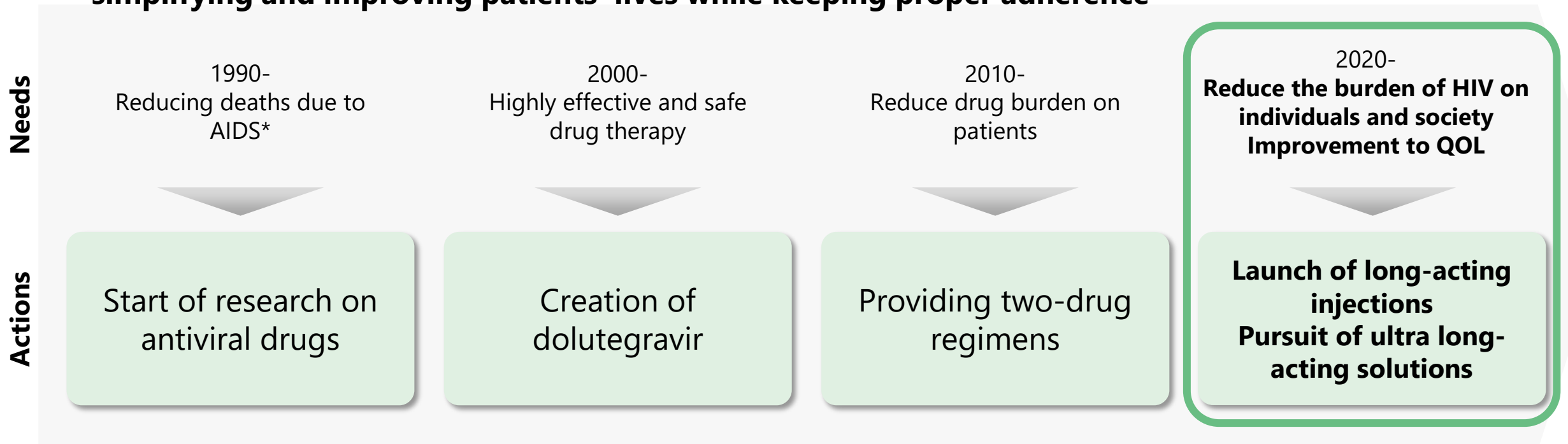
**John Keller, Ph.D.,**  
Senior Vice President, R&D Supervisory Unit



# Changes in the HIV landscape

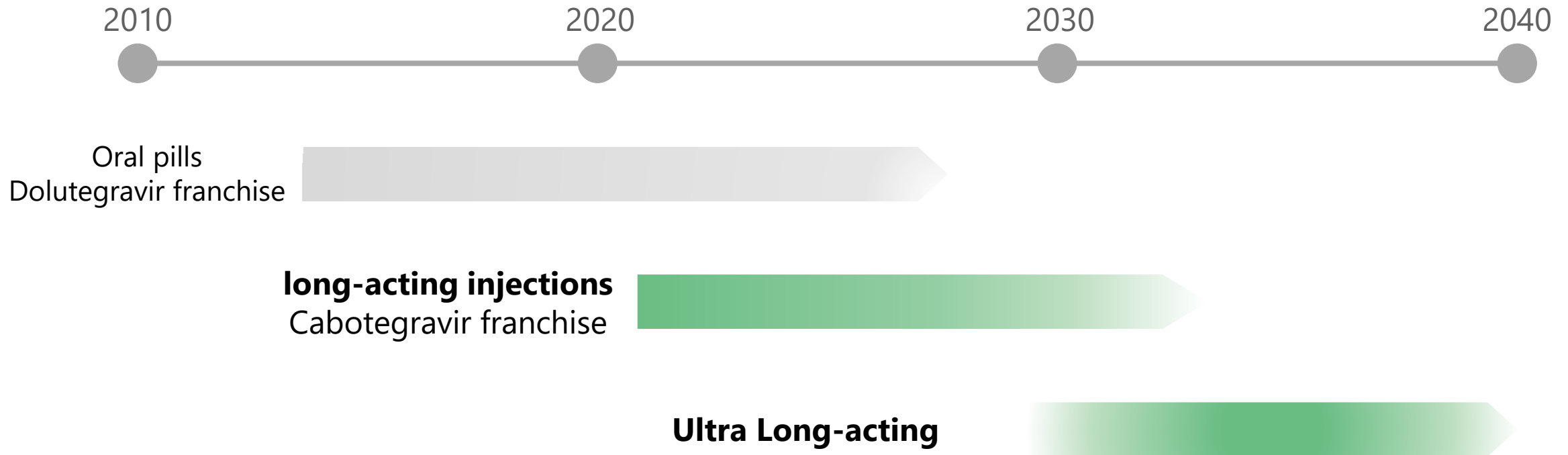
## Unmet needs in the HIV area and Shionogi/ViiV's efforts to address them

- Cooperating with ViiV to provide solutions that meet the hopes and expectations of people living with HIV
- Long-acting formulations (treatment and prevention) emerging that reduce the burden of HIV, simplifying and improving patients' lives while keeping proper adherence



# Pipeline of new products addressing patient needs

## Period from launch to patent expiry (US)



- **Address the needs of society by continuous introduction of new products centered on long-acting, ultra long-acting, and more convenient formulations**
- **Continuous flow of new products will sustain pipeline and reduce impact of dolutegravir patent cliff**

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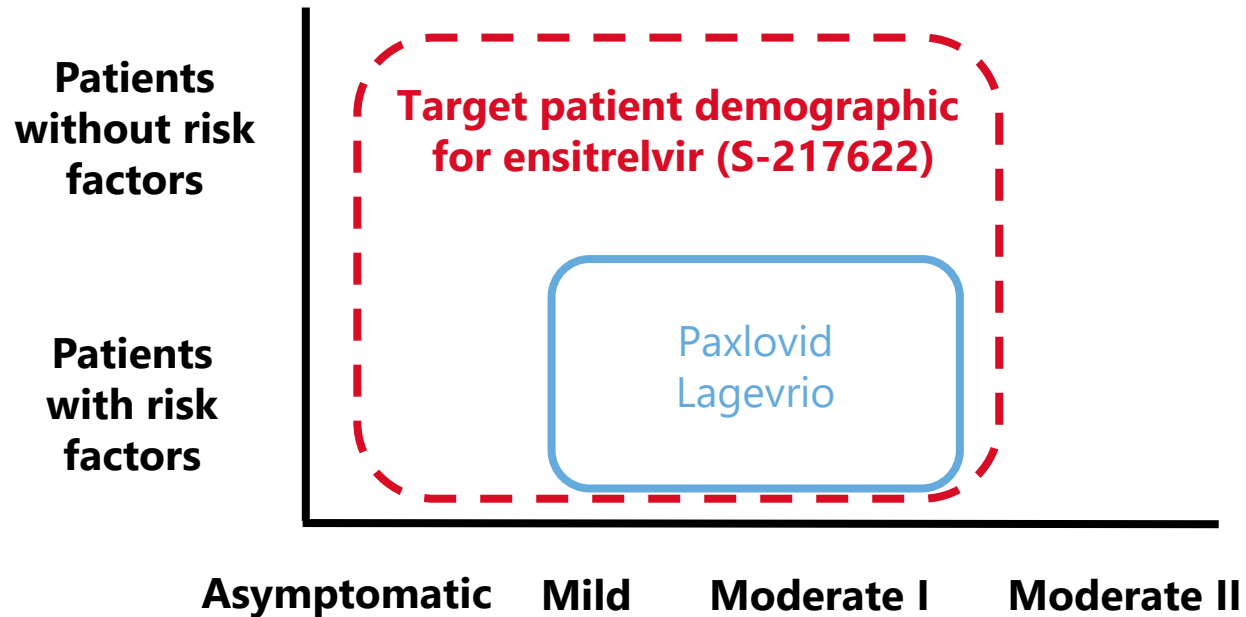
Chief Executive Officer

# Progress of COVID-19 related R&D



**Takeki Uehara, Ph.D.,**  
Senior Vice President, Drug Development and  
Regulatory Science Division

# Positioning of COVID-19 oral drugs



## [Current status of existing oral drugs]

- Clinical trials were conducted in unvaccinated patients in the pre-omicron stages of the epidemic
- Patients without risk factors were not eligible

Severity	Oxygen saturation	Clinical condition
Mild	SpO <sub>2</sub> ≥ 96%	No respiratory symptoms or Cough only, no dyspnea
Moderate I	93% < SpO <sub>2</sub> < 96%	Dyspnea, pneumonia findings
Moderate II	SpO <sub>2</sub> ≤ 93%	Oxygen needed

COVID-19 Medical Treatment Guidelines Version 8.0 P.32 modified

- **Phase 2/3 trial of ensitrelvir was conducted during the Omicron stage of the epidemic and mainly in vaccinated patients (approximately 90%)**
- **Ensitrelvir studies cover a wide range of patients with and without risk factors**

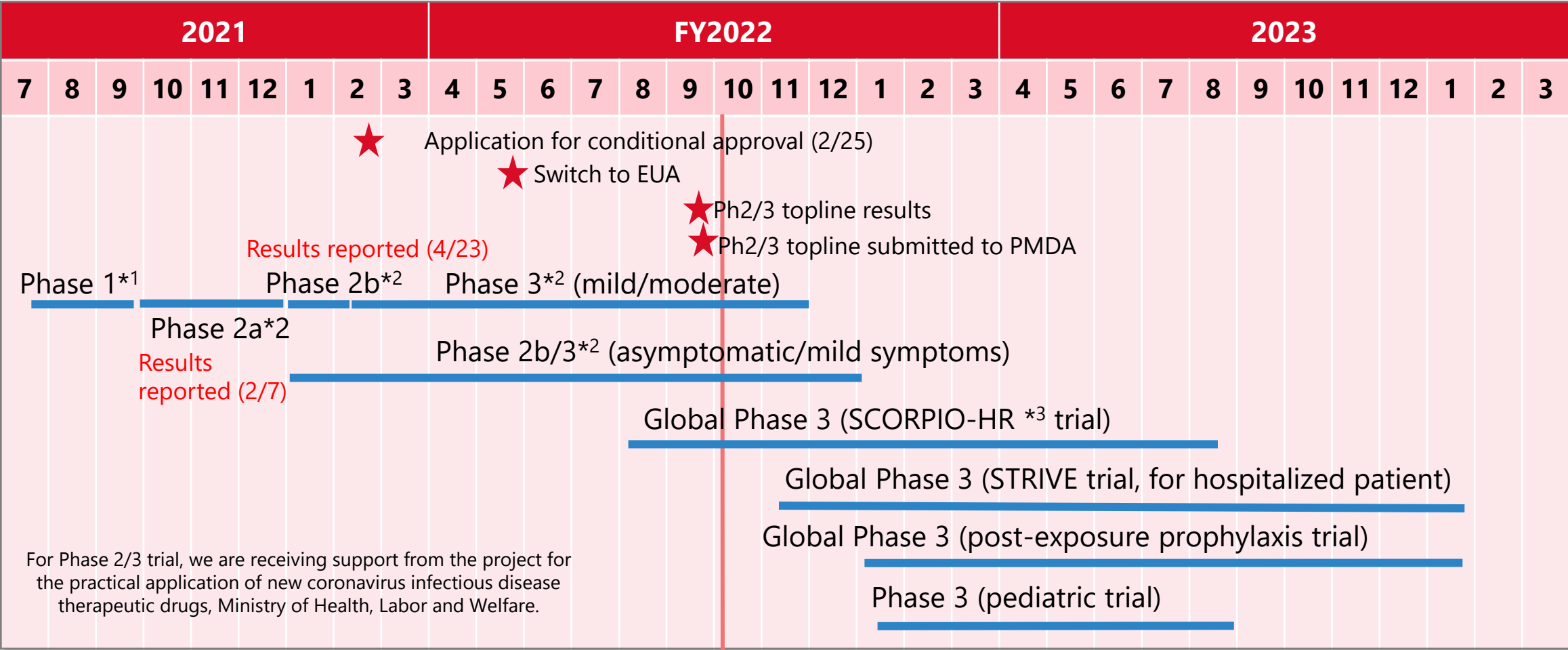
# Ensitrelvir: Antiviral effect against mutant strains\*

In vitro antiviral evaluation using VeroE6T cells

virus strain	Ancestor	alpha strain	beta strain	gamma strain	delta strain	omicron strain					
						BA.1	BA.1.1	BA.2	BA.2.75	BA.4	BA.5
EC <sub>50</sub> (μM)	0.37	0.46	0.40	0.50	0.41	0.29	0.36	0.52	0.30	0.22	0.40

- **Ensitrelvir shows antiviral efficacy against a wide range of strains, including past prevalent strains and recent Omicron mutant strains (BA.4, BA.5, BA.2.75), whereas existing neutralizing antibody drugs have been reported to have reduced efficacy against Omicron mutant strains\*\*.**
- **Ensitrelvir shows antiviral efficacy against existing drug-resistant viruses (no cross-resistance)**

# Ensitrelvir: Progress summary



For Phase 2/3 trial, we are receiving support from the project for the practical application of new coronavirus infectious disease therapeutic drugs, Ministry of Health, Labor and Welfare.

As of October 12, 2022

Trial period: Start of patient enroll to completion of clinical trial report

\*1 [jRCT2031210202](https://www.clinicaltrials.gov/ct2/show/study/NCT0231210202)、\*2 [jRCT2031210350](https://www.clinicaltrials.gov/ct2/show/study/NCT0231210350)、\*3 [NCT05305547](https://www.clinicaltrials.gov/ct2/show/study/NCT05305547)



## Ensitrelvir: Phase 3 part - Establishment primary endpoints -

- For the evaluation of clinical effectiveness during the Omicron stage of the epidemic, no clear evaluation index had been established. For that reasons we repeatedly discussed appropriate primary endpoints with experts and regulators, and assessed scientifically and medically appropriate evaluation indicators and evaluation targets



- During the Omicron stage of the epidemic, 5 of the typically listed 12 symptoms of COVID-19 (these 5: stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) were confirmed as the most common and characteristic symptoms
- When infected with the Omicron strain, and in a predominantly vaccinated population, the virus proliferates and disappears in the body faster than in the past epidemic stages, and the remission of symptoms is relatively rapid



- **Primary endpoint** : **The time to resolution of five key COVID-19 symptoms**
- **Main analysis population** : Limited to subjects enrolled less than **72 hours** from onset of COVID-19 to randomization
- **Confirmatory dose** : 125 mg (Application dose)



# Ensitrelvir: Phase 3 part - Summary patient background for registered cases -

Background information in the ITT\* population

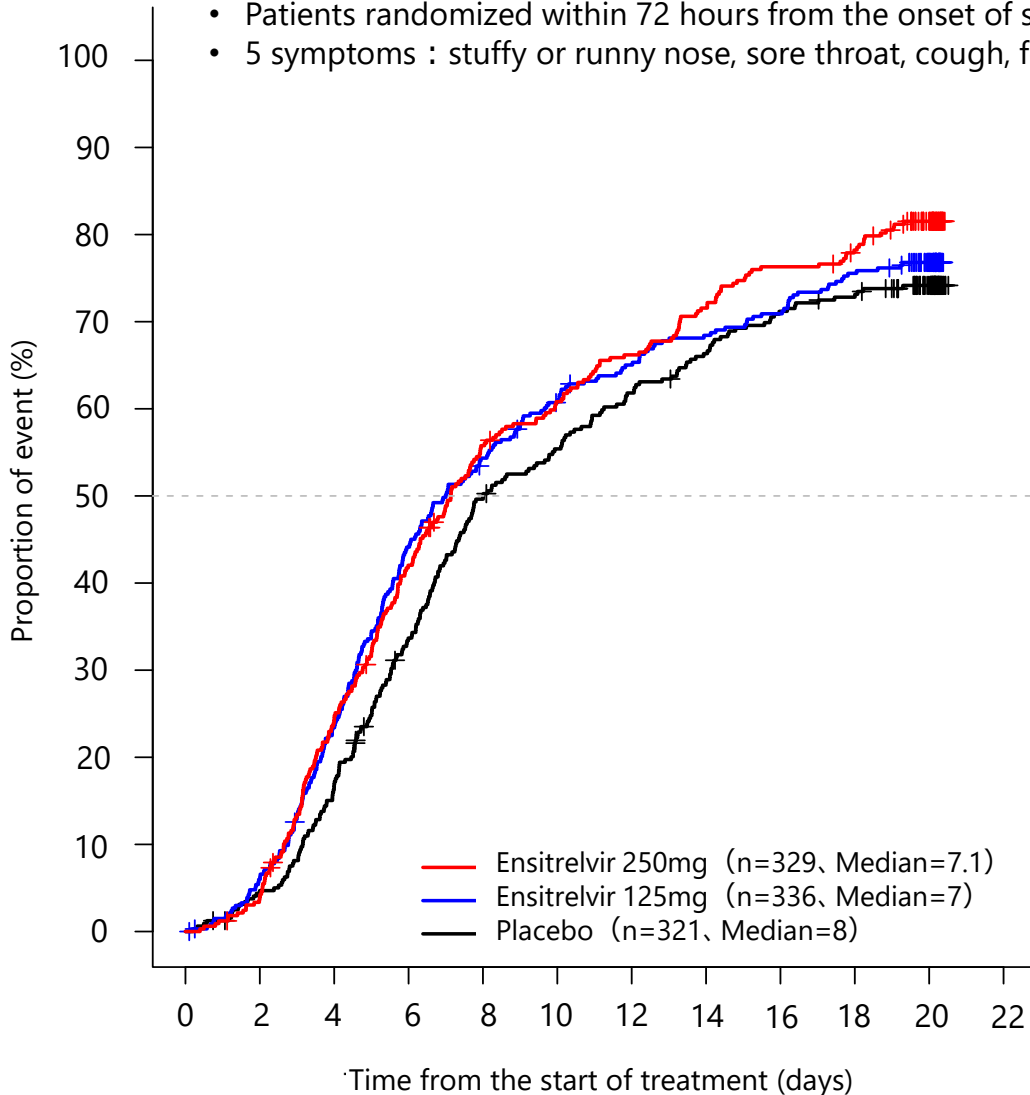
		125 mg N = 603	250 mg N = 595	Placebo N=600
Sex	Male	318	323	311
	Female	285	272	289
Mean of age		35.9	35.9	35.3
Vaccination of SARS-Cov-2		562 (93.2%)	551 (92.6%)	553 (92.2%)
Time from onset to randomization	< 72 hours	347	340	343
	≥ 72 hours	256	255	257

\* Intention-to-treat (ITT) : All subjects who were randomly assigned to the trial intervention and had a SARS-Cov-2 infection based on RT-PCR. 1,798 subjects excluding 23 subjects that were PCR negative at baseline from 1,821 subjects

# Ensirelvir: Phase 3 part - The time to resolution of all five key COVID-19 symptoms (Primary endpoint) -

## The time to resolution of all five key COVID-19 symptoms

- Patients randomized within 72 hours from the onset of symptoms
- 5 symptoms : stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness



### Target of primary endpoint

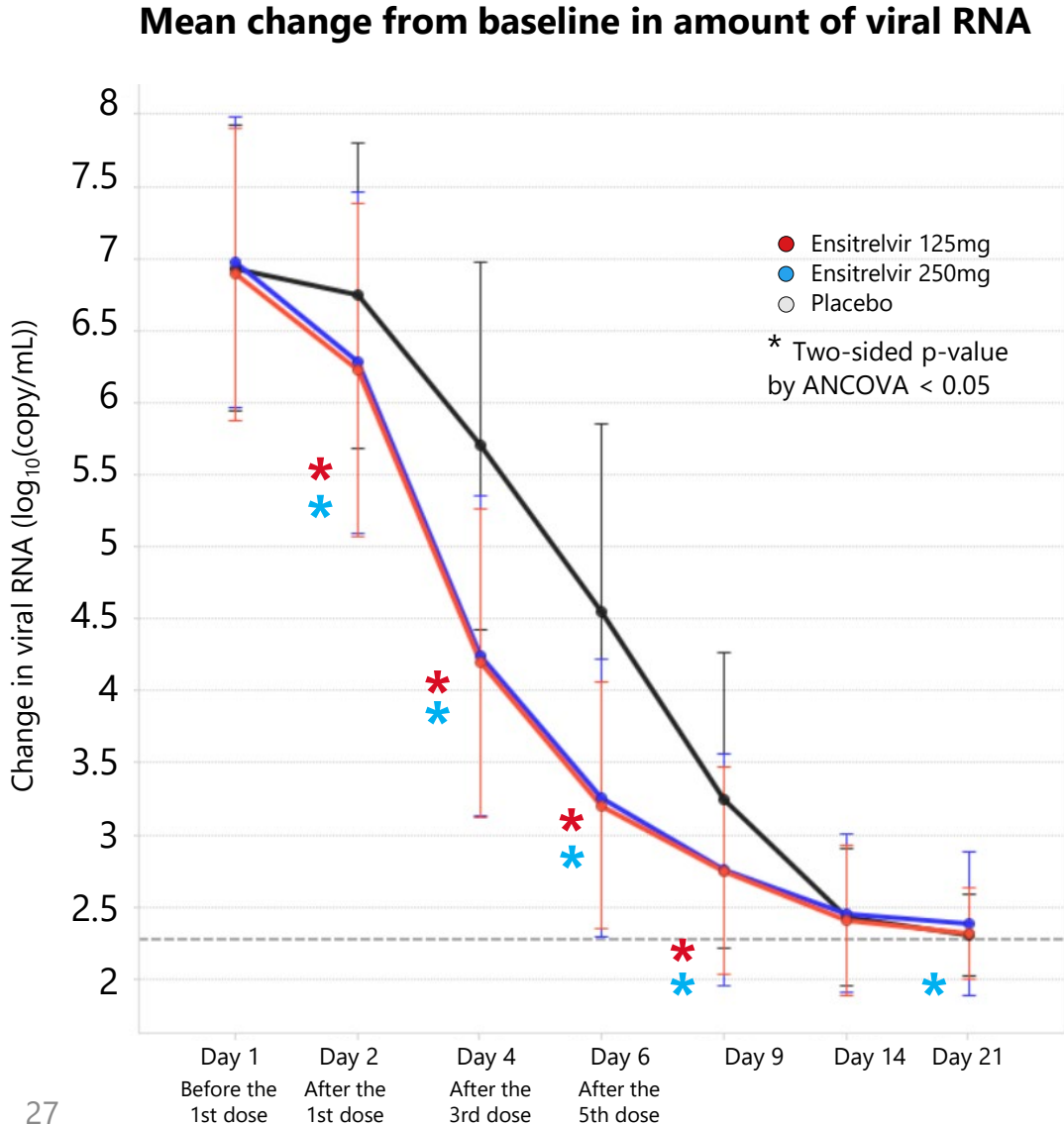
		125 mg N = 347	250 mg N = 340	Placebo N = 343
Median [95% CI]		167.9 [145.0, 197.6]	171.2 [150.8, 190.3]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]		<b>-24.3</b> [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	<b>0.0407</b>	0.0203	---

CI = Confidence Interval

[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

**Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)**

# Ensitrelvir: Phase 3 part - Change in viral RNA amount (Key secondary endpoint) -



**[Population within 72 hours from the onset of symptoms]**  
**Changes in viral RNA levels on day 4 of administration (after 3 doses)**

**Target of key secondary endpoint**

	125 mg N = 347	250 mg N = 340	Placebo N = 343
Mean (SD)	-2.737 (1.085)	-2.690 (0.974)	-1.235 (1.528)
ANCOVA vs. placebo [a]			
LS mean (SE)	-2.48 (0.08)	-2.49 (0.08)	-1.01 (0.08)
Difference in LS mean (SE) [95% CI]	<b>-1.47 (0.08)</b> [-1.63, -1.31]	-1.48 (0.08) [-1.64, -1.32]	---
P value	<b>&lt;0.0001</b>	<0.0001	---

UNIT: log<sub>10</sub> copies/mL

ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; LS = Least Squares; CI = Confidence Interval  
 Lower limit of quantification of viral RNA is 2.08 log<sub>10</sub> copies/mL.

If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed 2.27 and 2.08 log<sub>10</sub> copies/mL, respectively.

[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

**Ensitrelvir (125mg group) reduced viral RNA level to 1/300 compared to before administration on day 4 of administration (after the 3rd dose) (placebo decreased to 1/10)**

**Significantly reduced viral RNA levels on day 4 of administration (after 3 doses), confirming superior antiviral effects**

# Ensitrelvir: Phase 3 part summary

## Efficacy

- Population within 72 hours from the onset of symptoms
  - The median time to resolution of all five COVID-19 symptoms was significantly reduced in those treated with ensitrelvir (125mg group) . Achieved the primary endpoint in the Phase 3 part
    - ✓ The time to resolution of the 12 or 14 COVID-19 symptoms also showed a trend towards shortening for the 12 symptoms and a significant shortening for the 14 symptoms
    - ✓ Ensitrelvir also showed a significant reduction in viral RNA on day 4 (following the third dose) relative to placebo (greater than 1.4 log<sub>10</sub> copies/mL vs. placebo change from baseline on day 4)
- Population within 120 hours from the onset of symptoms
  - Time to resolution of 5, 12 or 14 symptoms of COVID-19 showed a numerical reduction in the 125 mg group compared with placebo (all with p-values greater than 0.05)

## Safety

- There were no serious adverse events or deaths in this trial.
- In the ensitrelvir 125mg group, the most common treatment-related adverse events were decreased high-density lipoprotein and increased blood triglycerides, as observed in previous trials

# Ensitrelvir: Further clinical trials

## SCORPIO

Stopping Covid Progression with early Protease Inhibitor treatment

### Phase 2/3 trial

- No criteria regarding vaccination, risk factor
- Japan, South Korea, Vietnam
- Start: Sep 2021

### SCORPIO-HR trial\* Phase 3

- Both high risk and standard risk can be enrolled
- No criteria regarding vaccination
- USA, EU etc.
- Start: Mar 2022

### SCORPIO-PEP trial Phase 3

- Prophylactic use
- Household members who has first symptomatic infection in the household
- Japan, USA, etc.
- Start: Dec 2022 (planned)

### STRIVE trial\* Phase 3

- Inpatient
- USA, EU etc.
- Start: Nov 2022 (planned)

### Pediatric trial (Japan) Phase 3

- Aged 6 to 12
- Mild / Moderate
- Japan
- Start: Nov 2022 (planned)

# Ensitrelvir: The SCORPIO-HR trial design

<b>Trial design</b>	A multicenter, randomized, double-blind, placebo-controlled
<b>Subject</b>	Non-hospitalized participants with COVID-19 (HR: 50%, OwH: 50%)
<b>Primary purpose</b>	To evaluate the efficacy of ensitrelvir against placebo for non-hospitalized COVID-19 patients
<b>Primary endpoint</b>	Time to sustained symptom resolution through Day 29
<b>Secondary endpoint</b>	<ul style="list-style-type: none"> <li>• Change From Baseline in Quantitative log<sub>10</sub> SARS-CoV-2 RNA Levels by PCR at Day 4</li> <li>• Hospitalization rate due to COVID-19, mortality rate due to all causes</li> </ul>
<b>Dosing group</b>	ensitrelvir, placebo
<b>Dosage</b>	Oral administration once daily for 5 days
<b>Target number of patients</b>	1,490 cases

- HR: High-risk subjects (50% of all enrolled subjects)
  - Vaccinated and un-vaccinated
  - Age 65+
  - Age 18-65
  - Obesity (BMI >30)
  - Diabetes, hypertension, cardiovascular disease, chronic lung disease
- OwH: Otherwise-healthy subjects (50% of all enrolled subjects)
  - Vaccinated and un-vaccinated
  - Age 18-64 without high-risk factors

# Ensitrelvir: Pediatric development plan

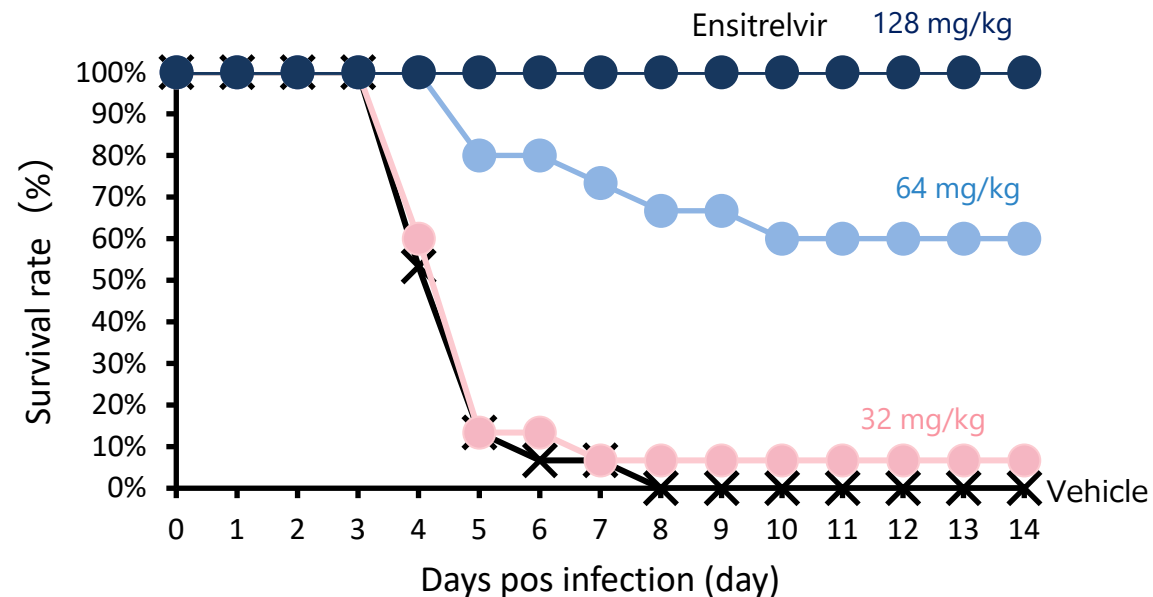
- To seek approval using the Phase 2/3 trial data in adolescents (12 to <18) in JP/EU/US
- To conduct the clinical trial for 6 to <12 in JP with higher priority than EU&US
- To plan the separated clinical trial in 0 to <12 for Global

Pediatric population	Japan		Global	
	Clinical trial	Formulation	Clinical Trial	Formulation
12 to <18	Phase 2/3 trial (ongoing)	Tablets	Phase 2/3 trial (ongoing)	Tablets
6 to <12	Phase 3 pediatric trial (in preparation)	Tablets (under consideration)	Global Phase 3 pediatric trial (under discussion)	Granules (under consideration)
0 to <6	Global Phase 3 pediatric trial (under discussion)	Granules (under consideration)		

# Ensitrelvir: Estimation of prophylactic effectiveness in humans

## Prophylactic Effect of ensitrelvir against Lethal Infection with SARS-CoV-2 in Mice

Condition : subcutaneously administrated 24 h post infection



A single subcutaneous dosing of 64 (Plasma concentration is 2.99  $\mu\text{g/mL}$  at the time of infection) or more significantly prolonged survival time compared to vehicle treatment.

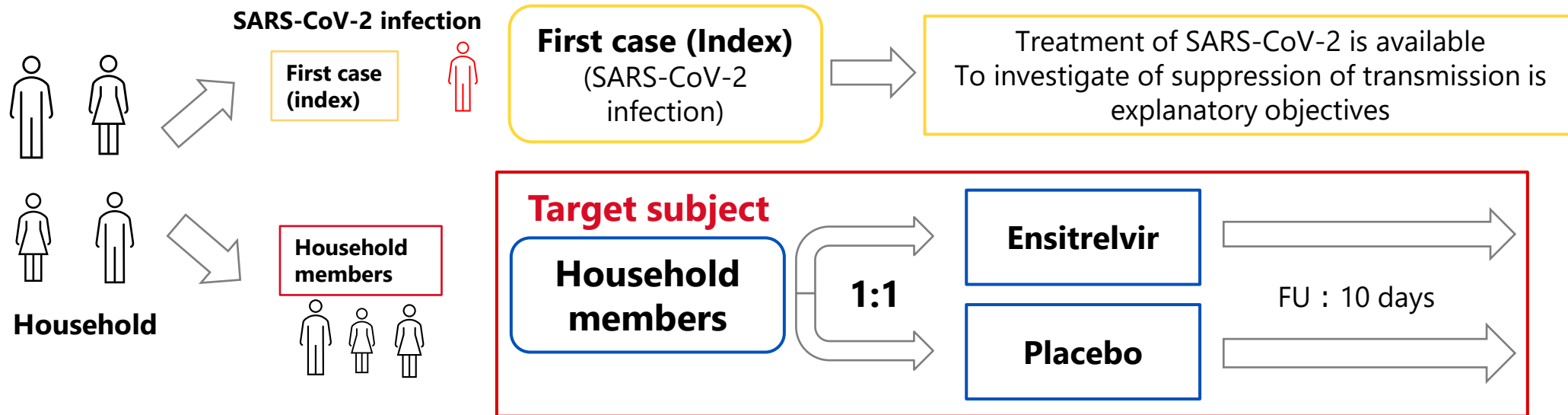
Prophylactic administration of ensitrelvir improved survival of SARS-CoV-2 infected mice

**Stop virus increasing/spreading, contribute to people getting back to normal life quickly**



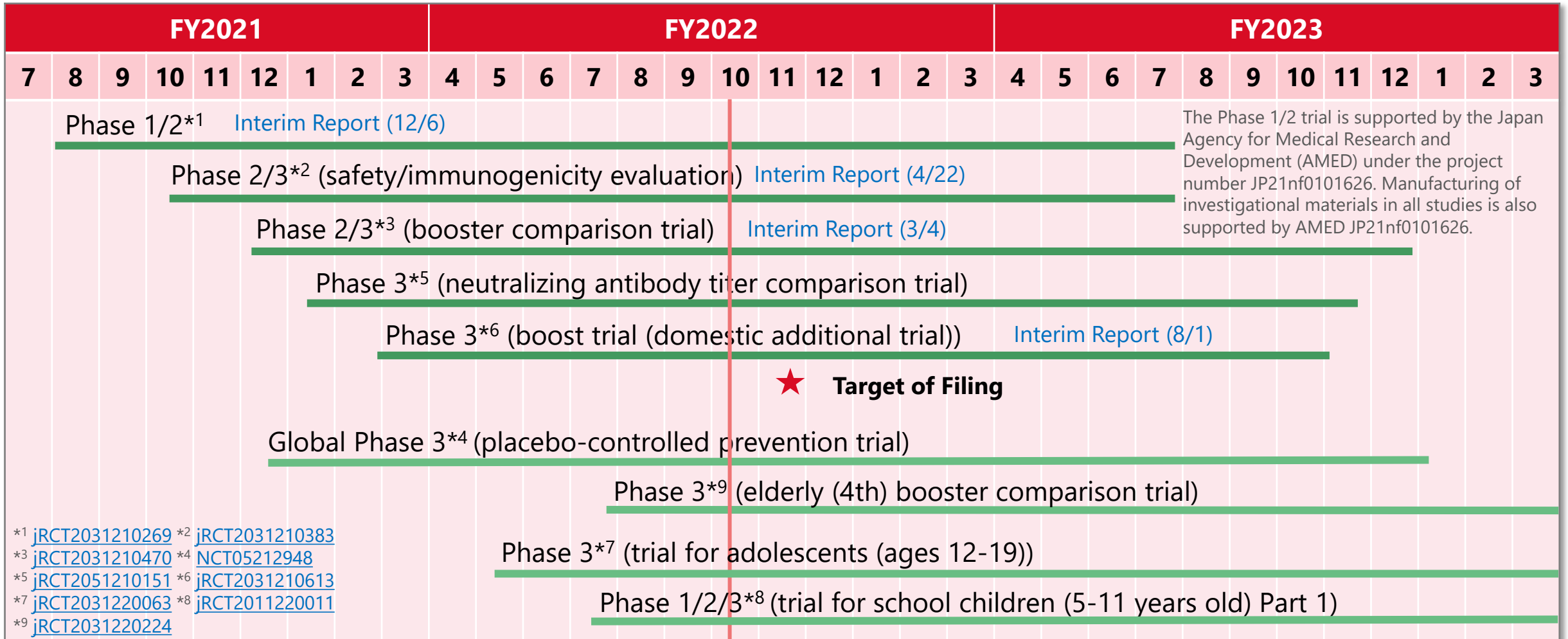
# Ensitrelvir: Post exposure prophylaxis trial (PEP) design

<b>Primary objective</b>	To compare ensitrelvir with placebo in the prevention of symptomatic SARS-CoV-2 infection in participants at Day10 after the first administration
<b>Target population</b>	Participants who are household members of SARS-CoV-2-infected patients
<b>Design</b>	Randomized, double-blind, multicenter, parallel-group, placebo controlled
<b>Sample size / Location</b>	2,040 participants (2 arms) Japan, USA, other several countries



**Target 2Q FY2023 for completion of enrollment, trial preparation on-going**

# S-268019 (recombinant protein vaccine): Progress summary



\*1 [jRCT2031210269](#) \*2 [jRCT2031210383](#)  
 \*3 [jRCT2031210470](#) \*4 [NCT05212948](#)  
 \*5 [jRCT2051210151](#) \*6 [jRCT2031210613](#)  
 \*7 [jRCT2031220063](#) \*8 [jRCT2011220011](#)  
 \*9 [jRCT2031220224](#)

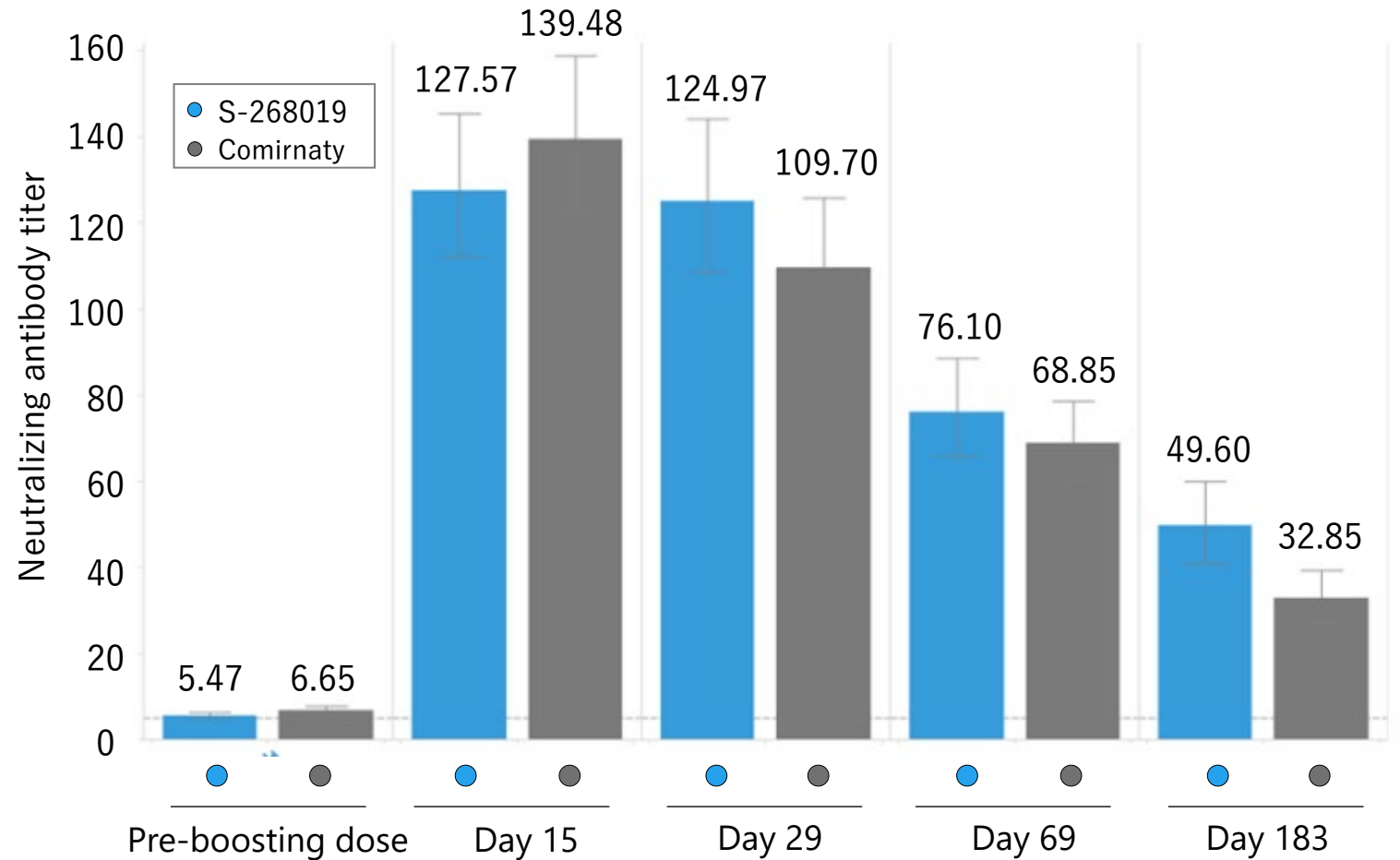
As of October 12, 2022

Trial period: Start of patient enroll to completion of clinical trial report

# S-268019: Phase 2/3 booster comparison trial

## - Neutralizing antibody titer after vaccination -

<b>Purpose</b>	Verification of non-inferiority of immunogenicity to intramuscular injection of S-268019 when boosted with Comirnaty
<b>Subjects</b>	Adults aged 20 years or older who have received two doses of Comirnaty intramuscular injection 6 months earlier or longer
<b>Dosing Regimen</b>	1 booster dose of S-268019 or Comirnaty Intramuscularly
<b>Target Number of Participants</b>	204 cases

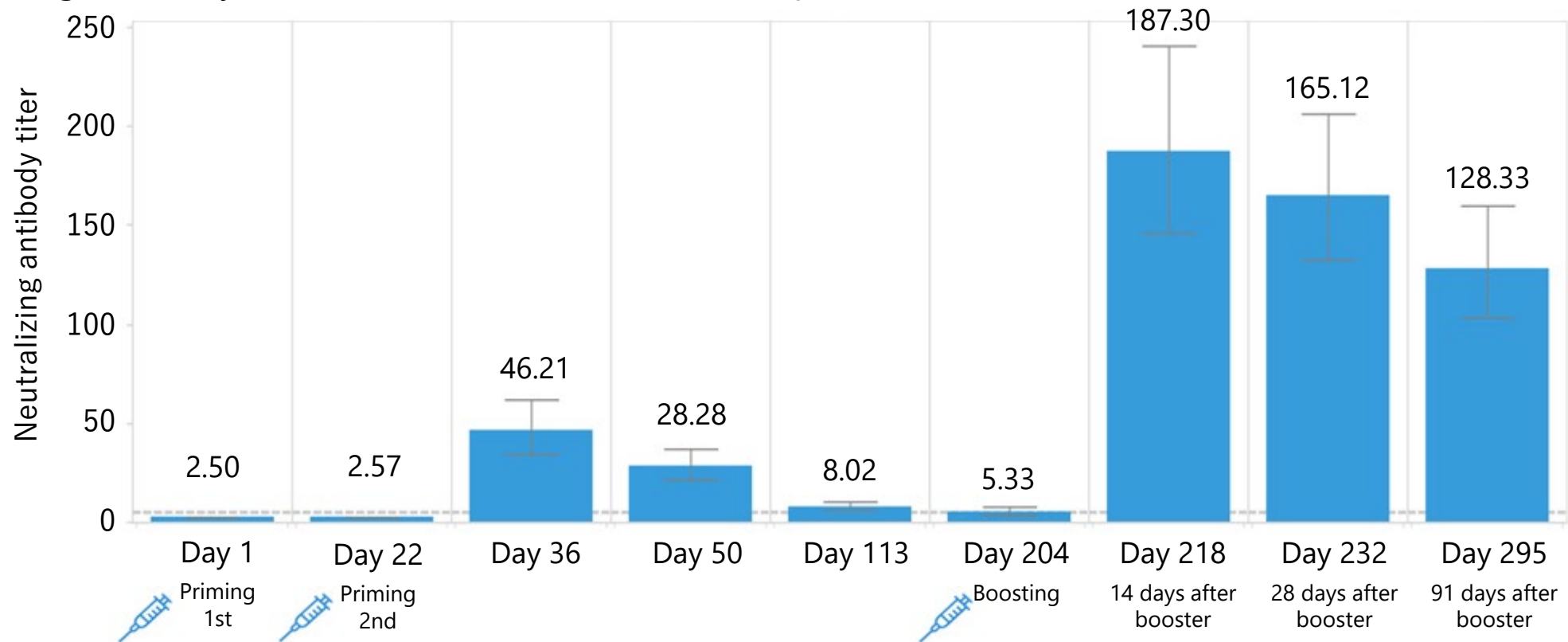


**Long-lasting neutralizing antibody titer was shown in booster dosing after Comirnaty priming**

# S-268019: Phase 1/2 trial

## - Neutralizing antibody titer after priming and boosting vaccination -

**Trial Outline:** Adults aged 20 years and over were vaccinated with S-268019 twice at 3-week intervals as the priming immunization, and then, after 6 months, were vaccinated with one dose of S-268019 as a booster. The neutralizing antibody titer was measured at each time point

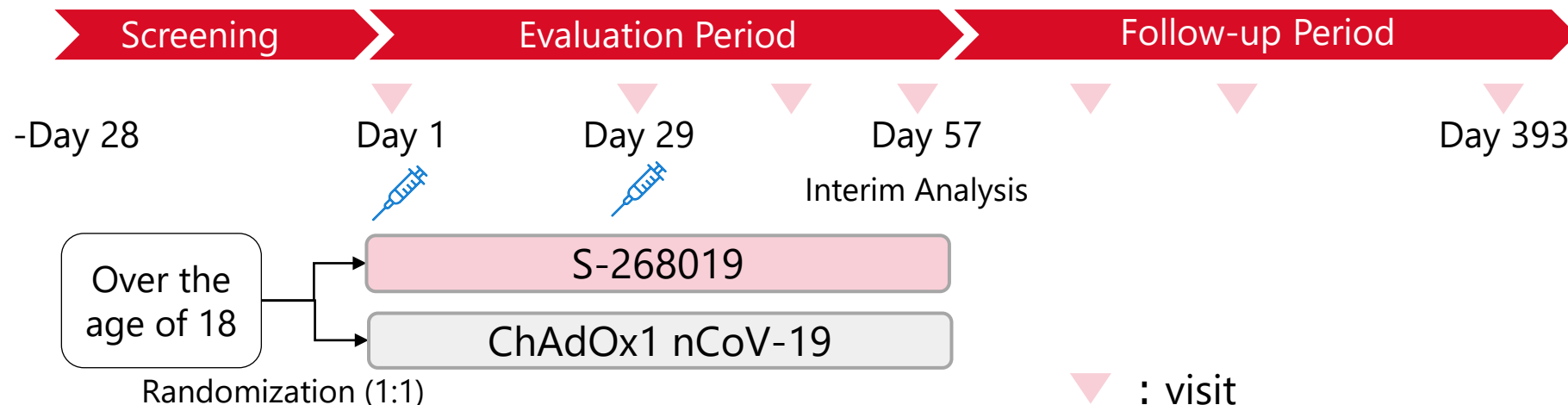


**Priming and boosting of S-268019 vaccination showed long-lasting and high neutralizing antibody titer**

# S-268019: Phase 3 neutralizing antibody titer comparison trial

## - Trial design -

<b>Purpose</b>	To assess the superiority of S-268019 over ChAdOx1 nCoV-19 intramuscular after 2 intramuscular injections
<b>Primary</b>	GMT of SARS-CoV-2 neutralizing antibody titer at 28 days following the 2 <sup>nd</sup> vaccination
<b>Key Secondary</b>	Seroconversion rate for SARS-CoV-2 neutralizing antibody titer at 28 days following the 2 <sup>nd</sup> vaccination
<b>Trial Design</b>	Active-controlled, parallel-group, observer-blind, multicenter
<b>Subjects</b>	Naïve men and women over the age of 18
<b>Target Number of Participants</b>	1,000 cases (500 cases: ChAdOx1 nCoV-19 intramuscular injection, 500 cases: S-268019)
<b>Dosing</b>	2 doses (Day 1, Day 29)



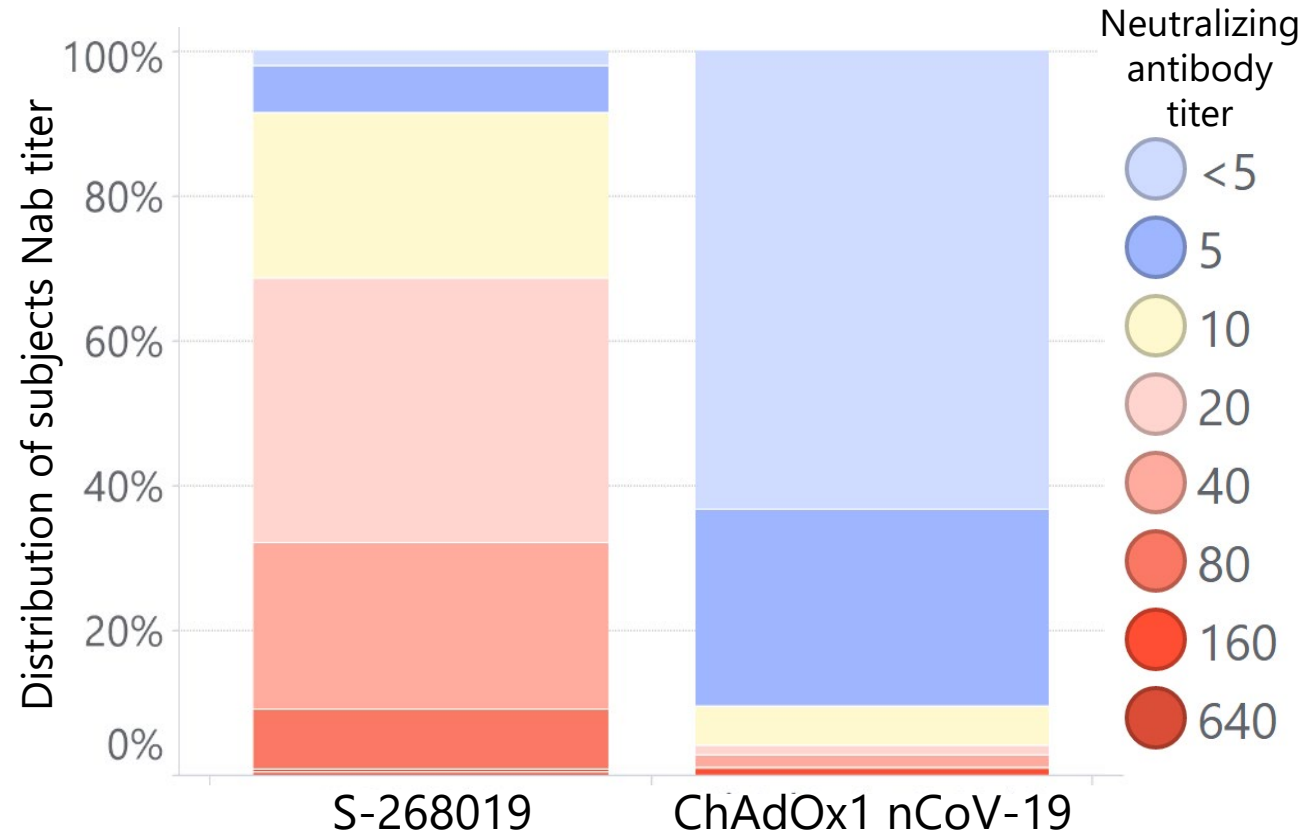
# S-268019: Design of neutralizing antibody titer comparison trial

## - Neutralizing antibody titer at 28 days following the second vaccination -

Planned Statics	S-268019	ChAdOx1 nCoV-19
Number	497	514
Geometric mean antibody titer (GMT)	19.92	-
95% confidence interval	(18.68, 21.23)	-
P-value*	<0.0001	-

\* Trial result of GMT ratio of S-268019 group to ChAdOx1 nCoV-19 group

**It was assessed that the neutralizing antibody titer in the S-268019 group was statistically significantly higher than that in the ChAdOx1 nCoV-19 group.**



# S-268019: Development status

## **Adult: Filing preparation**

- **Preconsultation completed**
  - Nonclinical Part: Pharmacology & Toxicology
- **Preconsultation in Progress**
  - Clinical Part: Ph1/2 trial, Ph2/3 trial, Booster comparison trial
- **CTD preparation**
  - CMC Part, Clinical Part: Neutralizing antibody titer comparison trial, Boost trial (domestic additional trial)



Filing Planned by the end of 2022

## **Pediatric: Clinical studies on-going**

- Started investigation in adolescents and is currently conducting dose finding trial in school children

## **Action to new variants**

- **Confirmed increase of neutralizing antibody titers against various variants in S-268019 clinical trial specimens**
  - Neutralizing antibody titer at booster is similar to neutralizing antibody titer at booster by community
- **Preparation of new variant antigen production**
  - Investigation of the antigen production process based on the genetic information of the Omicron variant is in the final stage
  - Mice booster immunogenicity test confirmed increasing of neutralizing antibody titer against new variants

# Agenda

## 1. Shionogi's R&D

- Opening
- Progress of COVID-19-related R&D
- Progress of Shionogi R&D
  - ✓ Development area
  - ✓ Research area
  - ✓ Vaccine Business
  - ✓ Summary of R&D

## 2. Summary

## 3. Q&A

**John Keller, Ph.D.,**

Senior Vice President, R&D Supervisory Unit

**Takeki Uehara, Ph.D.,**

Senior Vice President, Drug Development and Regulatory Science Division

**Takeki Uehara, Ph.D.,**

**Yasuyoshi Iso, Ph.D.,**

Senior Vice President, Research Division

**Yasunori Aoyama, Ph.D.,**

Senior Vice President, Biopharmaceutical Research Division

**John Keller, Ph.D.,**

**Isao Teshirogi, Ph.D.,**

Chief Executive Officer



# Progress in development areas



**Takeki Uehara, Ph.D.,**  
Senior Vice President, Drug Development and  
Regulatory Science Division

# Development area

Disease area	Project	Target disease	Stage	Posted page
Infection	<b>olorofim (F901318)</b>	Invasive aspergillosis	Global: Phase 3	P.43-45
Psychiatry/Nervous/Pain	<b>resiniferatoxin</b>	Pain associated with osteoarthritis	Global: Phase 3	P.46-48
	<b>sivopixant (S-600918)</b>	Intractable/Chronic with unknown cause cough	Global: Phase 2	P.49-50
	<b>zatolmilast (BPN14770)</b>	(1) Fragile X Syndrome (2) Alzheimer's dementia	(1) United States: Phase 2/3 (2) United States: Phase 2, Japan: Phase 2	P.51-53
	<b>zulanolone (S-812217)</b>	depression/depression	Japan: Phase 3	P.54-60
New growth area	<b>redasemtide (S-005151)</b>	(1) Dystrophic epidermolysis bullosa (2) Acute cerebral infarction (3) Knee osteoarthritis (4) Chronic liver disease (5) Cardiomyopathy	(1) Japan: Preparing for additional studies (2) Global: Preparing for Phase 3 trial (3)(4) Japan: Physician-initiated clinical trials underway (5) Japan: Preparing for investigator-initiated clinical trial	P.61-67
	<b>S-309309</b>	Obesity	United States: Phase 1	P.68-71
	<b>S-531011</b>	solid cancer	Japan/United States: Phase 1b/2	P.72-75
	<b>S-770108</b>	idiopathic pulmonary fibrosis	Japan: Phase 1	P.76-78

# Olorofim [F901318]: Profile



## Indication

- Invasive fungal infections with limited treatment options



## Product Characteristics

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



## Market

- Number of symptomatic patients: Tens of thousands are estimated as diagnosed invasive aspergillosis patients in Europe and China
- 90-day mortality of azole antifungal therapy is 20-30%\* and resistance is widespread



## 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



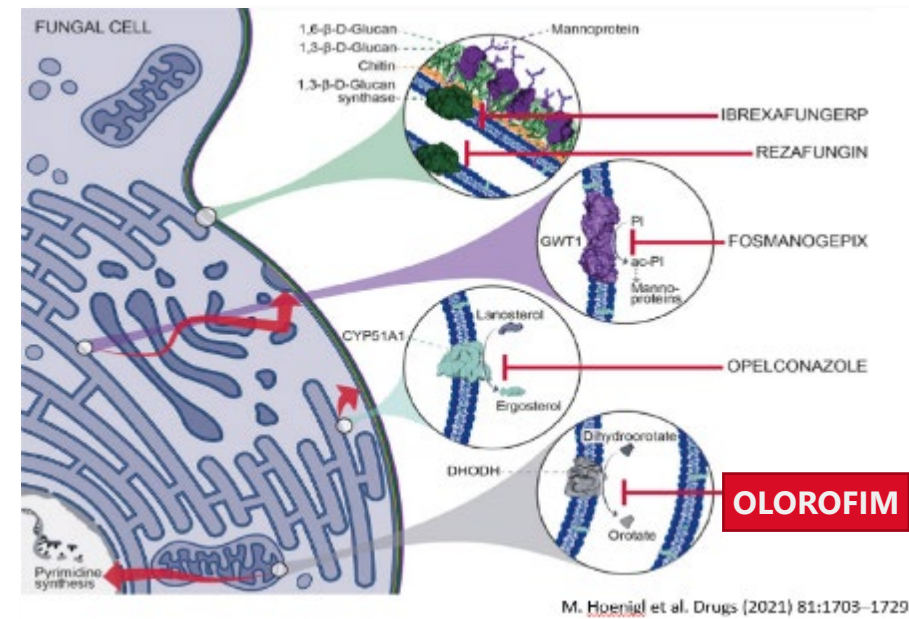
## Current Status

- Global Ph2b trial, Global Ph3 trial: On-going



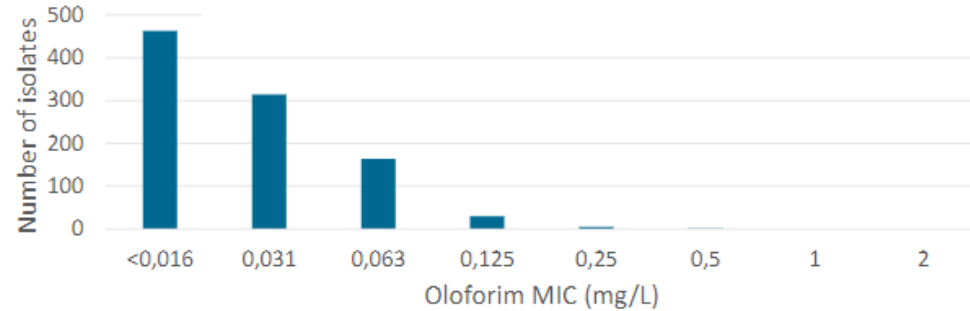
## Mechanism of Action

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

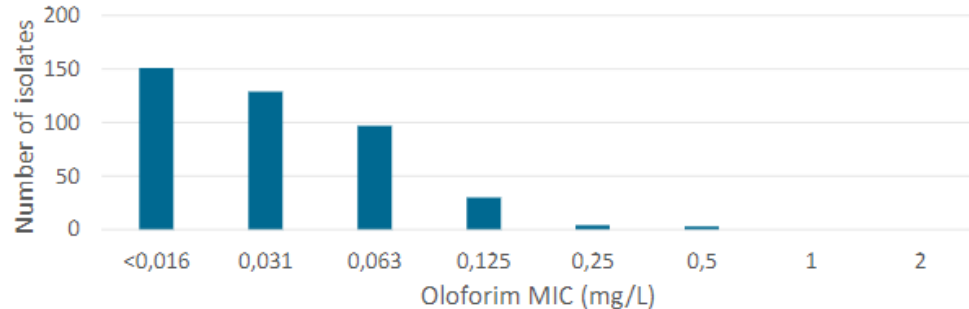


# Olorofim: Activity against *Aspergillus*

Susceptibility of olorofim to *A. fumigatus* (azole-susceptible strain) (n=987)



Susceptibility of olorofim to *A. fumigatus* (azole-resistant strain) (n=414)

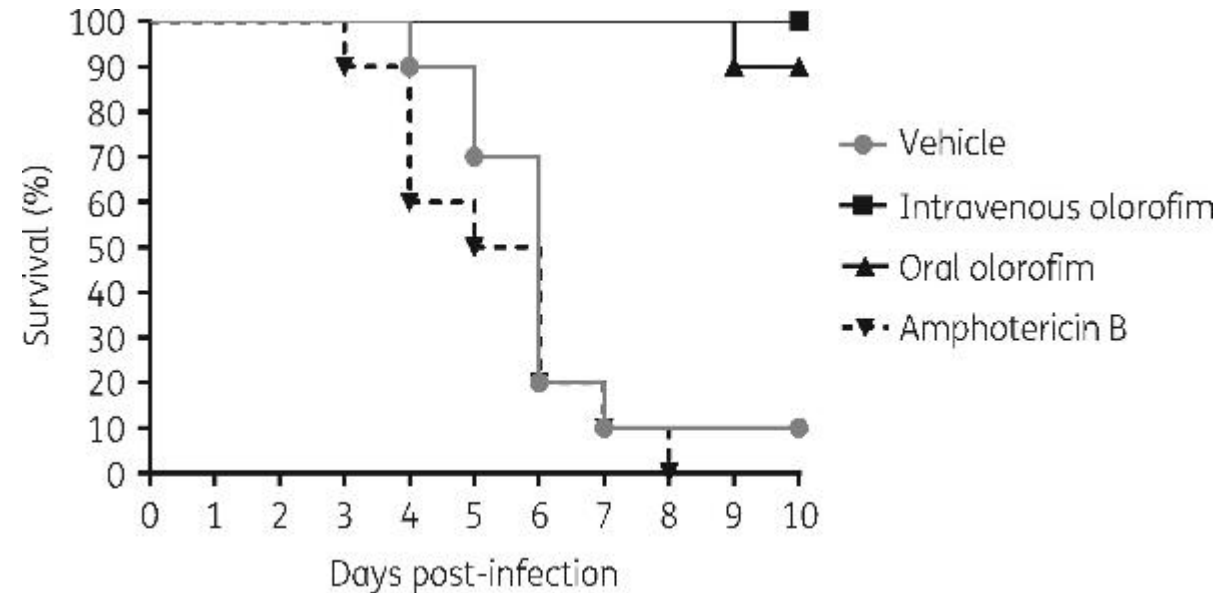


\*Susceptibility of *A. fumigatus* isolates with MICs  $\geq 0.25$  mg/L was  $<0.25$  mg/L in repeated testing

Buil et al., TIMM2019

**High antifungal activity regardless of azole resistance**

Survival rate (%) in *A. terreus sensu stricto* infected mice



Lackner et al., <https://doi.org/10.1093/jac/dky329>

**Olorofim showed high survival rate in infected mouse model**

# Olorofim: Summary of on-going studies

## **FORMULA-OLS (Phase 2b trial)**

---

### **Salvage trial in patients without treatment options**

- Official Title: Phase IIb Trial of F901318 as Treatment of Invasive Fungal Infections Due to *Lomentospora Prolificans*, *Scedosporium Spp.*, *Aspergillus Spp.*, and Other Resistant Fungi in Patients Lacking Suitable Alternative Treatment Options (NCT03583164)
- Target Number of Subjects: 200
- Trial Countries: US, Europe, APAC

## **OASIS (Phase 3 trial)**

---

### **RCT in invasive Aspergillosis when azole is difficult to use**

- Official Title: Phase III, Adjudicator-blinded, Randomised Trial to Evaluate Efficacy and Safety of Treatment With Olorofim Versus Treatment With AmBisome® Followed by Standard of Care in Patients With Invasive Fungal Disease Caused by *Aspergillus* Species (NCT05101187)
- Target Number of Subjects: 225
- Trial Countries: North & South America, Europe, APAC

**Joint development with F2G as a treatment for invasive fungal infections with limited treatment options**

# Resiniferatoxin: Profile



## Indication

- Osteoarthritis of the knee  
⇒ Moderate to severe pain associated with knee osteoarthritis in patients who have failed one or more prior therapies



## Special characteristics

- An injection that can reduce pain and improve functionality by injecting into the knee joint once every six months on average



## Market

- Number of symptomatic people : 25 million (Japan)
- Market size : Over 70 B 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

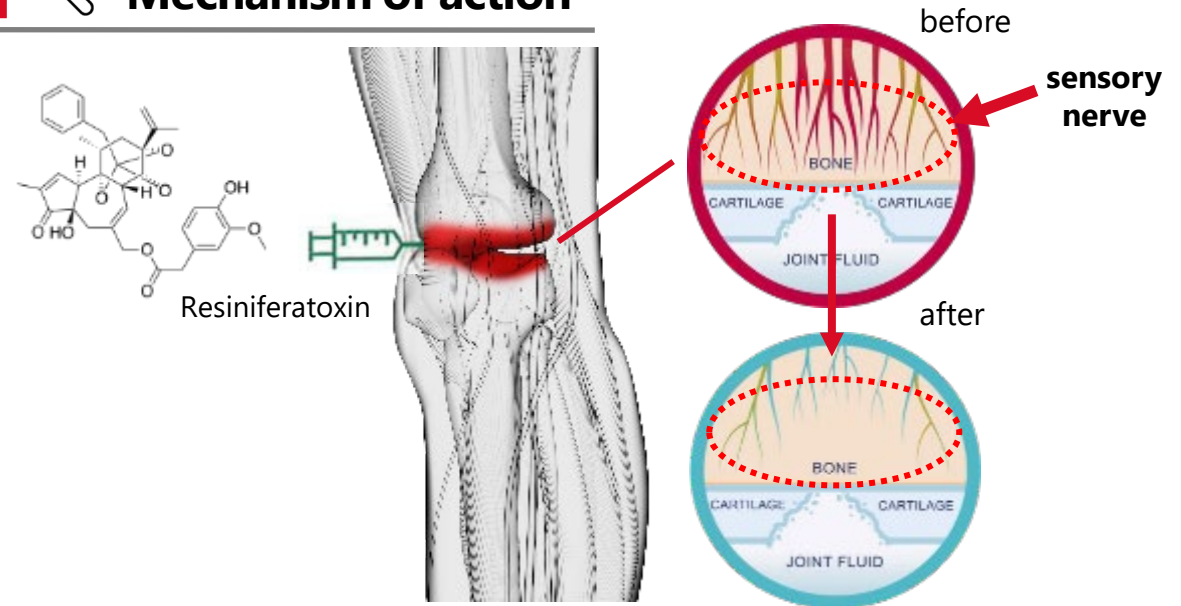


## Current status and future plans

- Global Phase 3 trials initiated in US and Europe, preparing for start in Japan later this year



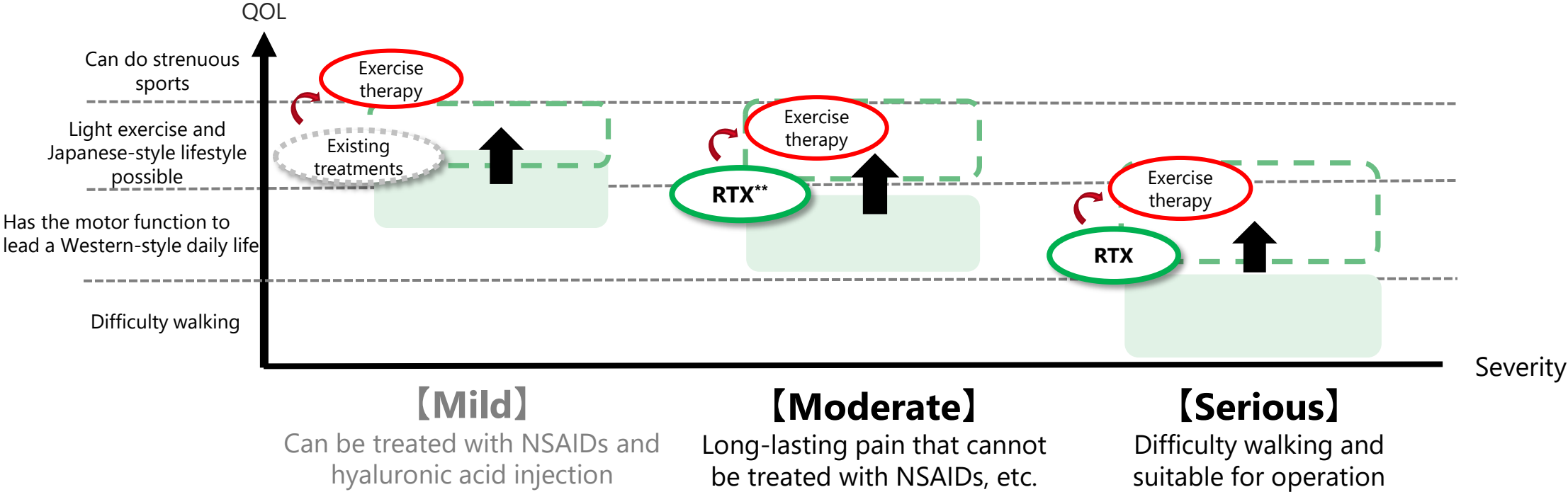
## Mechanism of action



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)

# Resiniferatoxin: Role in therapy

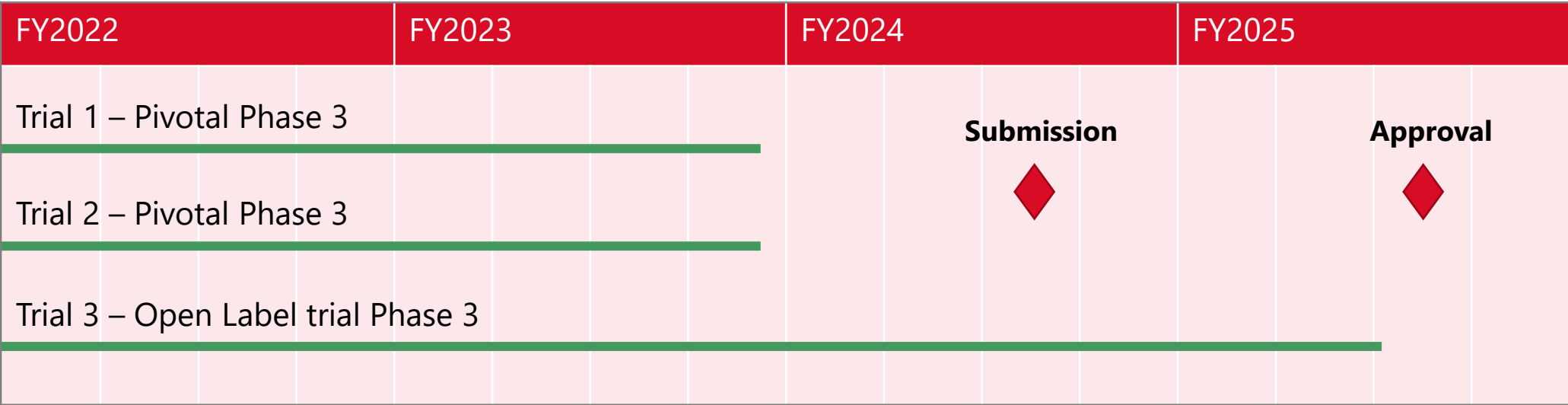
- Providing a new analgesic option for patients who have an inadequate response to existing treatments
- Improving patient QOL\* by reducing pain and improving functionality with injection once every 6 months on average
- Pain relief supports other therapeutic approaches such as exercise therapy and strength training



**Contributes to reducing pain, improving functionality and QOL and increasing activity levels in patients with moderate to severe disease**

# Resiniferatoxin: Future development plan

- Aligned with the development of S-005151 for osteoarthritis of the knee, to create a portfolio addressing both pain and cartilage regeneration
- Projected launch in launch in Japan in 2025



Trial period: Start of patient enroll to completion of clinical trial report

**Expected to contribute to domestic sales expansion after 2025 and drives top-line growth**



# Sivopixant [S-600918]: Profile



## Indication

- Refractory / unexplained chronic cough (RCC/UCC)



## Product property

- Well-tolerated and peripherally acting antitussive



## Market

- Chronic cough: 5%-10% of adult population  
RCC/UCC: 20%-40% of patients with chronic cough (estimated)



## Unmet medical needs

- There is no approved drug for RCC/UCC (other than Japan\*)
- Long-lasting use of central antitussives is not recommended due to safety concerns  
→ Efficacious and safe drug is needed



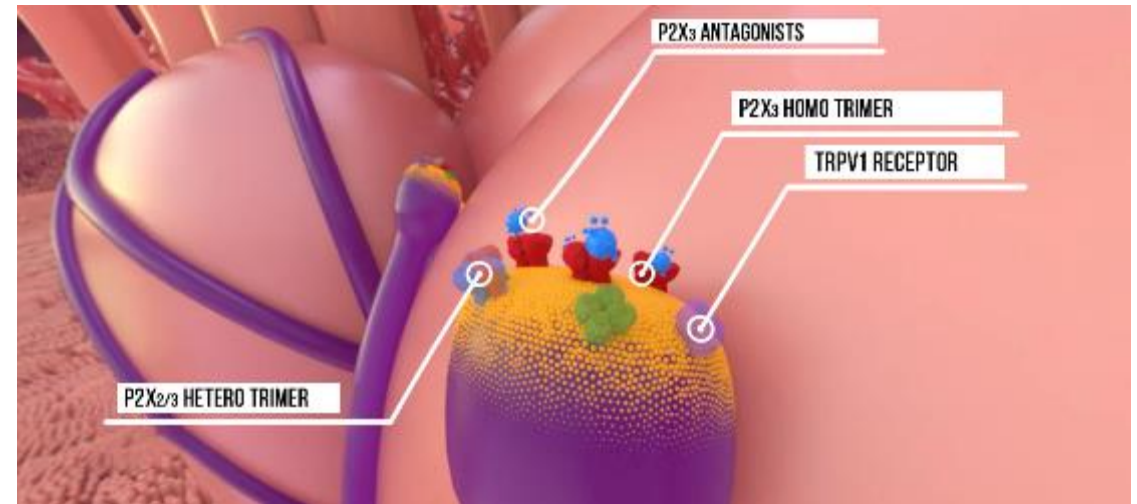
## Current status and future plans

- Regulatory meetings were held after Phase 2b completion
- In preparation for Phase 3 studies



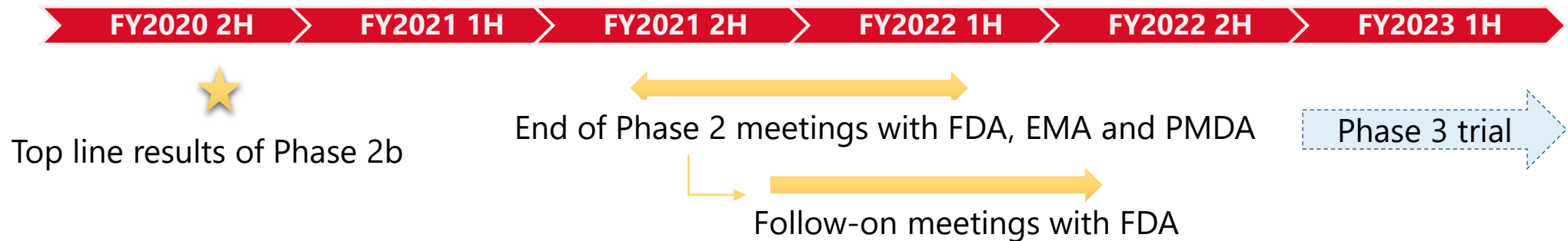
## Mechanism of action

- P2X3 receptor antagonist  
(Purinergic receptor subtype P2X3)



# Sivopixant: Development strategy

## Timeline for RCC/UCC



## Potential LCM indications

### • Pain

- Visceral pain
  - ✓ Interstitial cystitis
  - ✓ Bladder pain Syndrome
  - ✓ Endometriosis pain etc.
- Neuropathic pain

### • Cough

- IPF-associated cough
- ILD-associated cough
- Cough due to lung cancer
- Cough due to heart failure

### • Other

- Pruritus (atopic dermatitis, etc.)
- Hypertension

- In parallel with development for RCC, LCM strategy for above indications is under consideration
- **Whether to conduct Phase 3 trial will be determined in view of competitor landscape and regulators comments on endpoint**

# Zatolmilast [BPN14770]: Profile



## Indication

- Fragile X Syndrome (FXS<sup>\*1</sup>) / Alzheimer's disease (AD<sup>\*2</sup>)



## Product Characteristics

- Enhanced cognitive function, especially memory formation
- Well tolerated without notable GI side effects



## Market (FXS)

- Prevalence : About 1 in 10,000 have been diagnosed with FXS
- Market Size : \$187MM (US, Male, ≥18 years old)



## Unmet Needs (FXS)

- No approved treatments for FXS
- Treatment for severe behavioral symptoms (e.g., anxiety), cognition and communication disabilities



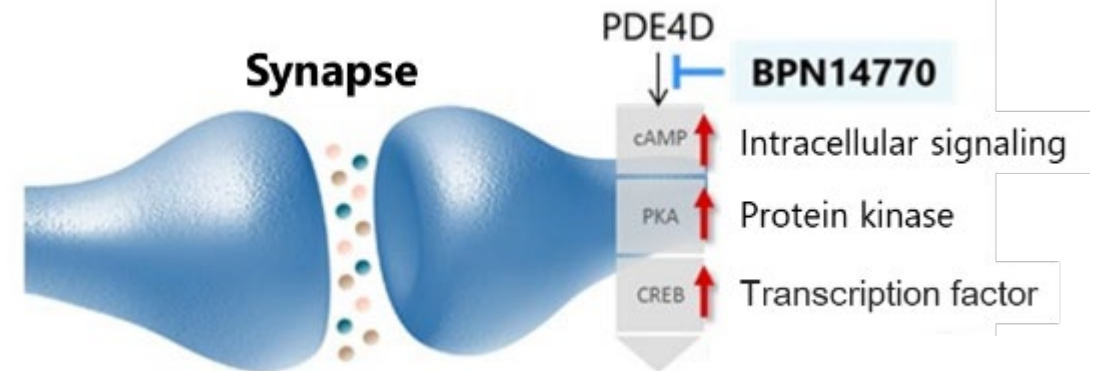
## Current Status and future plans

- FXS: US Phase 2/3 studies ongoing
- AD: Future development plan under consideration



## Mechanism of Action

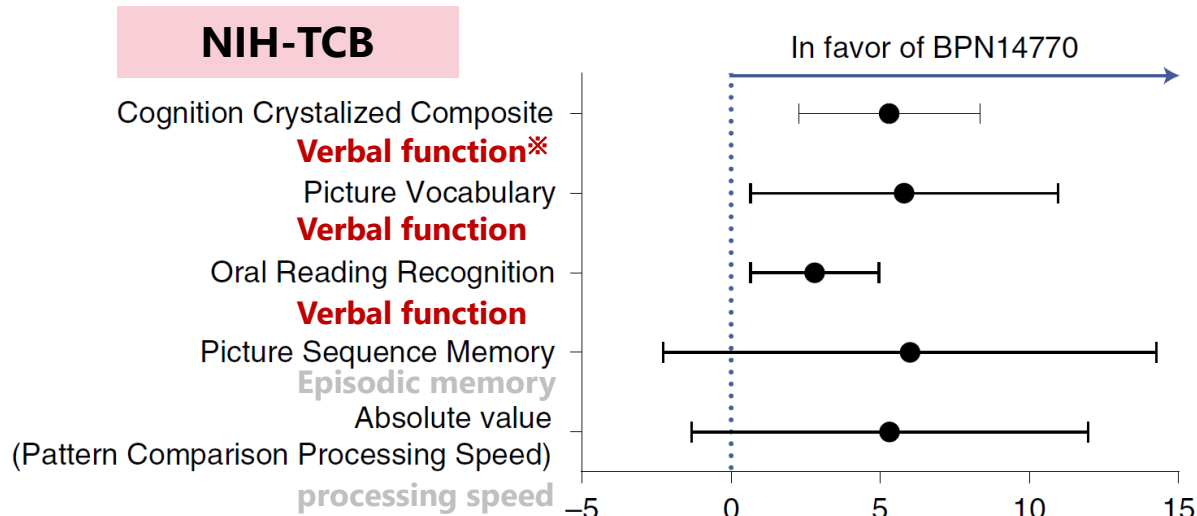
- PDE4D<sup>\*3</sup> allosteric inhibitor  
(phosphodiesterase subtype that hydrolyzes cAMP<sup>\*4</sup>)



1. Increase the cAMP signaling, and gene expression in neuron, resulting that the neuronal / synaptic function is enhanced
2. Improve the cognitive impairment / behavioral abnormality

# Zatolmilast: US FXS Phase2 trial (conducted by Tetra)

<b>Target population</b>	Male adult with Fragile X Syndrome (18~45 years old)
<b>Key efficacy endpoint</b>	NIH Toolbox cognitive battery (NIH-TCB, cognitive function)
<b>Trial design</b>	Single site, randomized, double-blind, cross-over (no washout period)
<b>No. of subject</b>	30 subjects
<b>Arms / Treatment period</b>	BPN14770 25 mg BID, Placebo / 12 weeks



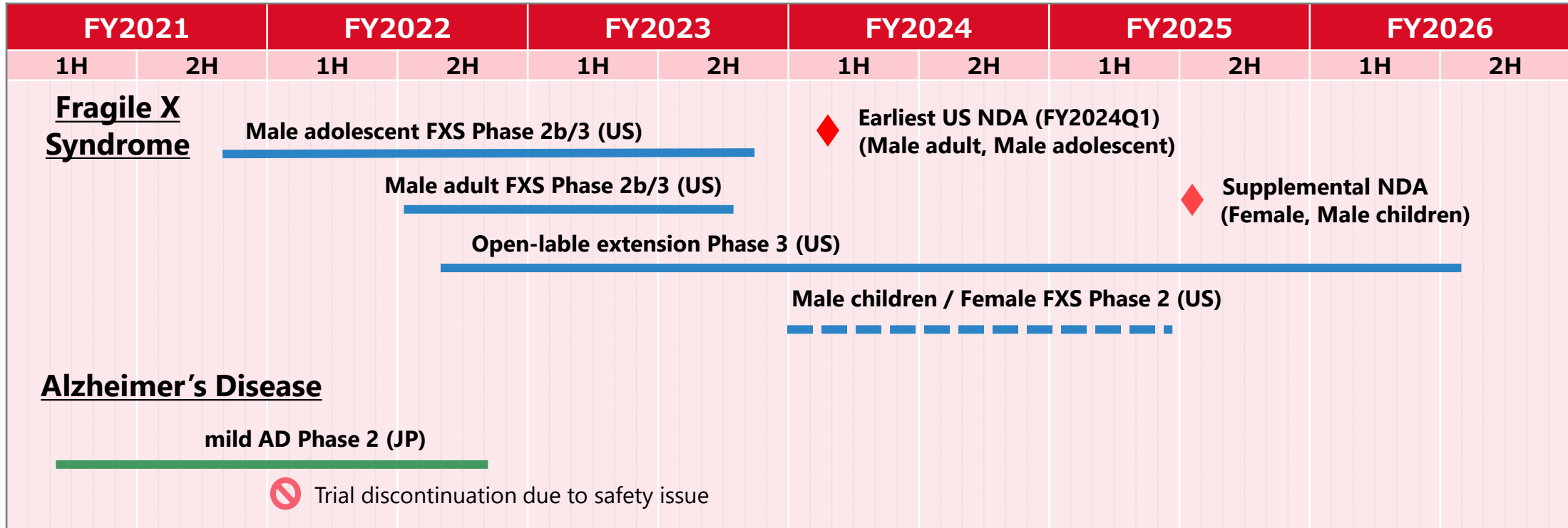
**At 25mg BID for 12 weeks, significant effect in NIH-TCB\* (verbal function) and caregiver VAS\*\* (assessment of language and daily function), BPN14770 has efficacy on verbal function and daily function in FXS patients.**

**US Phase 2b/3 studies with primary endpoint if NIH-TCB CCC (verbal function) being conducted (US NDA: ~2024).**

Berry-Kravis EM. et al., *Nat Med.* 2021 May;27 (5) : 862-870

\*Composite score calculated by Cognitive Crystallized Composite: Oral Reading Recognition & Picture Vocabulary

# Zatolmilast: Development schedule



Trial period: Start of patient enroll to completion of clinical study report

## Fragile X Syndrome (FXS)

- Conducting the male adolescent FXS Phase 2/3 trial, male adult FXS Phase 2/3 trial for US NDA
- Preparing for Phase 2 studies in male children / female

## Alzheimer's Disease (AD)

- Analysis of JP AD Phase 2 trial results for continuation of AD development

# Zuranolone [S-812217]: Profile



## Indication

- Major depressive disorder (depression)



## Characteristics

- Rapid onset of action (important unmet need)
  - Significant difference from placebo from the first observation after the treatment initiation (Day 3)



## Market

- Depression sufferers in Japan: Approx. 5 million\*<sup>1</sup>
  - Largest morbidity of any non-fatal ill-health disease
- Domestic antidepressant drug market: Approx. 160 B yen



## Unmet needs

- Low pharmacotherapy response rate: Remission rate at first antidepressant treatment 36.8% \*<sup>2</sup>
- Slow onset of action: Antidepressant effect takes 4-6 weeks, especially 8 weeks\*<sup>3</sup>



## Current status and future plans

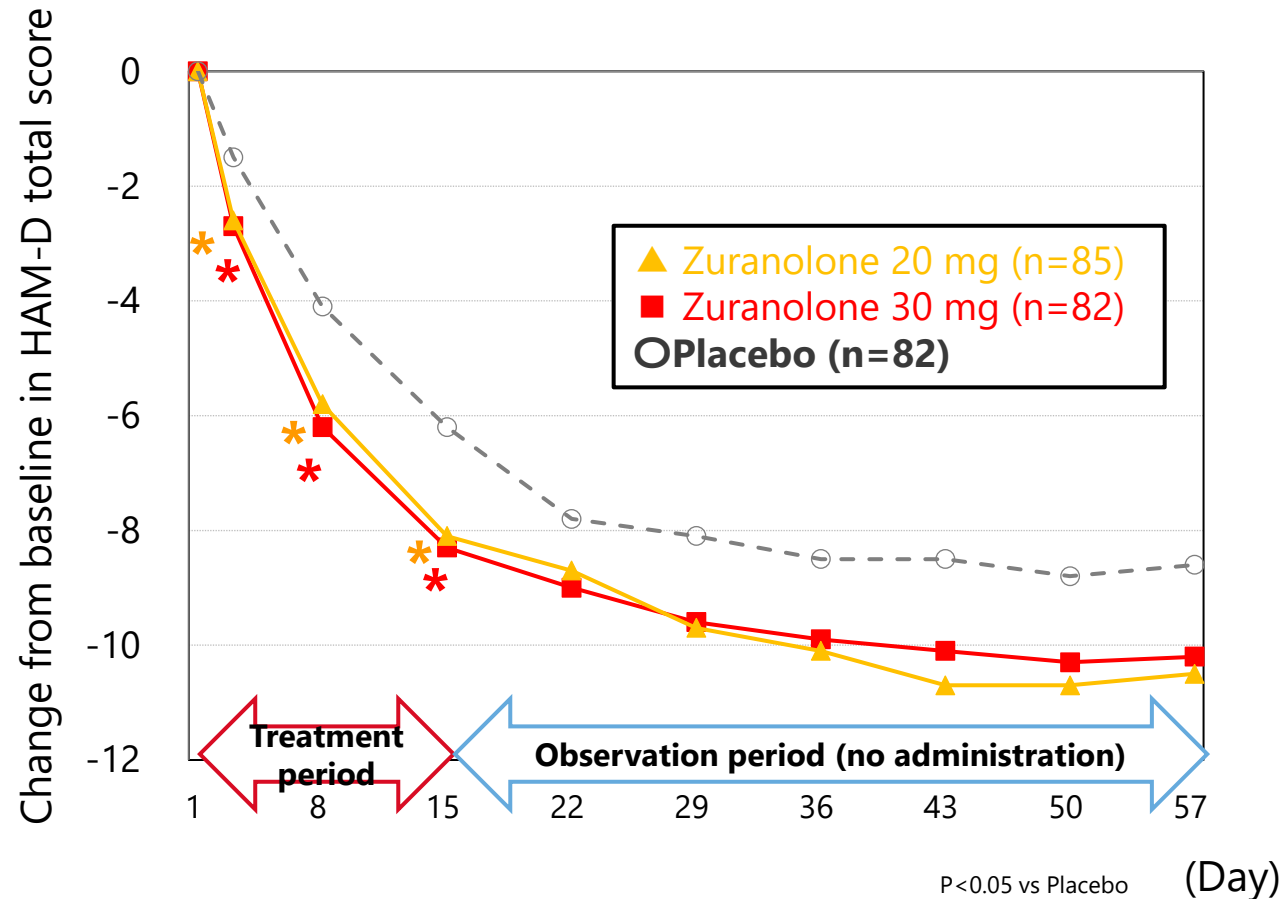
- US: Rolling submission initiated in April 2022, will be completed by the end of this year.
  - Indications: major depressive disorder, postpartum depression
- Japan: Aiming for NDA in 4Q 2023, Phase 3 is underway
  - Indication: Major depressive disorder
  - Phase 3 confirmatory trial: On track
  - Combination trial with antidepressants: FPI in 3Q 2022



## Mechanism of action

- Neuroactive steroid
  - Cerebrospinal fluid allopregnanolone decreased in depressed patients\*<sup>4</sup>
- GABA<sub>A</sub> receptor (γ-aminobutyric acid-gated chloride ion channel) positive allosteric modulator
  - Acts on synaptic/extrasynaptic receptors

# Zuranolone: Phase 2 trial in Japan



## Efficacy

- **Both 20 and 30mg achieved primary endpoints**
  - Significant improvement in change from baseline in HAM-D\* total score versus placebo at 20mg and 30mg from Day 3 (initial observation) to Day 15 (treatment completion)
  - Response rate\*\* significantly improved over placebo on Days 8 and 15
- ⇒ **Confirm the "rapid onset of action"**
  - During the observation period from Day 15 to Day 57, there was no significant difference from the placebo, but a tendency for the treatment effect to persist was shown.

## Safety

- **No safety concern**
  - All adverse events were mild or moderate and no new concern was raised

# Zuranolone: Characteristics and development strategy

## Strengths: Rapid onset of action (important unmet need)

- **Achieving efficacy in 2 weeks that required 6 to 8 weeks of treatment with existing antidepressants**
- Early improvement after the treatment initiation indicates a favorable outcome\*, and is of great clinical significance.

## Ease of use: 2-week administration only when treatment is needed contributes to convenience

- No need to adjust dosage, efficacy is confirmed in 2 weeks, **high adherence** is expected

## Development strategy: Seeking to establish a leading drug for acute treatment\*\* of depression

- Treatment concept: Improving depressive symptoms and leading to remission in a short period of time for patients with depression who require therapeutic intervention regardless of initial, relapse, or recurrence
- This drug covers a wide range of antidepressant treatment from the first-line to the second-line and third-line
  - Conduct clinical trials to evaluate efficacy and safety under the following conditions
    - ✓ Monotherapy for Naive Depressed Patients
    - ✓ Combined treatment with antidepressants for patients with insufficient response to antidepressant monotherapy

\*J Clin Psychiatry 2009;70(3):344-353

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



# Zuranolone: Clinical trial program




Major Depressive Disorder (MDD)


Postpartum depression (PPD)

Major Depressive Disorder (MDD)					Postpartum depression (PPD)	
Monotherapy/Add-on to existing drugs				Simultaneous initiation with other antidepressants	Monotherapy/add-on to existing drugs	
MDD-201	MOUNTAIN MDD-301A	WATERFALL MDD-301B	SHORELINE MDD-303 30mg/50mg Efficacy/ Safety assessment including retreatment	CORAL MDD-305	ROBIN PPD-201	SKYLARK PPD-301
30mg Verification of efficacy and safety	20mg/30mg Verification of efficacy and safety	50mg Efficacy/safety Verification		Verification of efficacy and safety of 50mg	30mg Verification of efficacy and safety	50mg Efficacy/ Safety verification
completion	completion	completion	in progress	completion	completion	completion



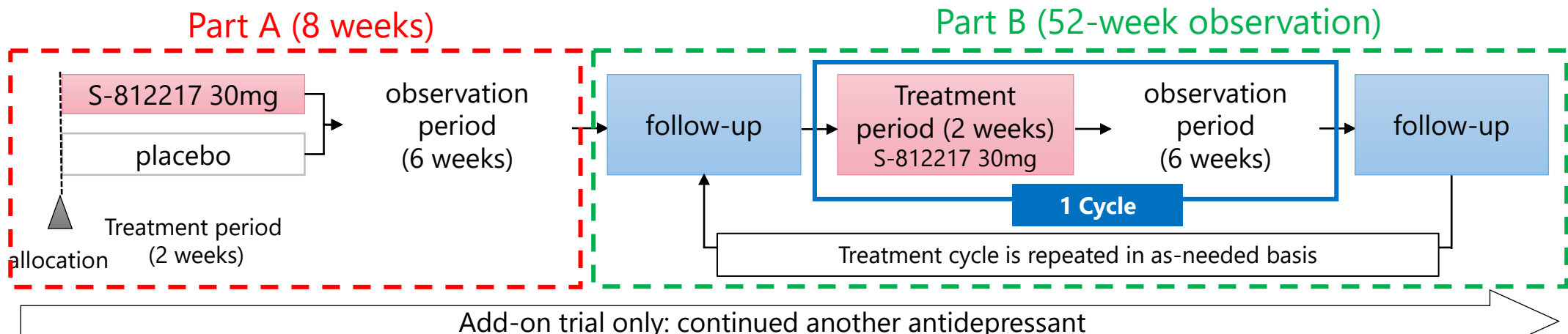
monotherapy		Add-on to existing drugs
Phase 2	Phase 3 confirmatory	Phase 3 combination with antidepressants
20mg/30mg Efficacy/safety Verification	Efficacy/safety of 30mg Safety verification including retreatment	Assessment efficacy and safety of 30mg
completion	in progress	in progress

 Conducted by SHIONOGI in Japan

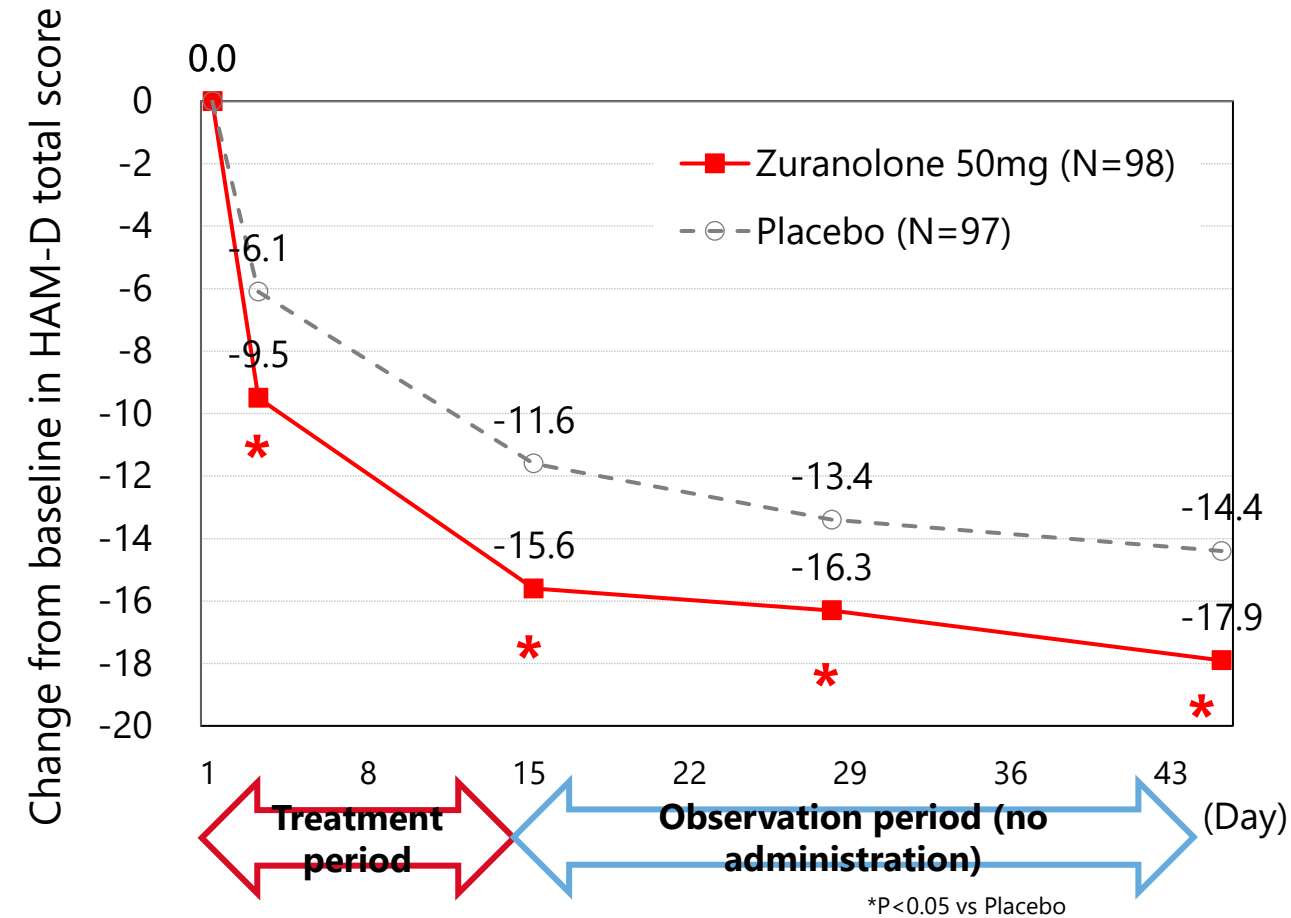
 Conducted by Sage in the United States

# Zuranolone: Overview of Phase 3 trial in Japan

	Phase 3 confirmatory trial	Phase 3 Add-on trial
<b>subject</b>	Patients with moderate to severe major depressive disorder	Patients with major depressive disorder on other antidepressants
<b>Purpose</b>	[Part A] Examination of superiority of Zuranolone over placebo [Part B] Examination of safety and tolerability of re-administration when necessary	Consider the following when adding Zuranolone to other antidepressants [Part A] Efficacy vs placebo [Part B] Safety and tolerability of re-administration when needed
<b>clinical trial design</b>	[Part A] A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial [Part B] Multicenter, open label	
<b>Dosing group</b>	Zuranolone 30mg group, placebo group	
<b>Sample size</b>	200 in each group, 400 in total	50 in each group, 100 in total
<b>Dose administration</b>	Oral administration once a day for 14 days after dinner	



# Zuranolone: US postpartum depression Phase 3 trial (SKYLARK, PPD-301)



## Effectiveness

- **Met primary and secondary endpoints**
  - Significant improvement over placebo in change from baseline in HAM-D total score from Day 3 (initial observation) to Day 45 (4 weeks after the end of administration)
  - Achieved the primary endpoint at Day 15
    - ✓ **Confirmed rapid onset of action and durable effect**
- Significant improvement in clinical global severity (CGI-S\*) compared to placebo on Day 15 (treatment completion)

## Safety

- **No safety concern**
  - The 50mg dose was well tolerated with no new concerns

# Zuranolone: Creation evidence and indications

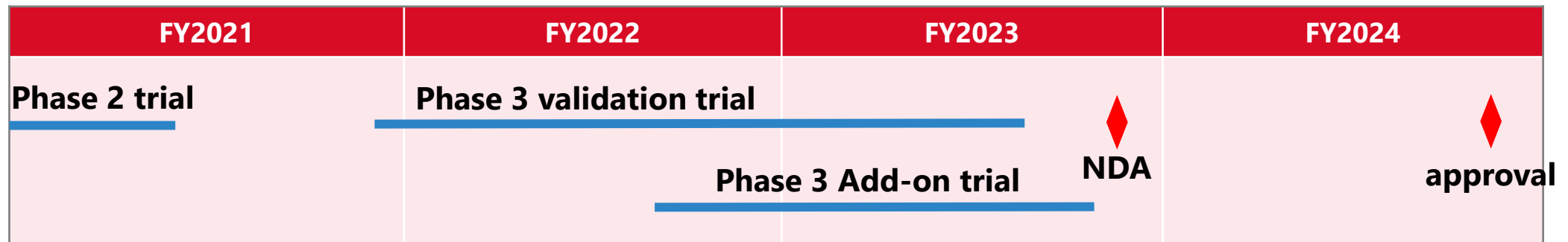
## Evidence

- **Major depressive disorder**
  - Broad acquisition of data on monotherapy and combination therapy
- **Postpartum depression**
  - Clear efficacy confirmed in clinical trials (rapid onset of action, durable effect)

## Indication

- **US (Sage) : Major depressive disorder, postpartum depression**
  - Following ZULRESSO (brexanolone\*) injective CIV, which is the only drug indicated for postpartum depression, Sage is seeking postpartum depression indication for this oral drug
- **Japan (SHIONOGI) : Depression**

## Japan development schedule



# Redasemtide [S-005151]: Challenges and developmental significance for regenerative medicine

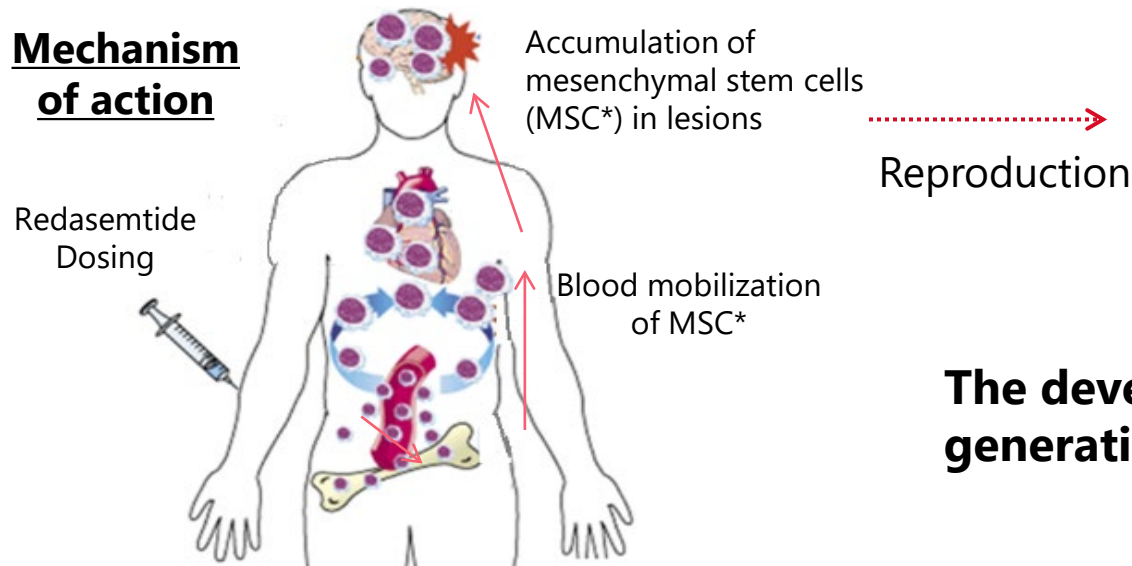
Conventional regenerative medicine  
(transplantation, regenerative medicine products, etc.)

cost	High
therapeutic opportunity	Limited accessibility <ul style="list-style-type: none"> <li>To medical institutions, doctors</li> <li>To early transplantation treatment</li> </ul>
others	Difficult to manage cell quality

Regeneration-inducing drug  
(Redasemtide)

<b>Low</b>
<b>Easy accessibility</b> <ul style="list-style-type: none"> <li>To medical institutions, doctors (No special equipment required)</li> </ul>
<b>Easy to manage the quality because of a chemically synthesized product</b>

## Mechanism of action



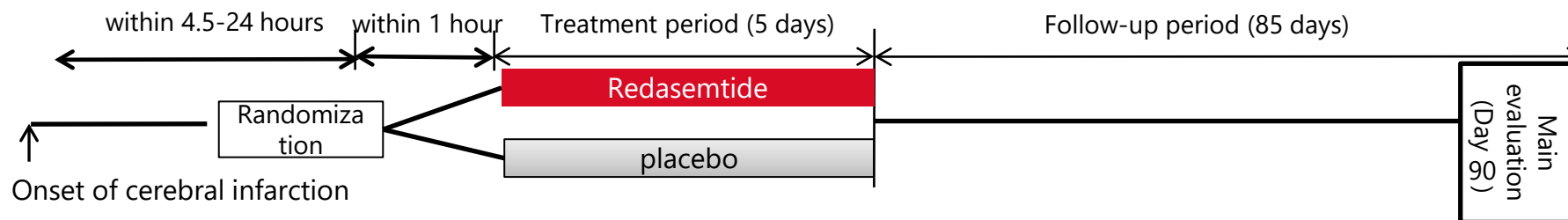
- Acute Ischemic Stroke
- Epidermolysis Bullosa
- Chronic Liver Disease
- Knee Osteoarthritis
- Cardiomyopathy etc.

Disease under development

**The development of this drug is of great significance as a next-generation drug that can induce regenerative ability stably at a lower cost.**

# Redasemtide: Acute Ischemic Stroke Phase 2 Trial Overview

<b>Clinical trial design</b>	Multicenter, randomized, placebo-controlled, double-blind
<b>Main purpose</b>	Efficacy and safety of redasemtide in patients with acute ischemic stroke
<b>Target patient</b>	<ul style="list-style-type: none"> <li>• Can be administered within 4.5-25 hours from the onset of symptoms at age 60-84 older</li> <li>• Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability)</li> <li>• Intravascular recanalization therapy (t-PA* treatment, endovascular treatment) cannot be performed</li> </ul>
<b>Administration group/ number of cases</b>	<ul style="list-style-type: none"> <li>• Redasemtide (1.5 mg/kg) group : 75 cases</li> <li>• Placebo group : 75 cases</li> </ul> <p style="text-align: right;">total 150 cases</p>
<b>Dosing method/duration</b>	Intravenous administration once daily for 90 minutes for 5 days
<b>Primary endpoint</b>	<b>Modified Rankin Scale (mRS) after 90 days of administration</b>
<b>Secondary endpoint</b>	Presence or absence and frequency of adverse events, NIHSS**, Barthel Index (BI)***, mRS (Day365), days to discharge, QOL assessment
<b>Country</b>	Japan
<b>Period</b>	April 2019 - December 2021



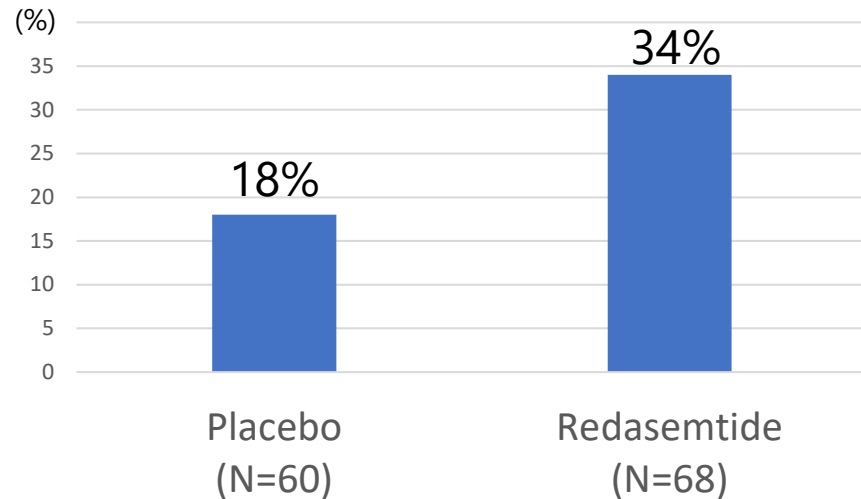
\* tissue plasminogen activator: used to treat cerebral infarction as a thrombolytic drug

\*\* National Institutes of Health Stroke Scale (NIHSS): Stroke Neurological Severity Rating Scale (42 points in total, the higher the score, the more severe)

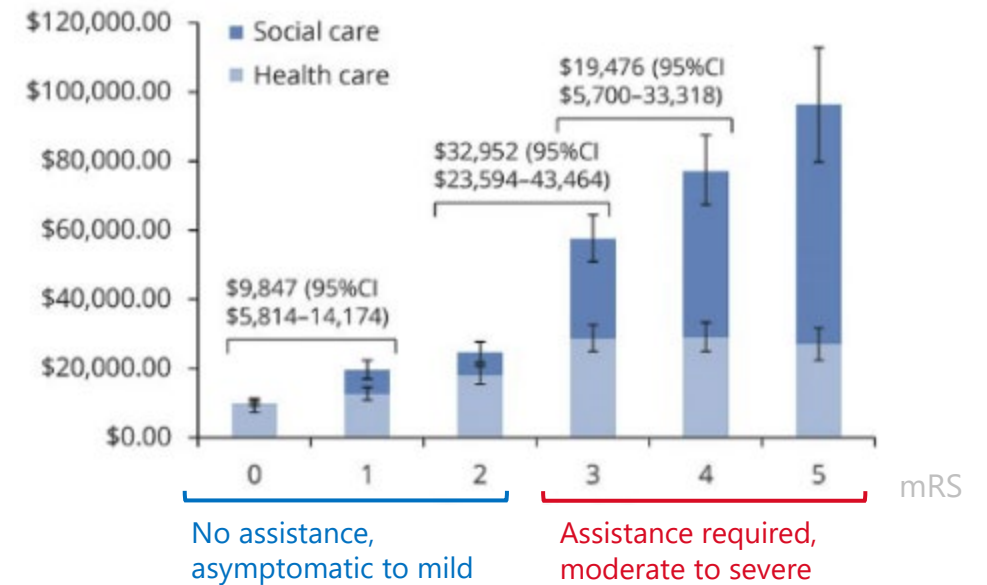
\*\*\* Barthel Index (BI) : Evaluation scale for activities of daily living such as eating, bathing, and toileting (total 100 points, the higher the score, the more independent the person is, and the guideline for complete independence is 95 points)

# Redasemtide: Acute ischemic stroke Phase 2 trial results

Percentage of patients requiring care after 6 days of administration who became care-free (mRS\* ≤2) after 90 days



mRS at 3 months after ischemic stroke and 5-year social and medical costs (per person)



Neurology 2018; 91. (21)

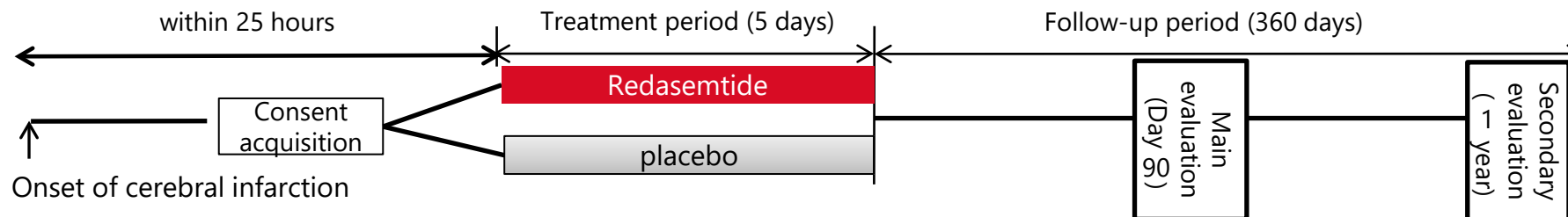
※Reference

- Prevalence(number) : 1.65 million
- (estimate for Japan, the US, and Europe in 2021)
- Market size: 735MM USD
- (estimate for Japan, the US and Europe in 2021)

- The percentage of patients requiring long-term care who improved to a socially independent level that required no assistance increased compared to the placebo group.
- The deterioration of mRS due to ischemic stroke has a large impact on the increase in social and medical costs, and the improvement of mRS using this drug is of great social significance.

# Redasemtide: Acute Ischemic Stroke Global Phase 3 Trial Overview (Draft)

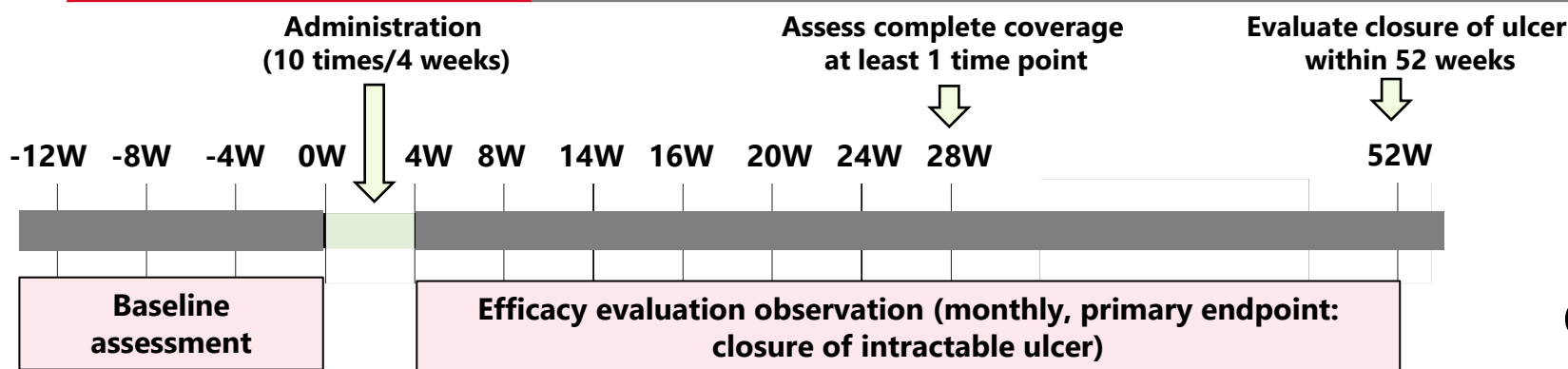
<b>clinical trial design</b>	Multicenter, randomized, placebo-controlled, double-blind
<b>main purpose</b>	<b>Verification of efficacy of redasemtide in patients with acute ischemic stroke</b>
<b>Target patient</b>	<ul style="list-style-type: none"> <li>• Can be administered within 25 hours from the onset of symptoms at age 18 or older</li> <li>• Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability)</li> <li>• Intravascular recanalization therapy (t-PA treatment, endovascular treatment) cannot be performed</li> </ul>
<b>Administration group/ number of cases</b>	<ul style="list-style-type: none"> <li>• Redasemtide (1.5 mg/kg) group : 678 cases</li> <li>• Placebo group : 678 cases</li> </ul> <p style="text-align: right;">total 1356 cases</p>
<b>Dosing method/duration</b>	Intravenous administration once daily for 90 minutes for 5 days
<b>Primary endpoint</b>	<b>Modified Rankin Scale (mRS) after 90 days of administration</b>
<b>Secondary endpoint</b>	NIHSS, Barthel Index (BI), mRS (Day365), days to discharge, QOL assessment
<b>country</b>	Japan, Europe, North America, China, etc.





# Redasemtide: Dystrophic epidermolysis bullosa additional Phase 2 trial (domestic) started

<b>Clinical trial design</b>	Multicenter, open-label, uncontrolled
<b>Main purpose</b>	Evaluation of efficacy and safety of redasemtide in patients with dystrophic epidermolysis bullosa with intractable ulcers
<b>Administration group/ number of cases</b>	Redasemtide (1.0 mg/kg) group: ≥3 subjects
<b>Dosing method/ duration</b>	Intravenous administration once daily for 30 minutes, 10 times/4 weeks [First week of administration: 4 days, Weeks 2-4 of administration: 2 days/week (once every 3-4 days)]
<b>Primary endpoint</b>	Closure of intractable ulcer*



**July 2022: Clinical trial notification submitted**

**Q4 2022 (FY) : FPI scheduled**

# Redasemtide: LCM vision

**Investigator-initiated studies are underway based on evidence accumulated in non-clinical research in academia**

## **Chronic liver disease**

- Investigator-initiated Phase 2 trial (final observation in November 2022)
- Improvement of liver function by suppressing liver fibrosis in chronic hepatitis
- Providing new treatment opportunities for patients for whom there are no effective treatments

## **Knee osteoarthritis**

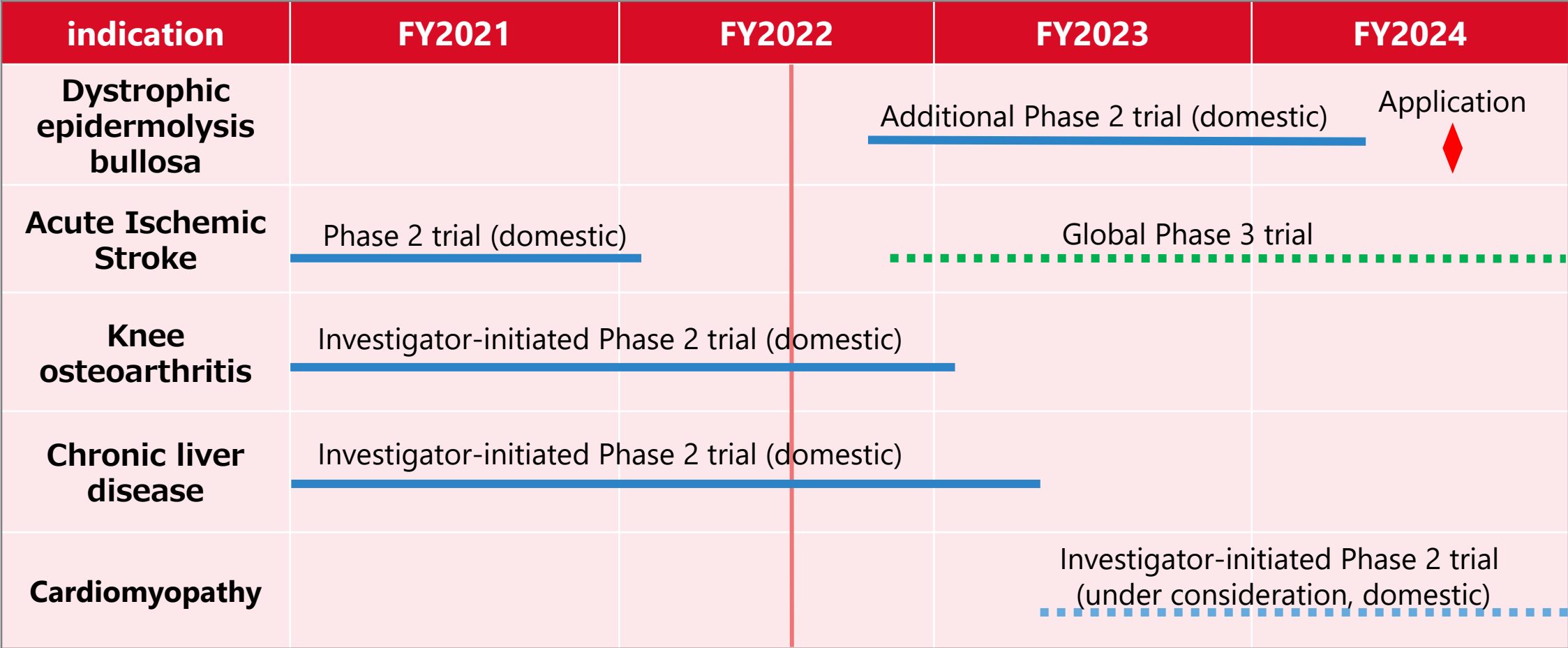
- Investigator-initiated Phase 2 trial (final observation in December 2022)
- Improvement of Morphological/joint function in knee osteoarthritis
- Providing new treatment opportunities that can contribute to improving QOL in an aging society

**An investigator-initiated trial for cardiomyopathy is being planned to maximize the value of this drug as a regeneration-inducing drug**

## **Cardiomyopathy**

- Improvement of cardiac function by suppressing cardiac fibrosis
- Considering targeting patients with ischemic cardiomyopathy with symptoms of heart failure

# Redasemtide: Development schedule



As of October 12, 2022

Trial period: Start of patient registration to completion of summary report

# S-309309: Profile



## Indication

- Obesity



## Product characteristics

- Best-in-class efficacy among existing oral drugs (weight loss of 10% or more per year) with no safety concern
- Lower economic burden compared to GLP-1<sup>\*1</sup> injectables



## Market

- Obese patients<sup>\*1</sup>: 245 million (7MM<sup>\*2</sup>), 125 million (U.S.)
- Market size<sup>\*3</sup>: \$ 1,692 MM (2021) (including 93% in the US)



## Unmet needs

- There is a demand for a drug that has no safety concerns, shows a sufficient weight loss effect over a long period of time, and has a low out-of-pocket cost.

<sup>\*1</sup> glucagon-like peptide-1 <sup>\*2</sup> © 2021 DR/Decision Resources, LLC. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.

<sup>\*3</sup> 7 major markets; US, France, Germany, Italy, Spain, UK and Japan <sup>\*4</sup> Copyright © 2022 IQVIA. Calculated by SHIONOGI based on IQVIA Analytics Link 2021.1-12, Reprinted with permission <sup>\*5</sup> monoacylglycerol acyltransferase 2



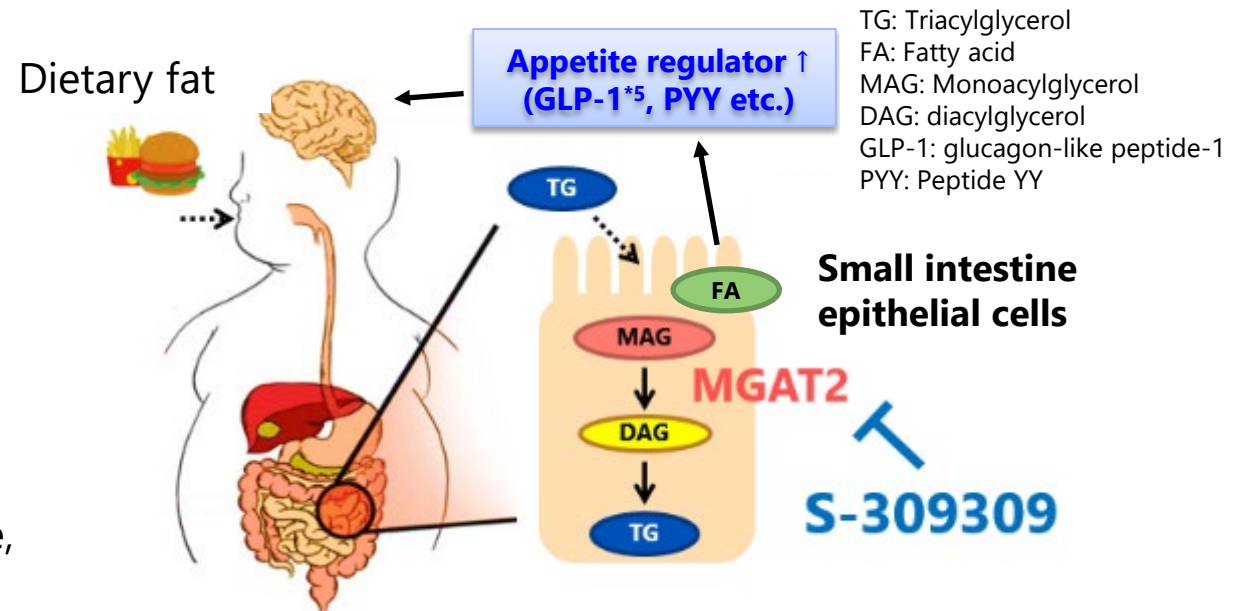
## Current status and future plans

- Phase 1 trial ongoing in the US
- Planning Phase 2 PoC trial

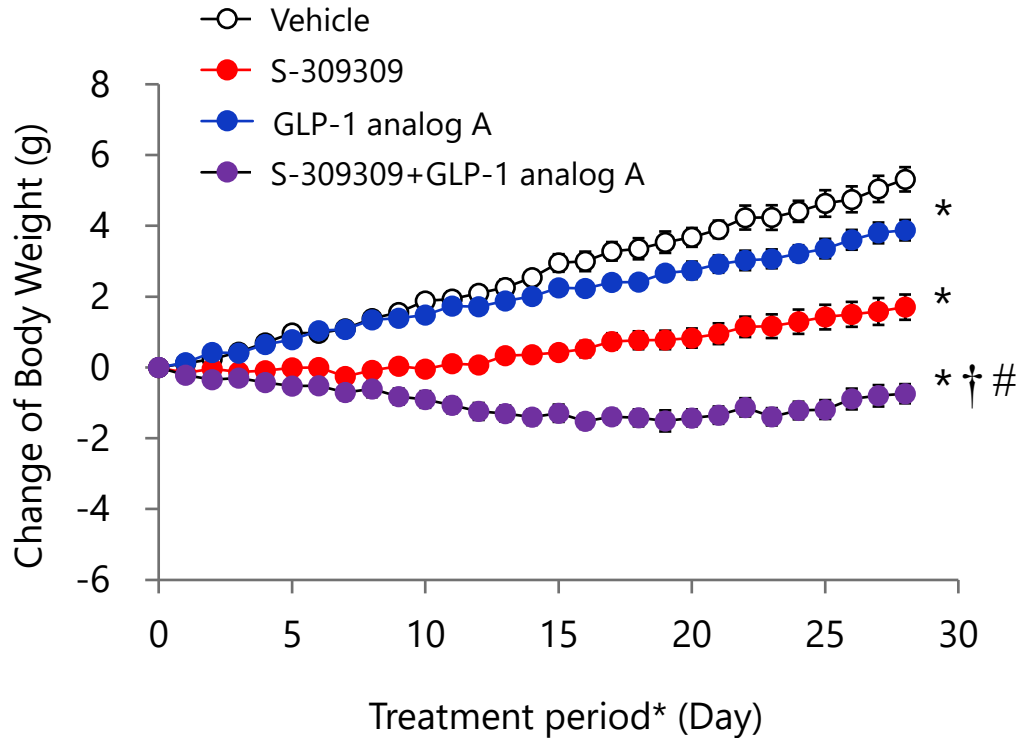


## Mechanism of action

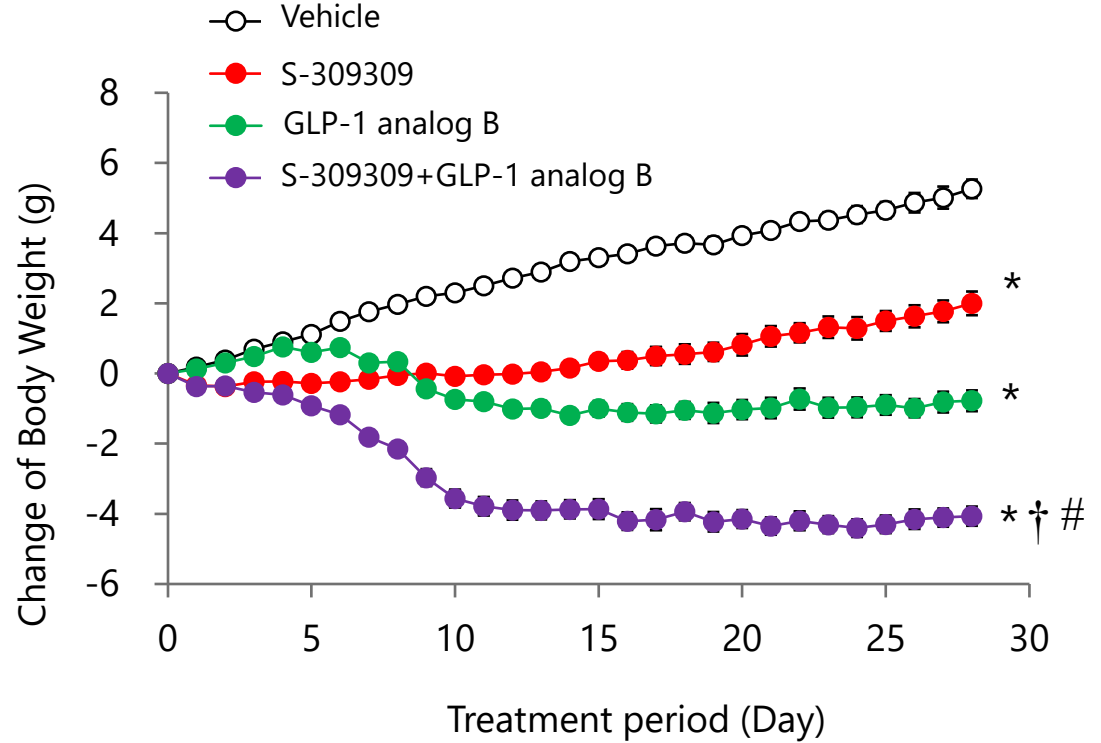
- Monoacylglyceroltransferase 2 (MGAT2<sup>\*5</sup>) inhibitor



# S-309309: Combination effect with GLP-1 analog



n=8-9, mean ± SE, \*P < 0.05 vs. Vehicle,  
 †P < 0.05 vs. S-309309, #P < 0.05 vs. GLP-1 analog A, Bonferroni



n=10, mean ± SE, \*P < 0.05 vs. vehicle,  
 †P < 0.05 vs. S-309309, #P < 0.05 vs. GLP-1 analog B, Bonferroni

**S-309309 showed a combination effect on weight reduction with GLP-1 analogs**

# S-309309: Phase1 SAD/MAD trial status

## Part 1 Single dose trial

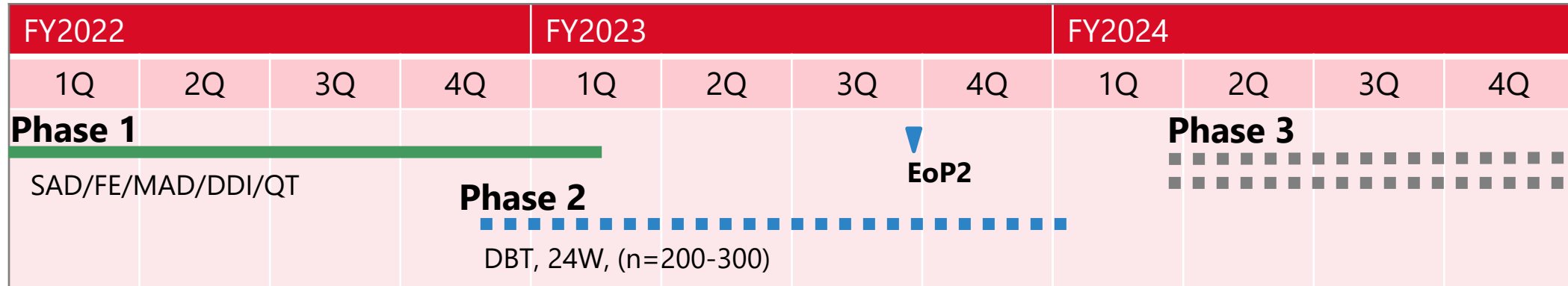
- AUC increased in dose-proportional manner between 1 – 300 mg.
- There are no significant food effect on the PK

## Part 2 Repeated dose trial

- Ongoing

<b>Country</b>	U.S.
<b>Trial design</b>	Phase 1 (single/multiple), single-center, randomized, double-blind, placebo-controlled trial <ul style="list-style-type: none"><li>• Part 1: Single dose (1-300 mg/person): Healthy adults</li><li>• Part 2: Multiple doses (50, 100 mg/person, 14 days): Healthy adults and obese but otherwise healthy adults</li></ul>
<b>Evaluation content</b>	<ul style="list-style-type: none"><li>• Safety and tolerability with single and multiple doses</li><li>• PK after single and multiple doses</li><li>• Food effect, QT analysis, Drug-drug interaction (midazolam)</li></ul>
<b>Trial period</b>	January 2022 (FPI) to October 2022 (LPO)

# S-309309: Upcoming schedule



Trial period: Start of patient enroll to completion of clinical trial report

## Phase 2 trial design (draft)

- **Primary objective**
  - Examination of weight loss effect of S-309309
- **Trial design**
  - Multicenter, randomized, placebo-controlled, double-blind
- **Primary endpoint**
  - The percent change from baseline in body weight at Week 24

- **Key inclusion criteria**

- Adults with BMI = 30 or greater
  - Adults with BMI to 27 or greater with the presence of dyslipidemia or hypertension
- (excluding patients with diabetes, secondary obesity, and obesity drug treatment)

# S-531011: Profile



## Indication Disease

- Solid tumors



## Product Properties

- A humanized anti-human CCR8\* monoclonal antibody
- Strong anti-tumor effect with no major safety concerns
  - CCR8 is expressed in tumor-infiltrating regulatory T cells (Treg) in a wide variety of cancer types regardless of staging.



## Unmet Needs

- High unmet medical needs for advanced cancer patients who have no approved ICI\*\* therapy or limited efficacy of ICI



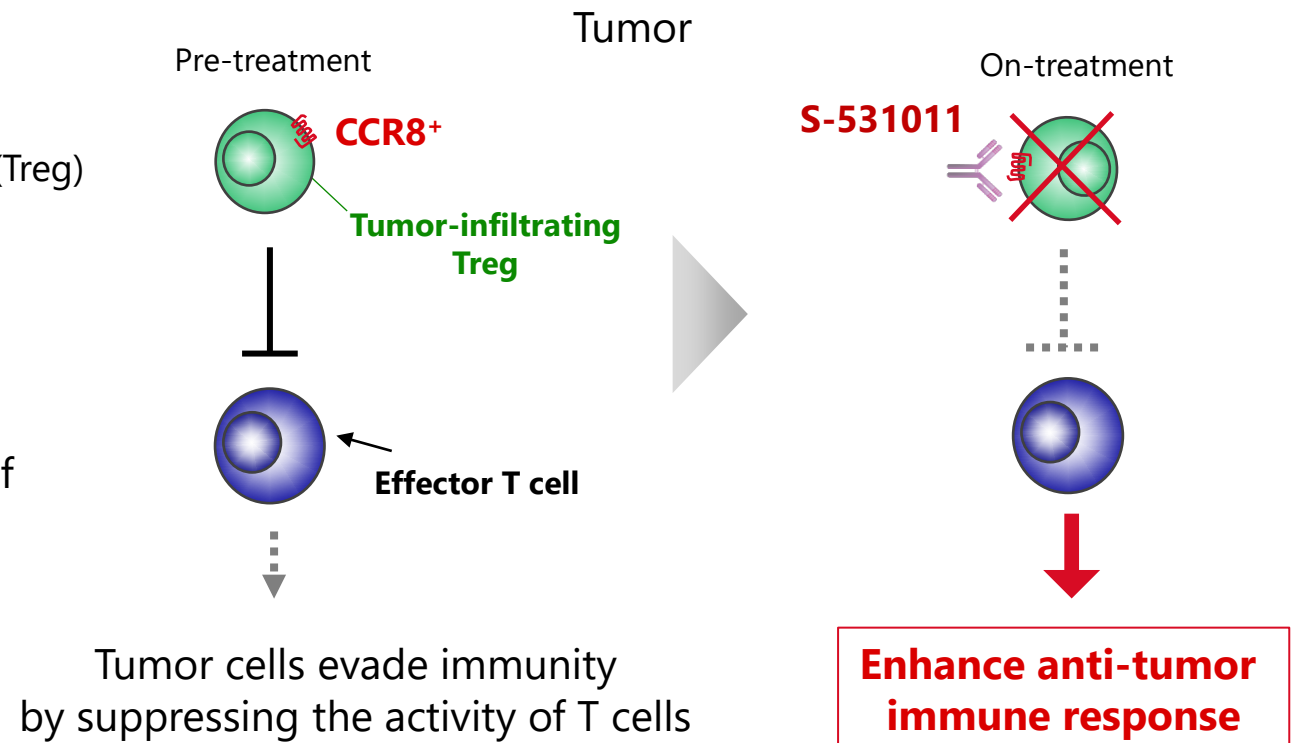
## Current status and future plan

- Phase 1b/2 trial is ongoing for 12 solid tumors



## Mechanism of Action

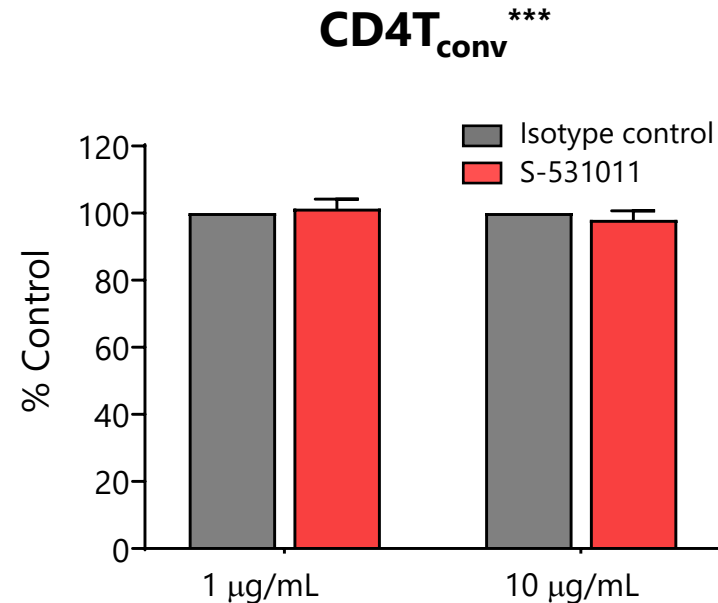
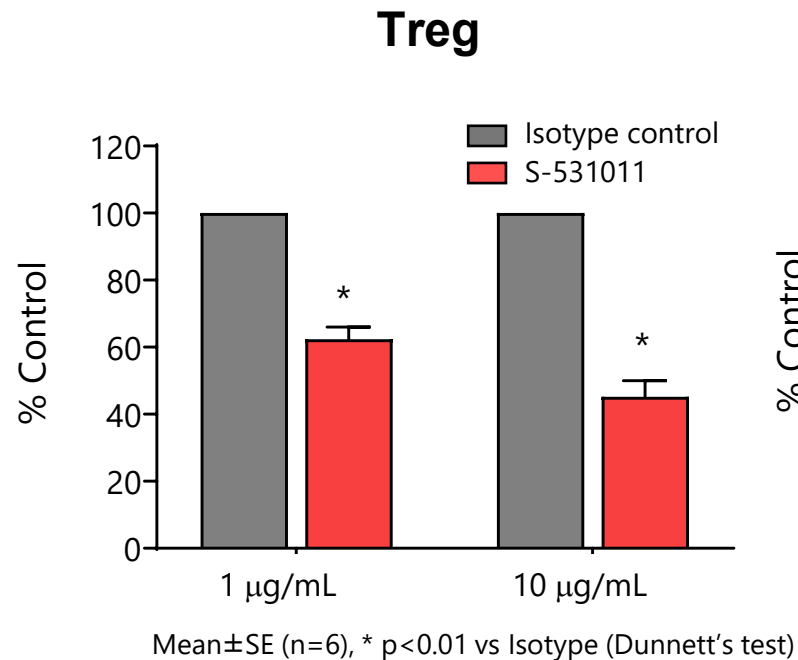
- Selective depletion of tumor-infiltrating Tregs by S-531011 is anticipated to restore antitumor immunity without inducing autoimmunity.



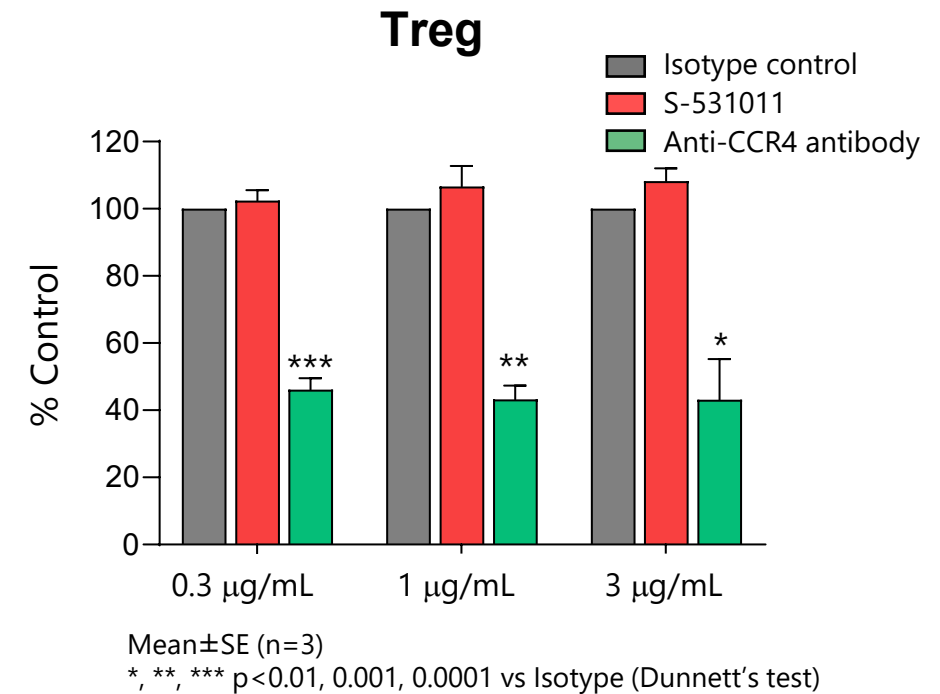


# S-531011: Antibody-dependent cellular cytotoxicity activity using human samples

## Tumor-infiltrating lymphocytes from lung cancer patients\*



## human PBMCs\*\*



**S-531011 is anticipated to selectively deplete tumor-infiltrating Tregs but not other effector T cells or peripheral Tregs**

# S-531011: Development plan and positioning

The purpose of the Phase 1b/2 trial is to evaluate the safety, tolerability and efficacy of S-531011 monotherapy and in combination with an anti-PD-1 antibody

## Monotherapy

Evaluate the safety and antitumor activity as monotherapy targeted on patients that have limited therapeutic option

## Combination with ICI

Evaluate the safety and antitumor activity in combination with an anti PD-1 antibody expecting the possibility of using S-531011 with current standard therapies

**S-531011 could be a promising new antitumor drug candidate for patients who are refractory or insufficiently treated with ICIs, either monotherapy or in combination with ICIs.**

# S-531011: Phase 1b/2 trial progress and upcoming schedule

## Safety

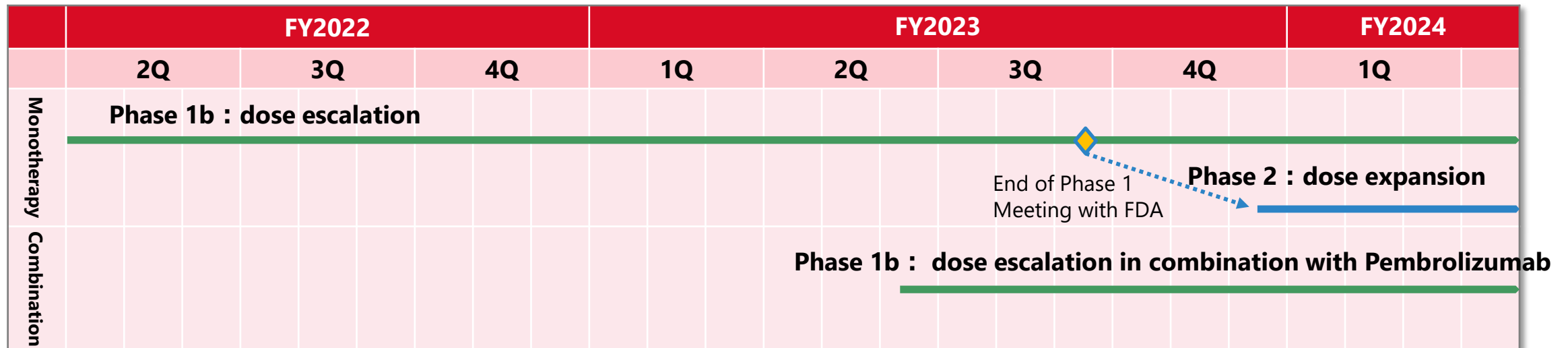
- No Dose Limiting Toxicity (DLT) occurred to date

## Pharmacokinetics

- Drug concentration and other parameters are confirmed and similar to prediction by animal scale up

## Pharmacodynamics and proof of mechanism

- Change in the proportion of tumor-infiltrating CCR8-positive Tregs using pre- and post-treatment biopsy samples; ongoing



# S-770108: Profile



## Indication

- Idiopathic Pulmonary Fibrosis (IPF)
- PF-ILD\* also under consideration



## Characteristics

- Dry-powder, inhaled formulation of Pirfenidone
- Greatly reduced dose, and systemic exposure compared to oral pirfenidone, reducing side effects (photosensitivity, gastrointestinal symptoms)



## Market

- Prevalence : 89,000 (US, JP, EU5 no. of diagnosed patients)
- Market Size : \$ 4.2 B (JP, US, EU5, 2021)



## Unmet Needs

- Existing treatments only slow down speed of lung function decline
- Combination therapy leading to improved treatment effect predicted to be the next phase in treatment of IPF



## Project Status and future plans

- Phase 1 Lung deposition trial - Complete (UK)
- Phase 1b IPF patient trial - Complete (JP)
- Phase 2 trial – Under preparation (Global)



## Mechanism of Action

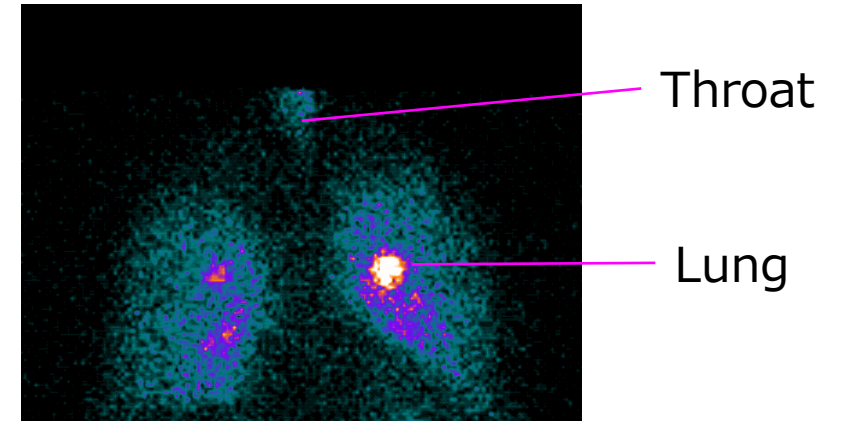
- Anti-fibrotic

# S-770108: Formulation development concept

## Formulation

- Capsule-based dry-powder formulation
- Convenient to use
- Particle size suited to delivery to lung periphery
- Confirmed transferability to the lungs in lung deposition trial

## Lung Deposition

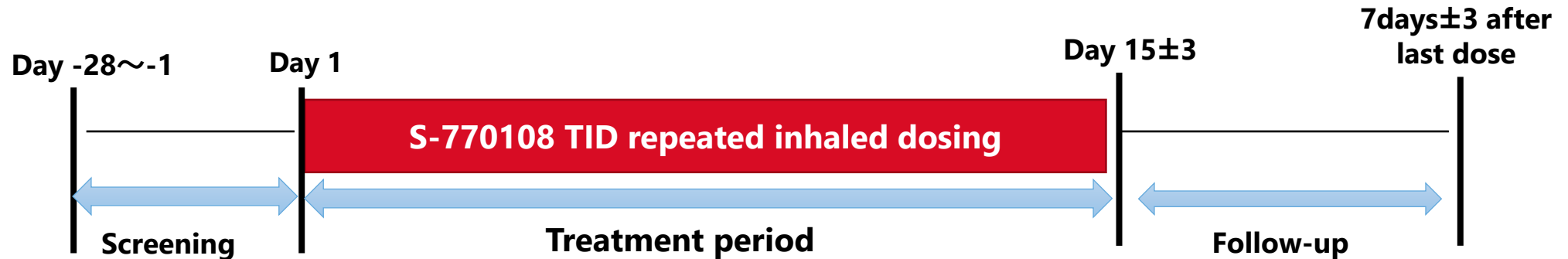


- By dosing pirfenidone directly to the lungs by inhalation, systemic exposure is greatly reduced (1%-2% of that seen with oral pirfenidone)
- Large reduction of oral pirfenidone associated side effects (photosensitivity, gastrointestinal symptoms) . Drug efficacy expected with sufficient lung concentration and good adherence
- IPF treatment is expected to move from mono- to combination-therapy in the near future, and as such inhaled pirfenidone is expected to have a good efficacy and safety profile, enabling use as both monotherapy, and in combined therapy with other approved agents.

# S-770108: IPF patient Japan Phase1b trial results

## Trial Design

25 IPF patients treated with S-770108 TID for 2 weeks (Feb-Jun 2022)



## Trial Results

- A cough was reported directly following dosing, but was transient and mild in all cases.
- 1 participants discontinued treatment due to an adverse event, but was deemed related to a concomitant medication, not to S-770108
- All participants achieved the target flow rate of 30\* L/min using the inhaler device

\* Based on in vitro, and clinical lung deposition trial data, flow rates of 30 L/min and above, were deemed to be sufficient to ensure adequate lung deposition of pirfenidone for efficacy

**All IPF patients in the trial achieved the target flow rates, and tolerability of S-770108 was confirmed. A Phase 2 trial is under preparation**

# Agenda

## 1. Shionogi's R&D

- Opening
- Progress of COVID-19-related R&D
- Progress of Shionogi R&D
  - ✓ Development area
  - ✓ Research area
  - ✓ Vaccine Business
  - ✓ Summary of R&D

## 2. Summary

## 3. Q&A

### **John Keller, Ph.D.,**

Senior Vice President, R&D Supervisory Unit

### **Takeki Uehara, Ph.D.,**

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### **Isao Teshirogi, Ph.D.,**

Chief Executive Officer

# Research area progress



**Yasuyoshi Iso, Ph.D.,**  
Senior Vice President, Research Division



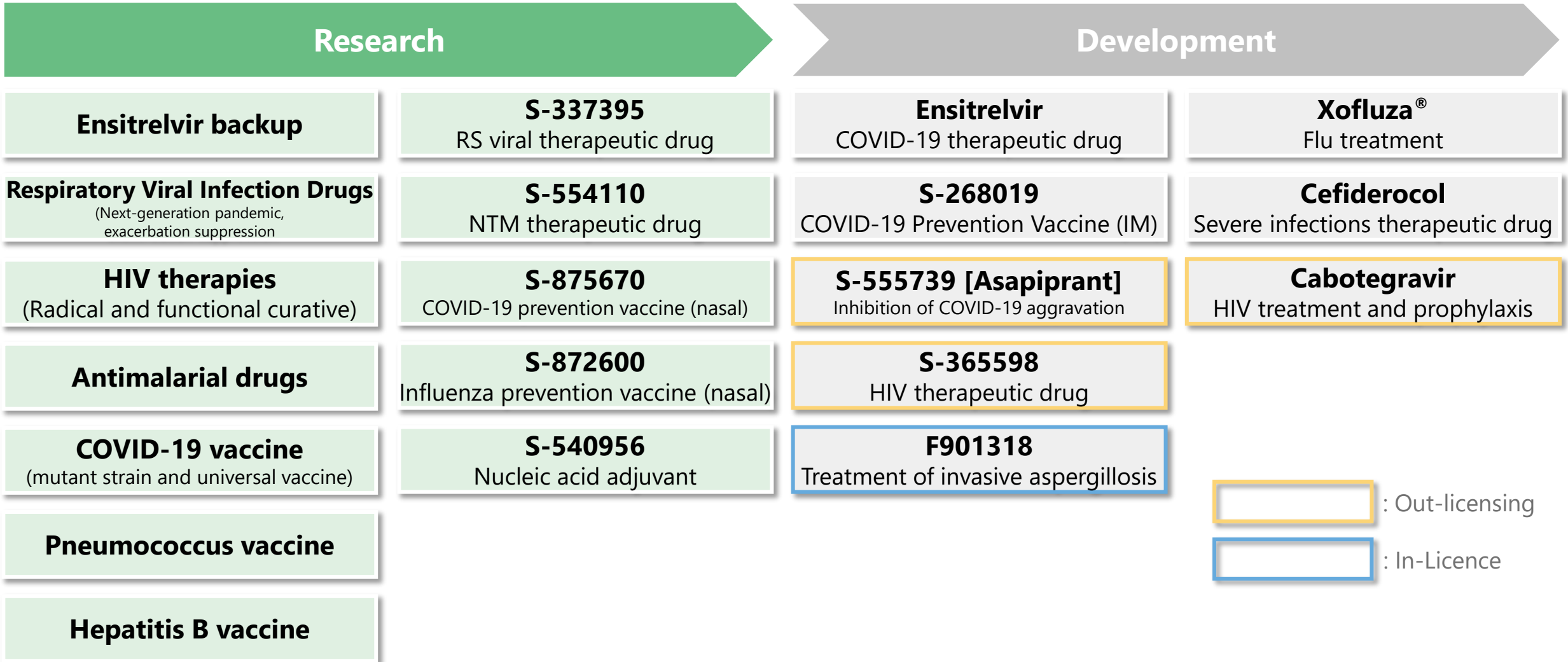
# Research part

Disease areas	Projects to be introduced today	Target disease	Posted page
Infection	<b>COVID-19 therapeutic drugs</b>	COVID-19	P.84-88
	<b>HIV Franchise (S-365598)</b>	HIV infections	P.89
	<b>S-337395</b>	RSV infections	P.90-93
Psychiatry/Nervous/Pain	<b>Pain Medicine (S-151128)</b>	Chronic pain	P.94-96

# Actions in the area of infectious diseases

Research Areas	Research Strategy	Target Diseases	
1. Acute Infection	<ul style="list-style-type: none"> <li>Building upon our know-how in infectious disease drug discovery, we continue to expand our pipeline for respiratory viral infections to address current medical needs and prepare for the next pandemic</li> </ul>	<ul style="list-style-type: none"> <li><b>COVID-19 medicine</b></li> <li><b>RS Viral infections</b></li> <li>Next pandemic</li> <li>Exacerbation suppression</li> </ul>	Research Department P.84-93
2. Chronic Infections	<ul style="list-style-type: none"> <li>Continuous creation of new anti-HIV drugs and pursuing HIV curative research by utilizing our infectious disease drug discovery know-how</li> <li>Advancing research in chronic infectious diseases (e.g., nontuberculous mycobacteria (NTM) and malaria)</li> </ul>	<ul style="list-style-type: none"> <li><b>HIV therapies</b> (combination candidates for S-365598)</li> <li><b>HIV curing</b></li> <li>Therapeutic drugs for NTM</li> <li>Antimalarial drugs</li> </ul>	
3. Infectious Disease Vaccine	<ul style="list-style-type: none"> <li>Progressing vaccine research based on our own infectious disease and immunology knowledge coupled with external collaboration</li> <li>Building vaccine platforms based on S-268019 R&amp;D experience</li> </ul>	<ul style="list-style-type: none"> <li><b>COVID-19</b></li> <li>Influenza</li> <li>S. pneumoniae</li> <li>Hepatitis B</li> </ul>	Biopharmaceuticals Research Department P.100-108

# Pipeline in infectious disease



## 1. Acute infection

# COVID-19 therapeutic drugs: Actions overview

Small molecule	Initial candidate compound	Fastest provision of COVID-19 specific therapeutic drug ⇒ Discontinued
	Ensitrelvir	Applicable to a wide range of patients therapeutically and prophylactically
	Ensitrelvir backup	Creation of oral therapeutic drugs that meet future needs
Peptide	S-880008	Broad-spectrum therapeutic drug with a more potent effect by using inhaled formulations, with one day dosing ⇒ Discontinued

# 1. Acute infection

## COVID-19 therapeutic drugs: Drug discovery targets for SARS-CoV-2

### Virus entry inhibitor

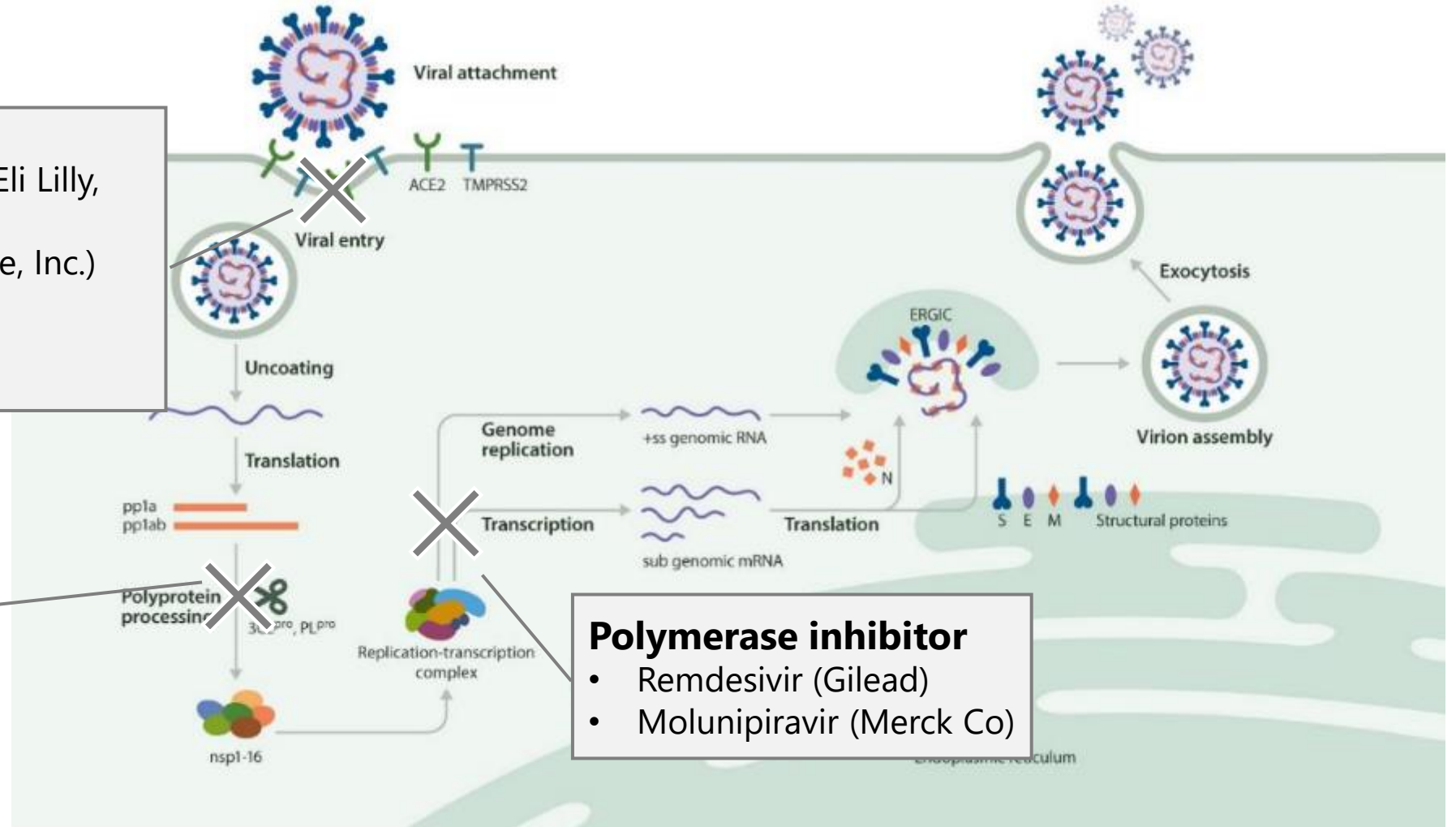
- Bamlanivimab/Etesevimab (Eli Lilly, Inc.)
- Sotrovimab (Glaxo SmithKline, Inc.)
- Tixagevimab/Cilgavimab (AstraZeneca)
- **S-880008**

### Protease Inhibitors

- Nirmatrelvir (Pfizer)
- **Ensitrelvir**

### Polymerase inhibitor

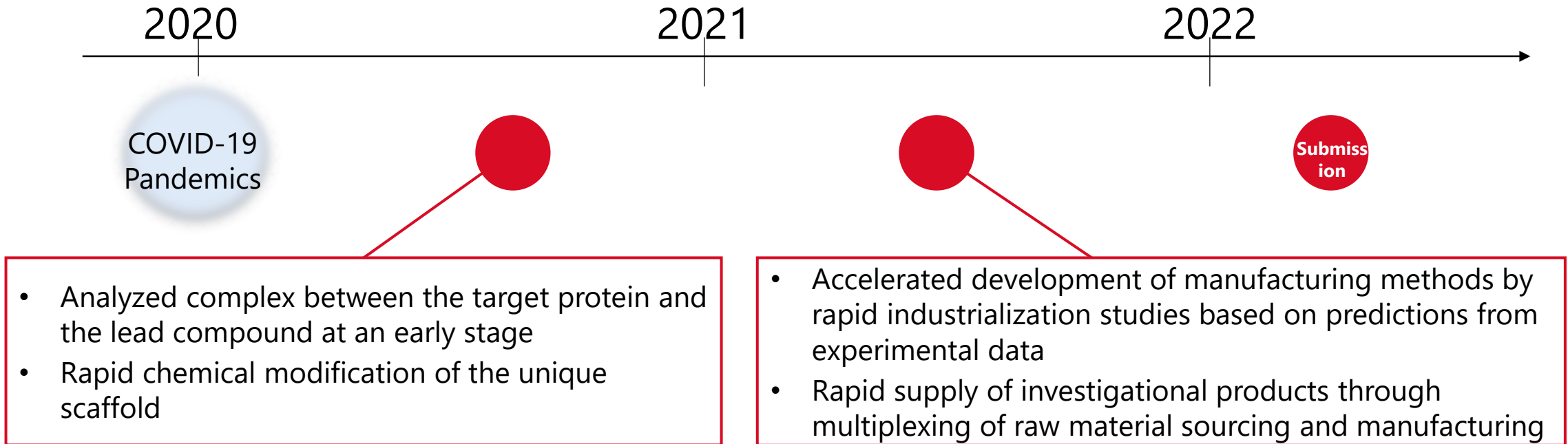
- Remdesivir (Gilead)
- Molunipiravir (Merck Co)



## 1. Acute infection

# COVID-19 therapeutic drugs: Factors for early identification of ensitrelvir

Discovered development candidates, including Ensitrelvir, in approximately 9 months from the start of the project (SAR\* initiated 4 months from the start of consideration)



**Building on our infectious disease drug discovery experience,  
upon selecting a SARS-CoV-2 specific compound, we entered clinical development  
at remarkable speed**

## 1. Acute infection

# COVID-19 therapeutic drugs: S-880008 (peptide)

### **Concept**

More effective therapeutic drugs delivered directly to target organs  
(upper and lower respiratory tracts, and lung)

**Inhalation formulation**



**Novel mechanism expected to have high potency and broad spectrum**

**Discovered Non RBD\* binding peptide S-880008 (SARS-CoV-2 incursion inhibitors)  
in a short period of time utilizing our peptide-drug discovery capabilities**

# 1. Acute infection

## S-880008: Reasons for discontinuing development

Although we were able to confirm potent in vivo efficacy, including against BA.1 strain, however, activity against a BA.2 strain with multiple amino acid mutations is reduced

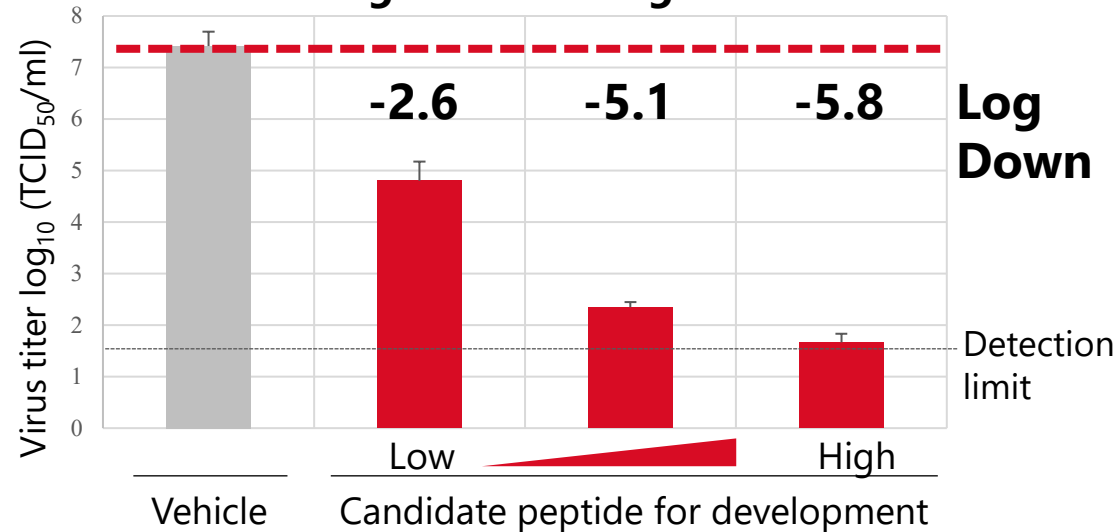
**Discontinued preclinical development because broad coverage cannot be assured for newly emerging variants**

### In vitro efficacy

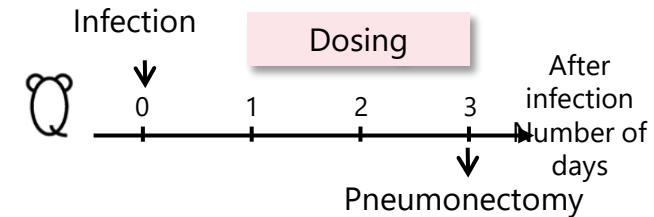
Viral strains	EC <sub>50</sub> (nM)
Conventional strains	4.2
Alpha strain	8.5
Beta strain	2.2
Gamma strain	6.4
Delta strain	7.8
Omicron BA.1 shares	6.4

### In vivo potency

#### Assessment using a mouse lung infection model\*



### Study design



Treatment condition: Treatment started 24 hours after infection  
Route of administration: Nasal administration



## 2. Chronic infections

# Actions in HIV research towards 2030 and beyond

## ViiV's medium-to long-term strategy and SHIONOGI actions



- ~2024
- **Partner selection for ULA**
    - Several novel mechanisms of action are under investigation

Around 2027

- **Provide ULA (once every three months or more)**
- **Provide a first administered LA regimen**
  - Cabotegravir + novel MOAs

2030 and beyond

- **Provide ULA (once every six months or more)**
- **Potential HIV cure**
  - S-365598 + novel MOAs
    - ✓ CY 2022: FTIH for S-365598



Focus on research into combination candidates for the creation of ultra long-lasting drugs

**S-365598**



**combination candidates**

Towards the creation of more convenient therapies and future "functional cures," multiple approaches under consideration

## 1. Acute infection

# S-337395: What is respiratory syncytial virus infection?

## **Disease overview**

---

- A respiratory viral infection with an infection rate of 100%\* by age 2
- RSV infection can cause severe symptoms, mainly inflammation of the lower respiratory tract, especially in the first few weeks to months of life\*
- It induces cold-like upper respiratory tract inflammation, and when it leads to lower respiratory tract inflammation, it causes severe bronchiolitis, pneumonia, recurrent wheezing, etc.



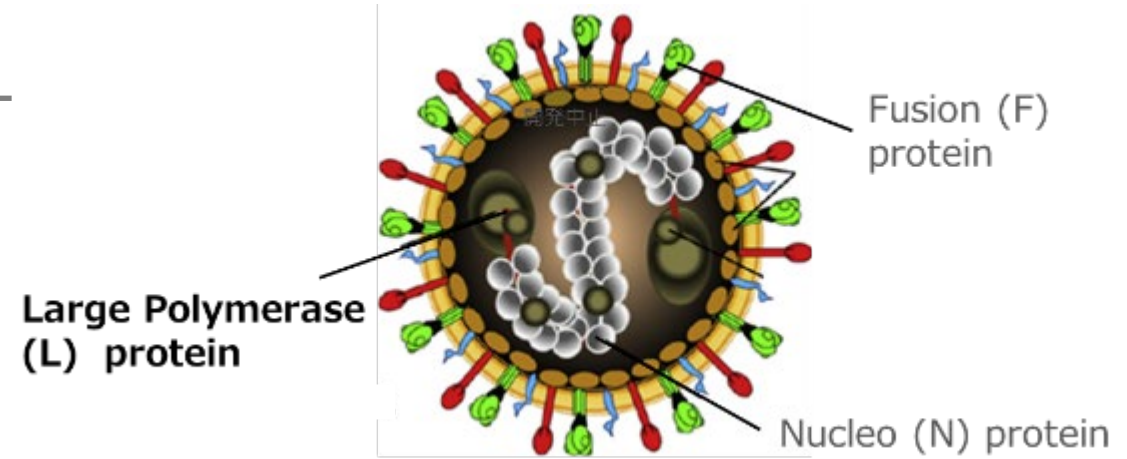
There is no effective antiviral drug against RSV,  
and RSV infection is one of the diseases with extremely high unmet medical needs

# 1. Acute infection

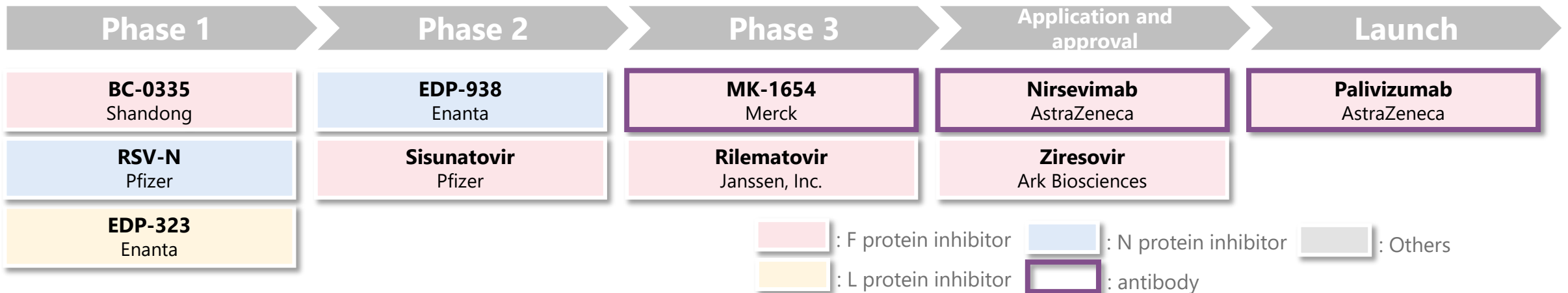
## S-337395: Concept and developmental status of competitors

### Concept and major development competitors\*

- F protein inhibitor antibodies on the surface of virus was launched only
- There are multiple developments centered on F protein targets
- By targeting the inhibition of the L protein, which is essential for viral propagation, wide-spectrum and potent antiviral effect on A and B types is expected



Microbes and Infection Volume 15, Issue 3, March 2013, Pages 230-242

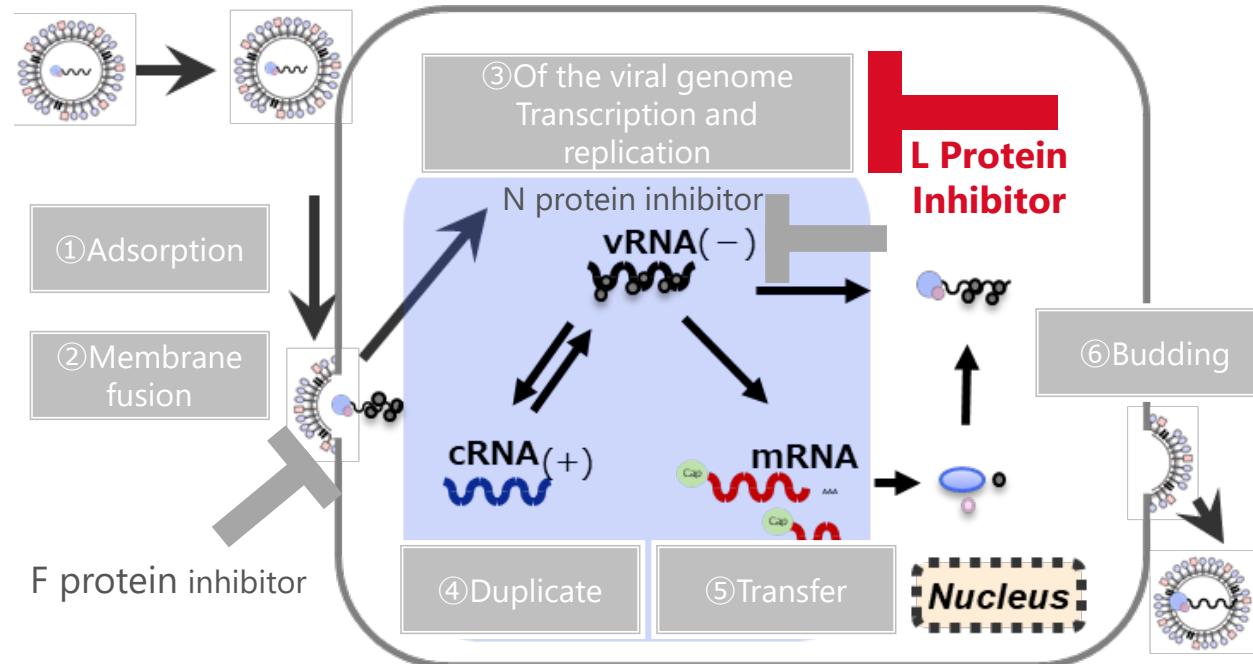


# 1. Acute infection

## S-337395: Compound summary

### RS viral replication processes and mechanisms of action

Synthesis of mRNA by RdRp\* activity of L protein, the first step essential for RS virus replication, is suppressed by inhibiting the function of L protein



# 1. Acute infection

## S-337395: Non-clinical data

### In vitro activity\*

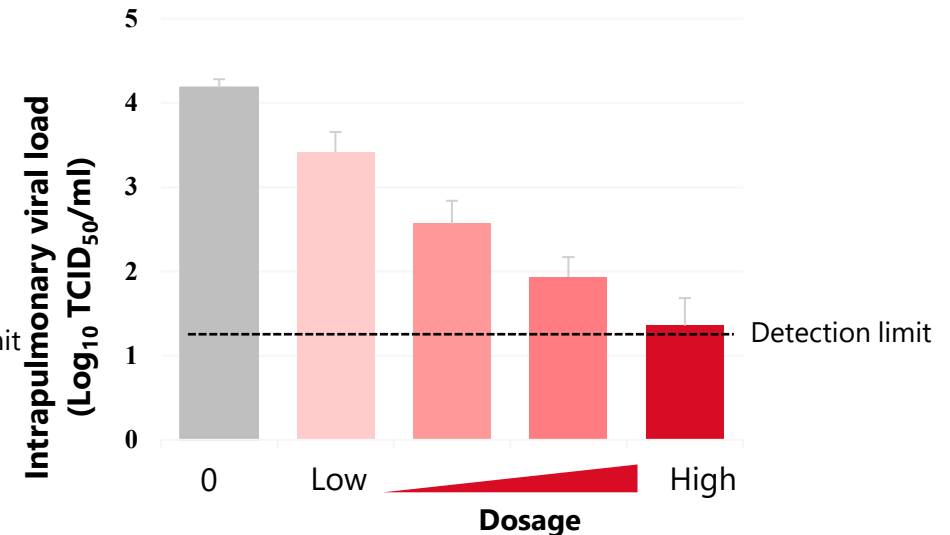
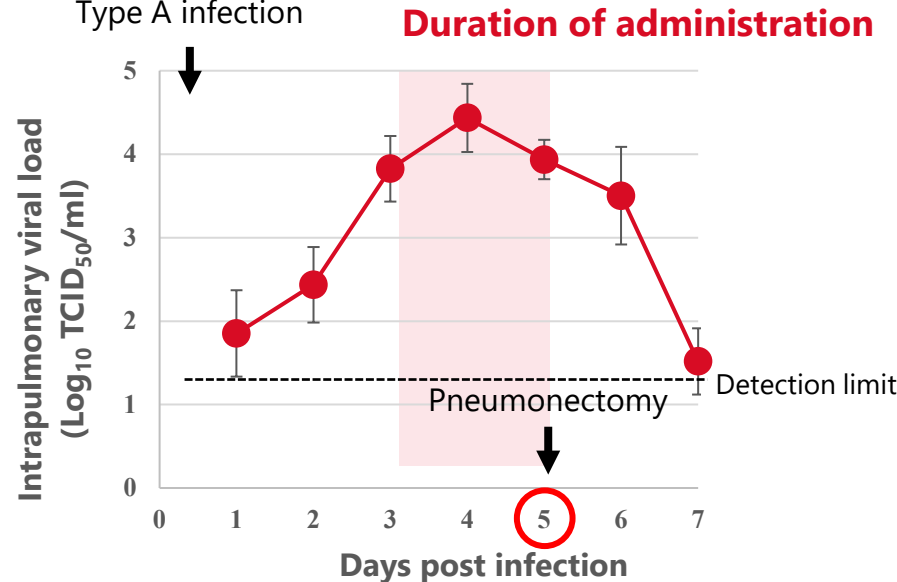
- For types A and B, strong antiviral activity was confirmed

Antiviral activity (EC <sub>50</sub> ; nM)	
A type	B type
0.35	0.76

### In vivo drug efficacy\* (murine)

- Viral growth is suppressed even when administered at a therapeutic timing around the peak of viral growth  
⇒ **Strong efficacy according to the dose was confirmed under conditions close to actual clinical conditions.**

Respiratory syncytial virus Type A infection



\* Exploratory studies that have not yet performed QA(QC completed)

QA: Quality Assurance

QC: Quality Control

# S-151128: Unmet needs and current status of pain treatments

## **Unmet need for pain medicines**

---

- Powerful analgesic effect in any kind of pain without side effects, dependence, or tolerance

## **Current status of pain treatment**

---

- In terms of analgesic effect, opioid drugs are considered to be the strongest, but abuse and dependence problems due to improper use have emerged in the U.S.\*
- Although the prescription volume of opioid therapeutics is greatly reduced, unnecessary suffering due to excessive prescription limitation/dose reduction (pain control poor\*<sup>2</sup>, increased rate of suicide and illicit drug use\*<sup>3</sup>) is a challenge
- Treatment satisfaction with existing non-opioid medications is low



Novel analgesics are required that resolve patients' pain without addiction risk

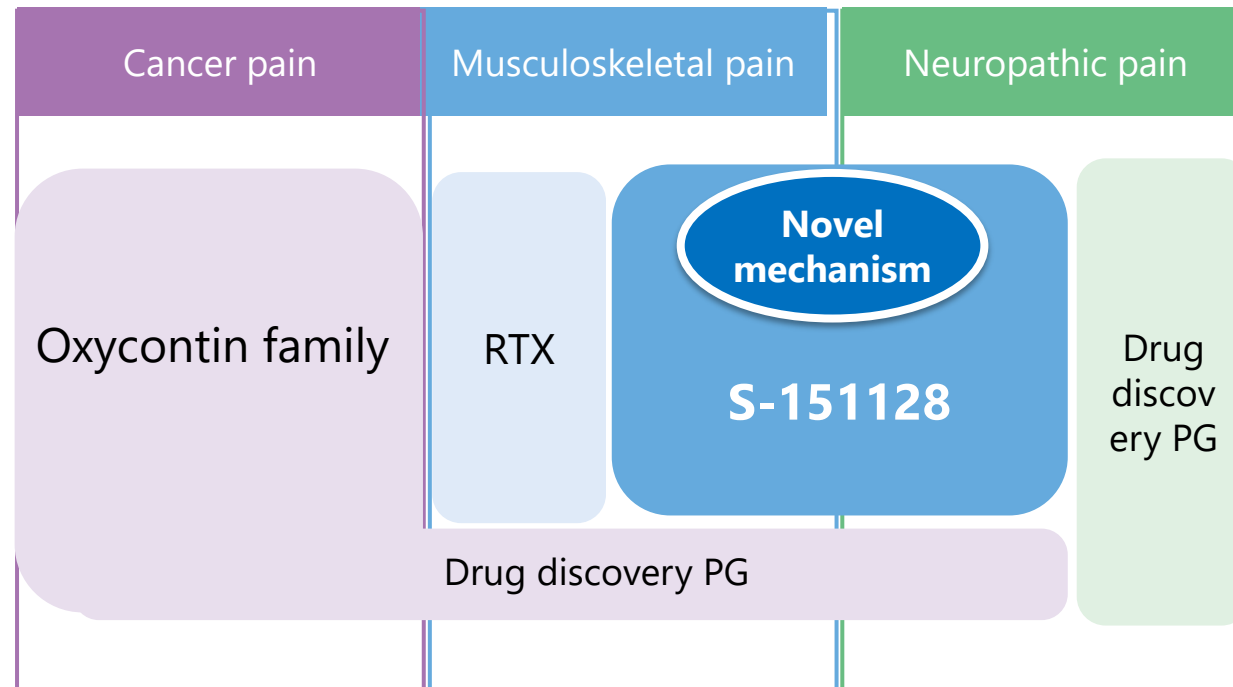
\* Centers for Disease Control and Preventio \*<sup>2</sup> Pain Med (2019) 1;20(4):724-735

\*<sup>3</sup> Health Professionals Call on the CDC to Address Misapplication of its Guideline on Opioids for Chronic Pain through Public Clarification and Impact Evaluation, <http://healthprofessionalsforpatientsinpain.org/the-letter-1>

# S-151128: Actions in the pain area

## SHIONOGI strategy for pain treatment

Provides treatment options from a pipeline of diverse mechanisms, freeing patients from the burden of pain

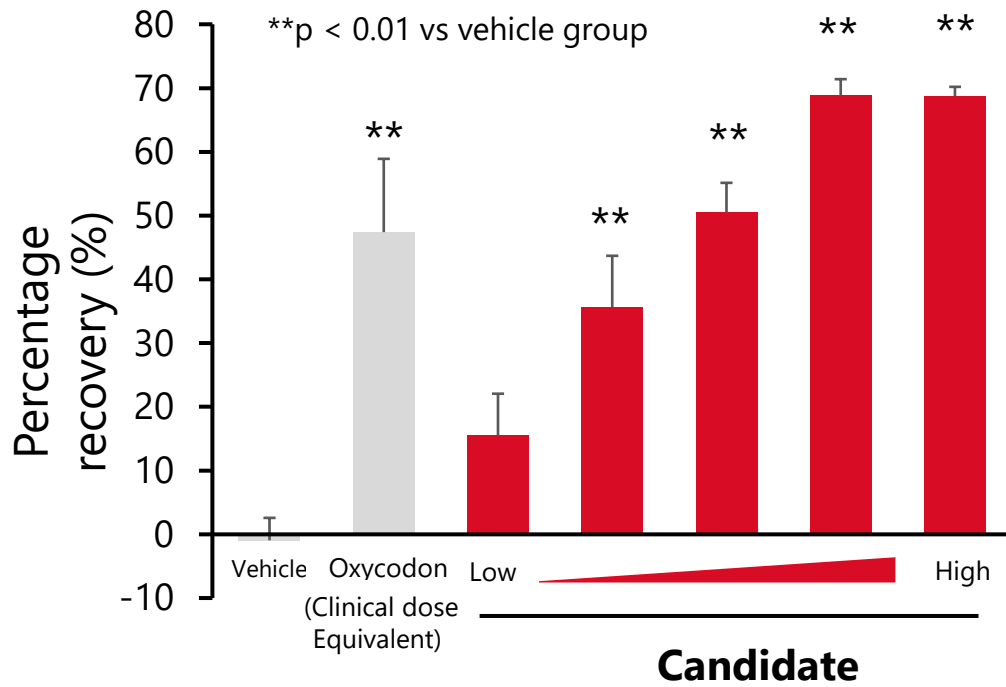


RTX: Resiniferatoxin

# S-151128: Analgesic with a novel mechanism

## In vivo potency (rat)

### Analgesic effects in a model of chronic pain



## Characteristics of S-151128

- Mechanisms of action that are yet to be marketed, such as ion-channels, GPCR<sup>\*2</sup>, and PPI<sup>\*3</sup>, which are highly challenging to discover
- High selectivity to other subtypes is more than 1000-fold
- High analgesic efficacy in multiple pain models

**S-151128 is expected to have an analgesic effect equal to or better than that of opioids without the damaging side effects**



# Timeline until the start of Phase 1 trial

Project	Target disease	FY2022	FY2023	FY2024	FY2025	FY2026
<b>S-337395</b>	RS Viral infections		★ (1Q)			
<b>HIV curing</b>	HIV infection				★ (4Q)	
<b>HIV therapies</b> (combination candidates for S-365598)	HIV infection					★ (4Q)
<b>S-151128</b>	Pain		★ (1Q)			

★ Scheduled start of Phase 1 trial

# Agenda

## 1. Shionogi's R&D

- Opening
- Progress of COVID-19-related R&D
- Progress of Shionogi R&D
  - ✓ Development area
  - ✓ Research area
  - ✓ Vaccine Business
  - ✓ Summary of R&D

## 2. Summary

## 3. Q&A

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**Yasunori Aoyama, Ph.D.,**

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**John Keller, Ph.D.,**

**Isao Teshirogi, Ph.D.,**

Chief Executive Officer

# Progress of vaccine business



**Yasunori Aoyama, Ph.D.,**  
Senior Vice President, Biopharmaceutical Research  
Division

# What is a vaccine?

**Formulations that induce an immune response and prevent the onset or reduce the severity of infections**

## **Recombinant protein vaccine**

**S-268019**

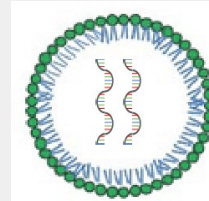


**Composed of antigen protein + adjuvant**

**Technology already in widespread vaccine use**

- Pathogen virus is not used
- Protein of interest only is manufactured as antigen for vaccine and administered to humans

## **mRNA vaccine**



**Composed of mRNA + lipid-molecules**

**First administered for COVID-19**

- Delivery of mRNA, a protein blueprint, to cells
- Antigenic proteins are produced in the human body after vaccination

# SHIONOGI's vaccine experience to date

**STEP 1: Entering the Vaccine-business  
(2017-2020)**

**STEP 2: Promote R&D of S-268019  
(2020-2022)**

## Building a vaccine research base

Research

- Started creation of influenza vaccine building on experience in drug discovery for the treatment of influenza

- By applying our drug discovery research capabilities in the areas of infectious diseases and immunity, created S-268019
- By merging in-house basic technology and external collaboration, ensure vaccines can respond to mutant strains

## Capital alliance with UMN Pharma

Manufacturing

- Acquisition of 'rhabdovirus-free' insect cell culture techniques
- Acquired manufacturing and research base

## Gaining expertise in vaccine production

- Process from antigenic search to GMP study drug substance manufacturing (UMN Akita Plant) completed
- Building knowledge and experience in manufacturing scale-up

# Newly acquired research ability through the creation of S-268019

Profile of S-268019	
<b>Antigen</b>	Recombinant antigen S-910823 of the full-length spike protein prepared in UMN Pharma's "rhabdovirus-free" insect cell culture
<b>Adjuvant</b>	Optimize response to A-910823 for increased neutralizing antibody titer



Acquired new capabilities and technologies through our efforts

## **Adjuvant selection**

- Rapid selection of the adjuvant
- Ability to change the adjuvant with flexibility

## **Neutralizing antibody titer assessment**

- Rapid response to the emergence of mutant viruses

## **Antigen production**

- Stable production and supply of investigational products

# Adjuvant studies essential for the creation of S-268019

## Previous adjuvant research

Accumulated knowledge of adjuvants including by S-540956 creation

## 1<sup>st</sup> adjuvant selection in S-268019

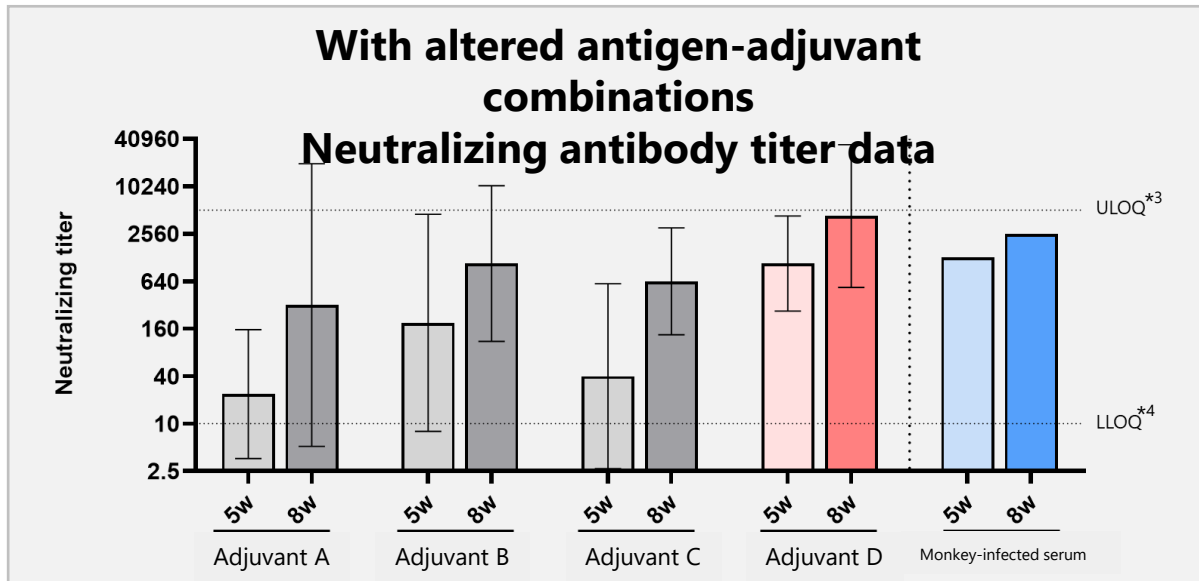
Selection of adjuvants based on VDE\*<sup>1</sup> risk and Th1\*<sup>2</sup> selectivity risk

## Clinical studies with 1<sup>st</sup> adjuvant 2<sup>nd</sup> adjuvant selection

Explored multiple combinations of antigens and adjuvants in parallel with Phase 1 trial

## Decided to change adjuvant

Higher neutralizing antibody titer induction



Approximately **4 months** from the decision to change adjuvant to the start of the second Phase 1 trial

**Appropriate adjuvant selection was achieved**

# Establishment of an evaluation system for the emergence of mutant viruses

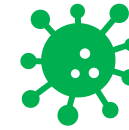
**Early detection of the virus**

- Continuous monitoring of the emergence of mutant viruses globally

Ancestor



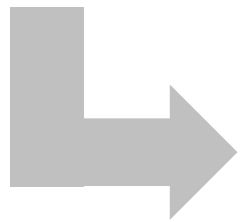
Delta



Omicron BA.1

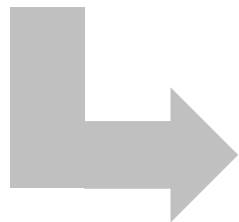


BA.2.12.1,  
BA.5,  
BA.2.75,  
BA.4.6...



**Construct a novel evaluation system**

- Production of Pseudovirus\* in SHIONOGI
- Providing live virus from the National Institute of Infectious Diseases
- Establishment of neutralizing antibody titer evaluation system for new mutant viruses



**Evaluate actual samples**

- Neutralization titers against mutant viruses in sera after S-268019 dose

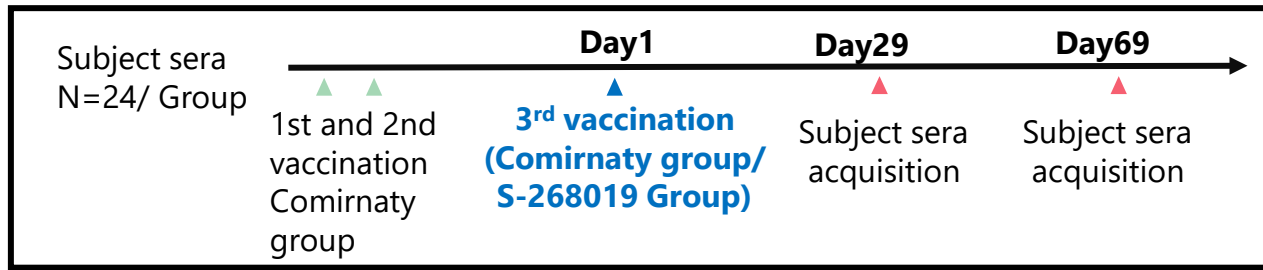
**Construct a seamless and rapidly assessable system for mutant viruses**



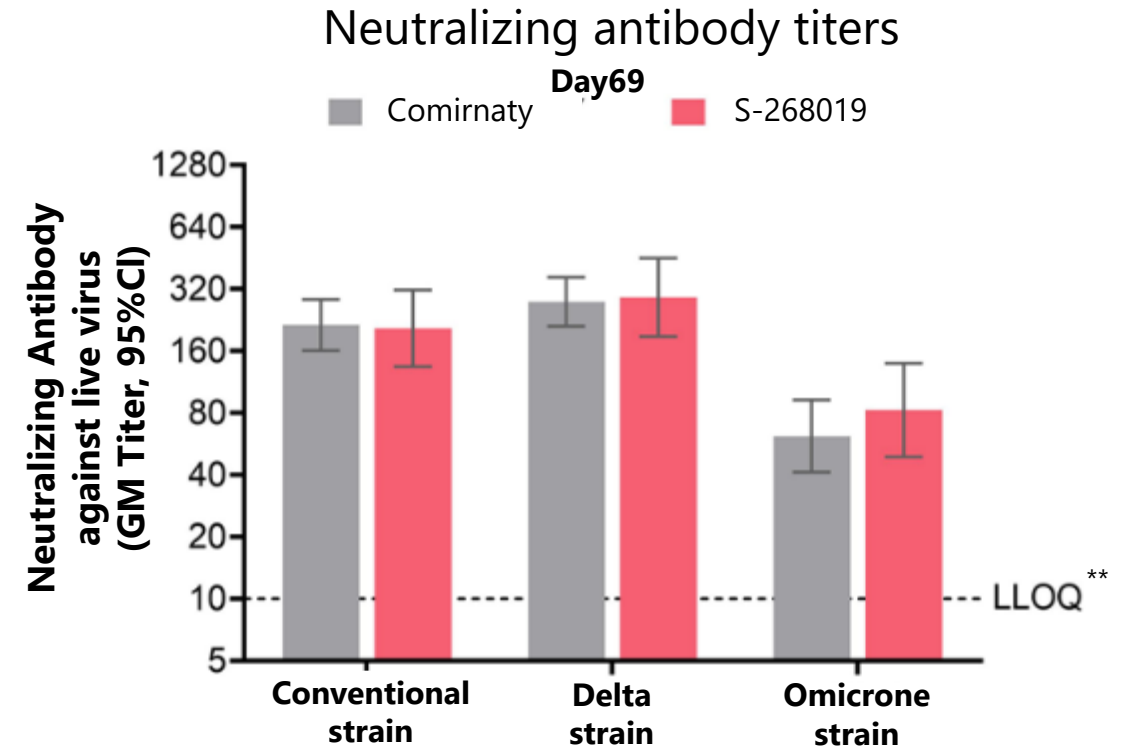
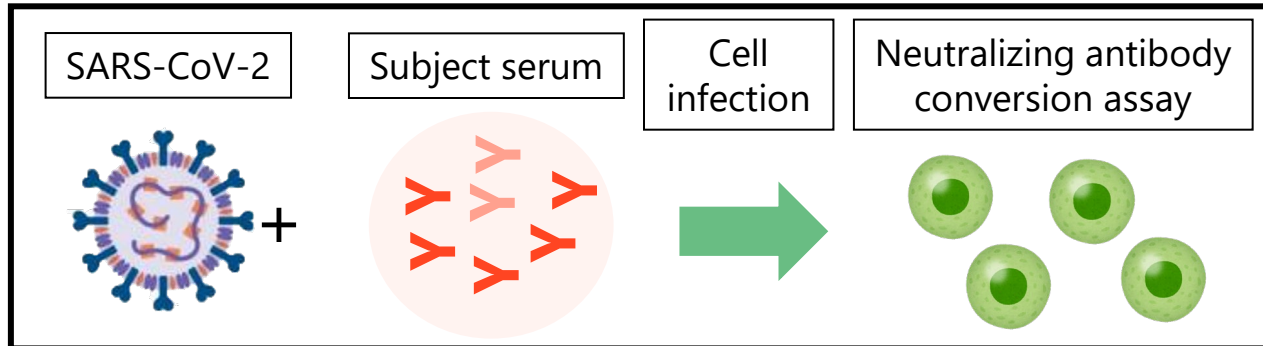
# Neutralization titers against S-268019 mutant viruses

Neutralization titers against mutant viruses were determined using subject serum from Phase 2/3 booster trial\*

## -A Phase 2/3 booster comparative trial-

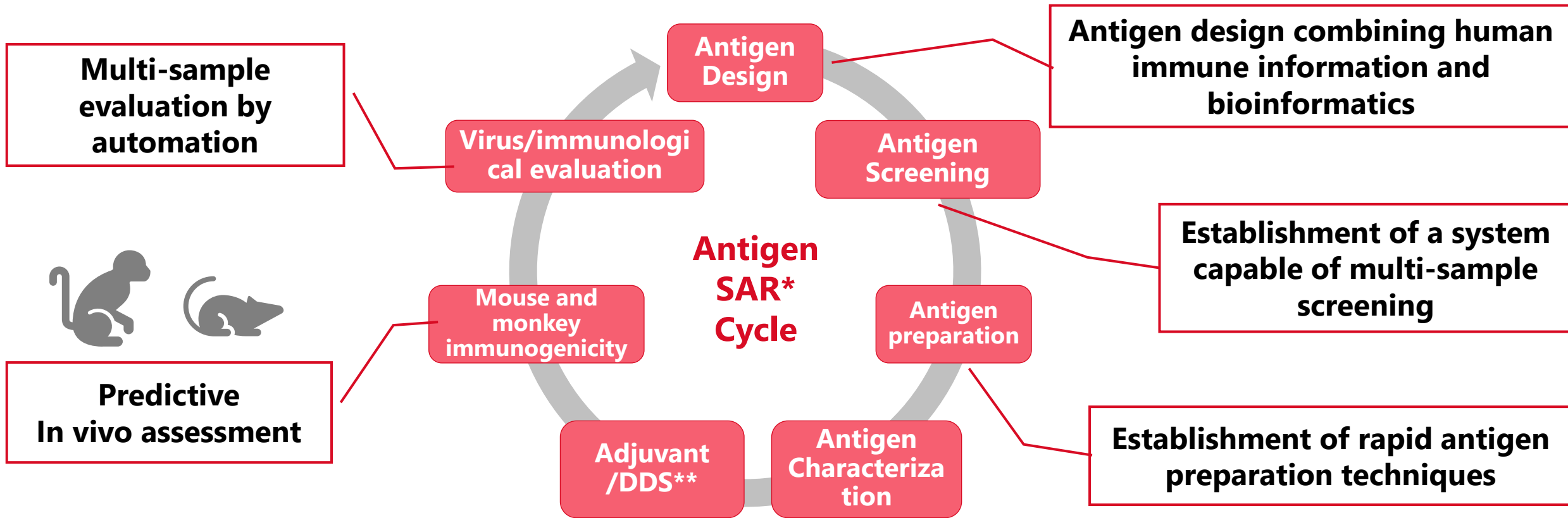


## -Neutralizing antibody titer test with serum-



**Booster administration of S-268019 suggests efficacy against mutant virus equivalent to that of Comirnaty administration**

# Construction of a novel antigen creation platform



**We set up a SAR cycle for vaccine-antigen generation  
Aim to establish a unique antigenic search platform for SHIONOGI**

# External cooperation

**Collaborating with world-leading research institutes and companies to build technical infrastructure and create new vaccines**



## Elucidation of human immune mechanisms

Analysis of vaccine mechanisms of action by immune profiling



## Construction of a mucosal immune platform

Practical application of a mucosal immunization-inducing vaccine in humans

Preparation of COVID-19<sup>\*2</sup> and pneumococcus vaccine-antigen<sup>\*3</sup> using cCHP<sup>\*1</sup>



## Universal antigen design<sup>\*4</sup>

The antigen is designed by back-calculating from immune factors induced in humans

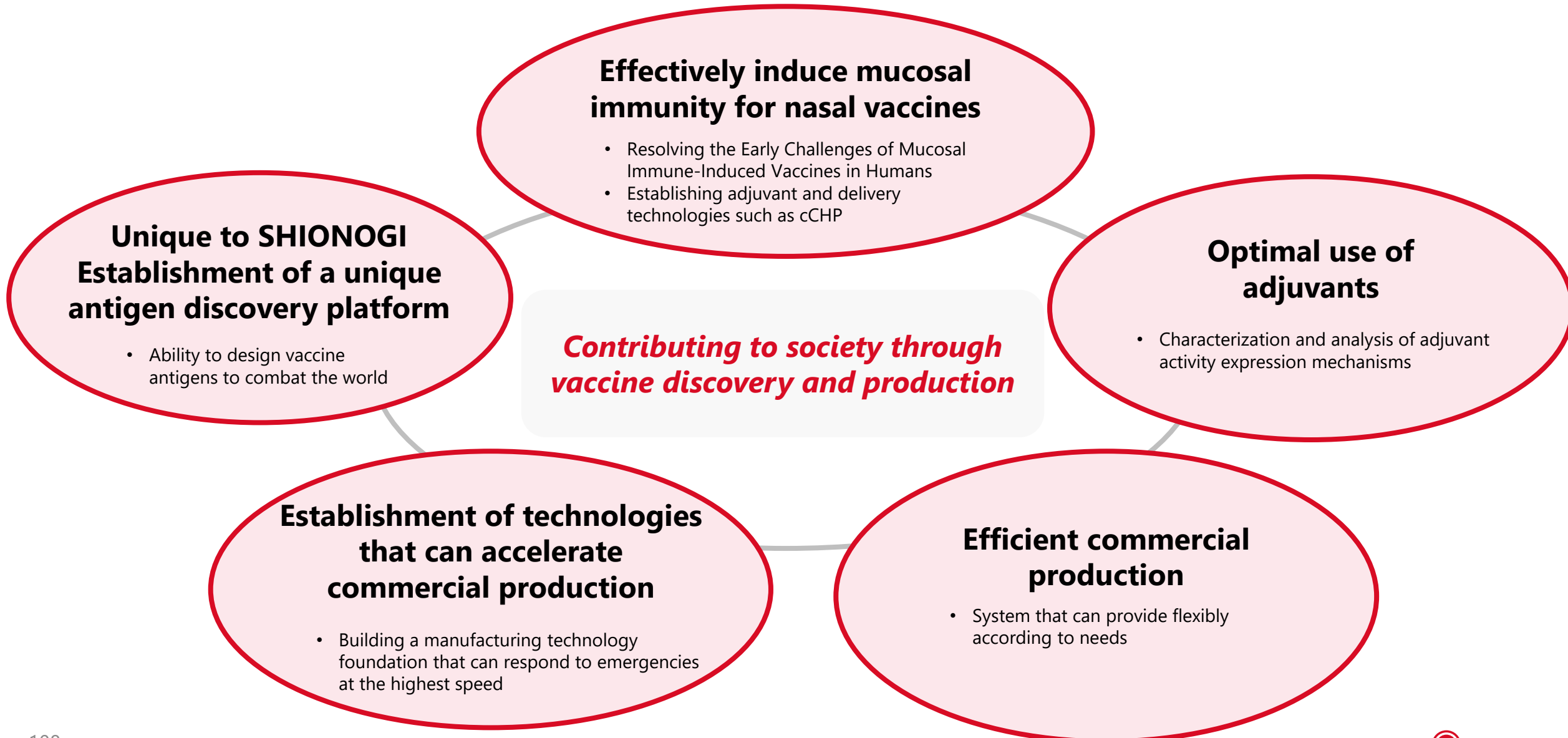


## Adjuvant studies

A platform to support optimal matching of adjuvants to antigens



# Aims of vaccine research



# Agenda

## 1. Shionogi's R&D

- Opening
- Progress of COVID-19-related R&D
- Progress of Shionogi R&D
  - ✓ Development area
  - ✓ Research area
  - ✓ Vaccine Business
  - ✓ Summary of R&D

## 2. Summary

## 3. Q&A

**John Keller, Ph.D.,**

Senior Vice President, R&D Supervisory Unit

**Takeki Uehara, Ph.D.,**

Senior Vice President, Drug Development and Regulatory Science Division

**Takeki Uehara, Ph.D.,**

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**John Keller, Ph.D.,**

**Isao Teshirogi, Ph.D.,**

Chief Executive Officer

# Summary of R&D



**John Keller, Ph.D.,**  
Senior Vice President, R&D Supervisory Unit

# Toward the achievement of the SHIONOGI Group Vision and sustainable growth

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**

---

## Results for STS Phase 1 (FY2020-FY2022Q2)

- Acquired the capability to deploy resources and expertise in an agile manner to support maximum focus, allowing us to develop Ensitrelvir and S-268019 at a remarkable speed ⇒ R&D transformation

## Toward the achievement of SHIONOGI Group Vision

- Utilize this new capability to advance growth drivers spanning the broader scope of the SHIONOGI Group Vision, while always meeting our commitment as an infectious disease company  
⇒ Growth from transformation

**Growing sustainably while bringing healthcare innovation to society**

# Upcoming pipeline events 1/2

As of Oct. 12, 2022 Not all plans are listed

Pipeline	Indication	Stage	FY2022 3Q-4Q	FY2023	FY2024
<b>olorofim (F901318)</b>	Invasive Aspergillosis	Phase 2b, Phase 3	★ Ph2b Interim report (3Q)		★ Ph3 Completion of case registration (4Q)
<b>S-337395</b>	RSV infection	Preclinical		● Ph1 start (1Q)	
<b>S-365598 (HIV franchise, out license)</b>	HIV infection	Preclinical	● Ph1 start (3Q)		
<b>resiniferatoxin</b>	Pain associated with knee osteoarthritis	Phase 3			★ Ph3 topline results (2Q) ◆ Submission (3Q)
<b>zatolmilast (BPN14770)</b>	①Fragile X Syndrome ②Alzheimer's disease	①Phase 2/3 ②Phase 2	①	★ Ph2b3 topline results (4Q)	
<b>zulanolone (S-812217)</b>	Depression	Phase 3		★ Ph3 topline results (3Q) ◆ Submission (4Q)	
<b>S-151128</b>	Chronic pain	Preclinical		● Ph1 start (4Q)	

● Timing of trial start    ★ Timing of topline results    ◆ timing of submission



# Upcoming pipeline events 2/2

As of Oct. 12, 2022 Not all plans are listed

Pipeline	Indication	Stage	FY2022 3Q-4Q	FY2023	FY2024
<b>redasemtide (S-005151)</b>	<ul style="list-style-type: none"> <li>① Epidermolysis bullosa</li> <li>② Acute ischemic stroke</li> <li>③ Knee osteoarthritis</li> <li>④ Chronic liver disease</li> <li>⑤ Cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>① Preparing for additional clinical trial</li> <li>② Preparing for Phase 3 trial</li> <li>③④ Investigator initiated clinical trial (Phase 2 trial) in progress</li> <li>⑤ Preparing for Investigator initiated clinical trial</li> </ul>	<ul style="list-style-type: none"> <li>①</li> <li>②</li> <li>⑤</li> </ul>	<ul style="list-style-type: none"> <li>Ph3 start (4Q)</li> <li>Ph2 start (2Q)</li> </ul>	<ul style="list-style-type: none"> <li>Submission (3Q)</li> </ul>
<b>S-309309</b>	Obesity	Phase 1	Ph1 topline results (3Q)	Ph2 start (4Q)	Ph2 topline results (3Q)
<b>S-531011</b>	Solid tumor	Phase 1b/2		Ph2 start (4Q)	
<b>S-770108</b>	Idiopathic pulmonary	Phase 1		Ph2 start (1Q)	

● Timing of trial start    ★ Timing of topline results    ◆ timing of submission

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Chief Executive Officer

# Appendix

# SDT-001: Profile



## Indication

- Children with Inattention symptoms in attention-deficit hyperactivity disorder (ADHD)



## Product characteristics

- Digital therapy application
- Running a video game-like application for approximately 25 min every day at home
- Improving inattentive symptoms in ADHD patients with activating the prefrontal cortex by performing dual tasks whose difficulty is adjusted for each person
- Treatment options with new evidence



## Market

- Up to 80,000 ADHD patients are eligible for this product



## Unmet needs

- Strong need for treatment without drugs (concerns about side effects and long-term administration), demand for other treatment options than drugs.
- Few medical institutions that can receive psychosocial treatment (conducted face-to-face with physician and medical personnel) due to lack of their resources.

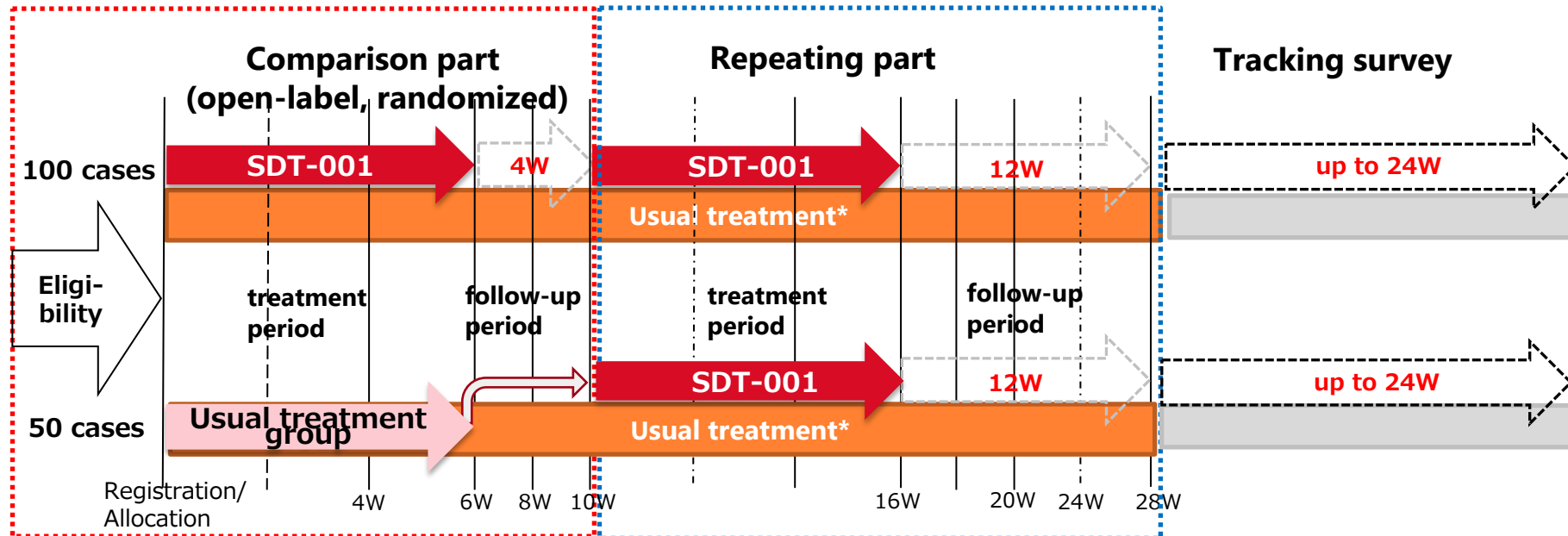


## Current status and future plans

- Phase 3 trial ongoing from April 2022
- Plan to apply in 2023
- Indication expansion for adult will consider based on the results of US adult studies (end of 2023)

# SDT-001: Phase 3 trial in pediatric ADHD patients (design)

<b>Subject</b>	Children (6-17 years old) with ADHD
<b>Primary purpose</b>	Verification of the efficacy (inattentive symptoms in ADHD-RS) of this device after 6 weeks of use in comparison with the usual treatment group
<b>Secondary purpose</b>	Evaluate efficacy, safety, and tolerability of repeated use of this device



\* Psychosocial treatment including environmental adjustment

# Pipeline: Infectious Disease

as of October. 12, 2022

## Preclinical

## Phase 1

## Phase 2

## Phase 3

## Submission

**S-872600**

Influenza nasal vaccine

**S-540956**

Nucleic acid adjuvant

**S-875670**

COVID-19 nasal vaccine

**S-337395**

RSV infections

**S-554110**

Nontuberculous  
mycobacterial infection



: Global development



**Out license**



**S-217622\***

[Ensitrelvir Fumaric Acid]  
COVID-19 treatment

**S-268019**

COVID-19  
Prophylactic vaccine



**S-268019**

COVID-19  
Prophylactic vaccine



**cefiderocol**

Aerobic Gram-negative  
bacterial infection (Pediatric)



**F901318**

[olorofim]  
Invasive Aspergillosis

**S-217622\***

[Ensitrelvir Fumaric Acid]  
COVID-19 treatment

\* Phase 2/3

**cefiderocol**

Various infectious diseases

**Xofluza®**

Influenza virus infection  
(Granules, < 20kg)

Stage change (change from August . 1, 2022)

S-365598 (HIV infection): Phase 2

S-880008 (COVID-19 treatment): Closed

**S-365598**

HIV infection

**S-555739**

Treatment by suppressing  
aggravation of COVID-19

**Xofluza®**

Influenza virus infection  
(Pediatric, < 1 year old)

**Xofluza® (US)**

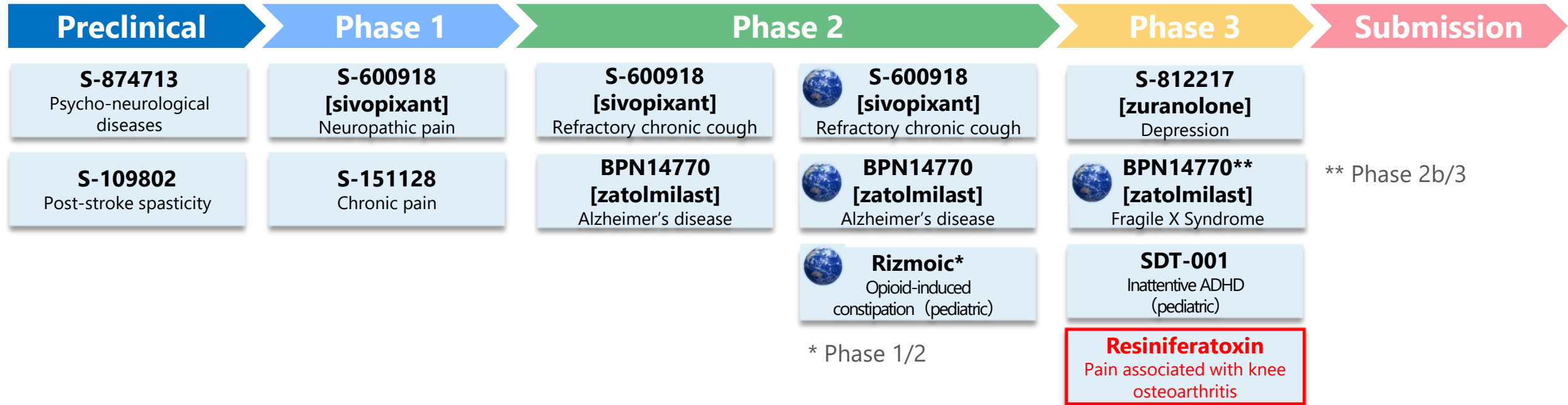
Influenza virus infection  
(Pediatric, < 1year old)

**Xofluza®**

Influenza virus infection  
(Transmission)

# Pipeline: Psycho-neurological disease

as of October. 12, 2022



: Global development

## Stage change (change from August . 1, 2022)

Resiniferatoxin (Pain associated with knee osteoarthritis): Phase 3  
 S-010887 (Neuropathic pain): Closed  
 S-120083 (Inflammatory pain): Closed  
 S-117957 (insomnia): Closed

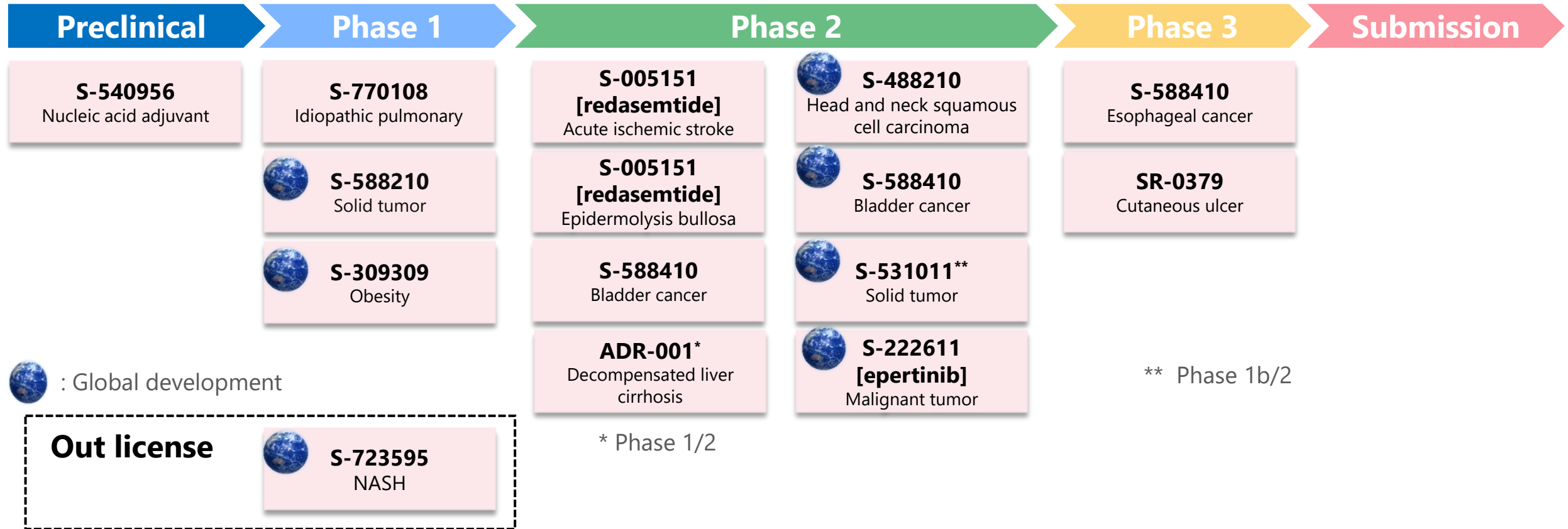
## Out license

**S-0373 [rovatirelin]**  
 Spinocerebellar Degeneration



# Pipeline: New growth areas

as of October. 12, 2022



Stage change (change from August . 1, 2022)

S-237648 (Obesity): Closed

# Forward-Looking Statements

- Forecast or target figures in this material are neither official forecasts of earnings and dividends nor guarantee of target, achievement and forecasts, but present the midterm strategies, goals and visions. Official earnings guidance should be referred to in the disclosure of the annual financial report (*kessan tanshin*) in accordance with the rules set by Tokyo Stock Exchange.
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