SHIONOGI R&D Day 2022

October 12, 2022
Shionogi & Co., Ltd.

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Agenda

1. Shionogi's R&D

➢ Opening	**John Keller, Ph.D.,** Senior Vice President, R&D Supervisory Unit
➢ Progress of COVID-19-related R&D	**Takeki Uehara, Ph.D.,** Senior Vice President, Drug Development and Regulatory Science Division
➢ Progress of Shionogi R&D	
✓ Development area	**Takeki Uehara, Ph.D.,**
✓ Research area	**Yasuyoshi Iso, Ph.D.,** Senior Vice President, Research Division
✓ Vaccine Business	**Yasunori Aoyama, Ph.D.,** Senior Vice President, Biopharmaceutical Research Division
✓ Summary of R&D	**John Keller, Ph.D.,**

2. Summary

Isao Teshirogi, Ph.D.,
Chief Executive Officer

3. Q&A

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Opening

- R&D transformation
- Environmental changes surrounding HIV business

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

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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

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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

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

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.)

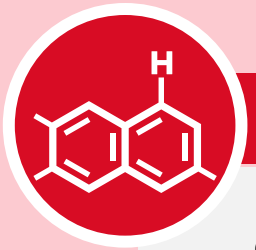
Build a model for stable earnings over the medium to long term

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

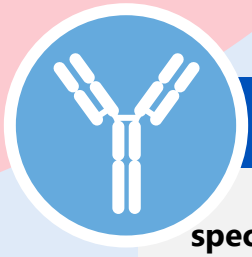
Xofluza®
ensitrelvir
HIV franchise

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

Areas to be strengthened in the future

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

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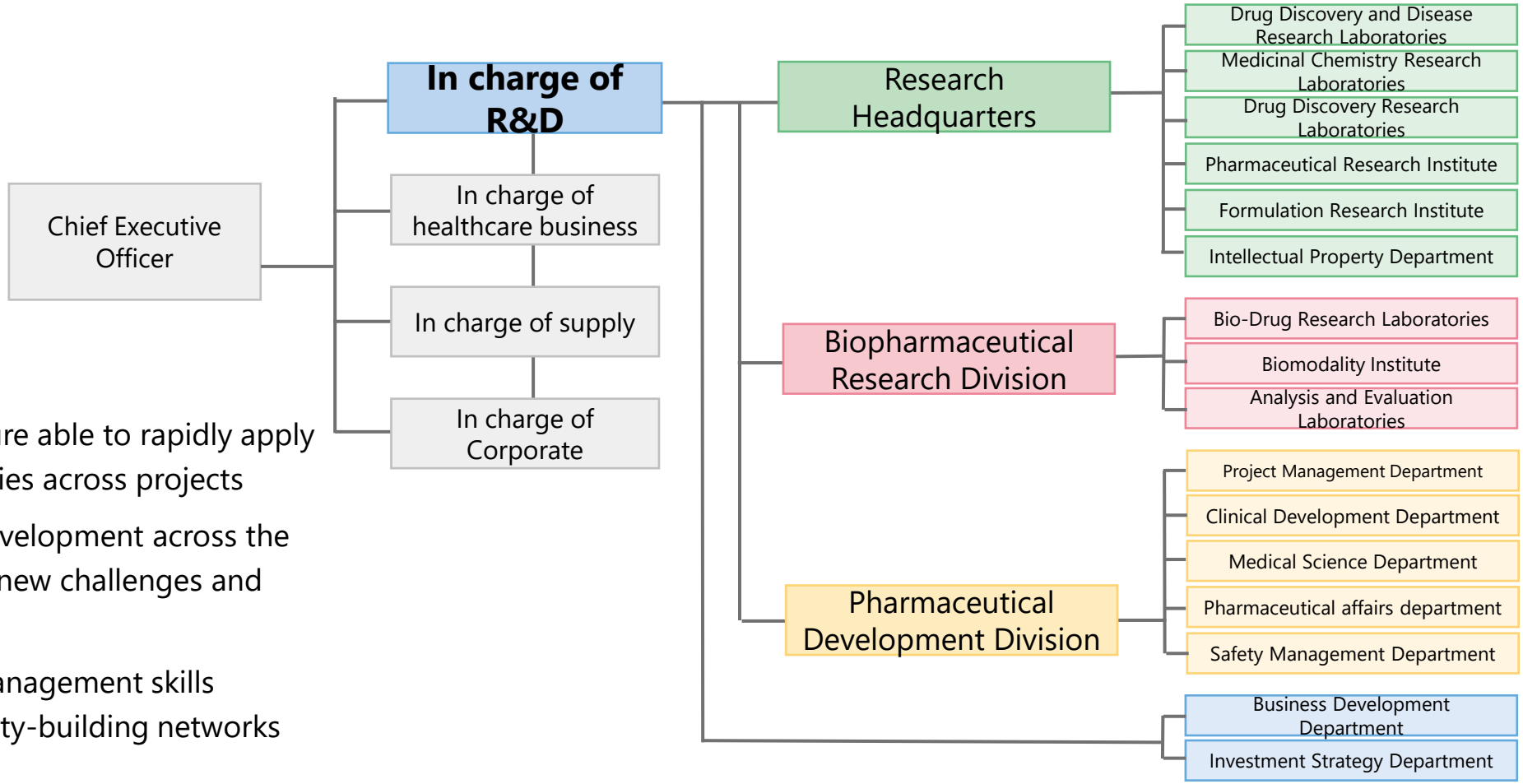
Approach to Realizing R&D Strategy - Organizational reform -

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

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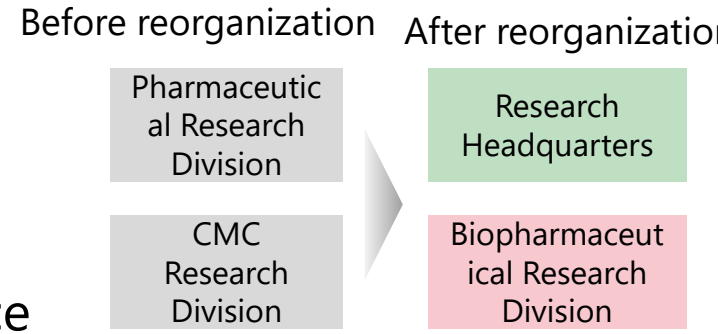
Approach to realizing R&D strategy - Organizational reform -

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

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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**

	1990-	2000-	2010-	2020-
Needs	Reducing deaths due to AIDS*	Highly effective and safe drug therapy	Reduce drug burden on patients	**Reduce the burden of HIV on individuals and society Improvement to QOL**
Actions	Start of research on antiviral drugs	Creation of dolutegravir	Providing two-drug regimens	**Launch of long-acting injections Pursuit of ultra long-acting solutions**

AIDS* : acquired immunodeficiency syndrome

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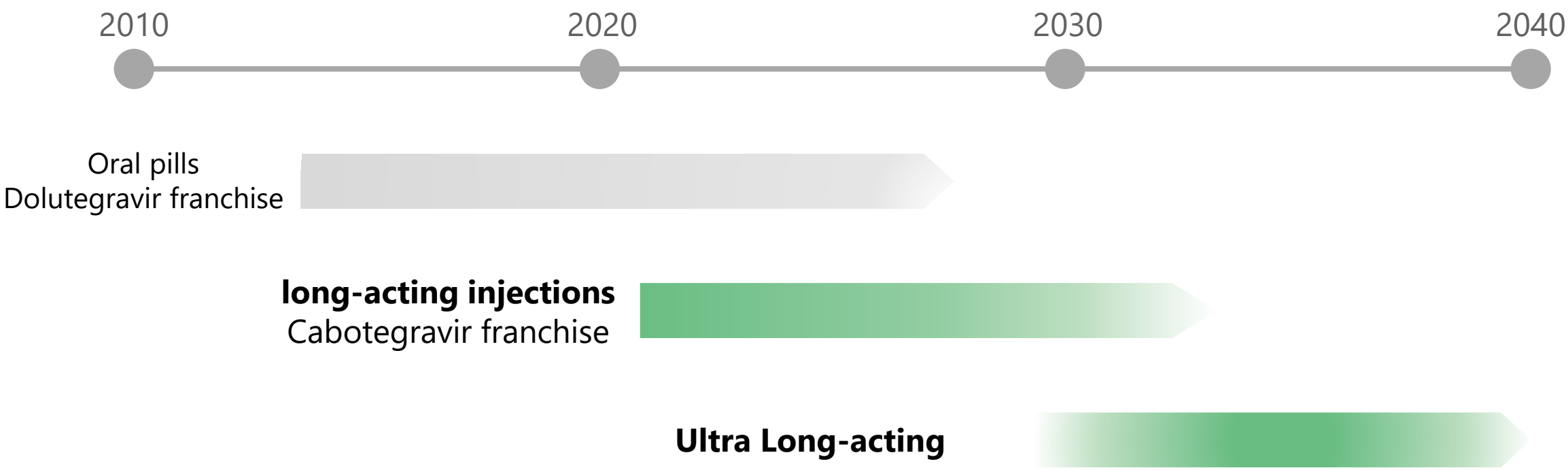
Pipeline of new products addressing patient needs

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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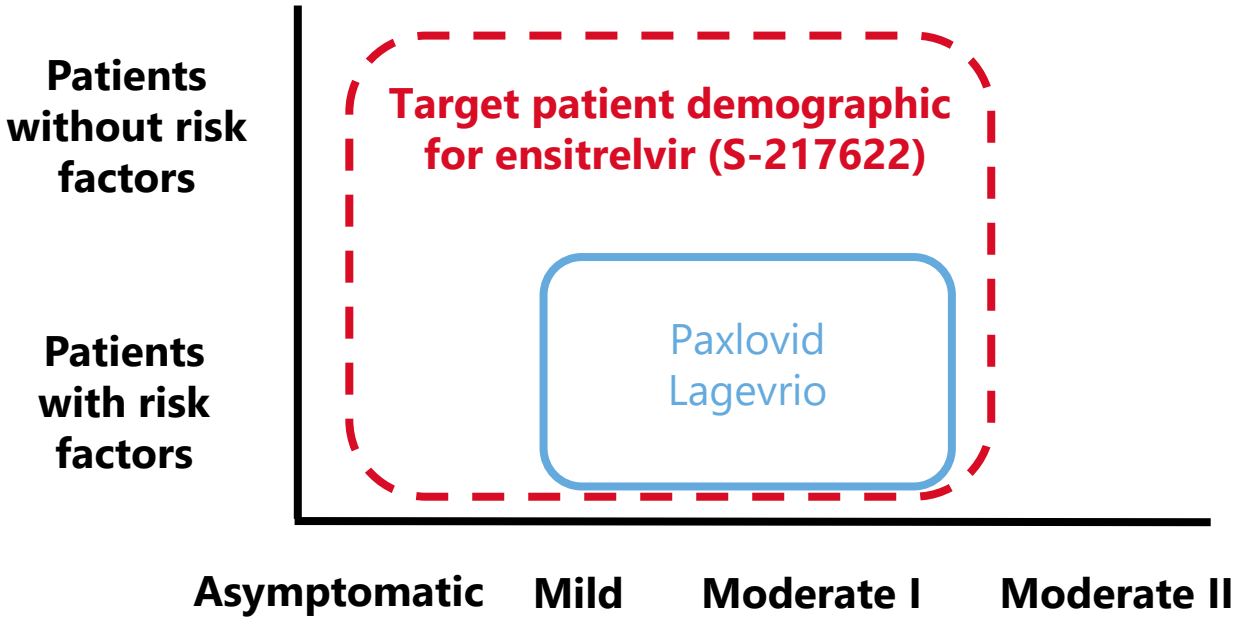
Progress of COVID-19 related R&D

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	$SpO_2 \geq 96\%$	No respiratory symptoms or Cough only, no dyspnea
Moderate I	$93\% < SpO_2 < 96\%$	Dyspnea, pneumonia findings
Moderate II	$SpO_2 \leq 93\%$	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**

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Ensitrelvir: Antiviral effect against mutant strains*

In vitro antiviral evaluation using VeroE6T cells

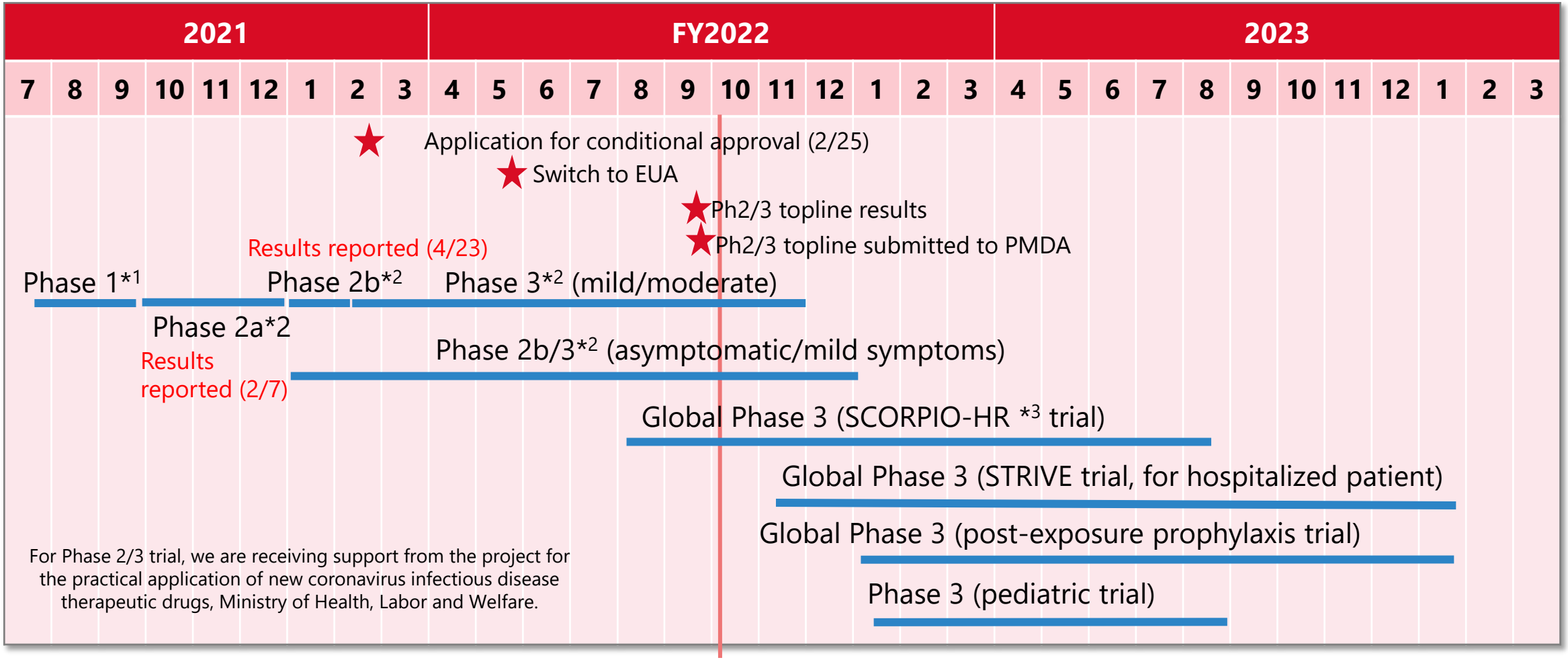
virus strain	Ancestor	alpha strain	beta strain	gamma strain	delta strain	omicron strain					
						BA.1	BA.1.1	BA.2	BA.2.75	BA.4	BA.5
EC_{50} (μM)	0.37	0.46	0.40	0.50	0.41	0.29	0.36	0.52	0.30	0.22	0.40

- **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)**

* Nakashima et al OPTIONS-XI P-205 Sep 2022

** Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2 | NEJM

Ensitrelvir: Progress summary



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

*1 jRCT2031210202、*2 jRCT2031210350、*3 NCT05305547

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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

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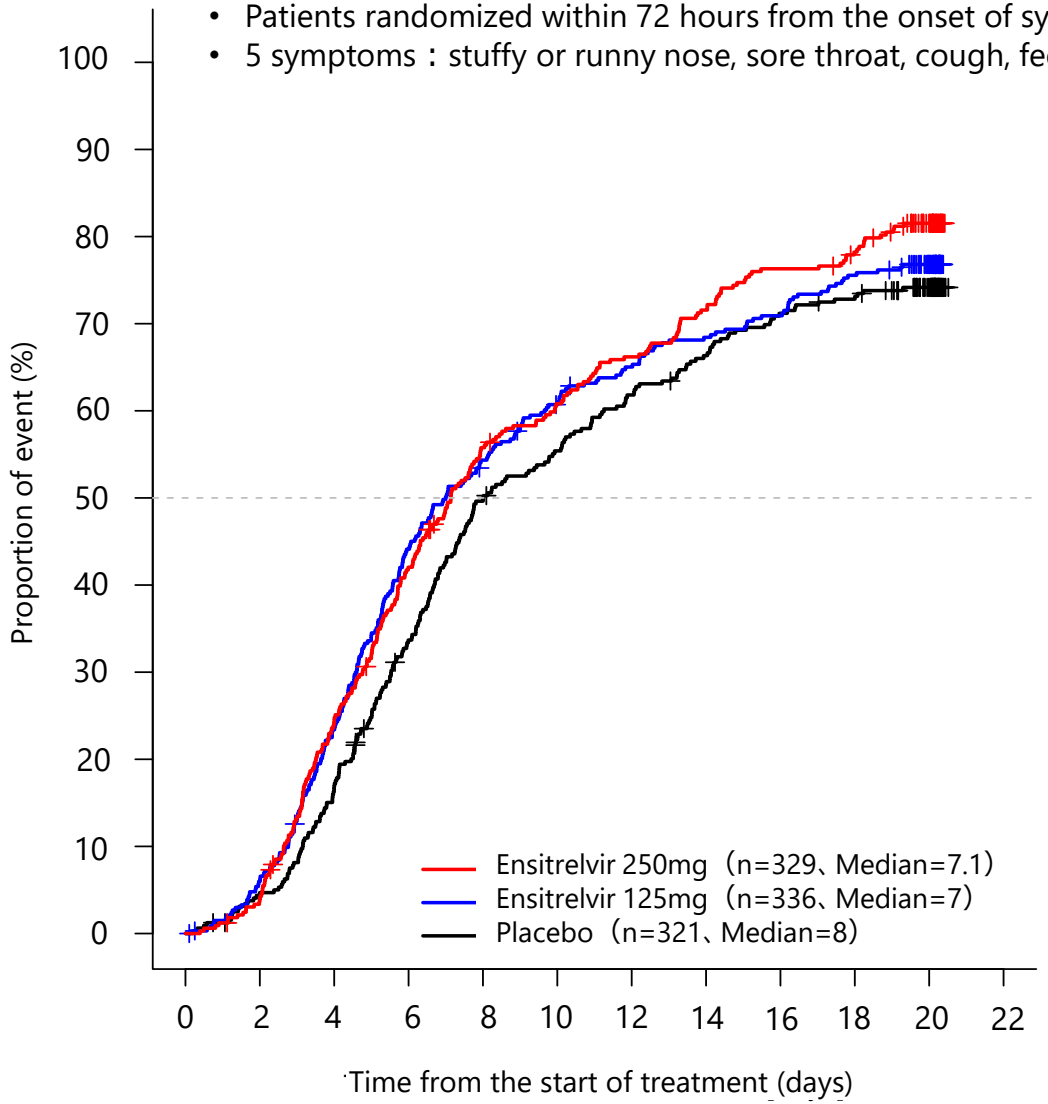
Ensitrelvir: Phase 3 part - The time to resolution of all five key COVID-19 symptoms (Primary endpoint) -

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]		**-24.3** [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	**0.0407**	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)

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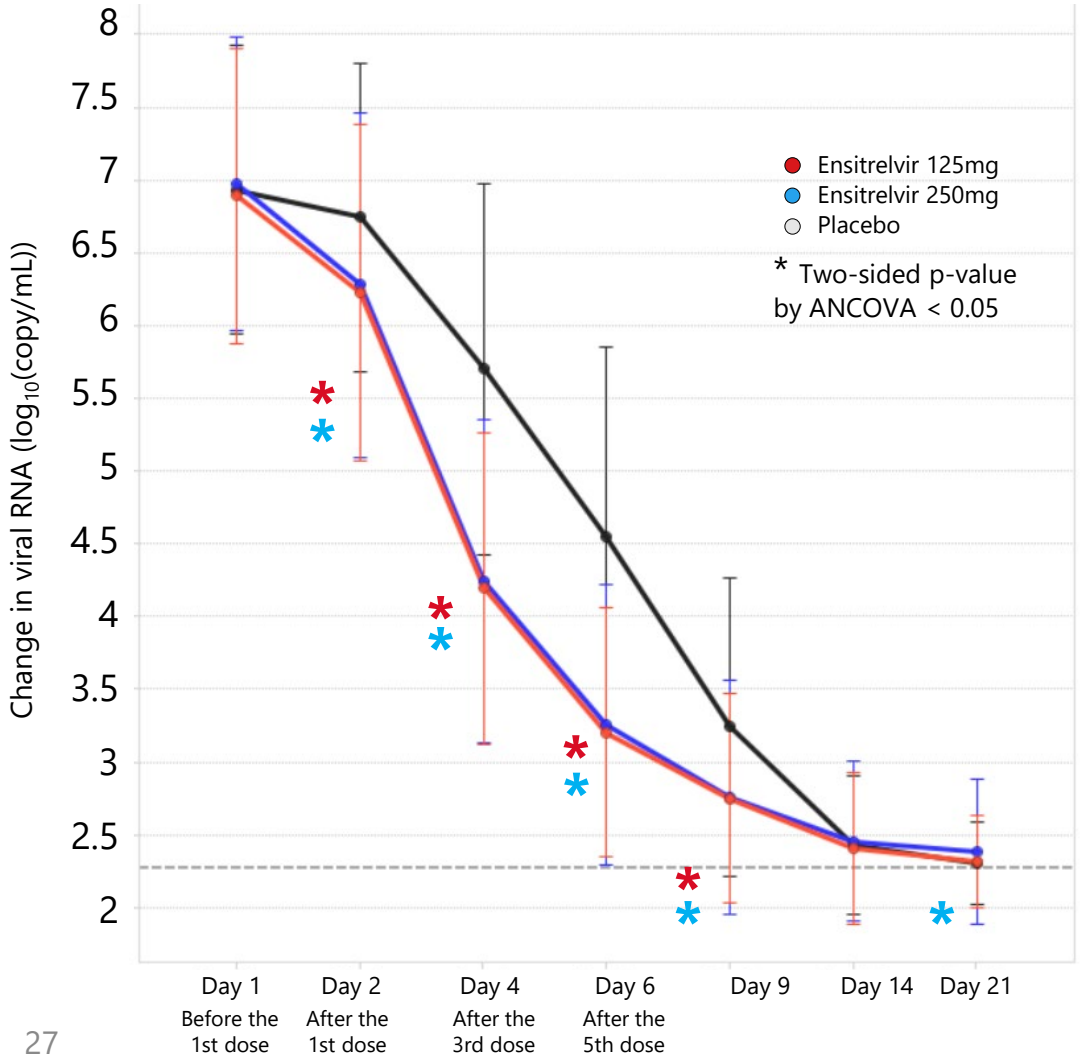
Ensitrelvir: Phase 3 part - Change in viral RNA amount (Key secondary endpoint) -

Mean change from baseline in amount of viral RNA



【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]	**-1.47 (0.08) [-1.63, -1.31]**	-1.48 (0.08) [-1.64, -1.32]	---
	P value	**<0.0001**	<0.0001	---

UNIT: log_{10} 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_{10} 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_{10} 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

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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 log10 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

STRIVE trial* Phase 3

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

SCORPIO-PEP trial Phase 3

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

Pediatric trial (Japan) Phase 3

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

Trial start：IND　* NIH sponsored trial

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Ensitrelvir: The SCORPIO-HR trial design

Trial design	A multicenter, randomized, double-blind, placebo-controlled
Subject	Non-hospitalized participants with COVID-19 (HR: 50%, OwH: 50%)
Primary purpose	To evaluate the efficacy of ensitrelvir against placebo for non-hospitalized COVID-19 patients
Primary endpoint	Time to sustained symptom resolution through Day 29
Secondary endpoint	・Change From Baseline in Quantitative $\log_{10}$ SARS-CoV-2 RNA Levels by PCR at Day 4 ・Hospitalization rate due to COVID-19, mortality rate due to all causes
Dosing group	ensitrelvir, placebo
Dosage	Oral administration once daily for 5 days
Target number of patients	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

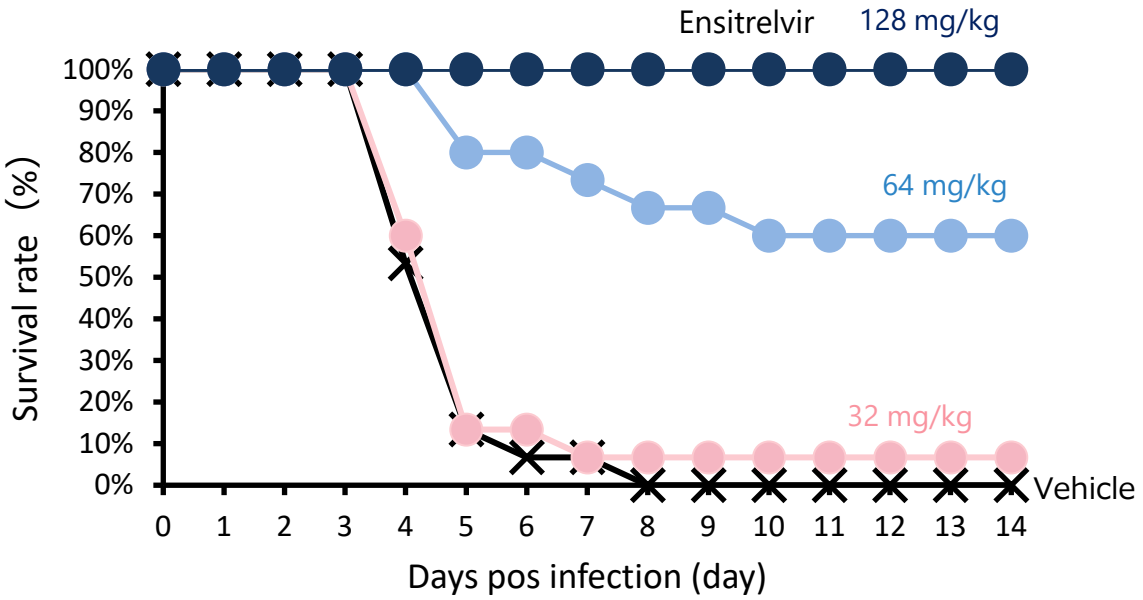
- To seek approval using the Phase 2/3 trial data in adolescents (12 to <18) in JP/EU/US
- To conduct the clinical trial for 6 to <12 in JP with higher priority than EU&US
- To plan the separated clinical trial in 0 to <12 for Global

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 μg/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

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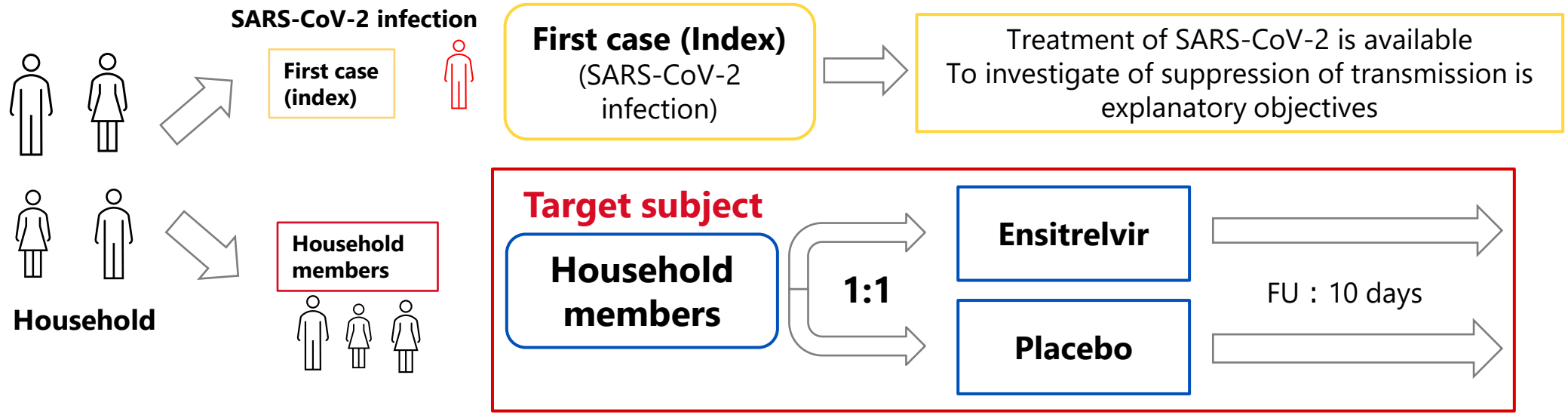
Ensitrelvir: Post exposure prophylaxis trial (PEP) design

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



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

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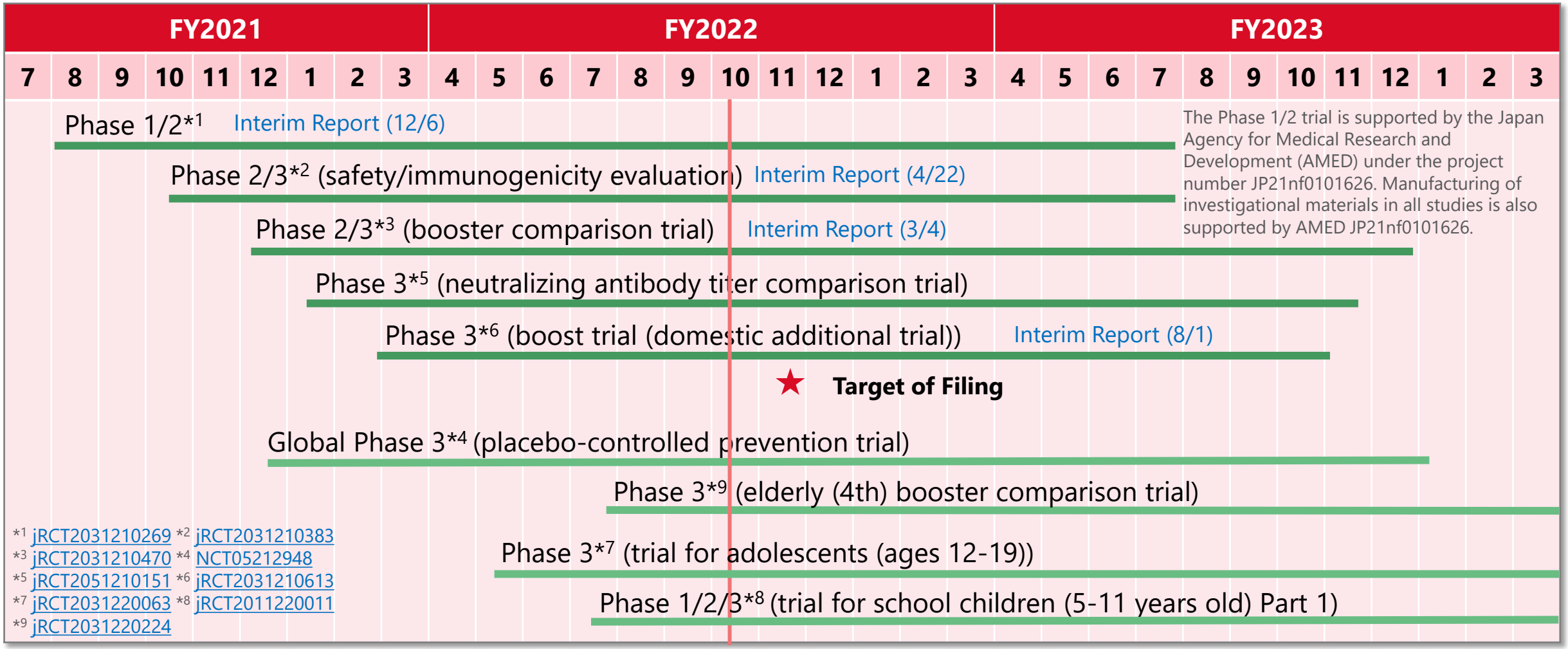
S-268019 (recombinant protein vaccine): Progress summary



The Phase 1/2 trial is supported by the Japan Agency for Medical Research and Development (AMED) under the project number JP21nf0101626. Manufacturing of investigational materials in all studies is also supported by AMED JP21nf0101626.

As of October 12, 2022

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

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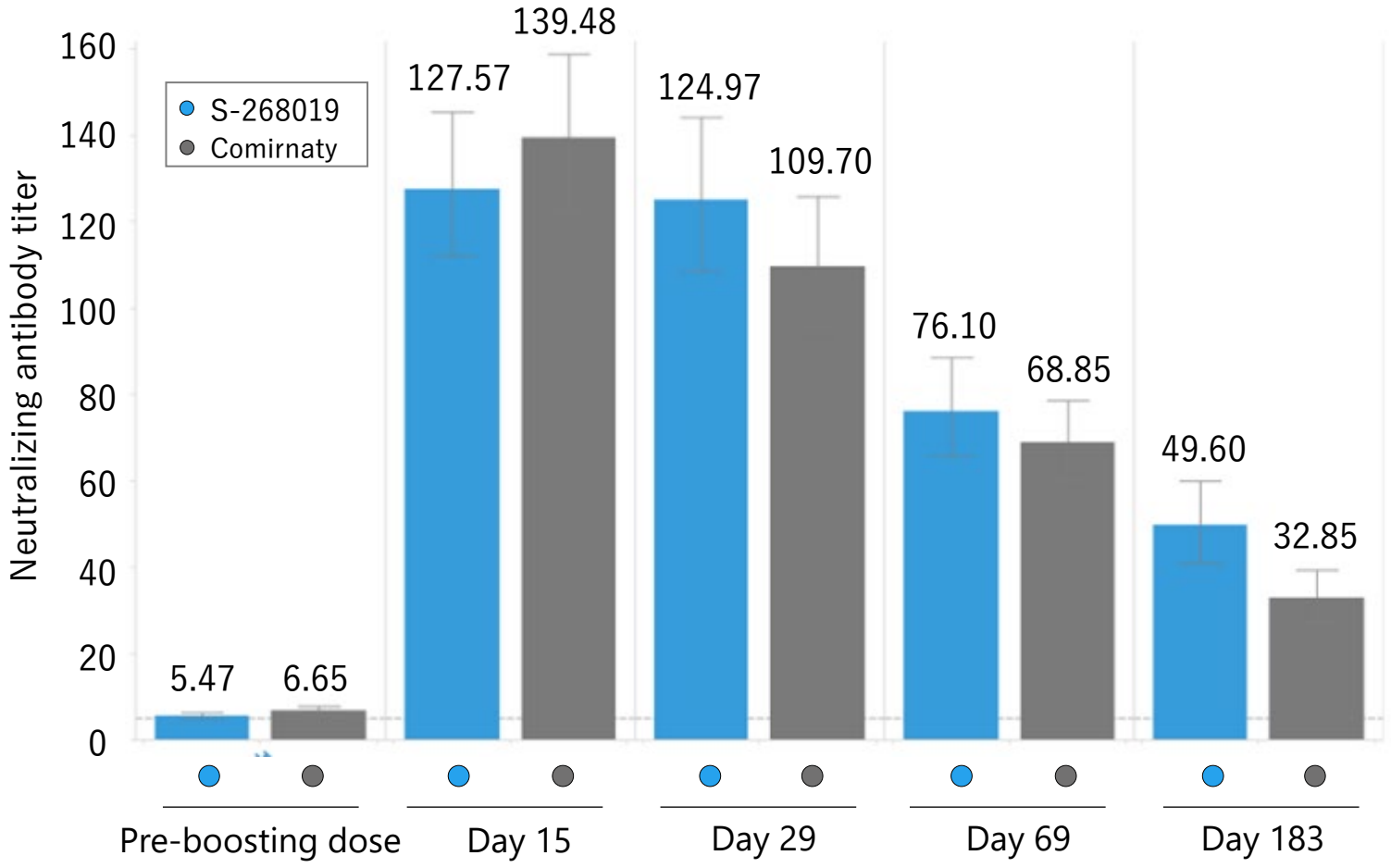
S-268019: Phase 2/3 booster comparison trial
- Neutralizing antibody titer after vaccination -

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



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

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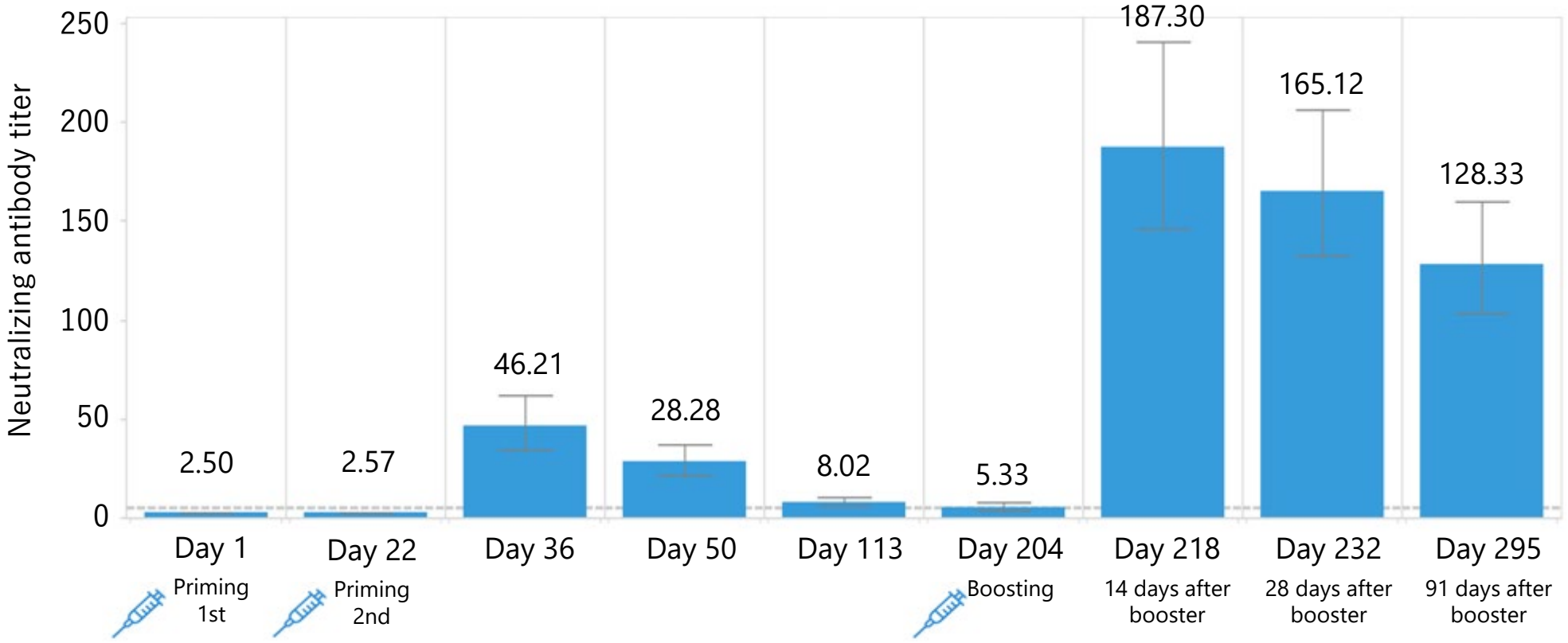
S-268019: Phase 1/2 trial
- Neutralizing antibody titer after priming and boosting vaccination -

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

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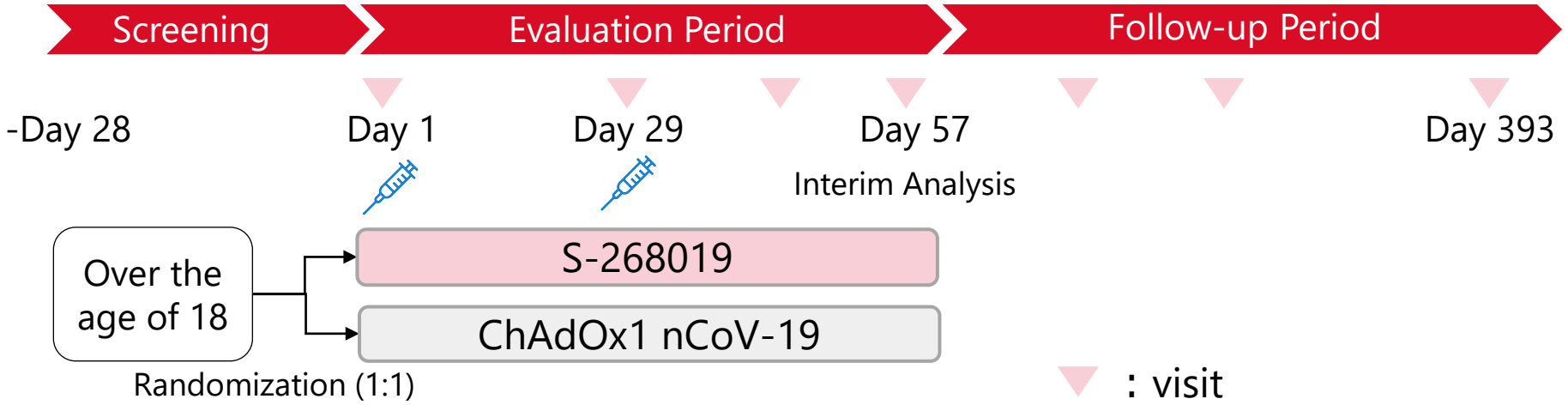
S-268019: Phase 3 neutralizing antibody titer comparison trial
- Trial design -

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



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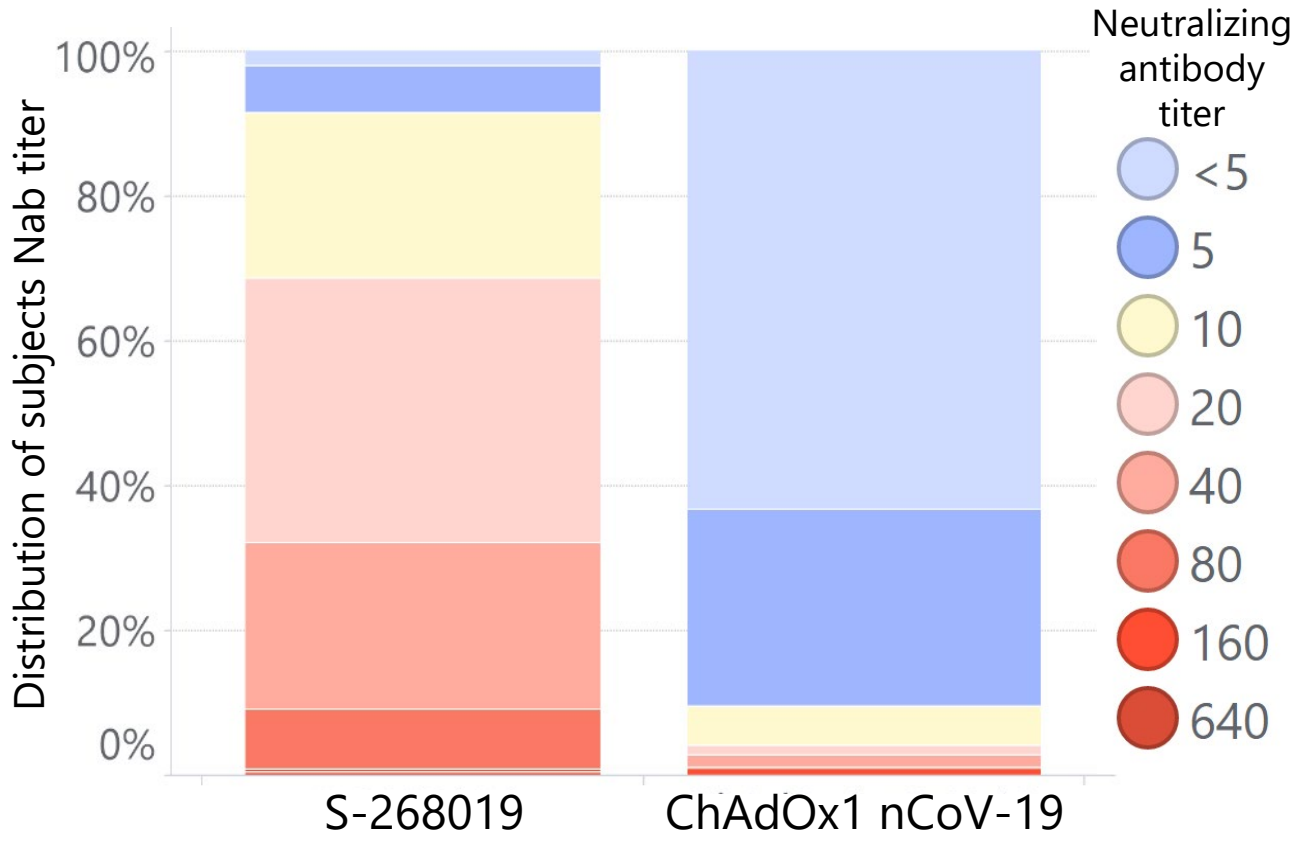
S-268019: Design of neutralizing antibody titer comparison trial
- Neutralizing antibody titer at 28 days following the second vaccination -

Planed 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.



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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	**John Keller, Ph.D.,** Senior Vice President, R&D Supervisory Unit
➢ Progress of COVID-19-related R&D	**Takeki Uehara, Ph.D.,** Senior Vice President, Drug Development and Regulatory Science Division
➢ Progress of Shionogi R&D	
✓ Development area	**Takeki Uehara, Ph.D.,**
✓ Research area	**Yasuyoshi Iso, Ph.D.,** Senior Vice President, Research Division
✓ Vaccine Business	**Yasunori Aoyama, Ph.D.,** Senior Vice President, Biopharmaceutical Research Division
✓ Summary of R&D	**John Keller, Ph.D.,**

2. Summary

Isao Teshirogi, Ph.D.,
Chief Executive Officer

3. Q&A

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Progress in development areas

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

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Development area

Disease area	Project	Target disease	Stage	Posted page
Infection	**olorofim (F901318)**	Invasive aspergillosis	Global: Phase 3	P.43-45
Psychiatry/Nervous/Pain	**resiniferatoxin**	Pain associated with osteoarthritis	Global: Phase 3	P.46-48
	sivopixant (S-600918)	Intractable/Chronic with unknown cause cough	Global: Phase 2	P.49-50
	zatolmilast (BPN14770)	(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
	zulanolone (S-812217)	depression/depression	Japan: Phase 3	P.54-60
New growth area	**redasemtide (S-005151)**	(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 incestigator-initiated clinical trial	P.61-67
	S-309309	Obesity	United States: Phase 1	P.68-71
	S-531011	solid cancer	Japan/United States: Phase 1b/2	P.72-75
	S-770108	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

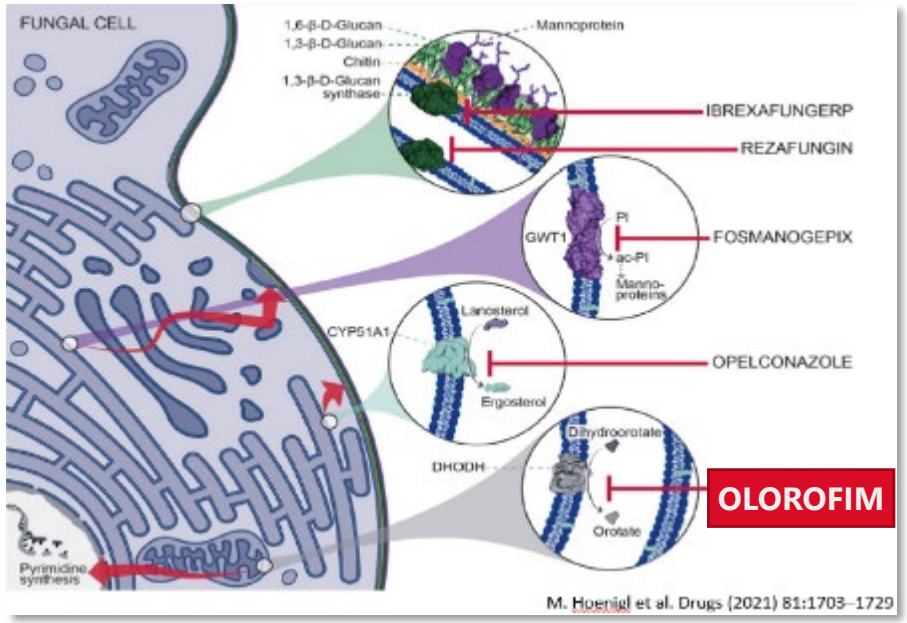
- Oral drug with a new MoA for invasive aspergillosis, where treatment options are limited due to resistance and tolerability issues
- A new treatment option for patients with rare fungal infections

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



* Lancet. 2016;387:760–769, N Engl J Med 2002; 347:408-415, Clin. Infect. Dis. 2010; 50:1091–1100

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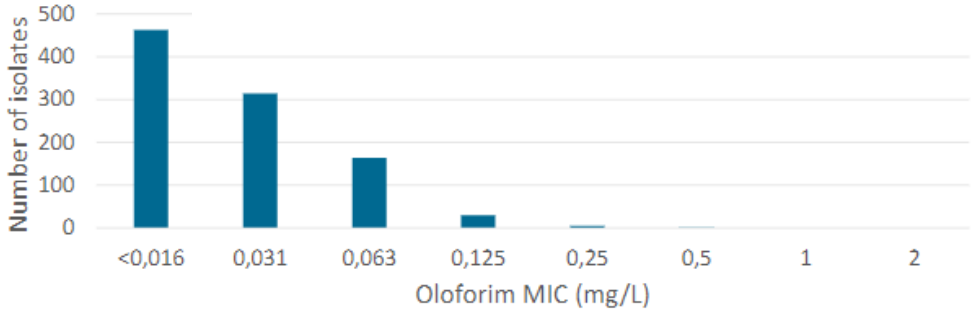
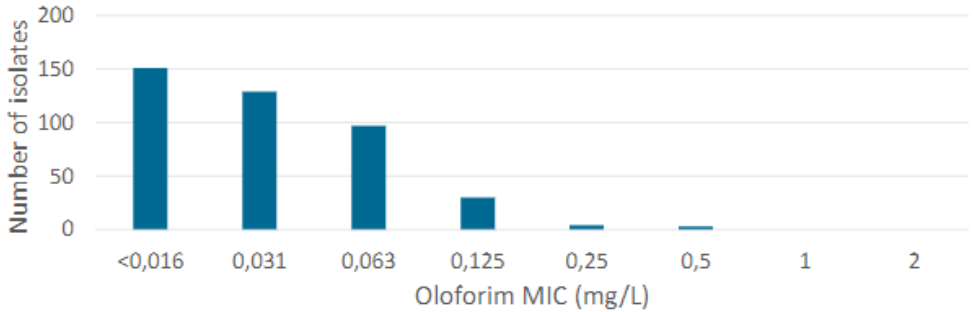
Olorofim: Activity against *Aspergillus*

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



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

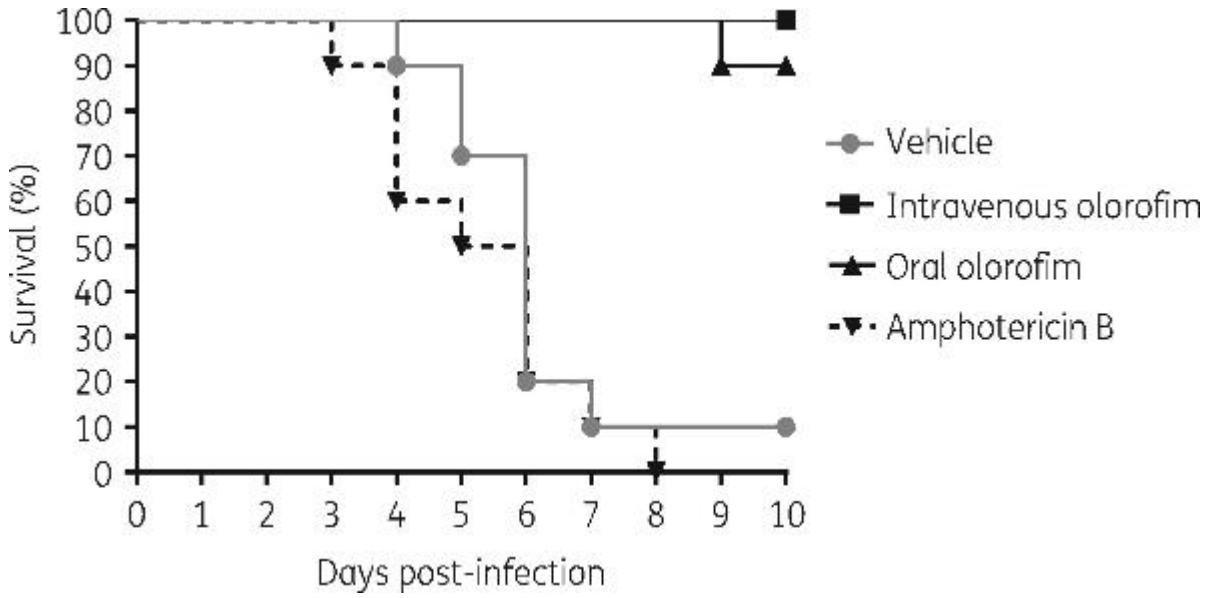


*Susceptiblity of *A. fumigatus* isolates with MICs ≥0.25 mg/L was <0.25 mg/L in repeated testing

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

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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)

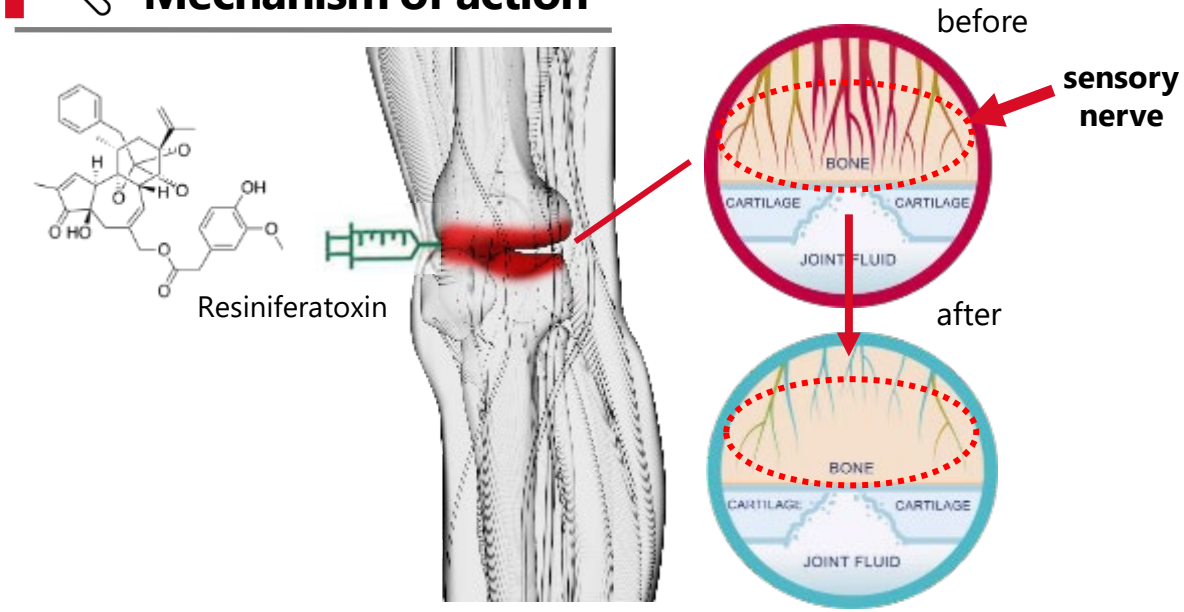
Unmet needs

- 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)

* Transient Receptor Potential Vanilloid 1

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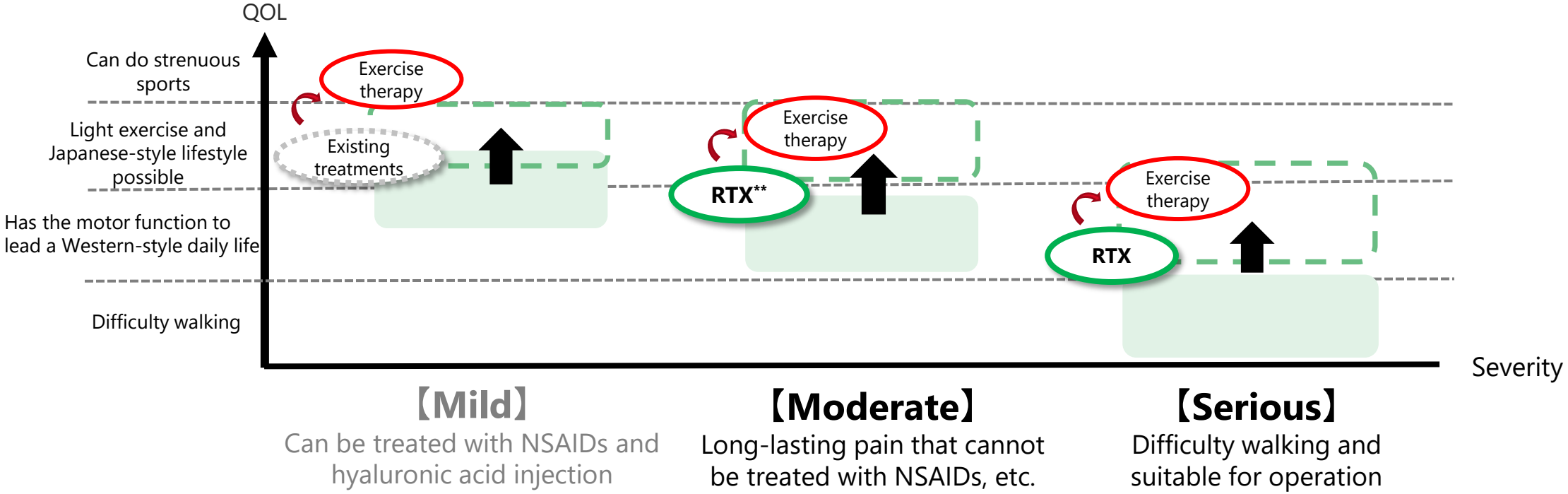
Resiniferatoxin: Role in therapy

- 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

* Quality of Life ** RTX : Resiniferatoxin

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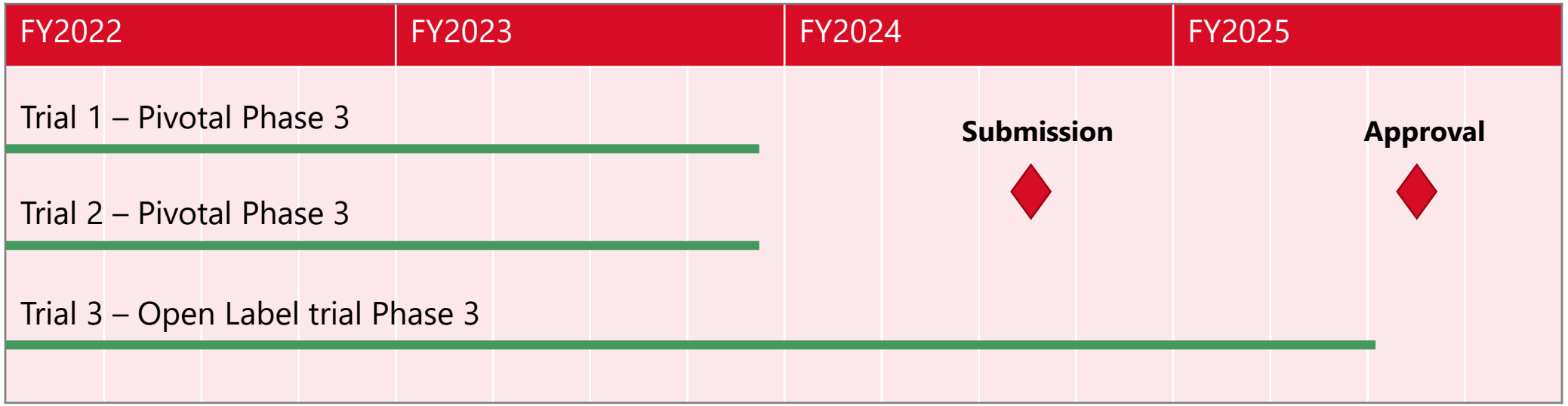
Resiniferatoxin: Future development plan

- 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 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

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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

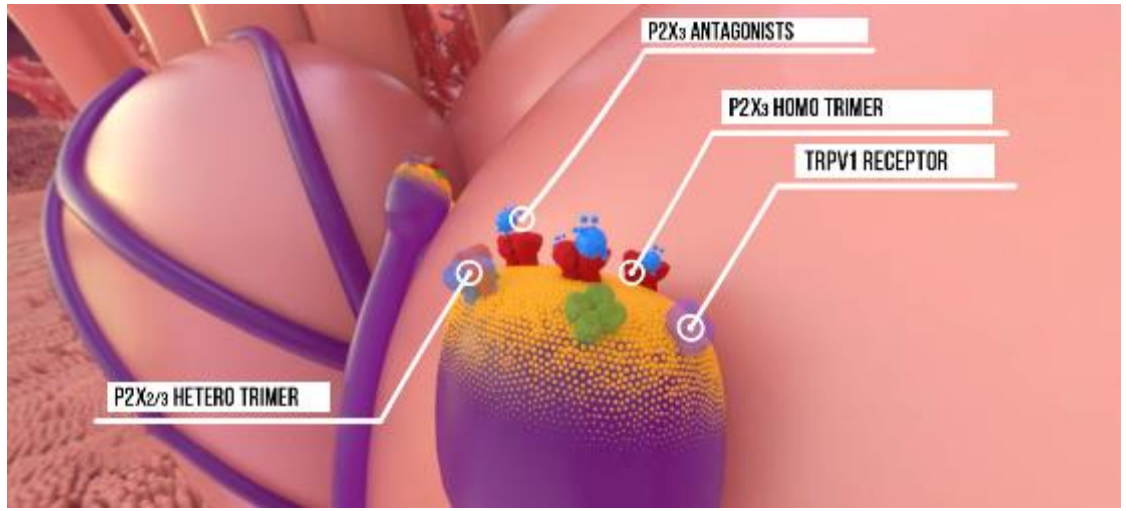
  → Efficacious and safe drug is needed

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)



* In 2022, gefapixant was approved in Japan

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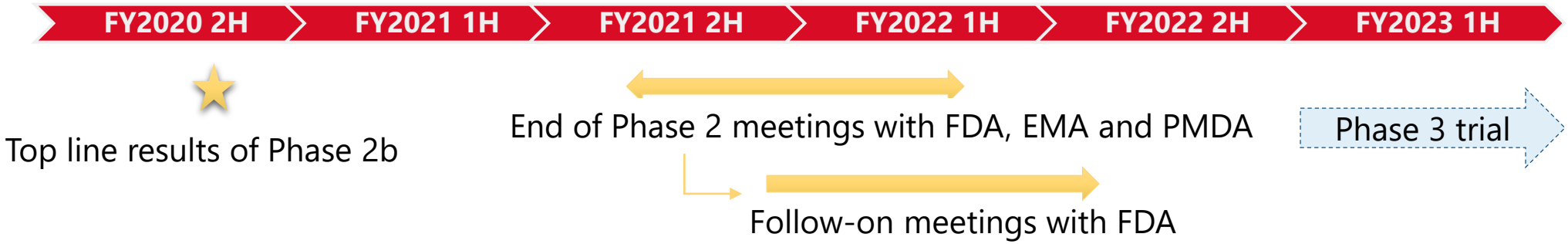
Sivopixant: Development strategy

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**

IPF : interstitial pulmonary fibrosis, ILD : interstitial lung disease

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Zatolmilast [BPN14770]: Profile

Indication

- Fragile X Syndrome (FXS*[1]) / Alzheimer's disease (AD*[2])

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)

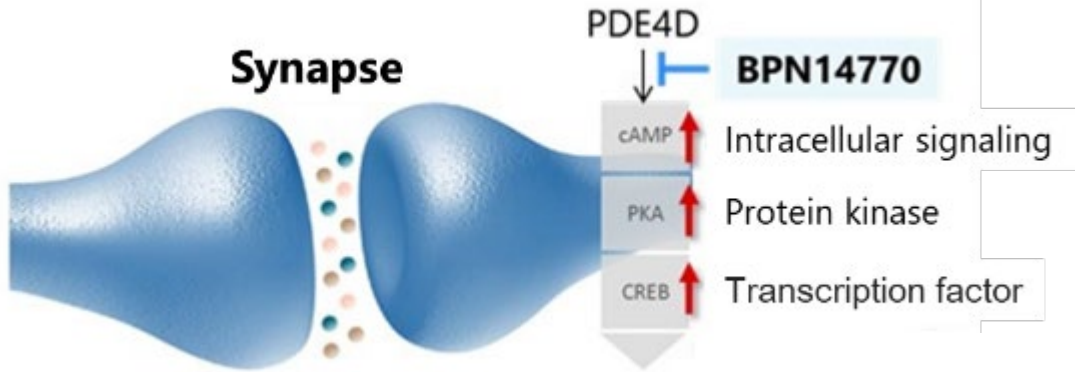
- No approved treatments for FXS
- Treatment for severe behavioral symptoms (e.g., anxiety), cognition and communication disabilities

Current Status and future plans

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

Mechanism of Action

- PDE4D*[3] allosteric inhibitor
  （phosphodiesterase subtype that hydrolyzes cAMP*[4]）



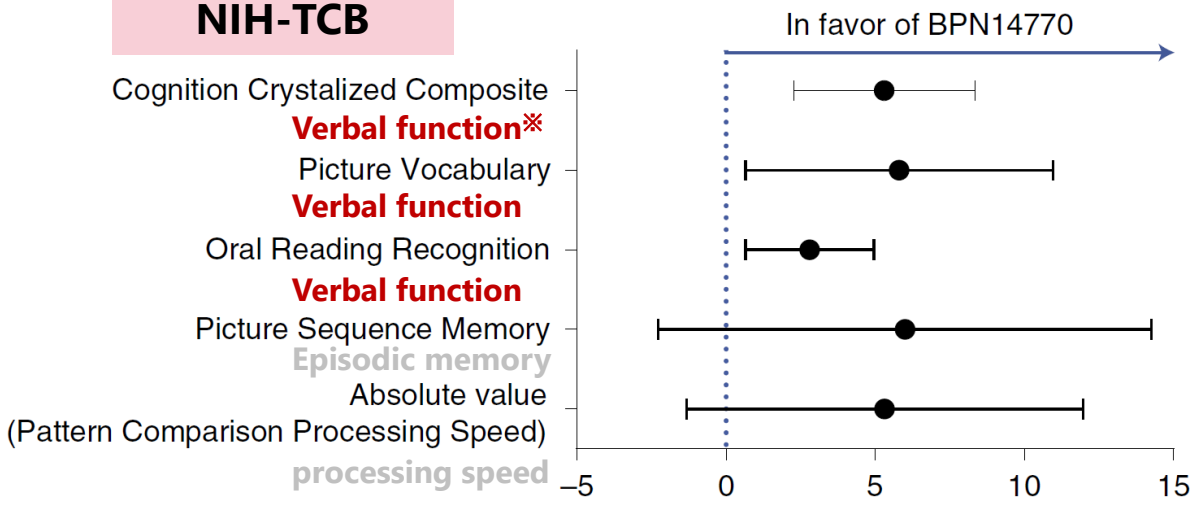
1. Increase the cAMP signaling, and gene expression in neuron, resulting that the neuronal / synaptic function is enhanced
2. Improve the cognitive impairment / behavioral abnormality

*[1] Fragile X Syndrome *[2] Alzheimer's disease *[3] Phosphodiesterase 4D *[4] cyclic adenosine 3,5-monophosphate

Zatolmilast: US FXS Phase2 trial (conducted by Tetra)

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

NIH-TCB



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 Crystalized Composite: Oral Reading RecognitionとPicture Vocabulary

* National Institutes of Health Toolbox Cognitive Battery ** Visual Analogue Scale

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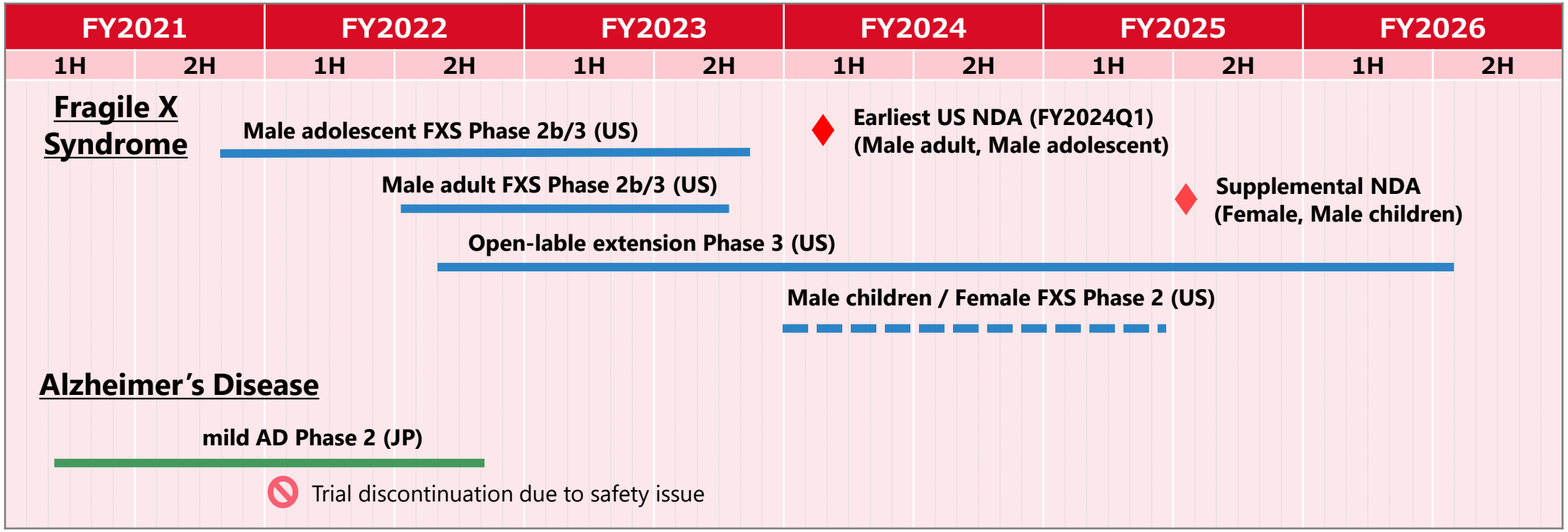
Zatolmilast: Development schedule



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

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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*[1]
  - ➢ 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% *[2]
- Slow onset of action: Antidepressant effect takes 4-6 weeks, especially 8 weeks*[3]

Current status and future plans

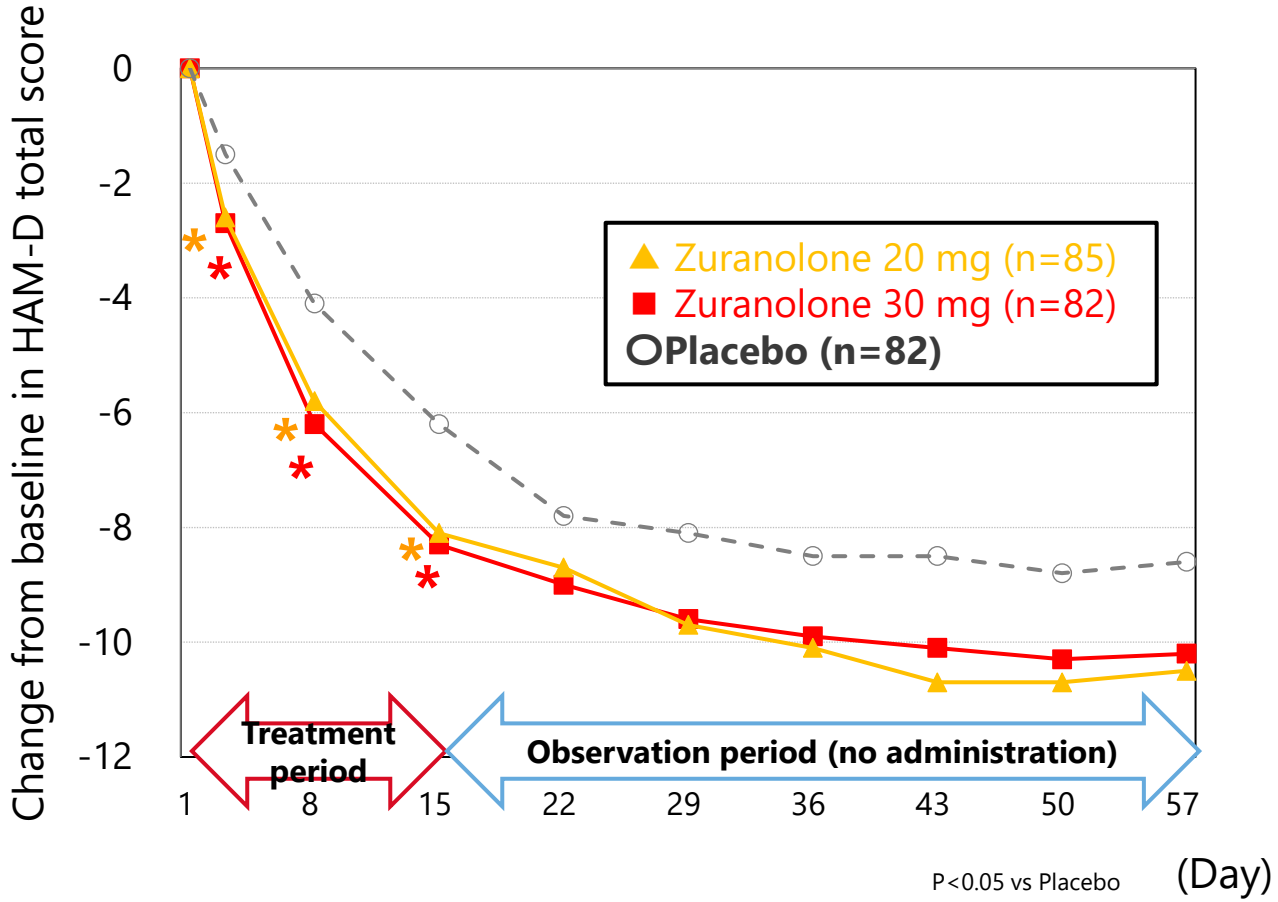
- US: Rolling submission initiated in April 2022, will be completed by the end of this year.
  - ➢ Indications: major depressive disorder, postpartum depression
- Japan: Aiming for NDA in 4Q 2023, Phase 3 is underway
  - ➢ Indication: Major depressive disorder
  - ➢ Phase 3 confirmatory trial: On track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

Mechanism of action

- Neuroactive steroid
  - ➢ Cerebrospinal fluid allopregnanolone decreased in depressed patients*[4]
- $GABA_A$ receptor (γ-aminobutyric acid-gated chloride ion channel) positive allosteric modulator
  - ➢ Acts on synaptic/extrasynaptic receptors

*[1] WHO, Depression and Other Common Mental Disorders Global Health Estimates
*[2] Am J Psychiatry 2006; 163:1905–1917 *[3] Japanese Depression Association Treatment Guidelines *[4] zunova et al., PNAS (1998)

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

* HAM-D: Hamilton Depression Rating Scale ** Percentage of cases with ≥50% improvement in HAM-D total score from baseline

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

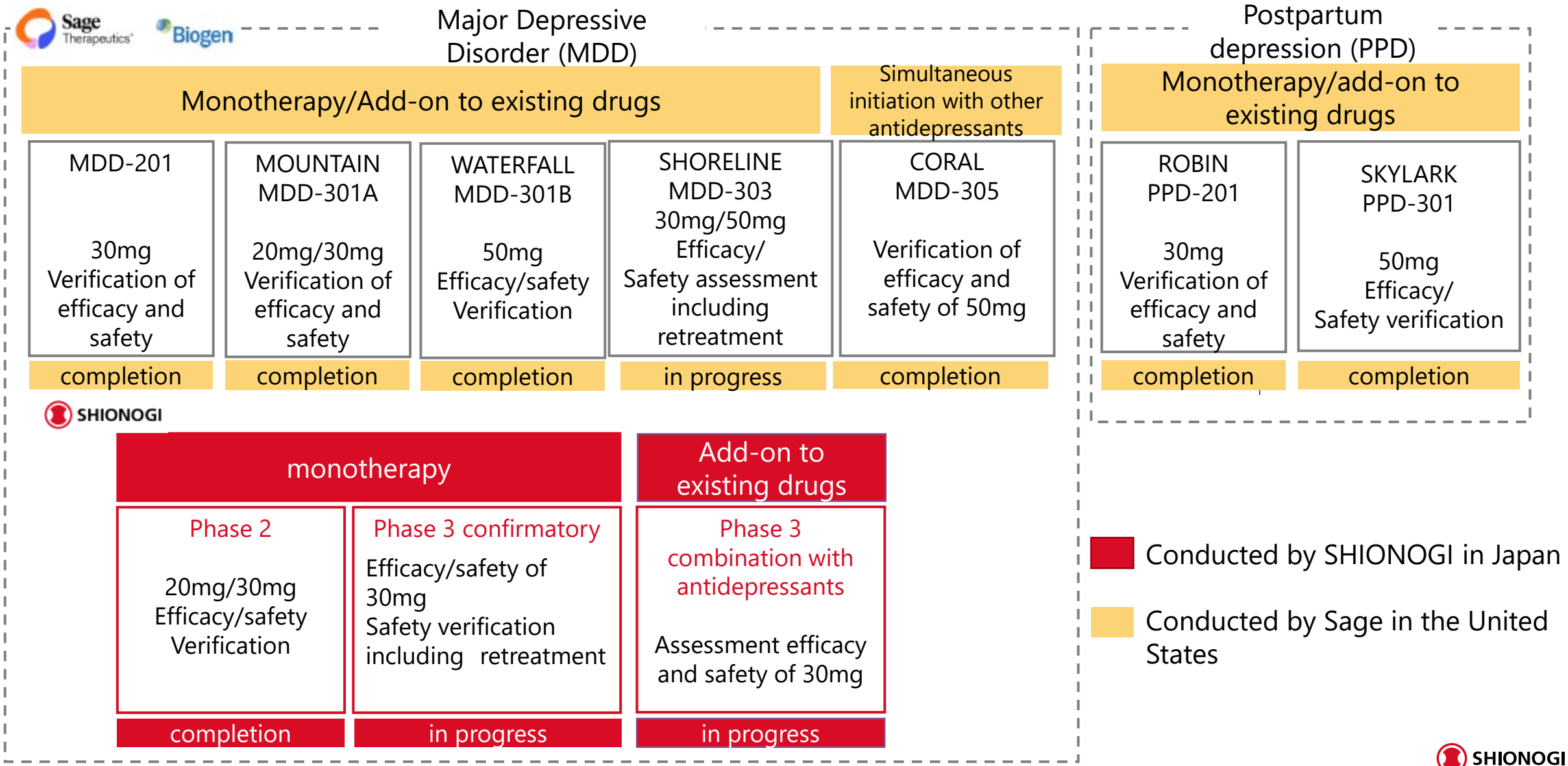
- No need to adjust dosage, efficacy is confirmed in 2 weeks, **high adherence** is expected

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



MDD: Major Depressive Disorder PPD: Postpartum Depression

※ Biogen is the partner of Sage to develop and commercialize zuranolone

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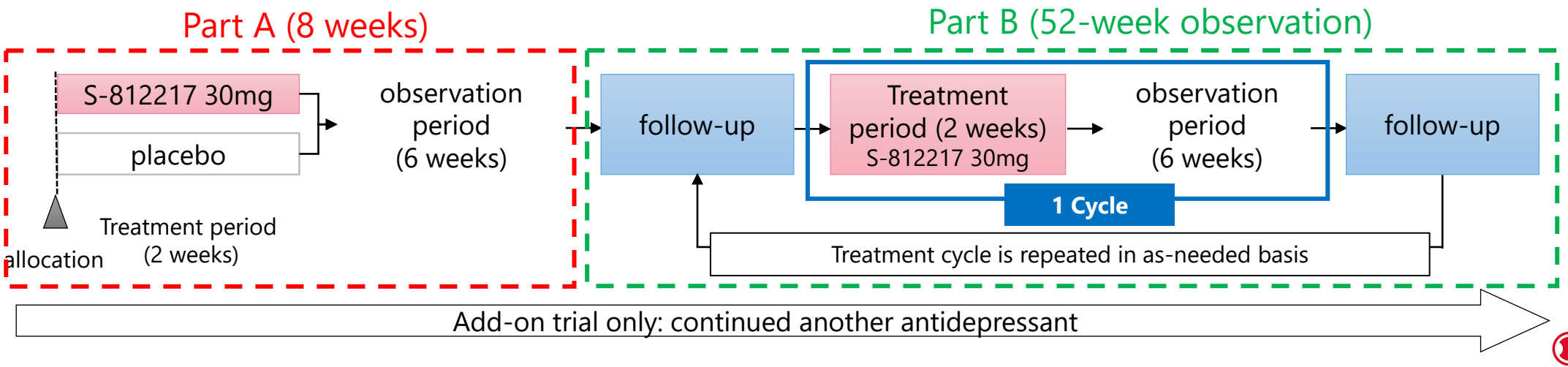
Zuranolone: Overview of Phase 3 trial in Japan

	Phase 3 confirmatory trial	Phase 3 Add-on trial
subject	Patients with moderate to severe major depressive disorder	Patients with major depressive disorder on other antidepressants
Purpose	[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
clinical trial design	[Part A] A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial [Part B] Multicenter, open label	
Dosing group	Zuranolone 30mg group, placebo group	
Sample size	200 in each group, 400 in total	50 in each group, 100 in total
Dose administration	Oral administration once a day for 14 days after dinner	



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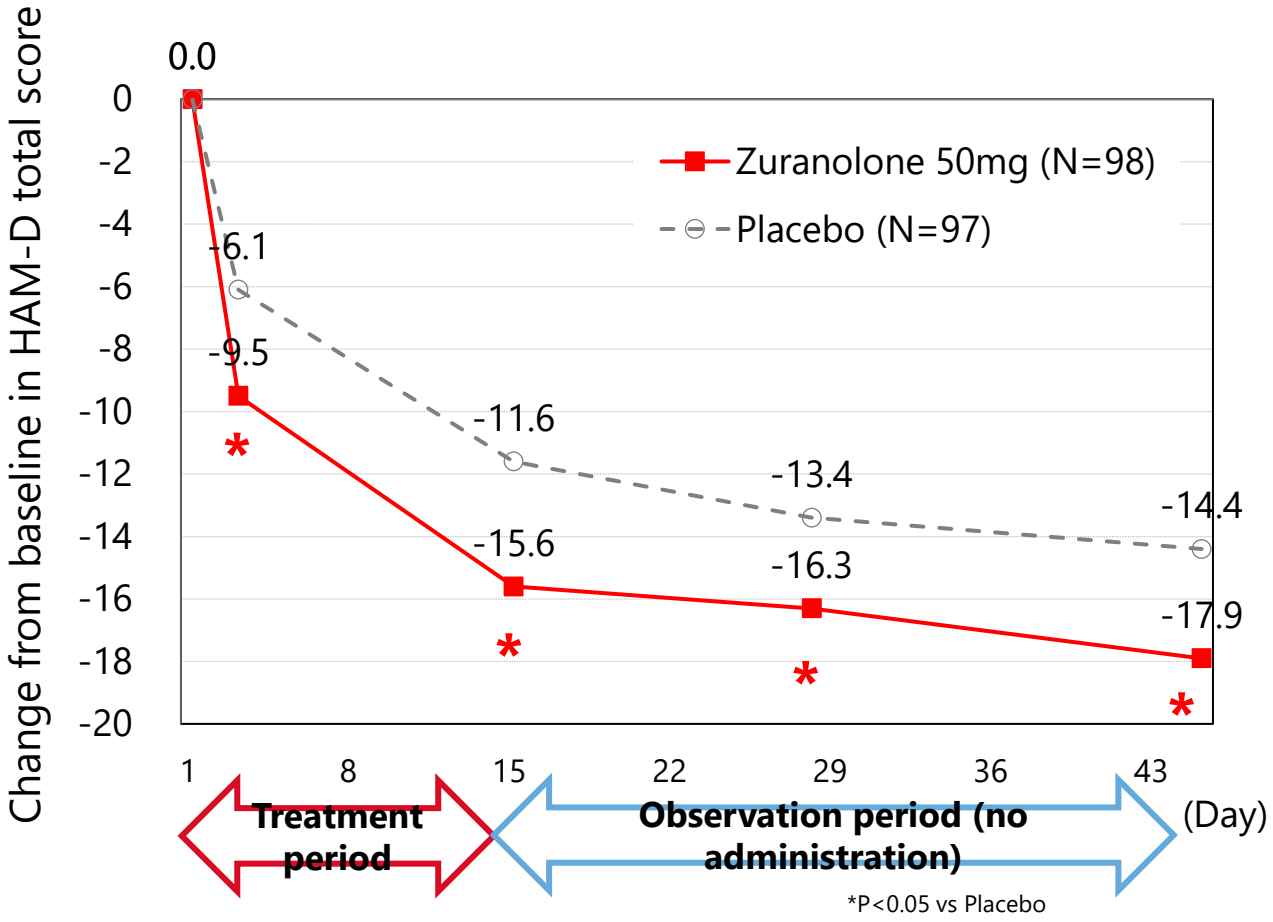
Zuranolone: US postpartum depression Phase 3 trial (SKYLARK, PPD-301)



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

* CGI-S : Clinical Global Impression – Severity

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Zuranolone: Creation evidence and indications

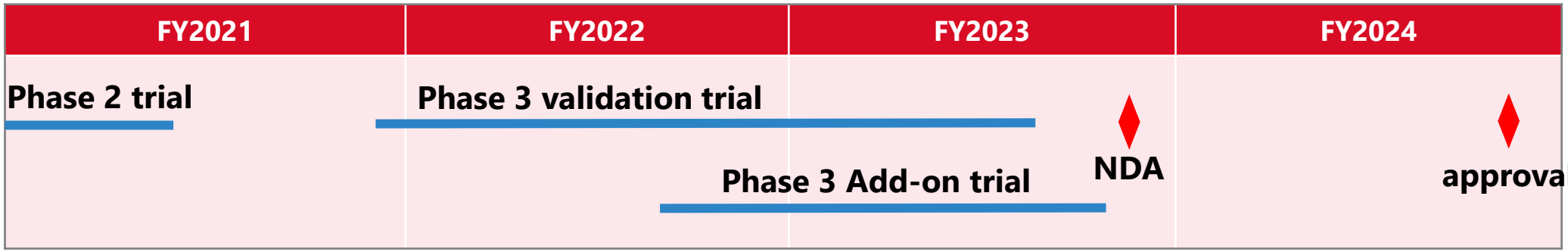
Evidence

- **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



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

* Brexanolone is chemically identical to endogenous allopregnanolone

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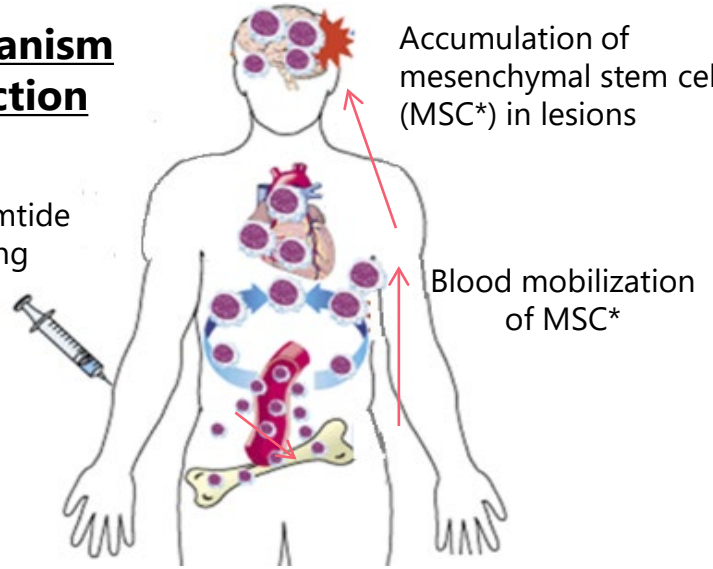
Redasemtide [S-005151]: Challenges and developmental significance for regenerative medicine

Conventional regenerative medicine (transplantation, regenerative medicine products, etc.)	
cost	High
therapeutic opportunity	Limited accessibility • To medical institutions, doctors • To early transplantation treatment
others	Difficult to manage cell quality

Regeneration-inducing drug (Redasemtide)
Low
Easy accessibility • To medical institutions, doctors (No special equipment required)
Easy to manage the quality because of a chemically synthesized product

Mechanism of action



Reproduction

- **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.

* Mesenchymal stem cells

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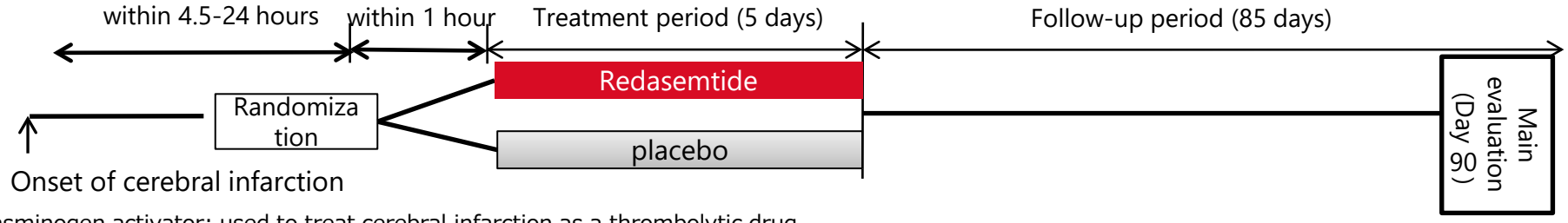
Redasemtide: Acute Ischemic Stroke Phase 2 Trial Overview

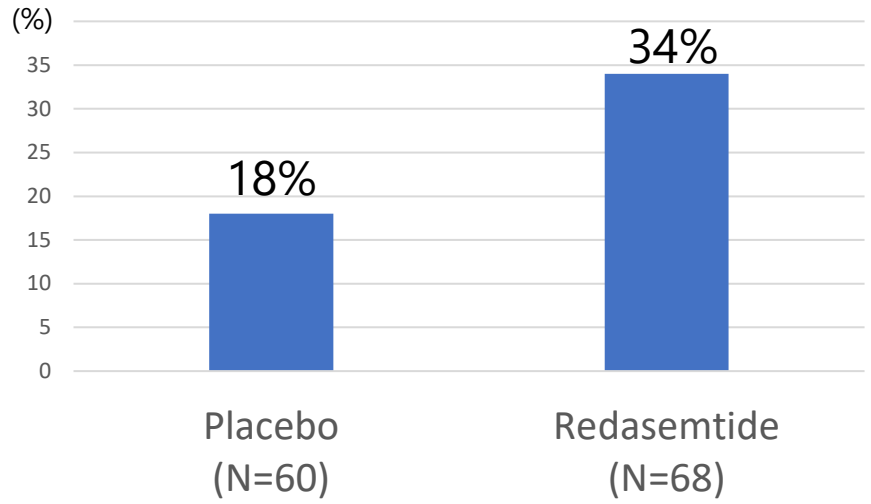
Clinical trial design	Multicenter, randomized, placebo-controlled, double-blind
Main purpose	Efficacy and safety of redasemtide in patients with acute ischemic stroke
Target patient	• Can be administered within 4.5-25 hours from the onset of symptoms at age 60-84 older • Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability) • Intravascular recanalization therapy (t-PA* treatment, endovascular treatment) cannot be performed
Administration group/ number of cases	• Redasemtide (1.5 mg/kg) group : 75 cases • Placebo group : 75 cases total 150 cases
Dosing method/duration	Intravenous administration once daily for 90 minutes for 5 days
Primary endpoint	**Modified Rankin Scale (mRS) after 90 days of administration**
Secondary endpoint	Presence or absence and frequency of adverse events, NIHSS**, Barthel Index (BI)***, mRS (Day365), days to discharge, QOL assessment
Country	Japan
Period	April 2019 - December 2021



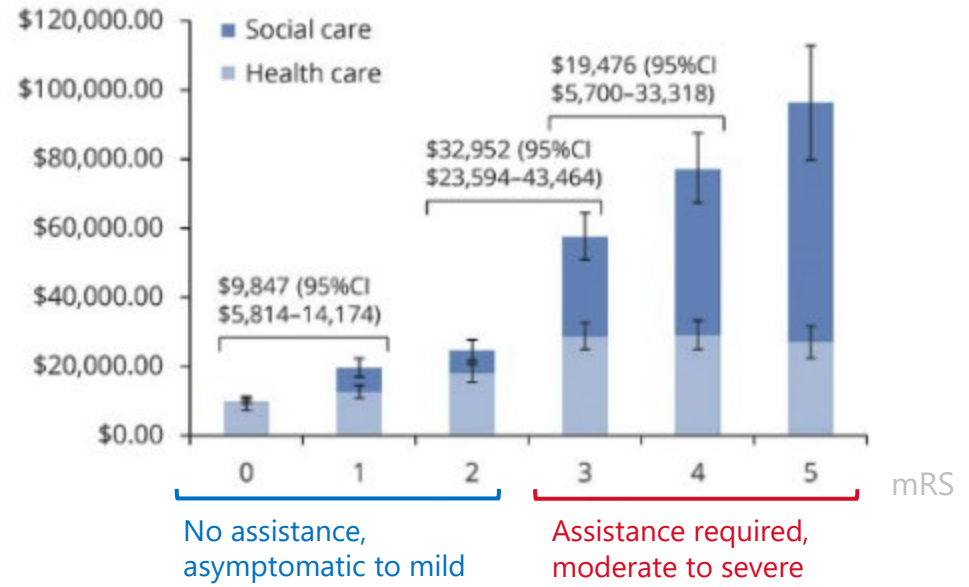
* tissue plasminogen activator: used to treat cerebral infarction as a thrombolytic drug
** National Institutes of Health Stroke Scale (NIHSS): Stroke Neurological Severity Rating Scale (42 points in total, the higher the score, the more severe)
*** Barthel Index (BI) : Evaluation scale for activities 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.**

* Modified Rankin Scale (mRS) : General prognostic rating scale (degree of social reintegration) ``Score 0 (no symptoms) to score 6 (death)'' in 7 grades

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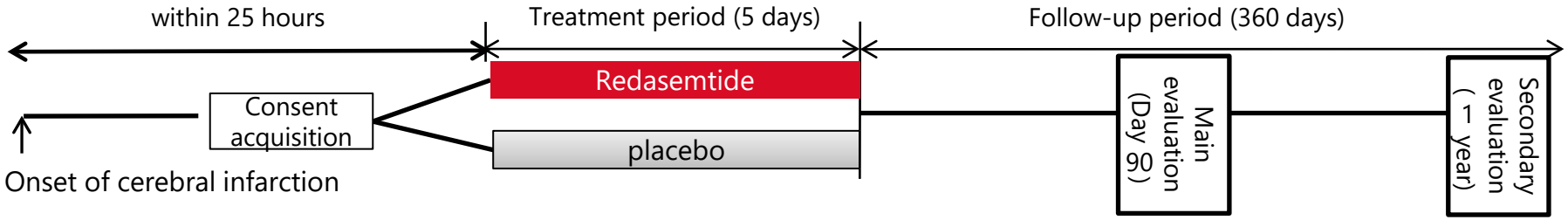
Redasemtide: Acute Ischemic Stroke Global Phase 3 Trial Overview (Draft)

clinical trial design	Multicenter, randomized, placebo-controlled, double-blind
main purpose	**Verification of efficacy of redasemtide in patients with acute ischemic stroke**
Target patient	• Can be administered within 25 hours from the onset of symptoms at age 18 or older • Presymptomatic mRS 0 or 1 (no symptoms, symptoms but no obvious disability) • Intravascular recanalization therapy (t-PA treatment, endovascular treatment) cannot be performed
Administration group/ number of cases	• Redasemtide (1.5 mg/kg) group : 678 cases • Placebo group : 678 cases total 1356 cases
Dosing method/duration	Intravenous administration once daily for 90 minutes for 5 days
Primary endpoint	**Modified Rankin Scale (mRS) after 90 days of administration**
Secondary endpoint	NIHSS, Barthel Index (BI), mRS (Day365), days to discharge, QOL assessment
country	Japan, Europe, North America, China, etc.



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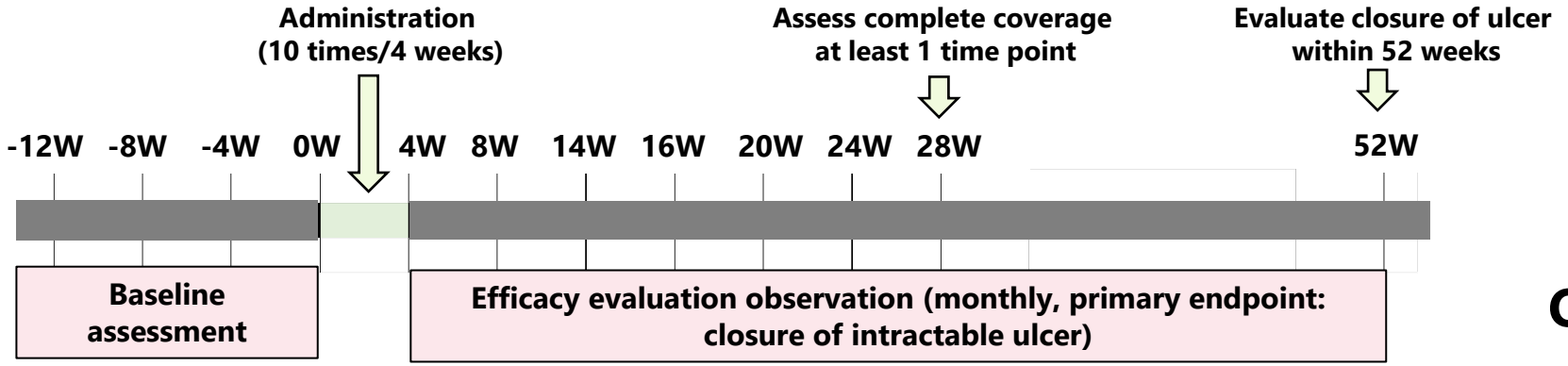
Redasemtide: Dystrophic epidermolysis bullosa additional Phase 2 trial (domestic) started

Clinical trial design	Multicenter, open-label, uncontrolled
Main purpose	Evaluation of efficacy and safety of redasemtide in patients with dystrophic epidermolysis bullosa with intractable ulcers
Administration group/ number of cases	Redasemtide (1.0 mg/kg) group: ≥3 subjects
Dosing method/ duration	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)]
Primary endpoint	Closure of intractable ulcer*



July 2022: Clinical trial notification submitted

Q4 2022 (FY) : FPI scheduled

* At least one time point of complete coverage within 28 weeks of administration and closure of intractable ulcer within 52 weeks of administration
Definition of closure: Complete coverage of the ulcer surface by the epidermis continues at 2 time points separated by 2 weeks or more

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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

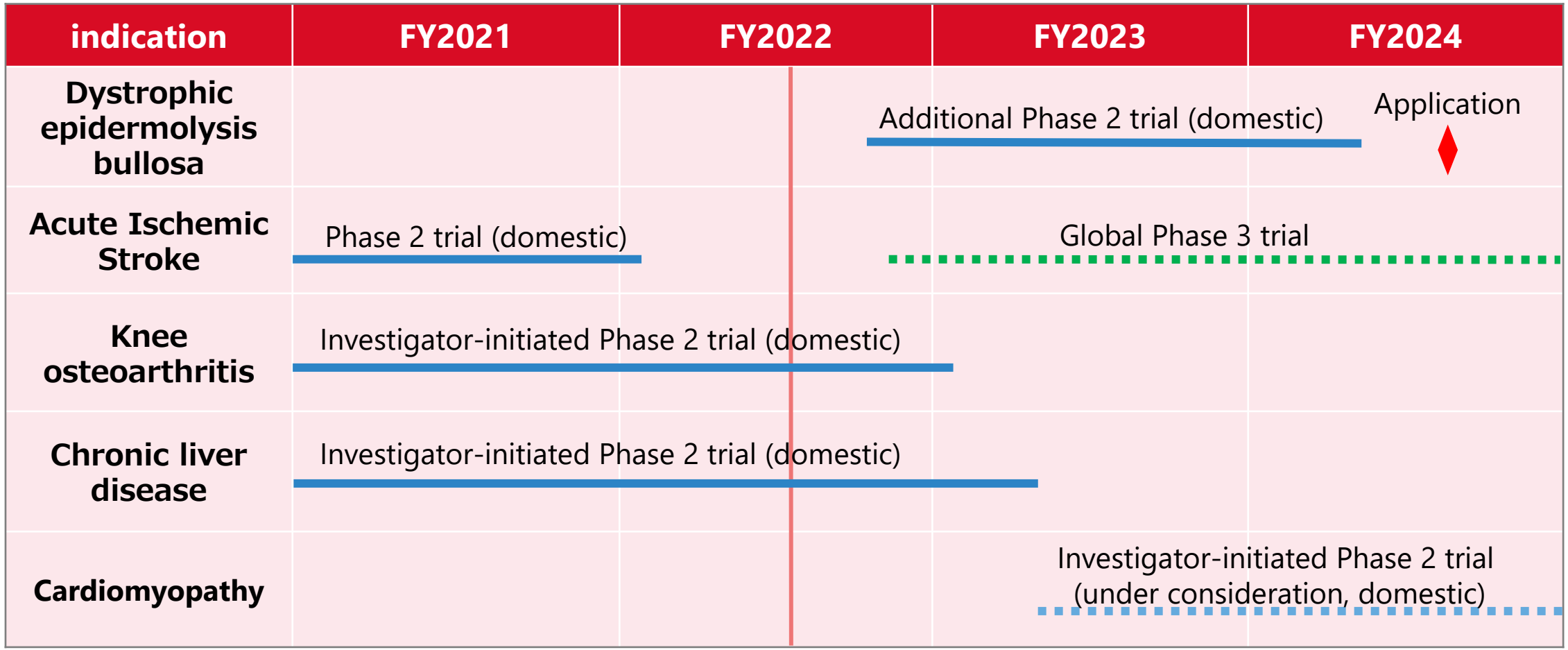
- Investigator-initiated Phase 2 trial (final observation in December 2022)
- Improvement of Morphological/joint function in knee osteoarthritis
- Providing new treatment opportunities that can contribute to improving QOL in an aging society

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

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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[*1] injectables

Market

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

Unmet needs

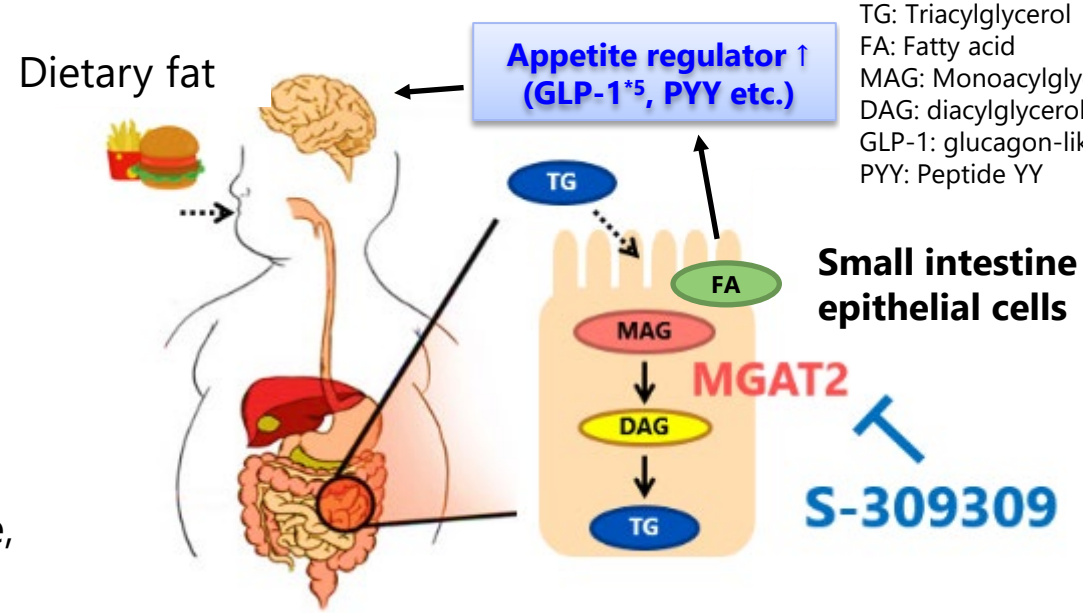
- There is a demand for a drug that has no safety concerns, shows a sufficient weight loss effect over a long period of time, and has a low out-of-pocket cost.

Current status and future plans

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

Mechanism of action

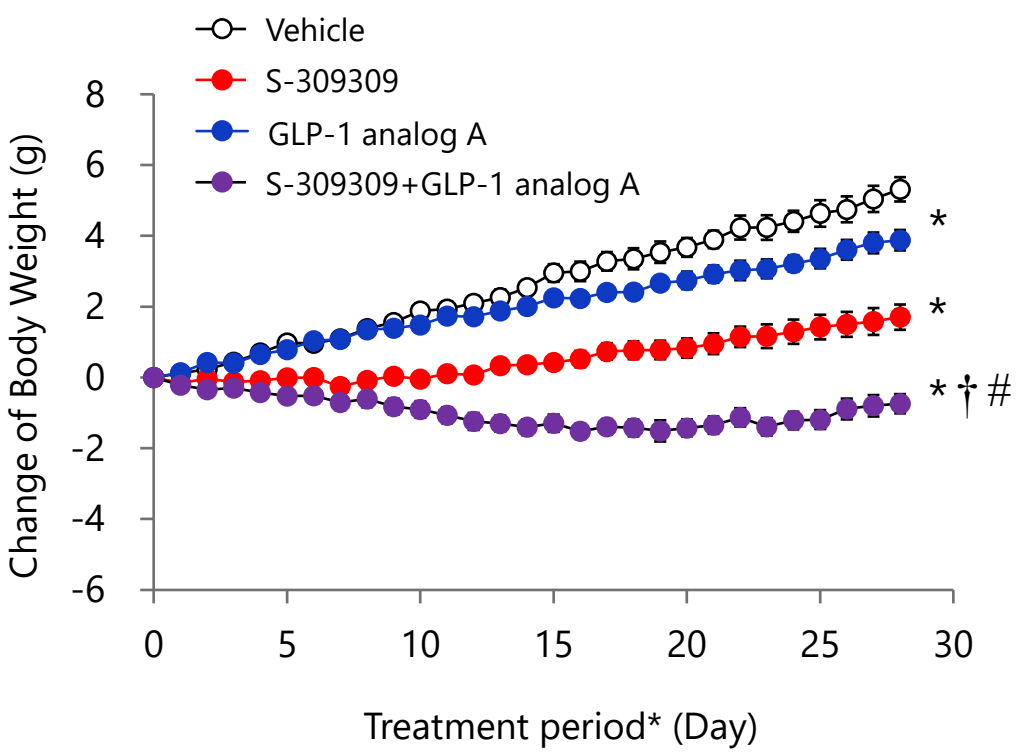
- Monoacylglyceroltransferase 2 (MGAT2[*5]) inhibitor



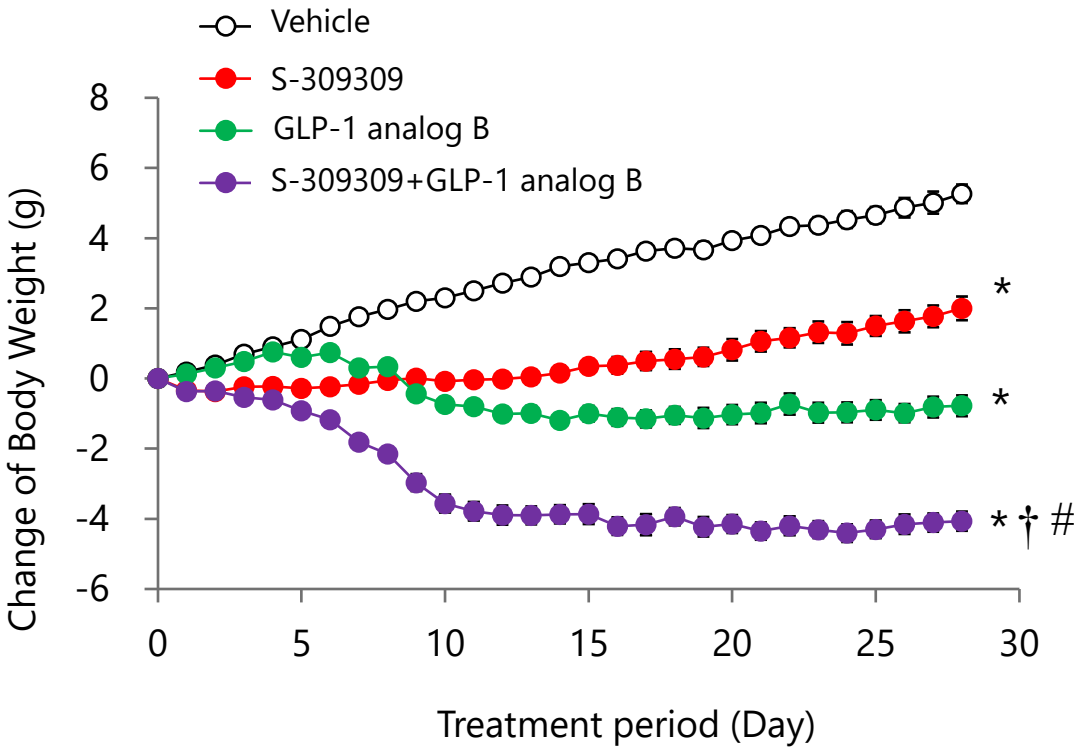
TG: Triacylglycerol
FA: Fatty acid
MAG: Monoacylglycerol
DAG: diacylglycerol
GLP-1: glucagon-like peptide-1
PYY: Peptide YY

*1 glucagon-like peptide-1 *2 © 2021 DR/Decision Resources, LLC. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.
*3 7 major markets; US, France, Germany, Italy, Spain, UK and Japan *4 Copyright © 2022 IQVIA. Calculated by SHIONOGI based on IQVIA Analytics Link 2021.1-12 , Reprinted with permission *5 monoacylglycerol acyltransferase 2

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 analogA, 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

* Administered for 4wks in high fat diet induced obesity mice

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S-309309: Phase1 SAD/MAD trial status

Part 1 Single dose trial

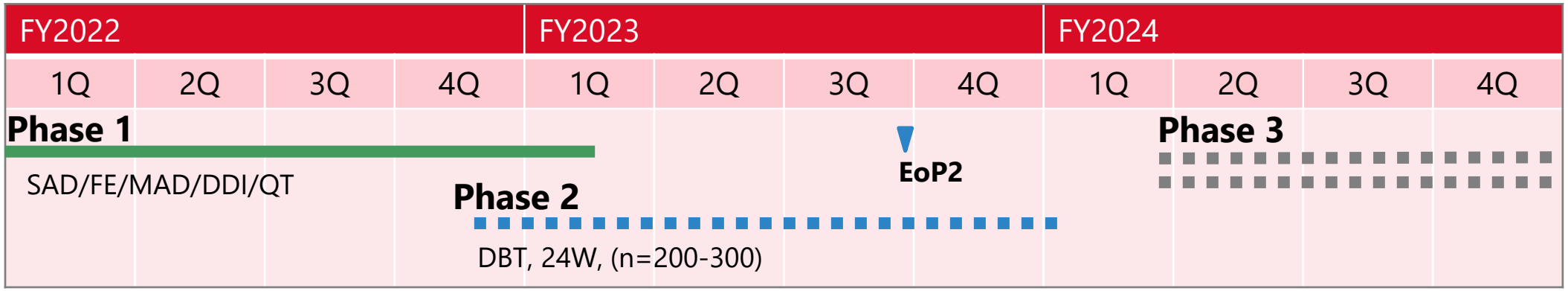
- AUC increased in dose-proportional manner between 1 – 300 mg.
- There are no significant food effect on the PK

Part 2 Repeated dose trial

- Ongoing

Country	U.S.
Trial design	Phase 1 (single/multiple), single-center, randomized, double-blind, placebo-controlled trial • Part 1: Single dose (1-300 mg/person): Healthy adults • Part 2: Multiple doses (50, 100 mg/person, 14 days): Healthy adults and obese but otherwise healthy adults
Evaluation content	• Safety and tolerability with single and multiple doses • PK after single and multiple doses • Food effect, QT analysis, Drug-drug interaction (midazolam)
Trial period	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)

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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

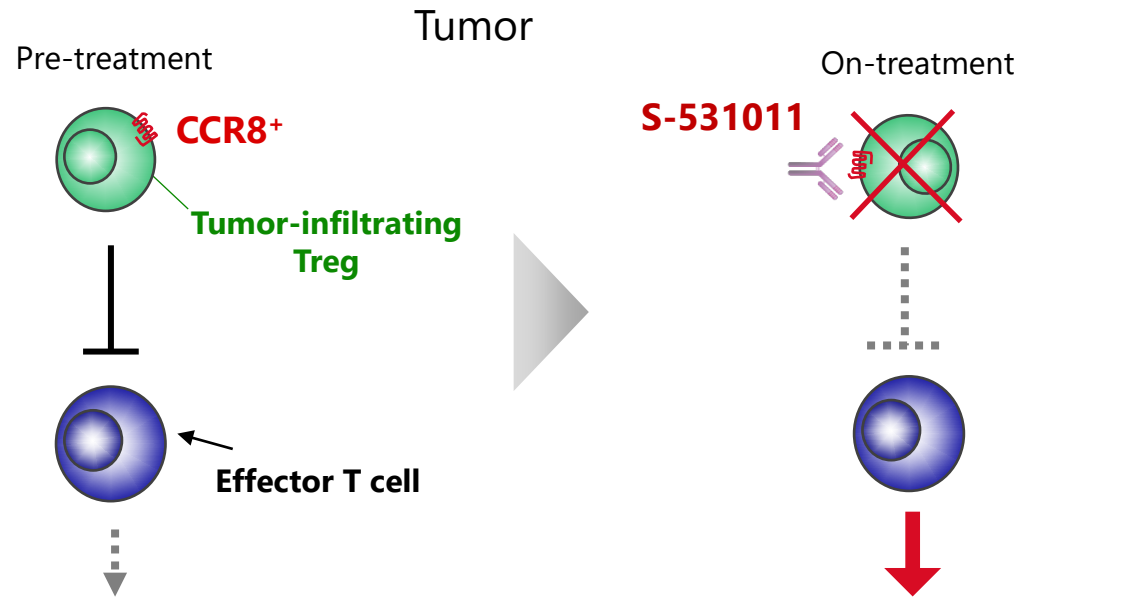
- High unmet medical needs for advanced cancer patients who have no approved ICI** therapy or limited efficacy of ICI

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.



* CCR8: Chemokine (C-C motif) receptor 8, **ICI: immune checkpoint inhibitor

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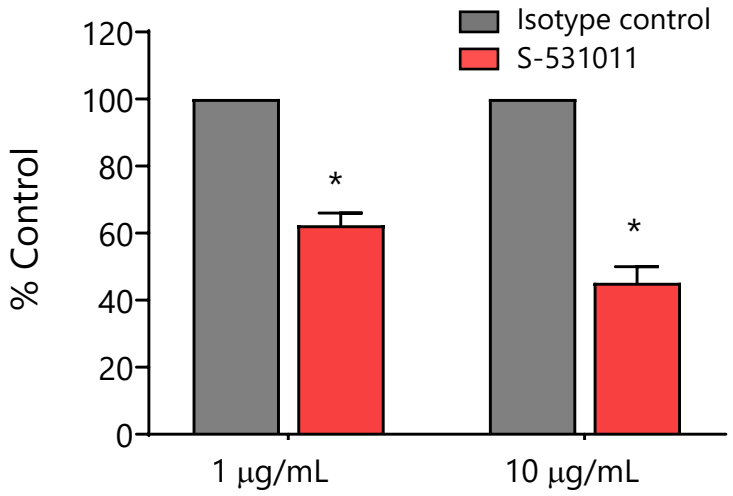
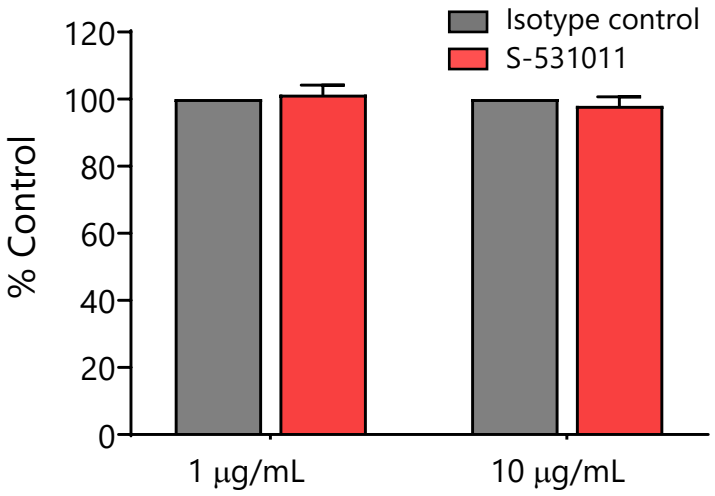
S-531011: Antibody-dependent cellular cytotoxicity activity using human samples

Tumor-infiltrating lymphocytes from lung cancer patients*

Treg



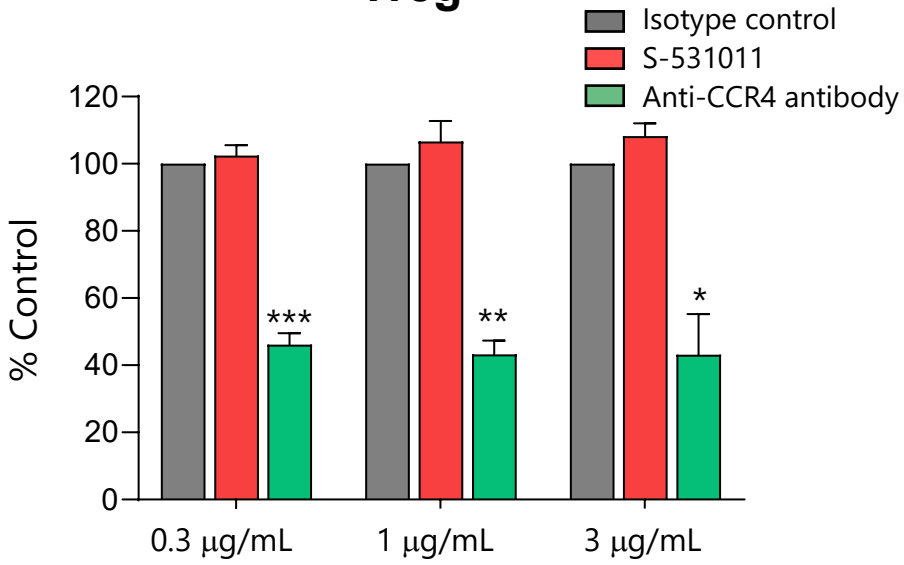
$CD4T_{conv}$***



Mean±SE (n=6), * p<0.01 vs Isotype (Dunnett's test)

human PBMCs**

Treg



Mean±SE (n=3)
*, **, *** p<0.01, 0.001, 0.0001 vs Isotype (Dunnett's test)

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

* Calculated percentage of Tregs or CD4 Tconv in $CD45^+$ cells ** Calculated percentage of Tregs in CD4T cells ***CD4T cells other than Tregs

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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

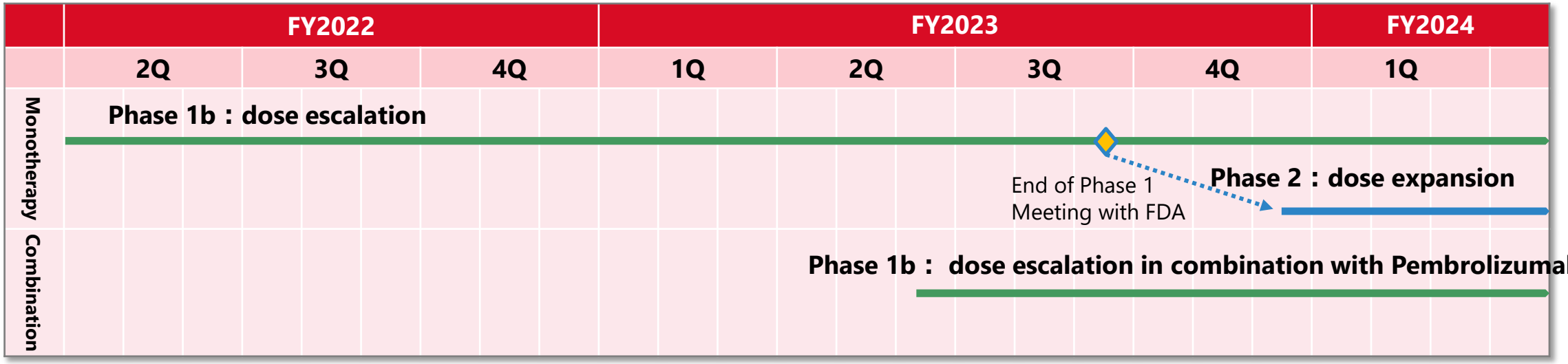
- No Dose Limiting Toxicity (DLT) occurred to date

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



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

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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

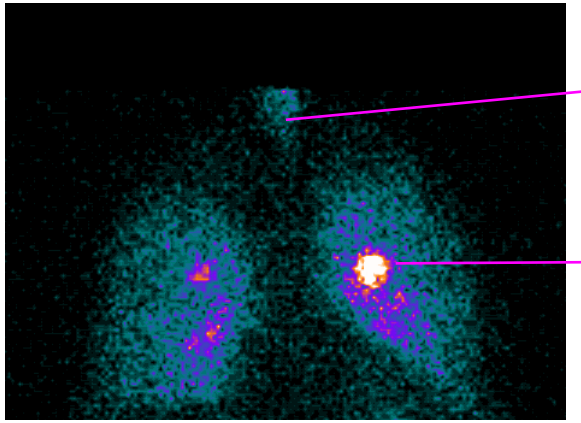
* Idiopathic pulmonary fibrosis ** Progressive Fibrosing Interstitial Lung Disease

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.

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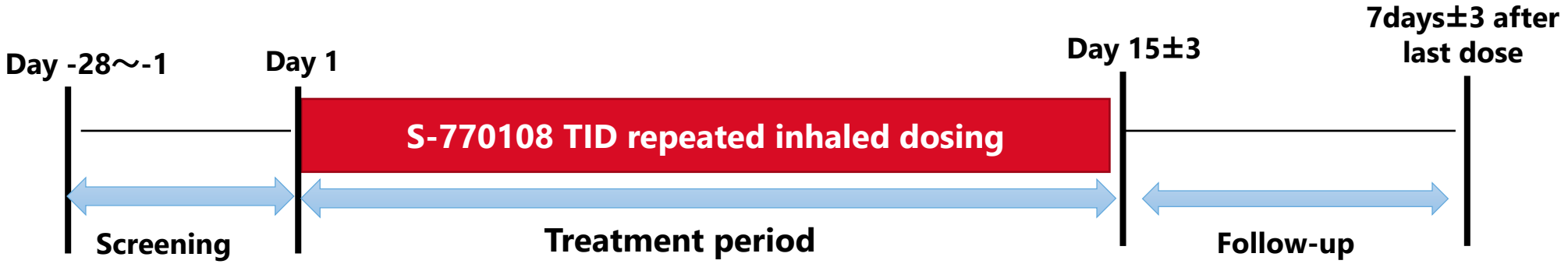
S-770108: IPF patient Japan Phase1b trial results

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

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Agenda

1. Shionogi's R&D

- Opening — **John Keller, Ph.D.,** Senior Vice President, R&D Supervisory Unit
- Progress of COVID-19-related R&D — **Takeki Uehara, Ph.D.,** Senior Vice President, Drug Development and Regulatory Science Division
- Progress of Shionogi R&D
  - ✓ Development area — **Takeki Uehara, Ph.D.,**
  - ✓ Research area — **Yasuyoshi Iso, Ph.D.,** Senior Vice President, Research Division
  - ✓ Vaccine Business — **Yasunori Aoyama, Ph.D.,** Senior Vice President, Biopharmaceutical Research Division
  - ✓ Summary of R&D — **John Keller, Ph.D.,**

2. Summary

Isao Teshirogi, Ph.D., Chief Executive Officer

3. Q&A

Research area progress

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

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Research part

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

Actions in the area of infectious diseases

Research Areas	Research Strategy	Target Diseases	
1. Acute Infection	• 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	• **COVID-19 medicine** • **RS Viral infections** • Next pandemic • Exacerbation suppression	Research Department P.84-93
2. Chronic Infections	• Continuous creation of new anti-HIV drugs and pursuing HIV curative research by utilizing our infectious disease drug discovery know-how • Advancing research in chronic infectious diseases (e.g., nontuberculous mycobacteria (NTM) and malaria)	• **HIV therapies** (combination candidates for S-365598) • **HIV curing** • Therapeutic drugs for NTM • Antimalarial drugs	
3. Infectious Disease Vaccine	• Progressing vaccine research based on our own infectious disease and immunology knowledge coupled with external collaboration • Building vaccine platforms based on S-268019 R&D experience	• **COVID-19** • Influenza • S. pneumoniae • Hepatitis B	Biopharmaceuticals Research Department P.100-108

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Pipeline in infectious disease

Research		Development	
Ensitrelvir backup	**S-337395** RS viral therapeutic drug	**Ensitrelvir** COVID-19 therapeutic drug	**Xofluza®** Flu treatment
Respiratory Viral Infection Drugs (Next-generation pandemic, exacerbation suppression	**S-554110** NTM therapeutic drug	**S-268019** COVID-19 Prevention Vaccine (IM)	**Cefiderocol** Severe infections therapeutic drug
HIV therapies (Radical and functional curative)	**S-875670** COVID-19 prevention vaccine (nasal)	**S-555739 [Asapiprant]** Inhibition of COVID-19 aggravation	**Cabotegravir** HIV treatment and prophylaxis
Antimalarial drugs	**S-872600** Influenza prevention vaccine (nasal)	**S-365598** HIV therapeutic drug	
COVID-19 vaccine (mutant strain and universal vaccine)	**S-540956** Nucleic acid adjuvant	**F901318** Treatment of invasive aspergillosis	
Pneumococcus vaccine			
Hepatitis B vaccine			

: Out-licensing

: In-Licence

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1. Acute infection

COVID-19 therapeutic drugs: Actions overview

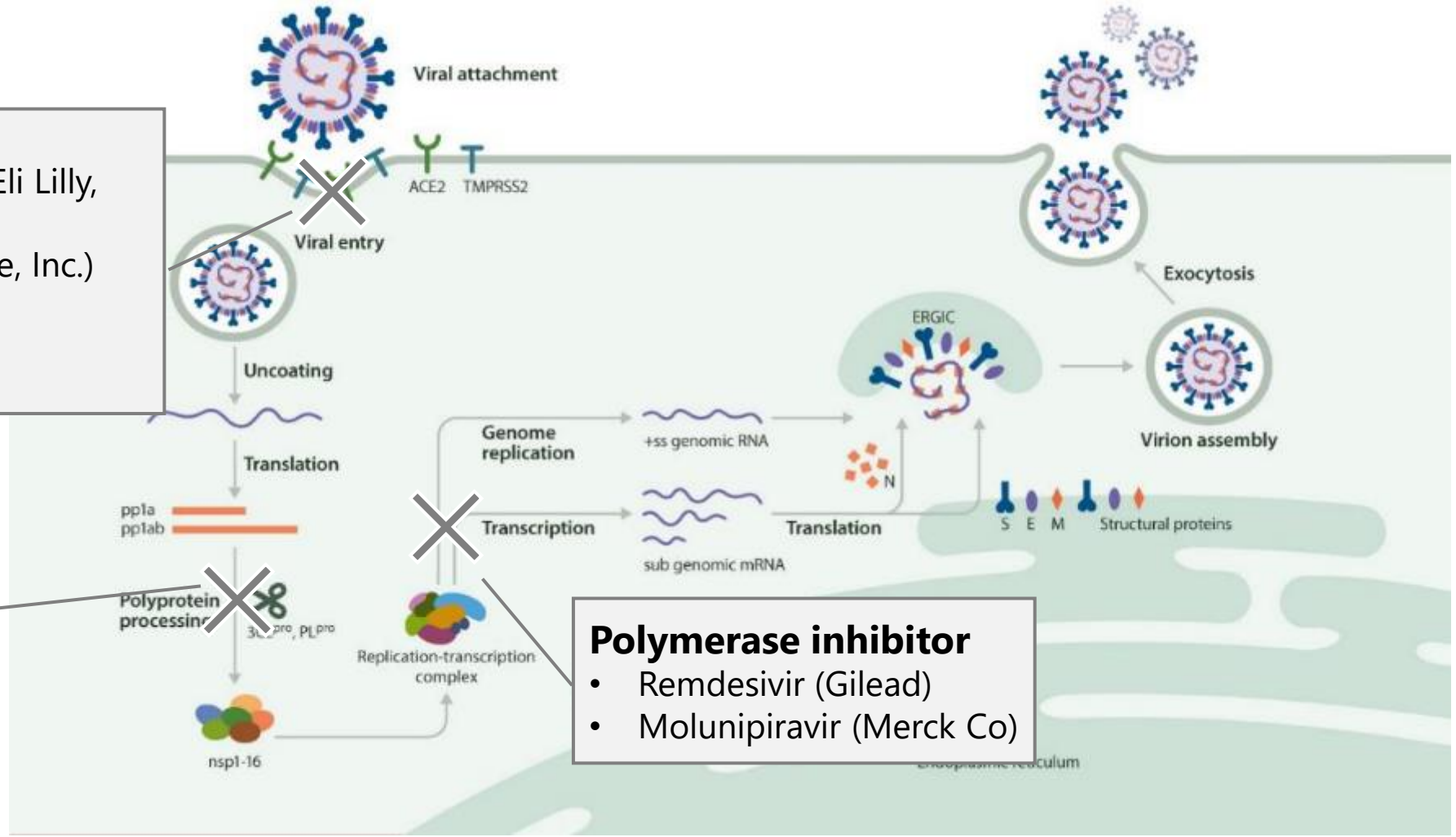
Small molecule	**Initial candidate compound**	Fastest provision of COVID-19 specific therapeutic drug ⇒ Discontinued
	Ensitrelvir	Applicable to a wide range of patients therapeutically and prophylactically
	Ensitrelvir backup	Creation of oral therapeutic drugs that meet future needs
Peptide	**S-880008**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

1. Acute infection

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

Virus entry inhibitor
- Bamlanivimab/Eteseviimab (Eli Lilly, Inc.)
- Sotrovimab (Glaxo SmithKline, Inc.)
- Tixagevimab/Cilgavimab (AstraZeneca)
- **S-880008**

Protease Inhibitors
- Nirmatrelvir (Pfizer)
- **Ensitrelvir**



Polymerase inhibitor
- Remdesivir (Gilead)
- Molunipiravir (Merck Co)

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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)

- Analyzed complex between the target protein and the lead compound at an early stage
- Rapid chemical modification of the unique scaffold

- Accelerated development of manufacturing methods by rapid industrialization studies based on predictions from experimental data
- Rapid supply of investigational products through multiplexing of raw material sourcing and manufacturing

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

* Structure activity relationship: Correlation between Structural and Antiviral Activity

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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

* Receptor Binding Domain: SARS-CoV-2 with human ACE2 receptors

1. Acute infection

S-880008: Reasons for discontinuing development

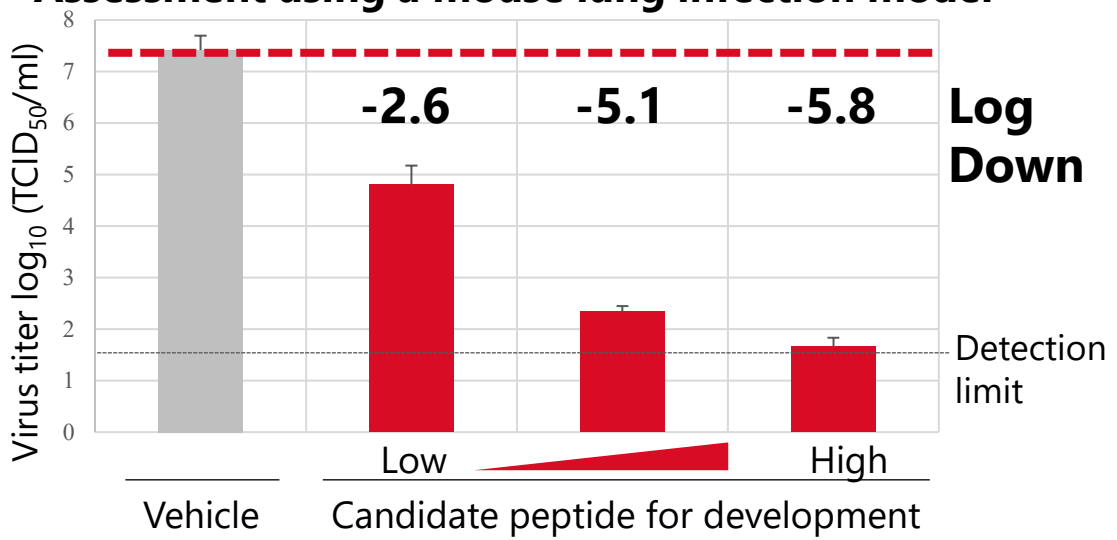
Although we were able to confirm potent in vivo efficacy, including against BA.1 strain, however, activity against a BA.2 strain with multiple amino acid mutations is reduced

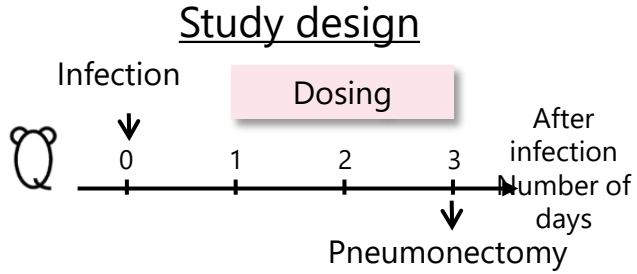
Discontinued preclinical development because broad coverage cannot be assured for newly emerging variants

In vitro efficacy

Viral strains	EC_{50} (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*





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

This research is supported by AMED under Grant Number JP20fk0108509

* SARS-CoV-2(WK-521 line) using virus acclimated in murine lung tissue

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2. Chronic infections

Actions in HIV research towards 2030 and beyond

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

ViiV Healthcare

~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

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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

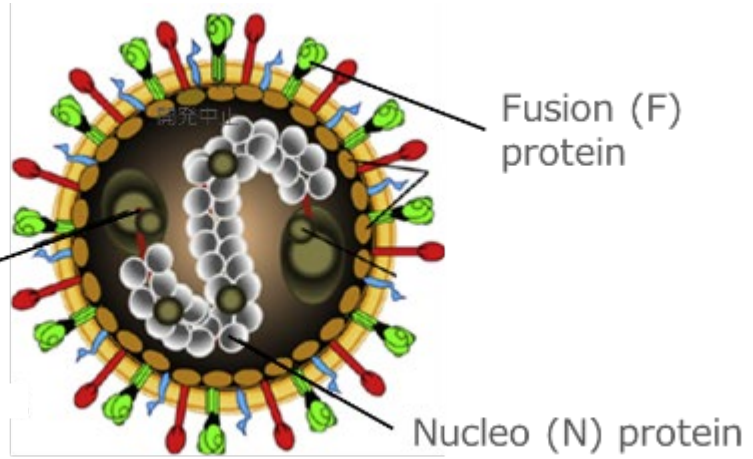
* World Health Organization.(2017).WHO Preferred Product Characteristics for Respiratory Syncytial Virus (RSV) Vaccines.

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

Phase 1	Phase 2	Phase 3	Application and approval	Launch
BC-0335 Shandong	**EDP-938** Enanta	**MK-1654** Merck	**Nirsevimab** AstraZeneca	**Palivizumab** AstraZeneca
RSV-N Pfizer	**Sisunatovir** Pfizer	**Rilematovir** Janssen, Inc.	**Ziresovir** Ark Biosciences	
EDP-323 Enanta				

: F protein inhibitor : N protein inhibitor : Others
: L protein inhibitor : antibody

* As of October 12, 2022

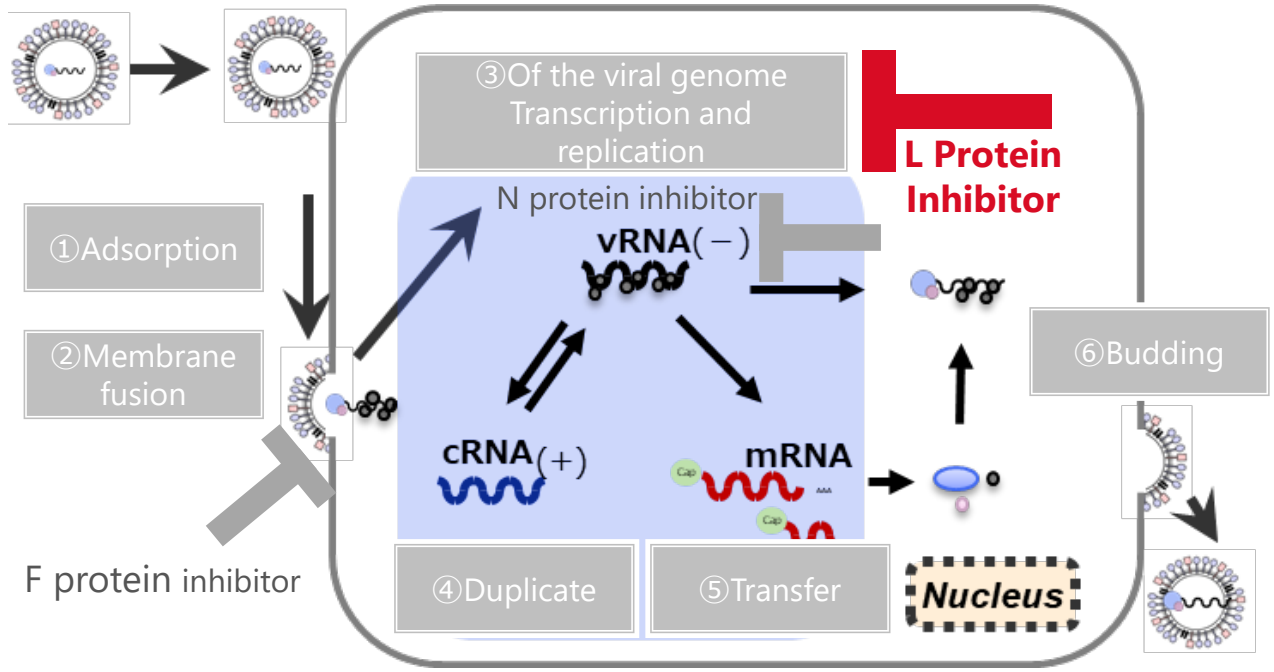
SHIONOGI

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



* RNA-dependent RNA polymerase

SHIONOGI

1. Acute infection

S-337395: Non-clinical data

In vitro activity*

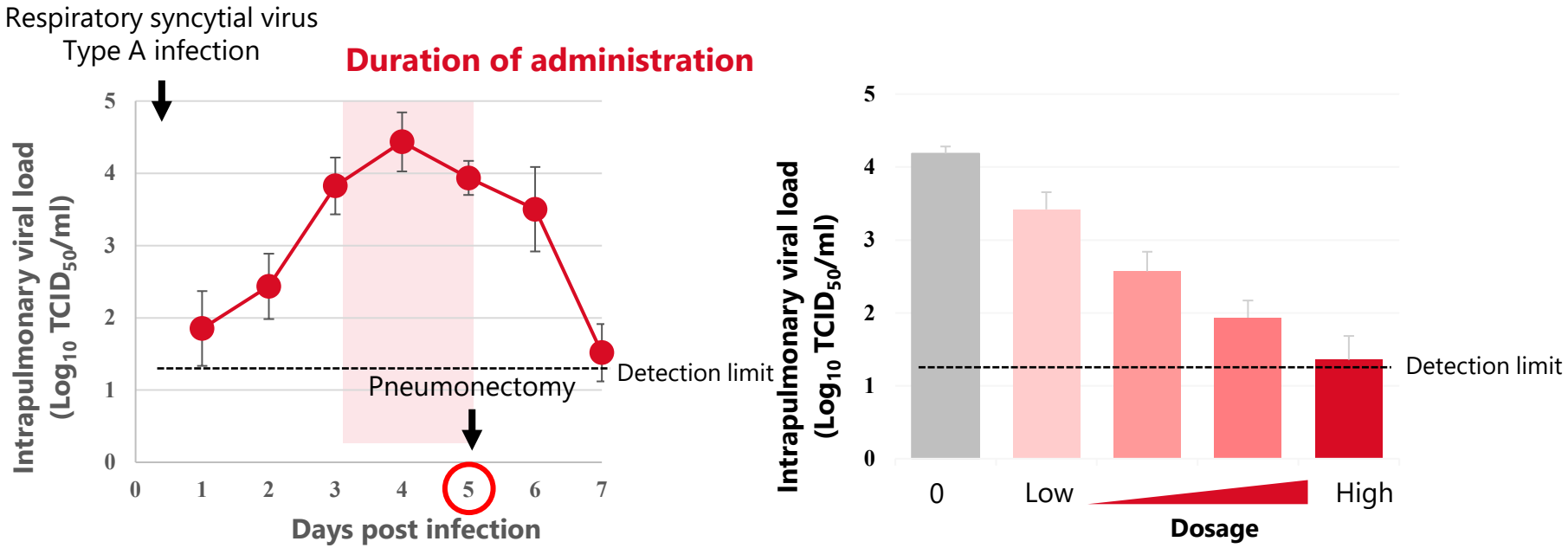
- For types A and B, strong antiviral activity was confirmed

Antiviral activity (EC_{50}; 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.



* Exploratory studies that have not yet performed QA(QC completed)
QA: Quality Assurance
QC: Quality Control

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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*2 , increased rate of suicide and illicit drug use*3) 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 *2 Pain Med (2019) 1;20(4):724-735
*3 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

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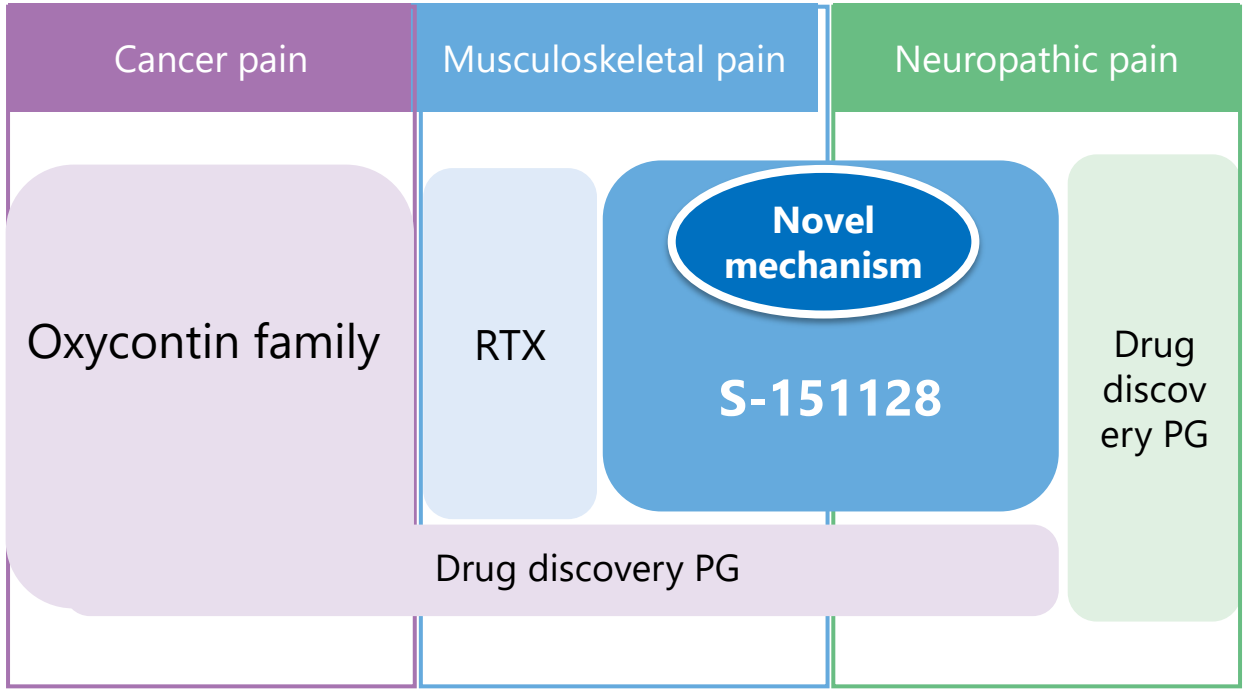
S-151128: Actions in the pain area

SHIONOGI strategy for pain treatment

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



RTX: Resiniferatoxin

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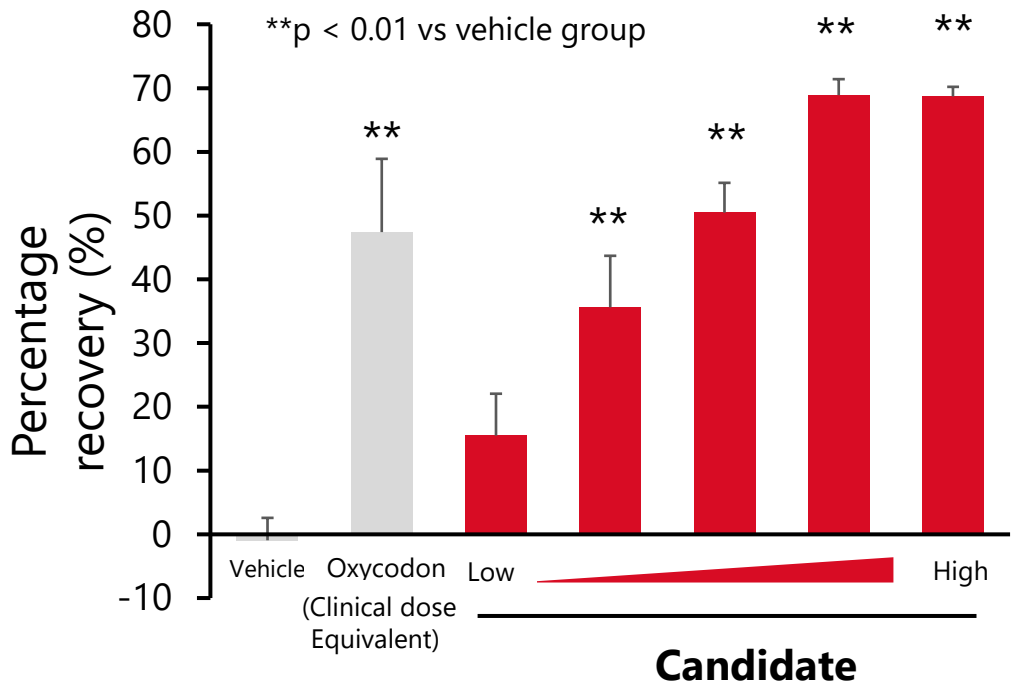
S-151128: Analgesic with a novel mechanism

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*2, and PPI*3, 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

* Exploratory studies that have not yet performed QA *2 G protein-coupled receptor:G Protein-Coupled Receptors
*3 Protein-protein interaction: Protein-protein interactions

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Timeline until the start of Phase 1 trial

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

★ Scheduled start of Phase 1 trial

Agenda

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- Progress of Shionogi R&D
  - ✓ Development area — **Takeki Uehara, Ph.D.,**
  - ✓ Research area — **Yasuyoshi Iso, Ph.D.,** Senior Vice President, Research Division
  - ✓ Vaccine Business — **Yasunori Aoyama, Ph.D.,** Senior Vice President, Biopharmaceutical Research Division
  - ✓ Summary of R&D — **John Keller, Ph.D.,**

2. Summary

Isao Teshirogi, Ph.D., Chief Executive Officer

3. Q&A

Progress of vaccine business

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

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What is a vaccine?

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

Recombinant protein vaccine

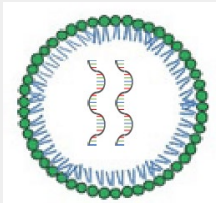
S-268019

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

* Adjuvants: Materials that increase immunogenicity

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	**Gaining expertise in vaccine production**
Manufacturing • Acquisition of 'rhabdovirus-free' insect cell culture techniques • Acquired manufacturing and research base	• 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	
Antigen	**Recombinant antigen S-910823 of the full-length spike protein prepared in UMN Pharma's "rhabdovirus-free" insect cell culture**
Adjuvant	**Optimaize response to A-910823 for increased neutralizing antibody titer**

Acquired new capabilities and technologies through our effors

Adjuvant selection

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

Neutralizing antibody titer assessment

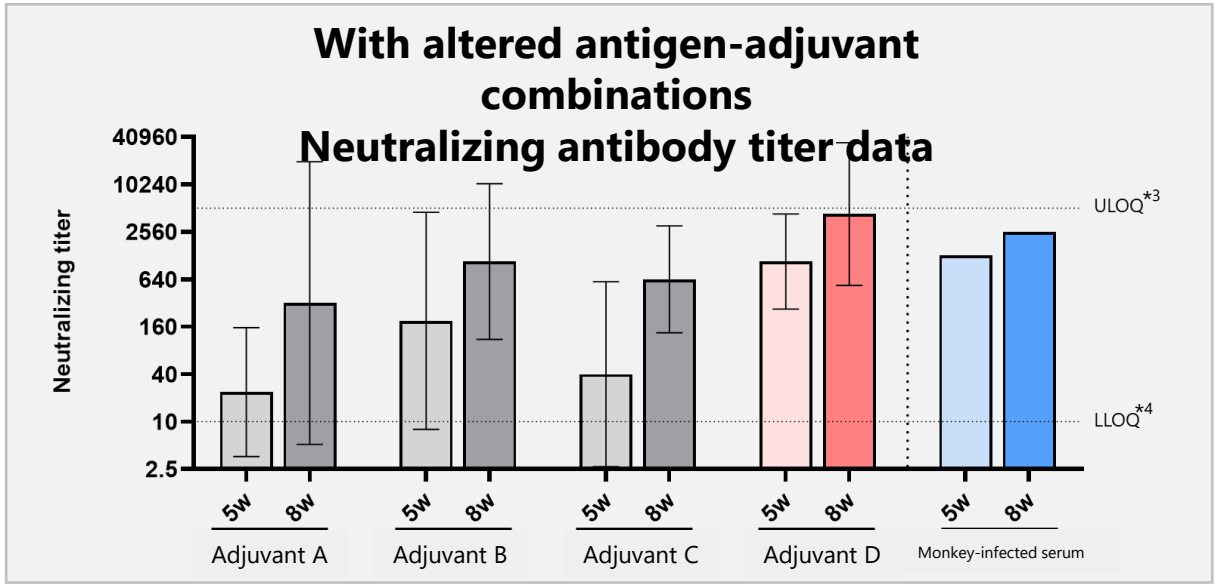
- Rapid response to the emergence of mutant viruses

Antigen production

- Stable production and supply of investigational products

Adjuvant studies essential for the creation of S-268019

Previous adjuvant research	1st adjuvant selection in S-268019	Clinical studies with 1st adjuvant 2nd adjuvant selection	Decided to change adjuvant
Accumulated knowledge of adjuvants including by S-540956 creation	Selection of adjuvants based on VDE*1 risk and Th1*2 selectivity risk	Explored multiple combinations of antigens and adjuvants in parallel with Phase 1 trial	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

*1 Vaccine induced Disease Enhancement *2 helper T1 cells *3 Upper limit of quantification *4 lower limit of quantification

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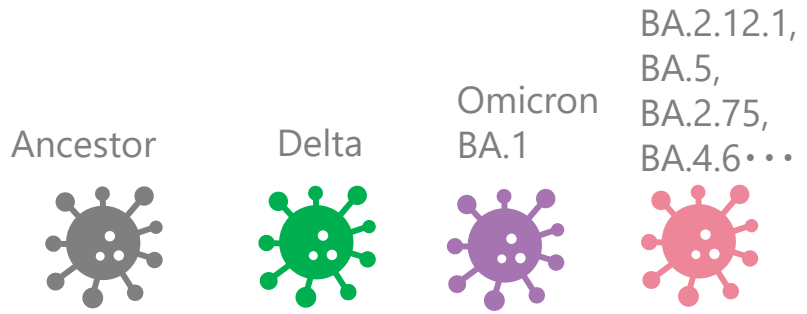
Establishment of an evaluation system for the emergence of mutant viruses

Early detection of the virus

- Continuous monitoring of the emergence of mutant viruses globally



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

* Viruses that have transiently expressed other viral envelope proteins or specific proteins on their surface instead of their own envelope proteins, also called pseudotyped viruses

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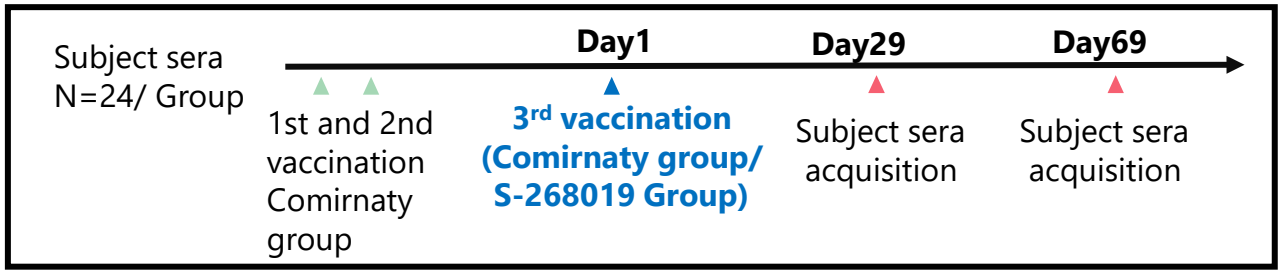
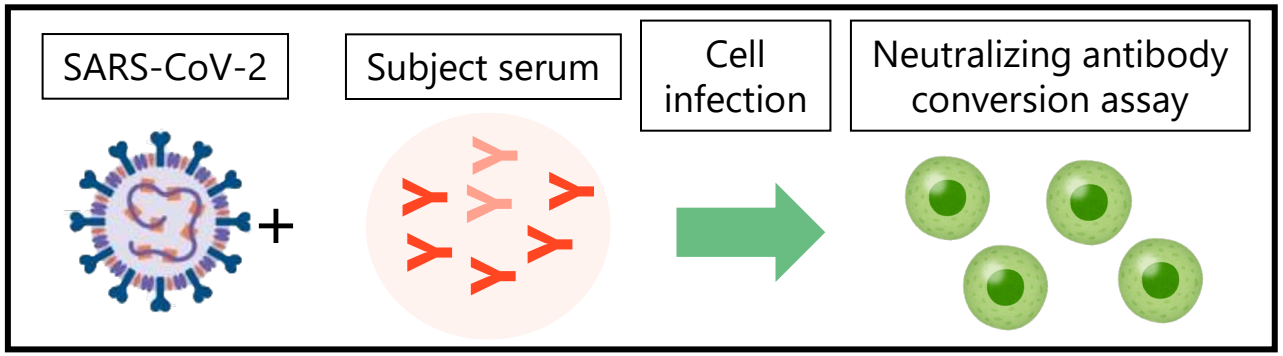
Neutralization titers against S-268019 mutant viruses

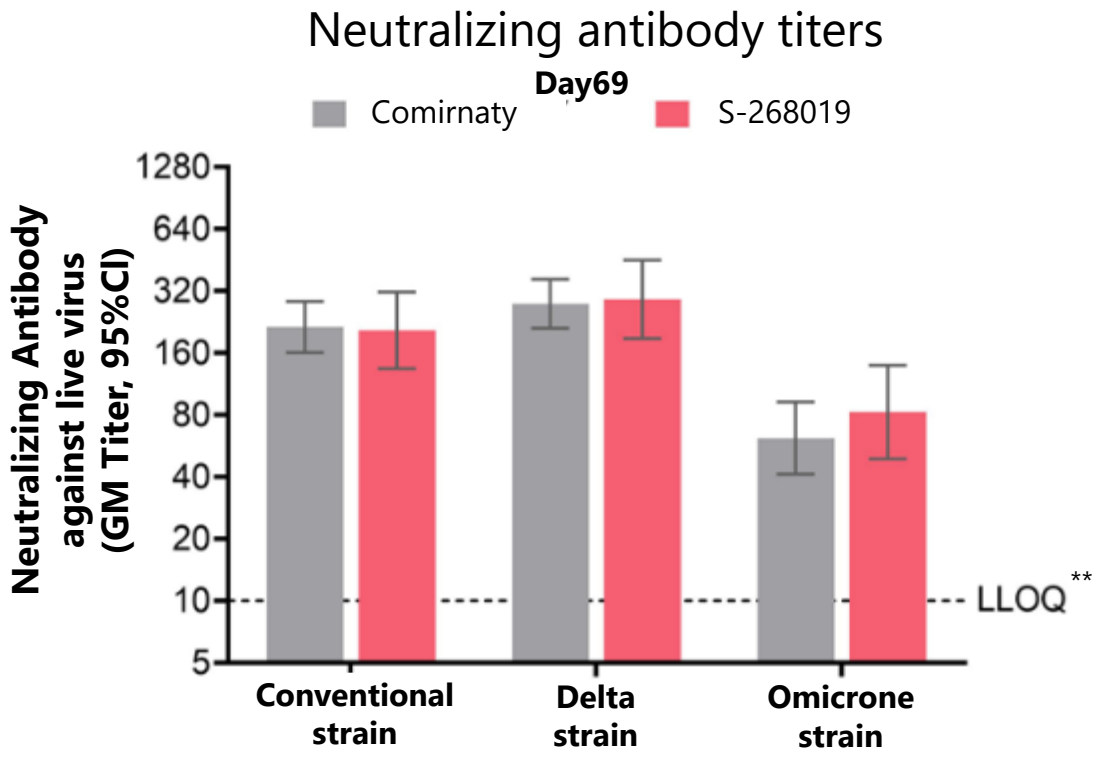
Neutralization titers against mutant viruses were determined using subject serum from Phase 2/3 booster trial*

-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

* jRCT2031210470 (Link) ** lower limit of quantification

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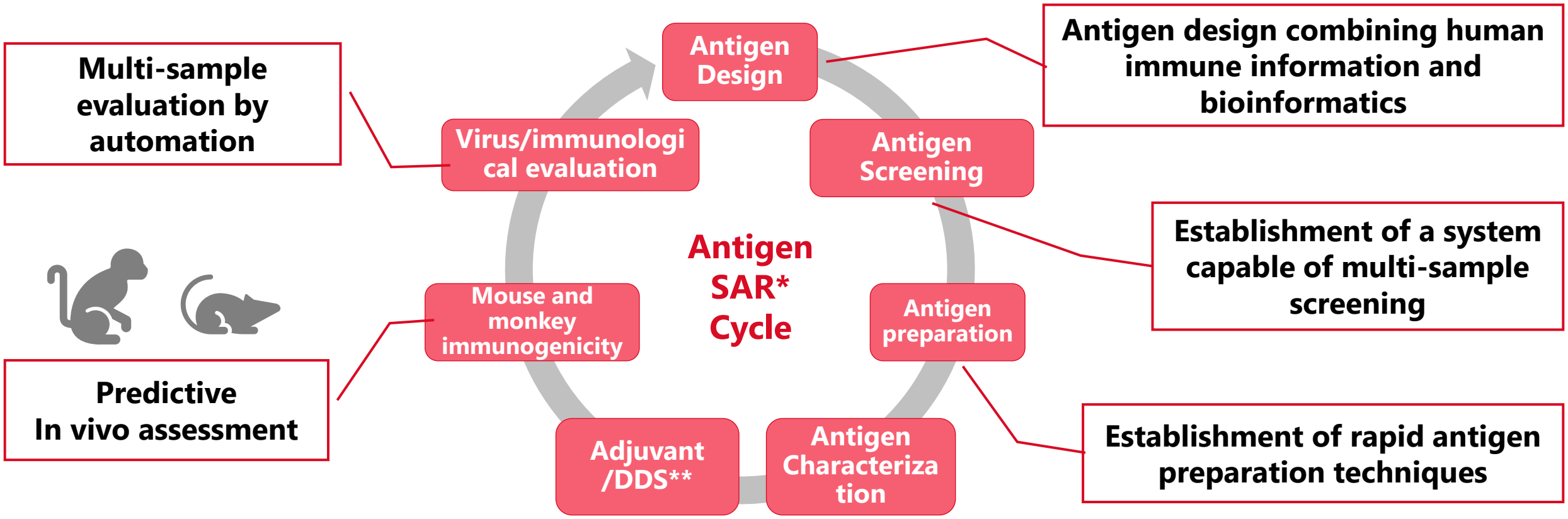
Construction of a novel antigen creation platform



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

* Structure–activity relationship ** Drug Delivery System

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

大阪大学 OSAKA UNIVERSITY　NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES　KOTAI

Construction of a mucosal immune platform

Practical application of a mucosal immunization-inducing vaccine in humans

Preparation of COVID-19[*2] and pneumococcus vaccine-antigen[*3] using cCHP[*1]

国立大学法人千葉大学 CHIBA UNIVERSITY　HanaVax　NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES

Universal antigen design[*4]

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

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

Adjuvant studies

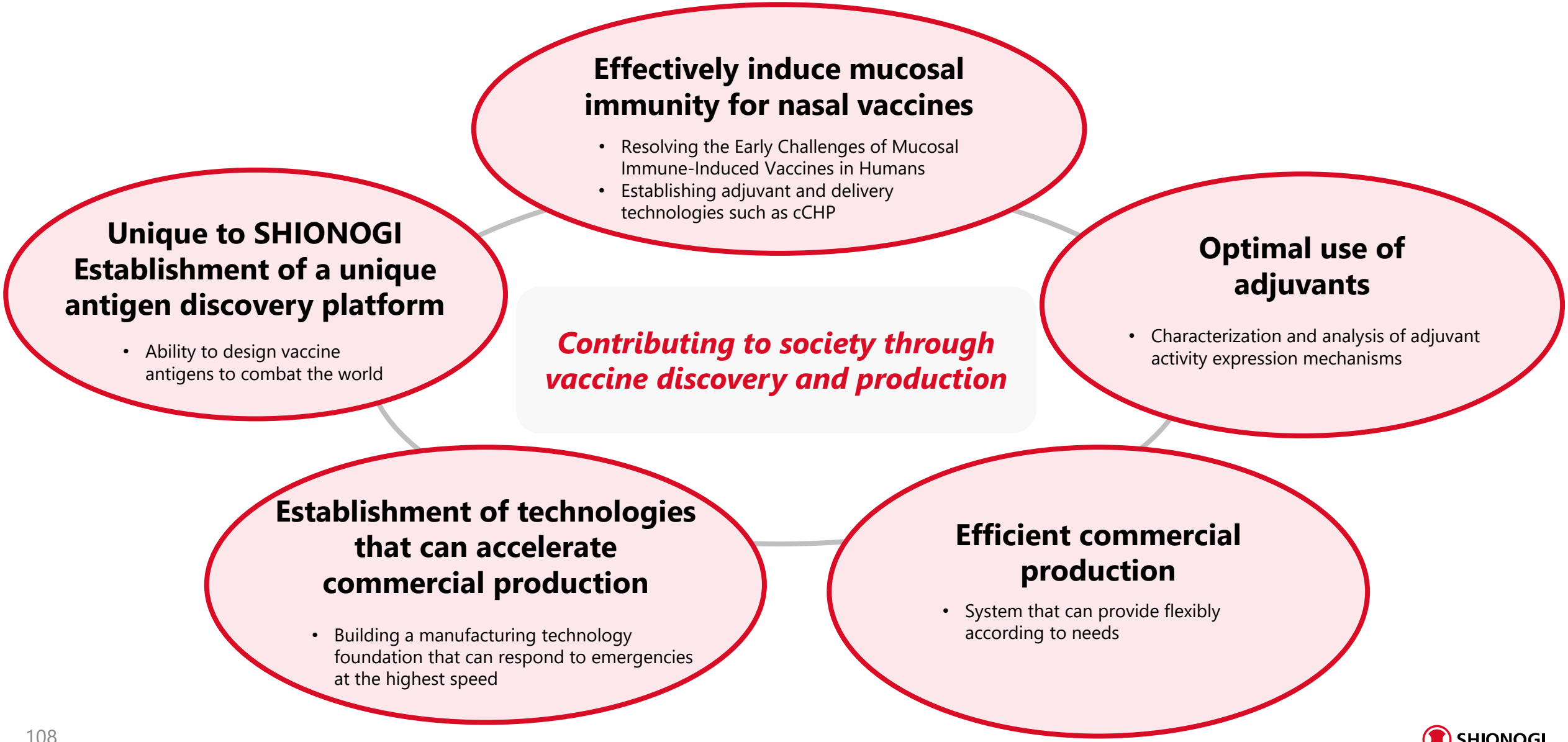
A platform to support optimal matching of adjuvants to antigens

東京大学医科学研究所 The Institute of Medical Science, The University of Tokyo

[*1] Cationic Cholesteryl Pullulan　[*2] Recombinant protein vaccine made with BEVS　[*3] pneumococcal surface protein A

[*4] Universal antigens: broad-spectrum antigens that cross over sarbecoviruses in general (Sarbecoviruses: Subpopulations around SARS coronaviruses)

Aims of vaccine research



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✓ Research area	**Yasuyoshi Iso, Ph.D.,** Senior Vice President, Research Division
✓ Vaccine Business	**Yasunori Aoyama, Ph.D.,** Senior Vice President, Biopharmaceutical Research Division
✓ Summary of R&D	**John Keller, Ph.D.,**
2. Summary	**Isao Teshirogi, Ph.D.,** Chief Executive Officer
3. Q&A	

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Summary of R&D

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

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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

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Upcoming pipeline events 1/2

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

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

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

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Upcoming pipeline events 2/2

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

Pipeline	Indication	Stage	FY2022 3Q-4Q	FY2023	FY2024
redasemtide (S-005151)	①Epidermolysis bullosa ②Acute ischemic stroke ③Knee osteoarthritis ④Chronic liver disease ⑤Cardiomyopathy	①Preparing for additional clinical trial ②Preparing for Phase 3 trial ③④Investigator initiated clinical trial（Phase 2 trial）in progress ⑤Preparing for Investigator initiated clinical trial	① ② ⑤	Ph3 start (4Q) Ph2 start (2Q)	Submission (3Q)
S-309309	Obesity	Phase 1	Ph1 topline results (3Q) Ph2 start (4Q)	Ph2 topline results (3Q)	
S-531011	Solid tumor	Phase 1b/2		Ph2 start (4Q)	
S-770108	Idiopathic pulmonary	Phase 1		Ph2 start (1Q)	

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

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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

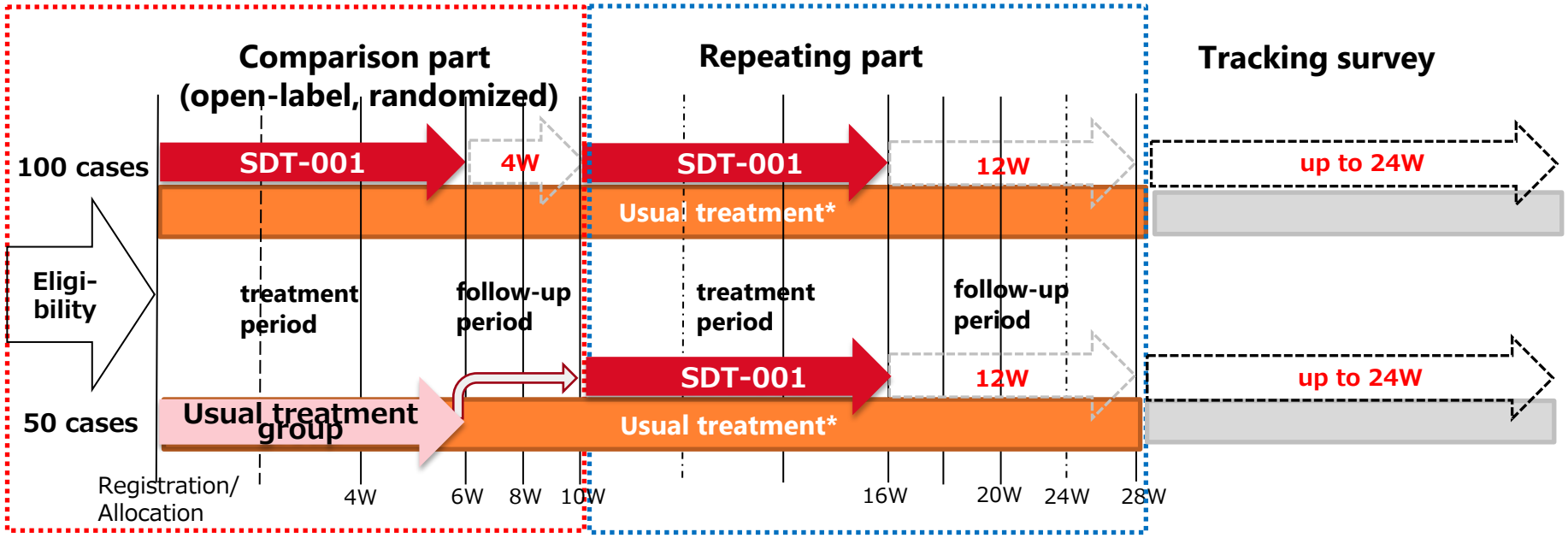
- Strong need for treatment without drugs (concerns about side effects and long-term administration), demand for other treatment options than drugs.
- Few medical institutions that can receive psychosocial treatment (conducted face-to-face with physician and medical personnel) due to lack of their resources.

Current status and future plans

- Phase 3 trial ongoing from April 2022
- Plan to apply in 2023
- Iindication 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)

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



* Psychosocial treatment including environmental adjustment

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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-217622*** **[Ensitrelvir Fumaric Acid]** COVID-19 treatment	**S-217622 **** **[Ensitrelvir Fumaric Acid]** COVID-19 treatment
S-875670 COVID-19 nasal vaccine	**S-337395** RSV infections		**S-268019** COVID-19 Prophylactic vaccine	* Phase 2/3, Phase 3 ** Phase 2/3
S-554110 Nontuberculous mycobacterial infection			**S-268019** COVID-19 Prophylactic vaccine	**cefiderocol** Various infectious diseases
			cefiderocol Aerobic Gram-negative bacterial infection（Pediatric）	**Xofluza®** Influenza virus infection (Granules, < 20kg)
			F901318 **[olorofim]** Invasive Aspergillosis	

Stage change (change from August . 1, 2022)
S-880008 (COVID-19 treatment): Closed

: Global development

Out license

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

Preclinical	Phase 1	Phase 2	Phase 3	Submission
S-874713 Psycho-neurological diseases	**S-600918 [sivopixant]** Neuropathic pain	**S-600918 [sivopixant]** Refractory chronic cough	**S-812217 [zuranolone]** Depression	
S-109802 Post-stroke spasticity	**S-151128** Chronic pain	**BPN14770 [zatolmilast]** Alzheimer's disease	**BPN14770** ** **[zatolmilast]** Fragile X Syndrome	** Phase 2b/3
		Rizmoic* Opioid-induced constipation (pediatric)	**SDT-001** Inattentive ADHD (pediatric)	
		* Phase 1/2	**Resiniferatoxin** Pain associated with knee osteoarthritis	

: Global development

Out license

S-0373 [rovatirelin]
Spinocerebellar Degeneration

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

: Progress from August. 1, to October. 12, 2022

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Pipeline: New growth areas

as of October. 12, 2022

Preclinical	Phase 1	Phase 2		Phase 3	Submission
S-540956 Nucleic acid adjuvant	**S-770108** Idiopathic pulmonary	**S-005151 [redasemtide]** Acute ischemic stroke	**S-488210** Head and neck squamous cell carcinoma	**S-588410** Esophageal cancer	
	S-588210 Solid tumor	**S-005151 [redasemtide]** Epidermolysis bullosa	**S-588410** Bladder cancer	**SR-0379** Cutaneous ulcer	
	S-309309 Obesity	**S-588410** Bladder cancer	**S-531011**** Solid tumor		
		ADR-001* Decompensated liver cirrhosis	**S-222611 [epertinib]** Malignant tumor		

: Global development

** Phase 1b/2

Out license

S-723595
NASH

* Phase 1/2

Stage change (change from August . 1, 2022)
S-237648 (Obesity): Closed

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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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- Risks and uncertainties include general industry and market conditions, and general domestic and international economic conditions such as interest rate and currency exchange fluctuations. Risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, technological advances and patents attained by competitors; challenges inherent in new product development, including completion of clinical trials; claims and concerns about product safety and efficacy; regulatory agency's examination period, obtaining regulatory approvals; domestic and foreign healthcare reforms; trend toward managed care and healthcare cost containment; and governmental laws and regulations affecting domestic and foreign operations.
- For products that are approved, there are manufacturing and marketing risks and uncertainties, which include, but are not limited to, inability to build production capacity to meet demand, lack of availability of raw materials, and failure to gain market acceptance.
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