Briefing Session on COVID-19

November 24, 2022

Shionogi & Co., Ltd.

SHIONOGI

Agenda

• Opening	**Isao Teshirogi, Ph.D.,** Chief Executive Officer
• Filled for domestic approval of COVID-19 vaccine S-268019 and Post-Marketing Safety Surveillance of Xocova® Tablets 125mg	**Takeki Uehara, Ph.D.,** Senior Vice President, Drug Development and Regulatory Science Division
• Xocova® Tablets 125mg Distribution System and Activities to Provide Information on Proper Use	**Toshinobu Iwasaki, Ph.D** Senior Executive Officer, Senior Vice President, Healthcare Business Supervisory Unit and Pharmaceutical Commercial
• Preparedness in Normal Times We Learned from the Pandemic	**Isao Teshirogi, Ph.D.,** Chief Executive Officer
• Q&A	

SHIONOGI

Filled for domestic approval of COVID-19 vaccine S-268019 and Post-Marketing Safety Surveillance of Xocova® Tablets 125mg

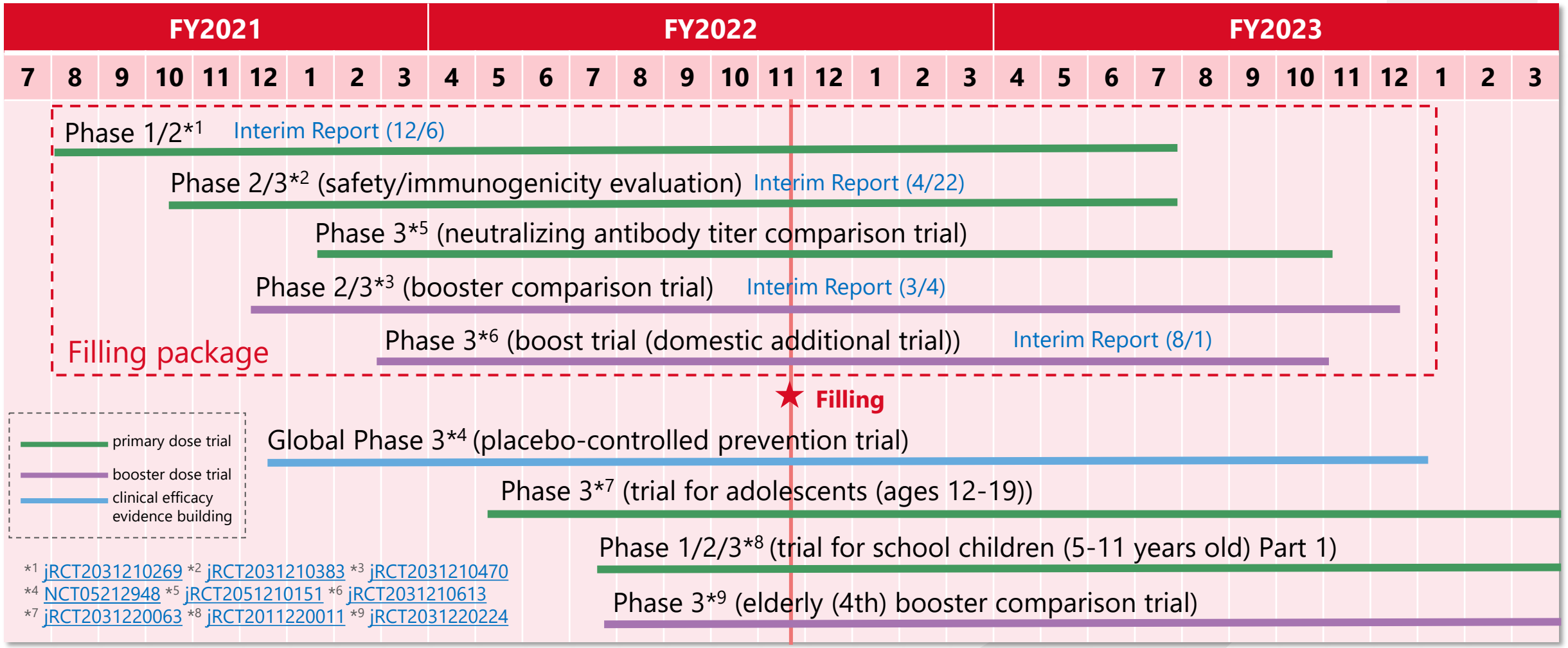
Takeki Uehara, Ph.D.
Senior Vice President, Drug Development and Regulatory Science Division

SHIONOGI

Filled for approval of COVID-19 vaccine S-268019 in Japan

SHIONOGI

S-268019: Progress summary



As of November 24, 2022

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

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.

SHIONOGI

S-268019: Development status in adults

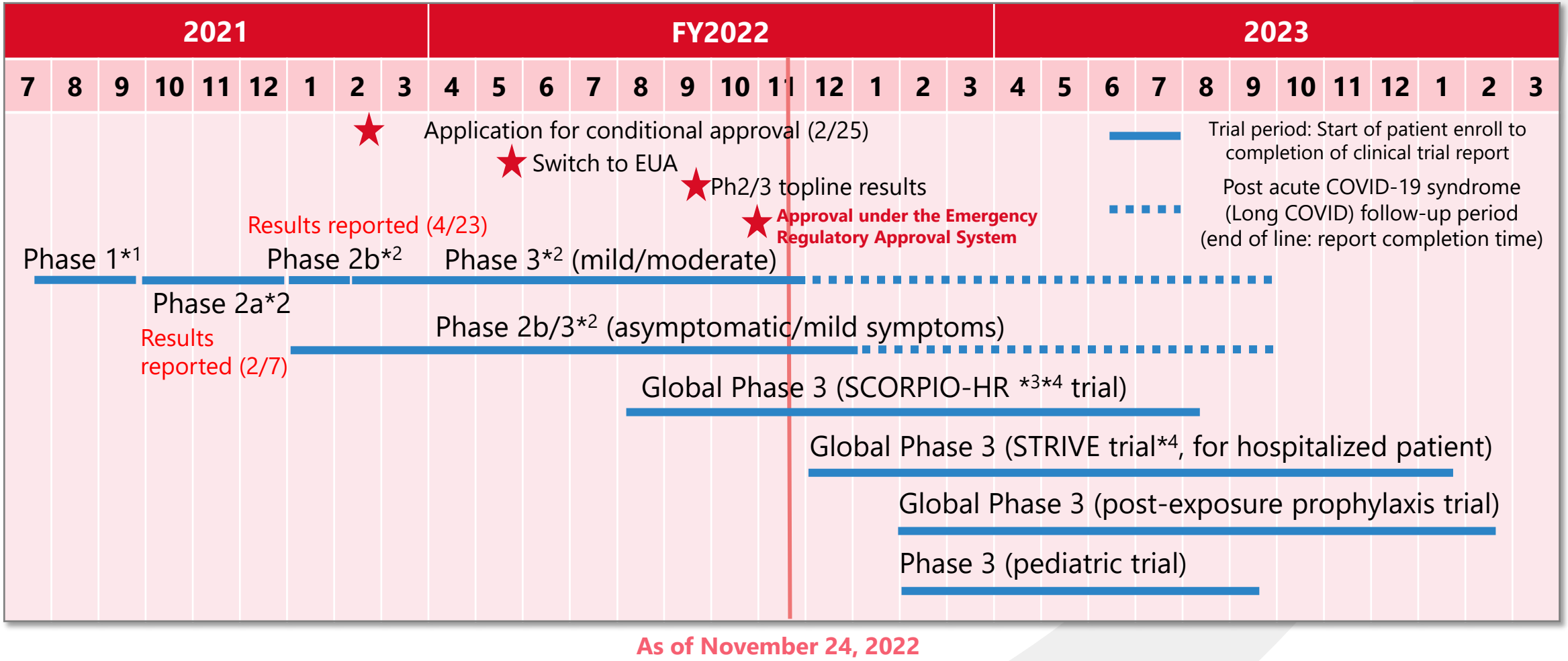
Filed for manufacture and sales approval of S-268019 in Japan on November 24, 2022

- Preconsultation with PMDA has started from Feb. 2022, and the data obtained so far has been submitted in advance
- **Filed for the indication of "prevention of COVID-19 by primary dose (1st and 2nd doses) and booster dose (3rd dose)"**
- Filed based on favorable results of 5 clinical trials conducted in Japan
  - Phase 1/2 trial (primary dose), Phase 2/3 trial (primary dose), Phase 2/3 trial (booster dose) , Phase 3 trial (booster dose), Phase 3 neutralizing antibody titer comparison trial (primary dose)

Collection and Disclosure of Post-Marketing Safety Information for Xokova® Tablets 125mg

SHIONOGI

Xocova: Progress Summary



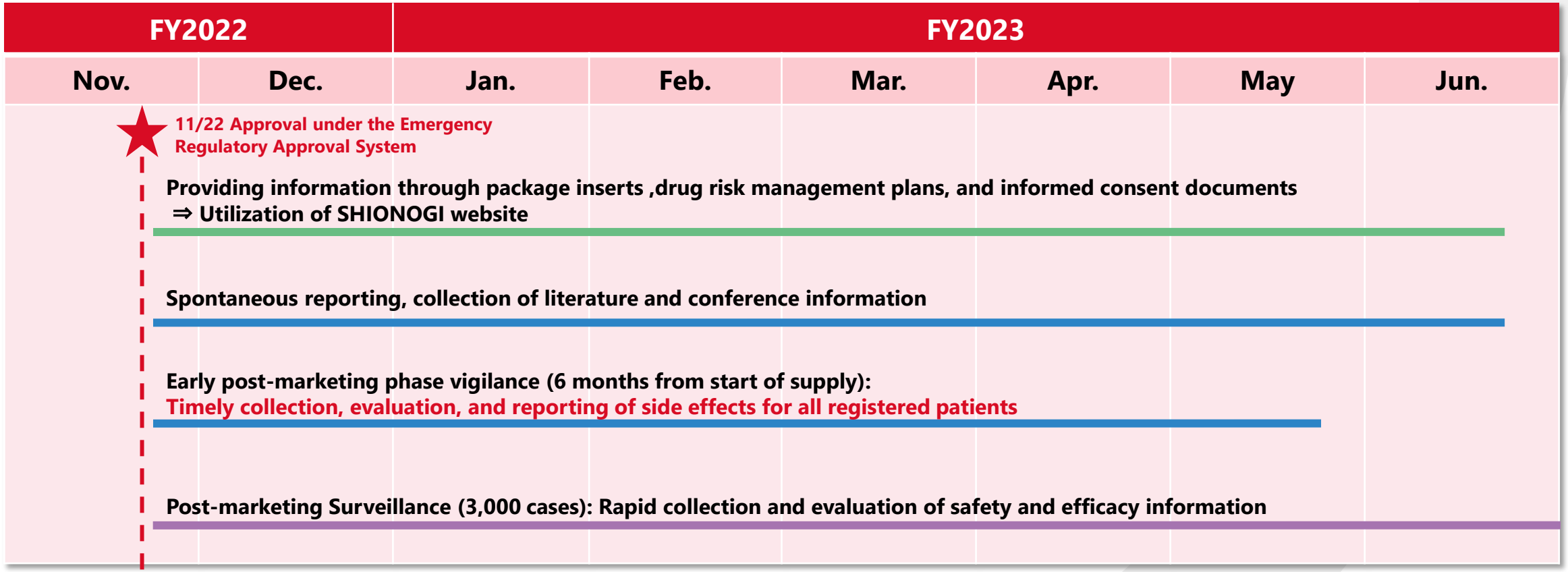
As of November 24, 2022

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

*1 jRCT2031210202 、*2 jRCT2031210350、*3 NCT05305547、*4 NIH sponsored trial

SHIONOGI

Overview of Post-Marketing Safety Surveillance Plan



Proactively engage in post-marketing surveillance, promptly collect and provide feedback on safety information under actual use

SHIONOGI

Risk Management Plan

	Xocova® Tablets 125mg
approval	emergency approval
Safety considerations	Important identified risks: None Important potential risk: Teratogenic Important missing information: Safety in patients with moderate or severe hepatic impairment
Efficacy Considerations	Efficacy in Phase 3 part of global Phase 2/3 study (Study T1221)
Additional drug safety surveillance activities*1	• Post-marketing Surveillance : 3000 cases [Purpose] A clinical pharmacological trial targeting subjects with liver dysfunction to confirm the safety and efficacy of Xocova under actual use as early as possible [Purpose] Confirm safety in patients with moderate or higher hepatic dysfunction
Additional risk minimization activities*2	• Implementation of explanation and understanding to the patient at the time of administration (informed consent document/patient handbook) • Preparing and providing "Requests regarding administration to "pregnant women, women who may be pregnant, or women who may become pregnant""

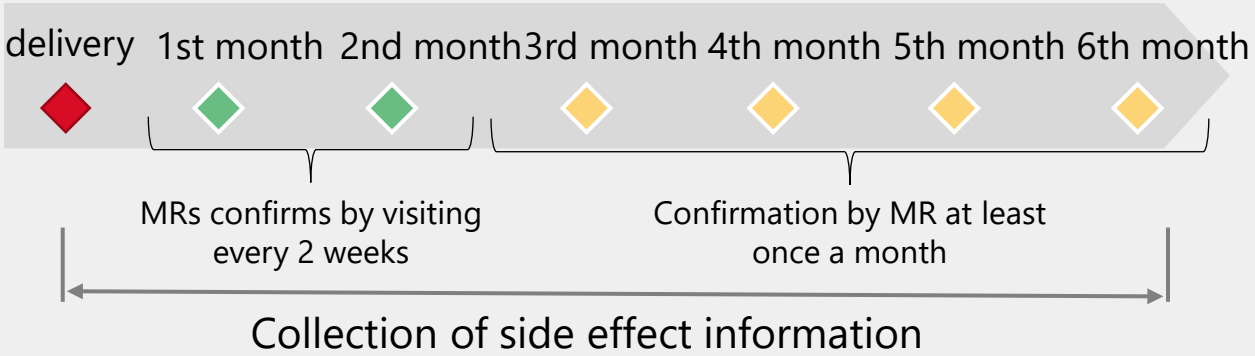
*1 Other than post-marketing surveillance
*2 Other than provision of Information or materials for post-marketing surveillance

SHIONOGI

Post-market Safety Monitoring - Post-Marketing Surveillance -

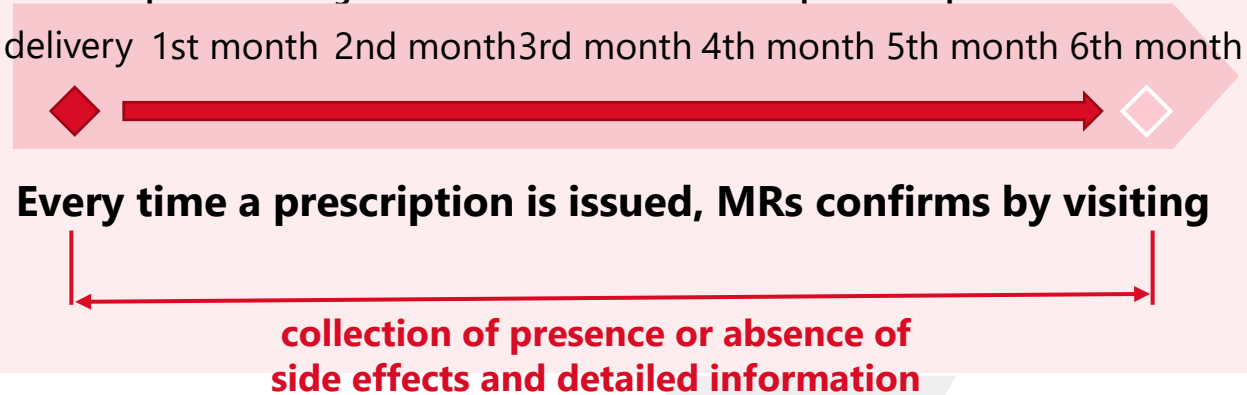
During the early post-marketing surveillance period (6 months from the start of supply), safety information will be collected for all prescription patients

Post-marketing surveillance



Early post-marketing surveillance of Xocova® Tablets 125mg

⇒ Routine post-marketing surveillance + confirmation of all prescribed patients



- Based on the patient information in the registration center, the MRs confirms and tallies the presence or absence and details of side effects for all prescription patients from medical professionals
- Disclosure of information to medical sites on SHIONOGI website, etc. every two weeks

Promptly collect, evaluate, and report safety information in actual use to ensure safety

SHIONOGI

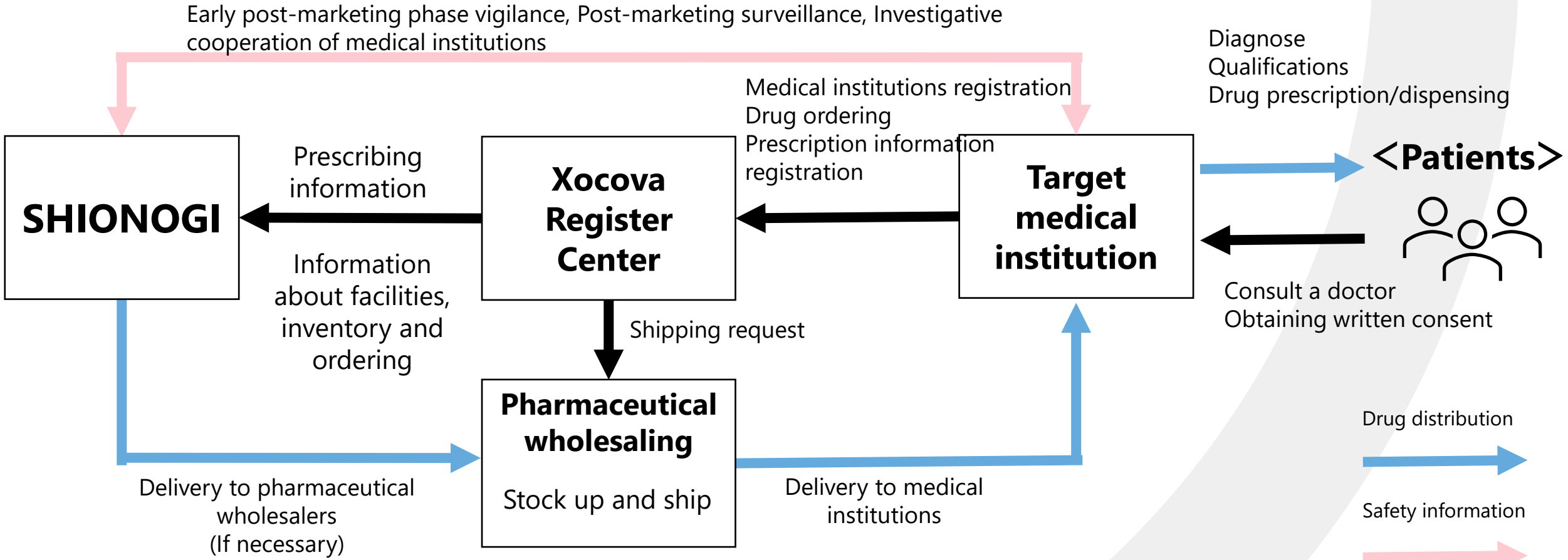
Xocova® Tablets 125mg Distribution System and Activities to Provide Information on Proper Use

Toshinobu Iwasaki, Ph.D
Senior Executive Officer, Senior Vice President,
Healthcare Business Supervisory Unit and Pharmaceutical Commercial

SHIONOGI

Regarding the Domestic Distribution System

- Supply under Purchase by the Government -



- Reliably manage distribution and prescription status under the medical institution registration system
- After confirming the medical institutions /prescription information registration, MR will promptly contact the target facility to confirm safety information after taking the drug
- **We will quickly grasp the actual usage of this drug, thoroughly confirm safety information, and promptly publish the collected information**

SHIONOGI

Activities to Provide Information on Proper Use

- **Thoroughly disseminate that this drug is an emergency approval drug**
  - Continuous collection of information, and prompt provision of safety information
- **Dissemination of the distribution system and medical institution registration system**
- **Thorough collection and provision of safety information**
  - Promotion of Early Post-marketing phase vigilance and Post-marketing Surveillance
- **Thorough provision of information on drug interactions, such as contraindications and precautions for co-administration and introduction of tools**
  - A drug interaction search page for this drug was opened on the SHIONOGI website "Information site for medical professionals"
  - It is possible to check whether the drug that the patient take corresponds to the contraindications and precautions for concomitant use of this drug
- **Provision of information on efficacy and safety necessary for decision-making on administration of this drug**
  - The results of the Phase 3 part of the study
  - Phase 2/3 trial cover a wide range of patients with and without risk factors for severe disease and with or without vaccination

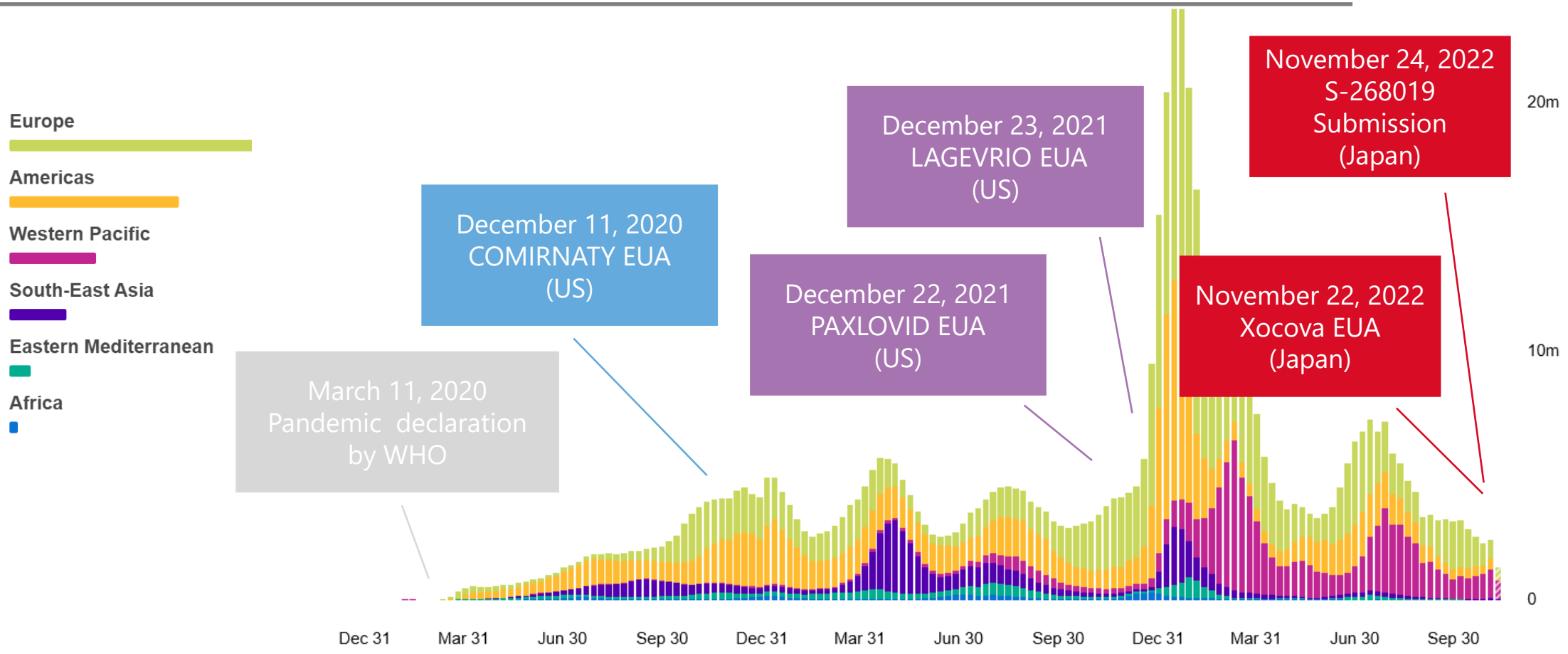
What we learned from the pandemic about being prepared in normal times

Isao Teshirogi, Ph.D.
Chief Executive Officer

SHIONOGI

Global Spread of COVID-19 and Development of Vaccines and Therapeutic Drugs

Change in the Number of New Infections by Region in the World (Weekly)*



* WHO Coronavirus Disease (COVID-19) Dashboard (As of November 21, 2022)

SHIONOGI

Background to the Early Development of COVID-19 Vaccines in the US

1. **Operation Warp Speed in the US**
   - Aggressive investment in promising candidates for the purpose of accelerating the development of vaccines, therapeutic drugs, and diagnostic drugs
2. **Focused on building a national system for emergencies such as pandemics even in normal times**
   - Recognition of national security issues, such as the threat of bioterrorism, in addition to public health
   - U.S. government organizations* dedicated to promoting research and development for preparedness and to building a crisis management system
   - Established the EUA legal framework and approval standards as a country at an early stage, and formulated and promoted development plans with FDA and industry working together

Cross-border collaboration between all stakeholders, including governments, academia, regulatory authorities, and the pharmaceutical industry, made early development and provision possible

* DARPA (Defense Advanced Research Projects Agency): an internal agency of the US Department of Defense, BARDA (Biomedical Advanced Research and Development Authority): an internal agency of the US Department of Health and Human Services

Background behind Japan's Delay in Vaccine Development

Problems revealed by this pandemic

Insufficient preparation in normal times for emergencies such as pandemics

- Continuous support for technological development from the perspective of national security is required

Creation of a system or mechanism designed for emergency response

- Existence such as emergency use authorizations (EUA) in the US
- Insufficient framework for conducting large-scale clinical trials

Barriers due to conventional approaches/systems in Japan

Substantial risks for reviewers and companies

- Litigation risk
- Loss of business opportunities due to the convergence of the target infectious disease

Insufficient education regarding vaccination (discussion of risk-benefit)

What We Learned from the Pandemic

- It is difficult to predict when, where, and what infectious disease will cause a pandemic
- Anyone can become infected, develop symptoms and die
- Considering global society, it is not enough just to implement local country measures against infectious diseases

Infectious disease control is a major public health issue, and it is necessary to build a *true global partnership*, not only among pharmaceutical companies, but also among all stakeholders, including governments, academia, and society

Threats of Infectious Diseases in the World

There are many infectious disease threats globally beyond COVID-19

Major global threats

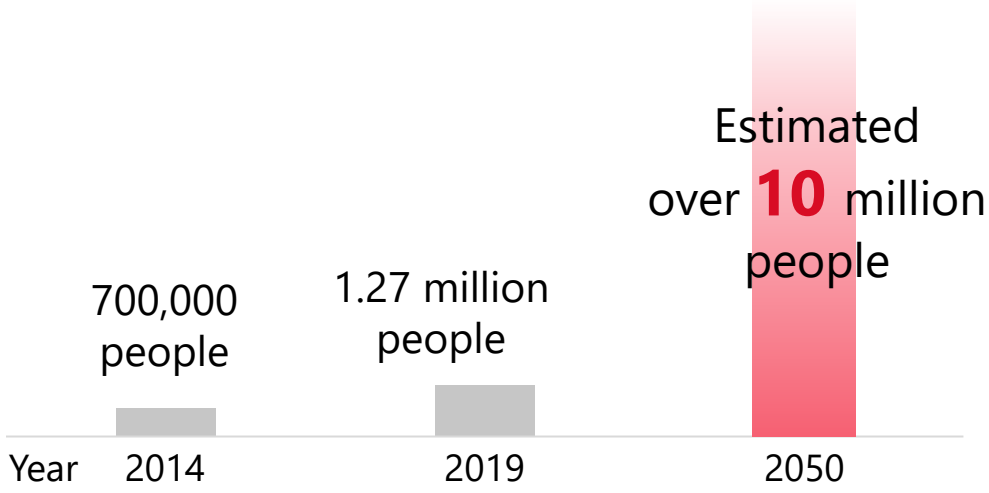
- **Three major infectious diseases (HIV/AIDS, malaria, tuberculosis)**
  - Prevalent in LMICs
  - Kill more than 2.5 million people each year
- **Neglected Tropical Diseases (NTDs)**
  - 20 diseases, such as dengue fever, rabies, and Chagas' disease, which are prevalent mainly in tropical regions and for which no cures have been developed
- **Antimicrobial Resistance**
  - Mutations in pathogenic bacteria make existing antibiotics less effective or ineffective

Threats of Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR)

AMR, called a “silent pandemic”, is a serious problem, as it is difficult to detect and spreads relatively

【Deaths due to AMR bacteria (annual)】



- AMR is estimated to have killed approximately 700,000 people* in 2014 and 1.27 million people** in 2019
- It is estimated that if effective AMR measures are not taken in the future, approximately 10 million people* will die annually by the year 2050, causing an economic impact of $100 trillion

Countermeasure on AMR is a “issue that must be addressed on a global scale”

* O’Neill J., “Tackling drug-resistant infections globally: final report and recommendations”, London: Review on Antimicrobial Resistance (2016)
** Antimicrobial Resistance Collaborators, “Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis”, The Lancet (2022)

SHIONOGI

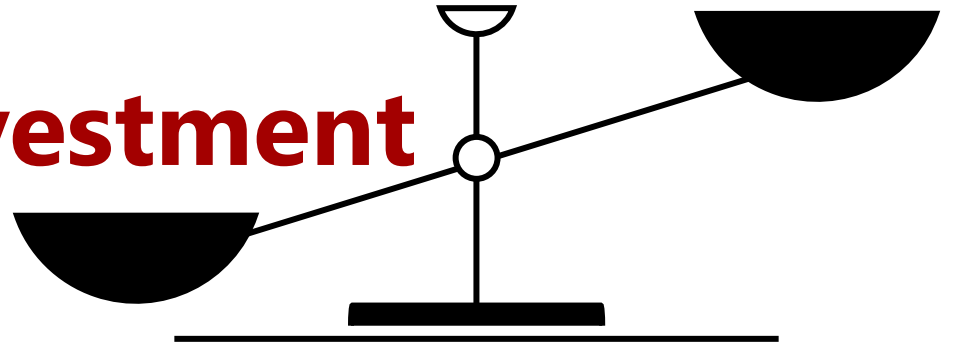
Acute Infectious Diseases Business Difficult to Continue

Dysfunctional business environment

Social needs

Huge R&D expenses

Maintenance cost of production equipment



Difficult to predict epidemics

Antibiotic stewardship

Promotion of switching to generics

Unable to sustain research and development because the investment cannot be recovered

Big Pharma withdraws from antimicrobial market

- **AstraZeneca** sold small molecule antimicrobial business to Pfizer (2016)
- **Sanofi** transferred ID department and 100 employees to Evotec (2018)
- **Novartis** withdraws from antimicrobial research (2018)

Bankruptcy or acquisition of biotech players

- **Achaogen** filed for bankruptcy (April 2019)
  - Within 1 year from plazomicin approval in July 2018
- **Melinta** Therapeutics filed for bankruptcy (December 2019)
- Acquisition of **Tetraphase Pharmaceuticals** (July 2020)
  - Eravacycline approved in August 2018

SHIONOGI

Do Not Repeat the Social Disruption Caused by Infectious Diseases

The need to strengthen preparedness for new pandemics “now”

- Accurate prediction of pandemics is difficult (COVID-19, flu, etc.)
- While the spread of COVID-19 has certainly raised public awareness of infectious diseases, preparation for the next pandemic remains insufficient

Infectious disease control is an important issue closely related to national security

- **Industry, government, and academia can work together to strengthen preparedness**
- **A framework is needed to prepare for emergencies arising from infectious diseases**
  - Incentives that enable sustained progress in research and development and stable production and supply
  - Construction of a clinical trial system that can respond quickly to emergencies
  - Development of laws that can flexibly adapt to both emergencies and normal times, and development of alternative evaluation criteria

Construction of a New Clinical Trial System and Development of Infrastructure for Emergencies

Issues and measures in the Xocova Phase 2/3 trial

- **There were few subjects for clinical trials at medical institutions**
  - Due to the special environment of a pandemic, isolation at accommodation facilities, homes and others
- **It was difficult to secure subjects during both the "recession" and the "wave" periods of infection**
  - Recession period: September to the end of December 2021 (after the 5th wave converges): Target new infections decreased
  - Wave period: From January 2022 (6th and 7th waves): The medical system was under strain, and it was difficult to secure medical resources

Conducted clinical trials at home/hotels and clinical trials in Asia (Korea/Vietnam)

- Completed the clinical trial with the cooperation of various stakeholders such as clinical trial doctors, local governments, and private companies

In anticipation of emergencies, it is necessary to build a clinical trial system and develop infrastructure, including online medical consultation, in order to secure subjects early and promote clinical trials

SHIONOGI

Maintaining a Production System in Preparation for Emergency Operations

The dilemma of maintaining production capacity

Mass production of vaccines, therapeutic drugs, etc. in a short period of time as an emergency measure for pandemic outbreaks

↳ Excessive costs to maintain production facilities for private companies after the emergency has passed and returned to normal

↳ It is difficult to rapidly produce a sufficient amount of vaccines and therapeutic drugs from dormant factories (humans and facilities)

In order to demonstrate sufficient manufacturing capacity in an emergency, it is necessary to operate the factory in an economically and functionally viable manner during normal times

Flexible and Bold Pharmaceutical Regulatory Actions in the US under the Emergency

Emergency Use Authorization (EUA)

- The EUA allows FDA to help strengthen the nation's public health protections against public health emergencies
- FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency when certain criteria are met, including that there are no adequate, approved, and available alternatives
- On the other hand, since it is "unapproved" after the declaration is lifted, the basis for authorization will be lost, and companies are recommended to accumulate data even after obtaining authorization and to get full approval promptly

EUAs issued by FDA

- Vaccine: 4 products
- Therapeutics: 14 products
- In vitro Diagnostic Agent: 414 products

Accumulation of evidence

Full approval/Cancellation of EUA due to change in prevalent strains

- Vaccine: 2 products approved
- Therapeutics: 2 products approved, 2 product under review, 3 products revoked
- In vitro Diagnostic Agent: 32 products revoked

Accelerated decision making based on consideration of risk and benefit to protect the country from the COVID-19 pandemic

Action in Japan to Overcome the Challenges Surfaced during the Pandemic

Domestic progress triggered by COVID-19

Creation of new emergency-ready systems		Preparation in normal times in anticipation of emergencies
Established a new method for validation of COVID-19 vaccines • Agreement on a study design comparing to approved vaccine with neutralizing antibody titer endpoint • Promoting development of purely domestic vaccines	**Establishment of Emergency Approval System** • A system to give rapid regulatory approval to promising medical products, such as therapeutics and vaccines, during a pandemic, prior to a full "normal" package becoming available	**Established SCARDA within AMED** • Extensive information collection and analysis on vaccine development • Strategic research funding

In terms of national security, various actions are in progress in Japan
It is very important to continue to promote these actions through collaboration between government, academia and the pharmaceutical industry

Taking the Example of Xocova -Development overview-

Mild/Moderate

FY2021									FY2022									
7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1

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

★ Application for conditional approval(2/25)

★ Switch to EUA submission

★ Phase 2/3 topline results

★ Phase 2/3 topline submitted to PMDA

Results reported(2/7)

Results reported(4/23)

Phase 1*1

Phase 2a*2

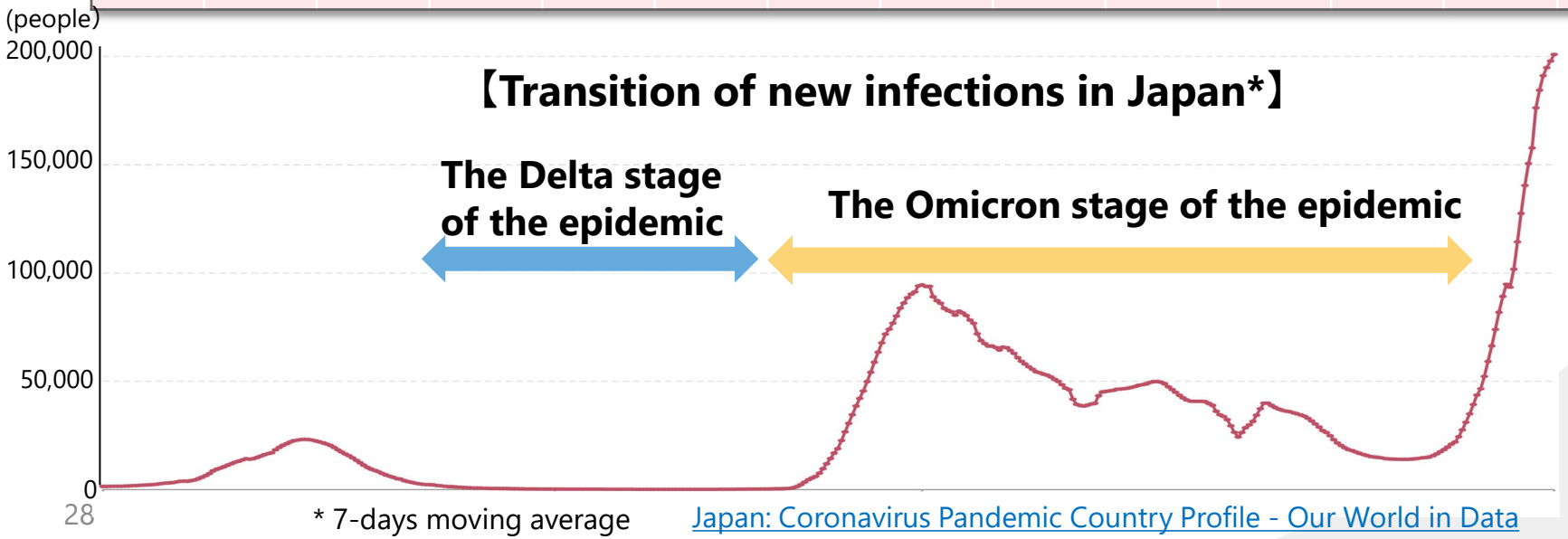
Phase 2b*2

Phase 3*2

★ **EUA**

Trial period:
Start of patient enroll to end of patient enroll

*1 jRCT2031210202 、*2 jRCT2031210350



* 7-days moving average

Japan: Coronavirus Pandemic Country Profile - Our World in Data

Conducted clinical trials in a rapidly changing external environment, such as infection status and prevalent virus strains

Coming up against difficulties we have never experienced

SHIONOGI

Challenges Faced in Drug Development during a Pandemic
-Accurate drug efficacy evaluation-

- Decrease in the rate of exacerbation due to rapid changes in vaccination status
- When infected with the Omicron strain, the virus multiplies and disappears in the body faster than the past epidemic strains, and the remission of symptoms is relatively quick
- Changes in major symptoms due to changes in epidemic strains
  - Common and characteristic symptoms during the Omicron epidemic are 5 of the 12 symptoms of COVID-19 (runny or stuffy nose, sore throat, respiratory symptoms of cough, fever or tiredness)

Regarding the evaluation of clinical efficacy during the Omicron strain epidemic, repeated discussions were held with medical experts, relevant ministries and agencies, and regulatory authorities in Japan and US, and evaluation items were set based on scientific and medical validity

⇒ Achieved primary endpoints in Phase 3 part

Role Japan Should Play

Globally provide necessary pharmaceuticals as one of the few countries can create new drugs

＜Related SHIONOGI actions＞

AMR initiatives

- Partnership with GARDP[*1] and CHAI[*2]
  - SHIONOGI and GARDP concluded a license agreement for non-exclusive rights to commercialize Cefiderocol in **135 countries**
  - SHIONOGI, GARDP, and CHAI entered into partnership agreement to provide sustainable access to patients in need of Cefiderocol

Initiatives against COVID-19

- Partnership with MPP[*3]
  - Concluded an agreement with MPP for the purpose of widely providing LMICs with the COVID-19 drug under development by SHIONOGI
  - After obtaining regulatory approval, this drug can be supplied to **117 countries** under this agreement
  - Waives royalties on sales in all countries covered by the agreement while COVID-19 remains classified as a Public Health Emergency of International Concern by the World Health Organization

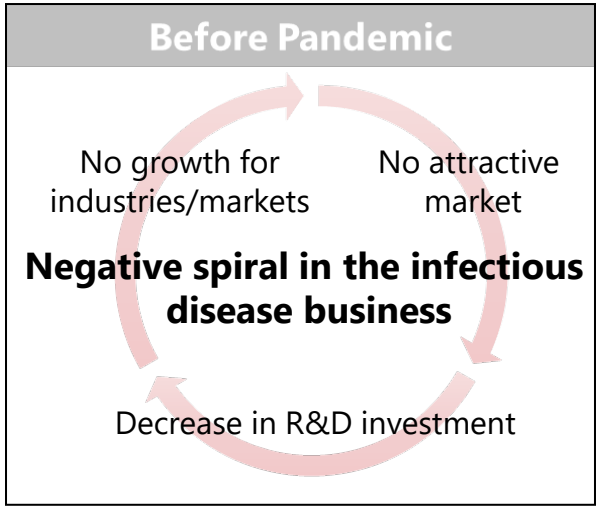
[*1] Global Antibiotic Research and Development Partnership [*2] Clinton Health Access Initiative, Inc. [*3] Medicines Patent Pool

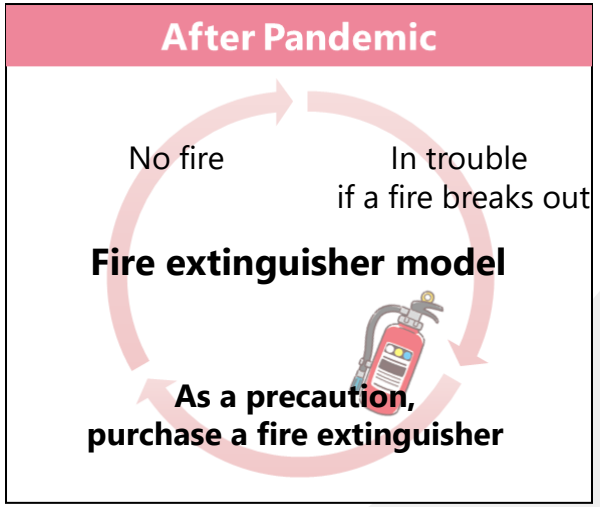
Establishment of Sustainable Acute Infectious Diseases Business

Building a new business model

- The current business model in acute infectious disease is unstable, influenced by epidemic and external factors, and insufficient return in normal times
- We should establish urgently a sustainable revenue structure that supports a healthy and productive R&D ecosystem even in the absence of a pandemic

  ⇒It is essential to introduce Pull Incentives, such as subscription models





It is necessary for all stakeholders to continue to tackle on infectious disease countermeasures in normal times

SHIONOGI


SONG
for you!
あしたの感染症と、
たたかっている。
感染症がこの世からなくなることはない。
パンデミックも、きっとまた起こる。
だからこそ、SHIONOGIは逃げずに向き合い続けます。
その時私たちの創るワクチンが、治療薬が、
強く、強く、ひとつでも多くのいのちを守れるように。
薬ができることの、その先へ。
SHIONOGI