Deliberation result report

February 12th, 3rd year of Reiwa
Pharmaceuticals and Life Sanitation Bureau Pharmaceuticals Examination and Management D

[Sales name] Community intramuscular injection
[General name] Coronavirus-modified uridine RNA vaccine (SARS-
CoV-2)
(Active ingredient name: Tojinameran)
[Applicant name] Pfizer Japan Inc.
[Date of application] December 18, 2nd year of Reiwa

[Deliberation result]
Infectious diseases caused by the new coronavirus (SARS-CoV-2) are prevalent worldwide in this product.
In the current situation, the quality, effectiveness and safety of pharmaceuticals, medical devices, etc.
(Act No. 145 of 1960; hereinafter referred to as the "Pharmaceuticals and Medical Devices Act"
That is.) It is expected that the approval will be based on Article 14-3, Paragraph 1.
There was an application for approval.
Regarding this product, the second meeting of the Pharmaceuticals Subcommittee held on February 12, 3rd year of Reiwa
Regarding the approval or disapproval of special cases pursuant to the provisions of Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Device
Was deliberated. As a result, on the premise that the following approval conditions are attached, we accept
Report to the Pharmaceutical Affairs Subcommittee of the Pharmaceutical Affairs and Food Sanitation Council
It was decided.
This item does not fall under any of the biological products or specific biological products, and is reexamined.
The period was 8 years, and both the drug substance and the drug were considered to be powerful drugs.

[Approval conditions]
1. Formulate a drug risk management plan and implement it appropriately.
2. This drug was approved based on the provisions of Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act.
It is a specially approved item, and information on long-term stability etc. is limited at the time of approval.
Therefore, continue to collect and report information after manufacturing and sales.
3. Due to limited knowledge at this time, books such as side effect information after manufacturing and sales
Collect drug safety data early based on a pre-determined plan
At the same time, submit it to the Pharmaceuticals and Medical Devices Agency, and the suitability of this drug
Take necessary measures for proper use. At that time, according to health surveys conducted by the government
Appropriately reflect the obtained information.

4. When the results of clinical trials currently being conducted or planned at home and abroad are obtained,
   Crabs will be submitted to the Pharmaceuticals and Medical Devices Agency
   In addition, the latest information on the efficacy and safety of this drug is provided to healthcare professionals and vaccinations.
   Take necessary measures to make it readily available to the person. Also done by the country
   Appropriately cooperate in disseminating information on the efficacy and safety of this drug.
   When.
5. Information on the efficacy and safety of this drug will continue to be accumulated when inoculating this drug.
   Based on the fact that it will be done, the latest effectiveness and the latest effectiveness for the vaccinated person or the surrogate person in advance
   Information on safety is explained in writing, and written consent on a medical examination slip, etc.
   Properly explain to your doctor that you will be vaccinated after you have obtained it.
6. The grace period for submitting materials based on Article 41 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act is acce
   It will be 6 months from the acquisition of approval. Submitted based on 2, 3 or 4 above
   If it is deemed necessary to change the approval items based on the materials, etc., the pharmaceutical doctor
   We may order changes to the approved items based on Article 74-2, Paragraph 3 of the Medical Equipment Law.
   thing.

February 9, 3rd year of Reiwa

Pharmaceuticals and Medical Devices Agency

Amendment table of the report on special approval

[Sales name] Community intramuscular injection

[General name] Coronavirus-modified uridine RNA vaccine (SARS-CoV-2)

(Active ingredient name: Tojinameran)

[Contractor] Pfizer Japan Inc.

[Date of application] December 18, 2nd year of Reiwa

The report on special approval of the above items dated February 8, 3rd year of Reiwa will be amended as follows. This repair

There is no positive change in the examination results.

Record

page	line		Revised			Before correction		
			N	GMT [both sides 95% CI]	GMFR [both sides 95% CI]	N	GMT [both sides 95% CI]	GMFR [both sides 95% CI]
57	Table 29	Pu La Se Bo Evaluation possible Noh immunity Original collection Team	40	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)	40	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)
		Pu In Se Bo All evaluations Immunogen Sex group	41	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)	41	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)

a) 1 month after the second inoculation at the time of sending the sample for immunogenicity measurement 1 month after the second inoculation at the time of sending the sample for immunogenicity measurement 1

Solutions for 40 cases, excluding 1 case for which the visit at the time was not completed Analysis excluding one case whose visit at the time of the month was not completed

Analysis results (evaluable immunogenicity population: 39 cases, all evaluated immunogens Results (evaluable immunogenicity population: 39 patients, all evaluated immunogens

Gender group: 40 cases) Gender group: 40 cases)

(Underlined part changed / Canceled line part deleted)

that's all

Page 4

Report on special approval

February 8, 3rd year of Reiwa

Pharmaceuticals and Medical Devices Agency

The results of examinations by the Pharmaceuticals and Medical Devices Agency for the following drugs for which approval has been submitted are as follows.

To.

Record

[Sales name] Community intramuscular injection

[General name] Coronavirus-modified uridine RNA vaccine (SARS-CoV-2)

(Active ingredient name: Tojinameran)

[Contractor] Pfizer Japan Inc.

[Date of application] December 18, 2nd year of Reiwa

[Dosage form / content] Injection containing 0.225 mg of Tojinameran in 1 vial

[Application category] Medical drugs (1) Drugs containing new active ingredients

[Book Quality] Tojinameran is a peaplomer analog of SARS-CoV-2 (Lys986Pro, Val987Pro)

It is an mRNA that encodes the total length. Tojinameran has a 5'cap structure and a poly A sequence.

All uridine residues were replaced with N_1 -methyl pseudouridine residues, including 4284

It is a single-stranded RNA consisting of single nucleotide residues.

Tozinameran is a mRNA encoding full length of spike protein analog (Lys986Pro, Val987Pro)

of SARS-CoV-2. Tozinameran is a single-stranded RNA consisting of 4284 nucleotide residues

including the 5'cap structure and poly A sequence in which all uridine residues are replaced by

N_1 -methylpseudouridine residues.

[Structure Construction]

The nucleic acid sequence of Pfizer-BioN.

Page 6

1-3: 5'Cap structure part

55-3879: Translation area

4175-4204, 4215-4284: Poly A transfer slip

Page 7

5'cap structure part

[Notices] This item is Article 14 (1) based on the provisions of Article 14-3 (1) of the Pharmaceuticals and Medical Devices Act. It was treated as an item that falls under the approval of the section.

[Examination Department] Vaccine Examination Department

[Examination outcome]

As shown in the attached sheet, from the submitted materials, the effectiveness of this product in preventing infectious diseases caused by SARS-CoV-2 is Safety is considered acceptable given the indicated and recognized benefits.

As a result of the examination by Pharmaceuticals and Medical Devices Agency, the following approval conditions have been added to this product. Therefore, it was judged that the following indications, dosages and administrations may be approved.

[Efficacy or effect]

Prevention of infectious diseases with SARS-CoV-2

[Dosage and administration]

Dilute with 1.8 mL of Japanese Pharmacopoeia saline and inoculate 0.3 mL once intramuscularly twice, usually at intervals of 3 weeks.

Page 8

[Approval conditions]

1. Formulate a drug risk management plan and implement it appropriately.
2. This drug is a specially approved item approved based on the provisions of Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act.

   Information on long-term stability, etc. is limited at the time of approval, so we will continue to collect information even after manufacturing and sales.

   And report.
3. Due to limited knowledge at this time, the safety information regarding the safety of this drug, such as side effect information, after manufacturing and marketing

   Data will be collected at an early stage based on a predetermined plan, and pharmaceuticals and medical devices will be collected.

   Submit to Pharmaceuticals and Medical Devices Agency and take necessary measures for proper use of this drug. At that time, health surveys conducted by the government, etc.

   Appropriately reflect the information obtained from.
4. When the results of clinical trials currently being conducted or planned in Japan and overseas are obtained, the results will be promptly transferred independently.

   Submit to the Pharmaceuticals and Medical Devices Agency and the latest information on the efficacy and safety of this drug.

   Take necessary measures to make it readily available to health care workers and vaccinated persons. Also, the country goes

   Properly cooperate in disseminating information on the efficacy and safety of this drug.
5. Based on the fact that information on the efficacy and safety of this drug will continue to be accumulated when inoculating this drug.

   The latest efficacy and safety information will be provided in writing to the recipient or surrogate in advance.

   Appropriately explain to your doctor that you will be vaccinated after obtaining written consent on a medical examination slip.
6. The grace period for submitting materials based on Article 41 of the Enforcement Regulations of the Pharmaceuticals and Medical Devices Act is calculated from the acquisition of approval 6

   Month. It is necessary to change the approval items based on the materials submitted based on 2, 3 or 4 above.

   If so, order the change of approval items based on Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

   There is.

Page 9

Attachment

Report on special approval (**1**)

January 29, 3rd year of Reiwa

The materials submitted by the applicant and the outline of the examination by Pharmaceuticals and Medical Devices Agency in this application are as follows.
It is as follows.

Application item

[Sales name] For intramuscular injection of community (multiple inoculations) (at the time of application)

[General name] Coronavirus-modified uridine RNA vaccine (SARS-CoV-2)

(Active ingredient name: Tojinameran)

[Contractor] Pfizer Japan Inc.

[Date of application] December 18, 2nd year of Reiwa

[Dosage form / content] Injection containing 0.225 mg of Tojinameran in 1 vial

[Efficacy / effect at the time of application]

Prevention of infectious diseases with SARS-CoV-2

[Dosage and administration at the time of application]

Dilute with 1.8 mL of Japanese Pharmacopoeia saline, and inoculate intramuscularly with 0.3 mL at a time, twice in total, at intervals of 3 weeks.

[table of contents]

[List of abbreviations, etc.]

As stated separately.

Page 10

1. Documents related to the origin or discovery process and usage status in foreign countries

Coronavirus is a single-strand positive-strand RNA virus belonging to the family Coronaviridae of the order Nidovirales.
is there. Human coronavirus (HCoV) that infects humans on a daily basis and causes colds
Four types of HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 were known, but in recent years.
Severe acute respiratory syndrome in 2003 as a coronavirus that infects humans from animals and causes severe pneumonia

(SARS) Coronavirus (SARS-CoV), Middle East Respiratory Syndrome (MERS) Coronavirus (MERS-) in 2012
CoV) has been identified.

On December 31, 2019, WHO reported an unexplained pneumonia outbreak in Wuhan, Hubei Province, China.

On January 12, 2020, WHO announced that the pneumonia was due to the new coronavirus (WHO:

https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ (Last confirmed date: January 21, 2021).

On January 30, the same year, WHO announced that the outbreak of new coronavirus-related pneumonia in Wuhan City, Hubei Province, China was international.

A public health emergency of concern (Public Health Emergency of International Concern) to [1] issued and corresponding to

Representation (https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (final confirmation

Date: January 21, 2021)), February 11, 2021, severe acute respiratory syndrome of the new coronavirus
The disease caused by coronavirus 2 (SARS-CoV-2) and SARS-CoV-2 was named coronavirus disease (COVID-19).

(Https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (last confirmed date: January 21, 2021)). January 17, 2021 Date and time

In terms of points, the total number of infected people in the world is 93,217,287, and the total number of deaths is 2,014,957.

The ratio of the number of infected people and the number of deaths to the total number of infected people and the total number of deaths is 44% and 47% in the United States.

-Roppa 33% and 33%, Southeast Asia 13% and 9%, Eastern Mediterranean 6% and 6%, Africa 2% and 3%, West Onishi

Western 1% and 1% (https://www.who.int/publications/m/item/weekly-epidemiological-update---19-january-2021 (Last confirmed date: January 21, 2021).

In Japan, the first patient with SARS-CoV-2-related pneumonia was confirmed on January 15, 2020, and February 1 of the same year.

Japan, Coronavirus Infectious Diseases [2] is the Act on Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases

Designated infectious diseases based on the law) [3] and quarantine infectious diseases based on the quarantine law [4] Was specified. Also revised on April 7, the same year.

The first state of emergency was declared based on the Law on Special Measures for New Influenza, etc., and it was urgent on May 25 of the same year.

A declaration of cancellation was made [5] . Although the number of newly infected persons (the number of positive PCR tests) has been on a downward trend,

The same year on the increase again around October, the second time of the emergency declaration has been made on January 7, 2021 [6] .

1) An abnormal situation defined as follows in the International Health Regulations (IHR) established by WHO.
(1) Situations recognized as bringing public health risks to other countries due to the international spread of diseases
(2) Situations that potentially require adjustment of international measures

2) The pathogen is a betacoronavirus genus coronavirus (in January 2nd year of Reiwa, the People's Republic of China has the ability to transmit to WHO to humans.
Only newly reported to do.).

3) Infectious diseases that are already known (excluding infectious diseases such as first-class infectious diseases, second-class infectious diseases, third-class infectious diseases, and new influenza).
If all or part of the provisions of the Disease Law are not applied mutatis mutandis, the spread of the disease may have a serious impact on the lives and health of the people.
What is specified by Cabinet Order (Article 6 of the Infectious Diseases Control Law)

4) Among infectious diseases that do not reside in Japan, it is necessary to test for the presence or absence of the pathogen in order to prevent the pathogen from invading the country.
What is specified by Cabinet Order (Quarantine Law, Article 2, Item 3)

5) The areas where emergency measures were implemented were initially Saitama, Chiba, Tokyo, Kanagawa, Osaka, Hyogo, and Fukuoka, but were temporarily expanded nationwide.
It was.

6) As of January 20, 2021, the areas where emergency measures are implemented are Tochigi prefecture, Saitama prefecture, Chiba prefecture, Tokyo, Kanagawa prefecture, Gifu prefecture, Aichi prefecture, Kyoto prefecture, Osaka prefecture, Hyogo prefecture, Fukuoka prefecture.

Page 11

As of January 19, 2021, the number of infected people in Japan was 332,231 and the number of deaths was 4,547. In addition, airport quarantine

In 2,082 cases, 15 cases were confirmed as returnees from overseas by charter flights, of which a total of 334,328 cases died.

There are reported 4,548 cases, including one death from airport quarantine. Also arrived at Yokohama Port on February 3, 2020.

The number of infected passengers on the cruise ship "Diamond Princess" was 712, and the number of deaths was reported to be 13.

(Https://www.mhlw.go.jp/stf/newpage_16163.html (Last confirmed date: January 21, 2021)).

The initial symptoms of COVID-19 resemble influenza and the common cold and are difficult to distinguish early onset.

The incubation period from SARS-CoV-2 exposure to onset is 1 to 14 days, and it usually develops in about 5 days.

(Https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations (Last confirmation date: January 21, 2021). Infectious before onset, between onset

It is said that the cause of community-acquired infection is that it is highly infectious at a time when it is not present and that it may be asymptomatic.

It makes it difficult to control the transmission of su. Fever, cough, malaise, dyspnea, dysgeusia, olfactory dysfunction, etc.

Symptoms are observed in many patients, and about 80% of patients remain mild and heal in about a week, but about 20% have pneumonia.

Exacerbates, leading to acute respiratory distress syndrome and multiple organ failure requiring mechanical ventilation in about 5% and fatal in 2-3%

Follow the course (JAMA 2020; 323: 1239-42). As of January 20, 2021, "by SARS-CoV-2" in Japan

Remdesivir is an approved drug for the treatment of "infectious diseases", and dexamethasone has an approved indication.

It can be used within the range of effect, but even with these treatments, the number of reported cases of infected, severely ill and dead in Japan

Continues to increase, and the tight medical system is also a problem. Therefore, as a measure against the spread of infection, SARS-

The CoV-2 vaccine is expected to prevent the onset of COVID-19, and early vaccine development is required.

Wakuchi approved in Japan as of January 2021 for the purpose of preventing infectious diseases caused by SARS-CoV-2

There are no medicines such as

This drug is a vaccine containing mRNA encoding the S protein of SARS-CoV-2 as an active ingredient. code

The base sequence of mRNA is optimized for continuous and efficient translation of the targeted protein, and the living body

LNP the mRNA to suppress RNA degradation within the cell and allow transfection of mRNA into cells

It is enclosed in. This drug is used by BioNTech in Germany and the United States for the purpose of preventing infections caused by SARS-CoV-2.

Development has been underway since March 2020 by Pfizer. Overseas clinical trials (C4591001 trials) began in April of the same year.

The internal clinical trial (Study C4591005) started in October of the same year, and as of January 20, 2021, all trials are ongoing.

Is.

The effect of preventing the onset of COVID-19 in the overseas C4591001 study and the safety factors 2 months after the second inoculation of this drug.

Based on the data, for the prevention of COVID-19, Emergency Use Authorization on December 11, 2020 in the United States

In Europe, conditional approval was granted on December 21, the same year.

This time, the Emergency Use Authorization by the US FDA was obtained, and as of the date of application for manufacturing and marketing approval, Europe

It was under review in the state, and a domestic C4591005 study to evaluate immunogenicity and safety is underway in Japan.

For this reason, Pfizer Japan Inc. filed an application for manufacturing and marketing approval in Japan on December 18, 2020.

It was. Some test results of the domestic C4591005 study were submitted during this approval review.

This report is "Handling of drugs for which special approval is being considered (request)" (December 17, 2nd year of Reiwa)

Based on the dated drug and crude drug trial 1217 No. 2), the examination was conducted based on the materials submitted by the applicant.

To.

2. Quality materials and outline of examination by PMDA

This drug is a vaccine in which the mRNA encoding the S protein S1 and S2 of SARS-CoV-2 is encapsulated in LNP.

is there.

2.1 API

Tolvaptan (BNT162b2) encodes the S proteins S1 and S2 of SARS-CoV-2 (derived from the Wuhan-Hu-1 strain).

2 amino acids substituted (K986P and V987P) to maintain optimal pre-fusion structure of S protein, which is mRNA

It is designed to be. In addition, a cap structure at the 5'end, an array for translation efficiency ( ), Vesicle

Signal sequence for body transport ( ), Sequence for RNA stabilization ( ) And poly A chain,

All UTPs have been replaced with m1 ΨTP to suppress immunogenicity to mRNA and promote translation .

2.1.1 Preparation and management of cell base materials used in raw material manufacturing

Cellbank is used to prepare a DNA template, which is one of the raw materials for pomalidomide. , , S1 and S2

protein, In addition, the plasmid DNA encoding the poly A chain was transferred to Escherichia coli( ) introduced to Co., Ltd.

After cloning, MCB was prepared. WCB was prepared by succession from MCB.

Characteristics analysis test of MCB and WCB (as well as Negation, host cell identification, survival rate,

, Restriction enzyme analysis, And gene sequence) and purity tests were performed.

Upon renewal, WCB will be confirmed to be compatible with the above characteristic analysis test and purity test.

2.1.2 Manufacturing method

The drug substance uses linear template DNA as a template. By the *in vitro* transcription reaction using , ATP, CTP, m1 ΨTP , GTP

Manufactured.

The manufacturing process of the drug substance is *in vitro* transcription reaction, , as well as And All are considered to be important processes. The linear template DNA is obtained by lysing the recovered Escherichia coli after culturing WCB and ringing it. Obtain the morphological plasmid DNA and obtain the circular plasmid DNA. , as well as After purification by Process and prepare. Properties (turbidity and color) as control items for linear template DNA Key), pH, absorbance ( ), Restriction enzyme analysis (Integrity), purity, residual protein content, microbial limits Endotoxin is set every time.

Process validation is carried out on the actual production scale for the manufacturing process of the API.

2.1.3 Safety assessment of foreign infectious substances

No biological raw materials are used in the manufacturing process of the API. In addition, it is derived from the organism used when producing raw materials. We also confirmed the raw materials. Used in the preparation of MCB and WCB Is healthy Because Come on Heat treatment at ℃ or higher for more than a minute, ℃ or higher for more than an hour Pathogens by drying at ℃ or higher Was inactivated.

Page 13

2.1.4 Development process of manufacturing process (equivalence / homogeneity)

The main changes in the manufacturing method during the drug substance development process are as follows.

The drug substance used in non-clinical and clinical trials is manufactured by Process 1, and the drug product to be marketed is described in Process 2. Manufactured by In Process 1, the drug substance is After *in vitro* transcription reaction using the template DNA prepared in After Purified by. In Process 2, the drug substance is made from plasmid DNA After *in vitro* transcription reaction using the linear template DNA as well as After as well as Purified by. When changing from Process 1 to Process 2, quality equivalence / homogeneity The sex has been confirmed.

In addition, the QbD method is used to develop the manufacturing process (see 2.3).

2.1.5 Characteristics

2.1.5.1 Structure and characteristics

The characteristic analysis shown in Table 1 was performed.

Table **1** Test items and test methods in characteristic analysis

item		Test method
Primary structure	RNA sequence	Oligonucleotide mapping (IP-RP-HPLC / ESI / MS / MS or LC-MS / MS) after RNase T1 treatment Next Generation Sequence (NGS)
	5'cap structure	After RNase H treatment, IP-RP-HPLC-UV / ESI MS and LC-UV / MS
	Poly A chain	After RNase T1 treatment, IP-RP-HPLC-UV / ESI MS and LC-UV / MS
Higher-order structure	Higher-order structure	Circular dichroism spectrum

2.1.5.2 Target substance-related substances / Impurities derived from target substances

Impurities derived from the target substance are classified as double-stranded RNA and are appropriately controlled according to the specifications and test methods of the drug substance.

2.1.5.3 Impurities derived from manufacturing process

The impurities derived from the manufacturing process are Process-derived impurities A *, Process-derived impurities B *, ATP, CTP, GTP, ml ΨTP, Process-derived impurities C *, Process-derived impurities D *, Process-derived impurities E *, Magnesium acetate, calcium chloride, ammo sulfate Nium, Triton X-100, Triton Hydrochloric Acid Buffer, Glycerol, Sodium Chloride, Potassium Chloride, Process-derived impurities F *, Process-derived impurities G * as well as Process-derived impurities H * was said.

Residual template DNA is properly controlled according to drug substance specifications and test methods. Process-derived impurities A * and Process-derived impurities B * has been confirmed to be sufficiently removed in the manufacturing process. Also, ATP, CTP,

GTP, m1 ΨTP, Process-derived impurities C *, Process-derived impurities D *, Process-derived impurities E *, Magnesium acetate, calcium chloride, sulfuric acid
Ammonium, Triton X-100, Tris Hydrochloric Acid Buffer, Glycerol, Sodium Chloride, Potassium Chloride, Process origin
Impurities F *, Process-derived impurities G * as well as Process-derived impurities H *, Even if it is assumed that impurities cannot be removed in the purification process,
It has been confirmed that there is no safety problem with respect to the seed amount.

* Replaced when new drug information is provided

2.1.6 Management of **API**

API specifications and test methods include content specifications, properties, confirmation test (RT-PCR), pH, and purity test (double-stranded RNA).
(Immune blot) and template DNA (qPCR)), 5'cap (reverse phase HPLC), poly A chain (ddPCR), RNA complete
Wholeness (capillary gel electrophoresis), endotoxin, microbial limit, quantification method (ultraviolet-visible absorbance measurement method)
Is set.

Five

Page 14

2.1.7 Drug substance stability

Table 2 outlines the main stability tests of the drug substance .

Table **2** Summary of major drug substance stability studies

Exam name	Manufacturing method	Number of lots	Storage conditions	Implementation period	Preservation form
Long-term storage test Accelerated test	Process 1	1	-20 ± 5 ℃ 5 ± 3 ℃	6 months	Container making
Long-term storage test Accelerated test	Process 1	1	-20 ± 5 ℃ 5 ± 3 ℃	3 months	Container making
Long-term storage test	Process 2	Four	-20 ± 5 ℃	3 months	Container making

For long-term storage tests, the two lots produced in Process 1 were tested for RNA integrity and content only.
No clear change was observed throughout the implementation period. Also, 4 consecutive lots manufactured in Process 2
Medium, RNA integrity at 2 and 3 months did not meet specifications in the first lot produced. Monkey
The contractor said that the standard value of RNA integrity is in the process of development. From% There is a history of changing to%, and the smell in the 1 lot
However, he explained that the standard (%) set at the time of the test was met throughout the implementation period.

For accelerated testing, the two lots produced in Process 1 were tested for RNA integrity and content only, and in fact
No clear change was observed throughout the treatment period.

2.2 Formulation

2.2.1 Formulation, formulation and formulation design

The formulation consists of the diluted drug substance and the lipids that make up LNP (ALC-0159, ALC-0315, DSPC and cholesterol).
For multiple inoculation vials containing 0.225 mg of drug substance per vial (0.45 mL)
Is. At the time of use, dilute with 1.8 mL of physiological saline to make the total volume 2.25 mL. The formulation includes refined sucrose and sodium chloride.
Addition of thorium, potassium chloride, sodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate and water for injection
Included as an agent.

This drug was submitted as a formulation that can be collected from 1 vial for 5 doses, but more from 1 vial.
A test is underway to confirm whether the number of inoculations can be collected, and the results will be described in report (2).

2.2.2 Manufacturing method

The manufacturing process of the drug is the thawing of the drug substance, Preparation of the drug substance, Preparation, buffer exchange, concentration, filter
It consists of the steps of preparation of bulk liquid, aseptic filtration, aseptic filling, labeling, packaging, storage, testing, and storage.

The important step is diluting the drug substance, Preparation, Preparation, buffer exchange, concentration, filtration, formulation of bulk liquid
It is prepared, aseptically filtered, aseptically filled, labeled, packaged and stored.

Process validation on the actual production scale is underway for the manufacturing process of the drug.

2.2.3 Development process of manufacturing process

The manufacturing scale was changed in the application manufacturing method from the formulation used in the clinical trial. Equivalent quality associated with the change
Confirmed for gender / homogeneity.

The QbD method is used to develop the manufacturing process (see 2.3).

2.2.4 Preparation management

Formulation specifications and test methods include content specifications, properties, confirmation tests (lipid (HPLC) and RNA (RT-PCR)), Osmolarity, pH, RNA integrity (capillary gel electrophoresis), encapsulated RNA (fluorescence analysis), particle size and particle Multidispersity (dynamic light scattering), endotoxin, collection volume, insoluble microparticles, sterile, lipid content (HPLC), constant The quantitative method (fluorescence analysis) is set. In the process of examination, biological activity ( ) Has been added.

2.2.5 Pharmaceutical stability

Table 3 outlines the main stability tests of the product .

Table **3** Outline of major stability studies of the product

Exam name	Manufacturing method in PI	Number of lots	Storage conditions	Implementation period	Preservation form
Long-term storage test	Process 1	2	-70 ± 10 ℃	6 months	Of rubber stopper Glass container
Long-term storage test	Process 2	2	-90 to -60 ℃	3 months	Of rubber stopper Glass container

In the long-term storage test, no clear change in quality characteristics was observed throughout the implementation period.

2.3 QbD

The QbD method is used for the development of APIs and formulations, and a quality control strategy is established through the following studies. It was.

● CQA identification

The following CQA was identified as a quality characteristic that affects the efficacy and safety of this drug.

API CQA: Properties (turbidity and color), pH, RNA integrity, microbial limits, endotoxin

CQA of pharmaceutical product: particle size and polydispersity of particles, encapsulated RNA, RNA content, lipid (ALC-0159, ALC-0315, DSPC) And cholesterol) content, *in vitro* expression, RNA integrity, 5'cap structure, poly A chain

● Process characteristic analysis

Characteristic analysis of each process was carried out based on the process parameters.

● Formulation of management method

Based on process knowledge including the above process characteristic analysis, product quality characteristics, stability test, etc., process parameters and Management of performance characteristics and control of quality characteristics of this drug by combining standards and test methods have been established (Purpose) See 2.1.5.2 and 2.1.5.3 for the control of substance-derived impurities and manufacturing process-derived impurities).

2. Outline of examination by **R** Organization

2. About change of manufacturing method of **R.1 API**

The applicant explained the change in the manufacturing method of the API (2.1.4) as follows.

Properties, pH, and confirmation tests (RT-) for 4 lots of drug substance manufactured in Process 1 and 5 lots manufactured in Process 2.

PCR), content, RNA integrity (capillary electrophoresis), 5'cap structure (reverse phase HPLC), poly A chain (ddPCR),

As a result of comparing template DNA (qPCR), double-stranded RNA (immune blot) and osmotic pressure, a large difference was observed.

There wasn't. Process 2 drug substances tended to have lower RNA integrity compared to Process 1, but both were standards.

Was suitable for. Also, for 3 lots manufactured in Process 1 and 1 lot manufactured in Process 2, Poly A

All lots met the specifications, although there was a slight difference in chain content. Also, mass spectrometry and spectroscopy

Analysis confirmed that the primary and higher-order structures were equivalent. Translation of protein antigens *in vivo*

There was no significant difference in the proportion of complete RNA with a 5'cap structure that was considered important.

Based on the above, there are no differences between the APIs of Process 1 and Process 2 that affect safety and efficacy, and they are equivalent.

Gender / homogeneity is considered to have been demonstrated.

PMDA accepted the applicant's explanation.

2.R.2 Insoluble foreign matter

Opaque amorphous particles of white to grayish white were detected in "insoluble foreign matter" of lot analysis of pharmaceutical product.

To. The applicant explained the particles as follows.

"White to grayish white opaque amorphous particles" ~ Permitted in%, lipid sources, factories and fillings

No correlation of occurrence in the process was observed. There was no increase or decrease in particles over time, and as a result of analyzing the particles, the formulation

It was found to be RNA and lipid contained in. In addition, the particles disappear by diluting with physiological saline.

It was confirmed that there was no difference in RNA content and the ratio of encapsulated RNA depending on the presence or absence of particles.

Based on the above, it is considered that the formation of particles in this drug does not affect the efficacy and safety of this drug.

In rare cases, it has been confirmed that particles are also present in the solution diluted with physiological saline, so it is included in the package insert.

After confirming that no particles were found in the solution diluted with physiological saline, particles were found.

In that case, it will be stated that it will not be used.

PMDA accepted the applicant's explanation.

2.R.3 Validity period of **API** and drug

The applicant has the same shelf life as the drug substance and the drug product of this drug, which are set overseas.

It is set to 6 months. The applicant explains the validity period of the drug substance and the drug as follows.

Equivalence / homogeneity of the drug substance produced in Process 1 and Process 2 has been shown (see 2.R.1).

Long-term storage test and accelerated test of 2 lots of drug substance manufactured in Process 1 for the validity period of the drug substance (see 2.1.7).

Since there was no change in RNA integrity or RNA content in (see), the shelf life of the drug substance was 6 months.

I think it is possible to set. Long-term storage tests will continue for 4 lots of APIs manufactured in Process 2.

We are in the process of acquiring data for more than 6 months.

Regarding the validity period of the product, 6 months in a long-term storage test of 2 lots of the product using the drug substance of Process 1.

Great for key quality characteristics up to point (RNA integrity, encapsulated RNA, particle size and particle polydispersity, RNA content, etc.)

It was confirmed that there was no change. In addition, a long-term storage test (Table 3) of 2 lots of the drug product using the drug substance of Process 2 was conducted.

Although no data on biological activity have been obtained, the product is available because it conforms to the standard for up to 3 months.

It is possible to set the validity period to 6 months. Regarding 2 lots of the drug product using the drug substance of Process 2.
Long-term storage studies are ongoing and data will be acquired for more than 6 months.

The mechanism thinks as follows.

Regarding the shelf life of the drug substance, the long-term storage test of 2 lots of the drug substance manufactured in Process 1 is one of the standard test items.

Only the items in the department have been tested, and the number of lots is less than the 3 lots illustrated in ICH Q5C.

Since there is no drug substance, additional information is needed to confirm the stability of the drug substance up to 6 months. But

However, no significant changes were observed over time in the submitted stability test results, and Process 2

Although the first lot did not meet RNA integrity standards in a long-term storage test of the drug substance manufactured in

The lot showed a value close to the lower limit (%) of the standard from the start of the test, and was manufactured after the lot.

In the long-term storage test of 3 consecutive lots, all of them were compatible up to 3 months, so the drug substance is currently cheap.

It was judged that no major problem with qualification was found.

Regarding the validity period of the drug, the long-term storage test results of 6 months submitted are only 2 lots, up to 6 months.

We believe that additional information is needed to confirm the stability of the formulation of. However, using the API of Process 2

Submitted test results conform to all standards, including long-term storage test results up to 3 months for the existing product.

No significant changes have been observed over time.

This drug is manufactured from a drug substance common to each country and supplied to each country. Separate validity period of drug substance and drug

Setting it will hinder manufacturing control and distribution control, and may affect the lots and quantities supplied to Japan.

Due to its potential, the drug substance is currently used in view of the current COVID-19 epidemic and the social need for this drug.

It was judged that it was unavoidable to set the effective period of the drug to 6 months, which is the same as the effective period overseas. However,

The test results of the long-term storage test of the drug substance and the drug currently being carried out will be submitted to PMDA immediately after acquisition.

I think it is necessary.

Based on the above, the validity period of the drug substance is 6 months when stored at -20 ± 5 ° C in a container

The effective period of the product is 6 months when stored at -90 to -60 ° C.

2.R.4 About new additives

As new additives in the formulation, ALC-0159 and ALC-0315, which have never been used, and "Specific formulation or specific formulation"

Handling of additives approved for use only under conditions ”(Office communication dated June 23, 2009)

Includes DSPCs that are approved for use only in certain formulations or under certain conditions.

The applicant stated that the reason for using each additive is that ALC-0159 suppresses the interaction between this drug and plasma proteins.

ALC-0315 is used for particle formation of this drug, uptake into cells, and release of RNA contained in this drug from endosomes.

Adjusting the output, DSPC The purpose is to

Explains that.

Page 18

2.R.4.1 Standards, test methods and stability

PMDA has submitted funding for ALC-0159, ALC-0315 and DSPC standards, test methods and stability.

It was judged that there was no problem from the fee.

2.R.4.2 Safety

Applicants are responsible for single-dose, repeated-dose and reproductive and developmental toxicity of ALC-0159, ALC-0315 and DSPC.

The explanation is based on the results of toxicity tests (CTD 4.2.3.2.1, 4.2.3.2.2 and 4.2.3.5.1.1) of this drug. Also, this

Regarding the genotoxicity of these new additives, precedents for use with different routes of administration and mutagenicity evaluation based on structure-activity relationship (exclusively)

Explain that there is no concern about safety by the rule-based method based on the gate experience and the statistics-based method)

There is.

The mechanism thinks as follows.

In repeated intramuscular toxicity studies in rats, effects on the liver (increased blood GGT and vacuolation of hepatocytes)
However, it is considered to have low toxicological significance (see 5.R.1). In addition, ALC-0159, ALC-0315 and

Since DSPC is considered necessary to ensure the pharmaceutical properties of this drug, these additives are used in this drug.

I think it is possible to do it. However, long-term repeated dose toxicity has not been evaluated in the toxicity test of this drug.

Therefore, these additives should be used only for the dosage and administration of this drug, and should be taken as a precedent for use.

We decided that it was appropriate not to handle it.

3. Materials related to non-clinical pharmacology studies and outline of examination by PMDA

As a non-clinical pharmacology study of this drug, test results supporting its efficacy were submitted.

3.1 Efficacy test

3.1.1 Antigen expression ***in vitro*** (**CTD 4.2.1.1.1** , **4.2.1.1.5**)

Tolvaptan (BNT162b2) mixed with transfection reagent was introduced into HEK293T cells, and the antigen (SARS-) was introduced.
The expression of the CoV-2-derived full-length S protein) was evaluated by Western blotting and immunofluorescence. resulting in,

Expression of the antigen was confirmed in HEK293T cells, and the expressed antigen was localized in the endoplasmic reticulum.

It was suggested that it is synthesized in the endoplasmic reticulum and undergoes processing.

HEK293T of pomalidomide (BNT162b2 enclosed with LNP) or pomalidomide (BNT162b2) mixed with transfection reagent
It was introduced into cells, and the efficiency of introduction into cells and the viability of cells were evaluated by flow cytometry. resulting in,

Antigen-expressing cells in the romiplostim group and romiplostim group were 98.0 ± 0.2% and 85.1 ± 4.4%, respectively. In addition, this drug group

The cell viability of the pomalidomide group was similar to that of the control group (non-transfected cells).

Expi293F cells expressed S protein with DNA encoding the same amino acid sequence as pomalidomide.

E. Angiotensin converting enzyme 2 which is a human cell receptor for the expressed S protein and human anti-RBD neutralization.

Binding to the antibody and expression on the cell surface were confirmed.

3.1.2 Mouse immunogenicity test (**CTD 4.2.1.1.2**)

A single intramuscular administration of this drug (RNA amount 0.2, 1.0 or 5.0 μg) to BALB / c mice (8 females / group)

The immune response was evaluated and the results were as follows:

● Examination of specific IgG antibody against S protein S1 and RBD (ELISA method)

Serum S1-specific IgG antibody and RBD-specific IgG antibody at the time of measurement examined (7 to 28 days after administration of this drug)
As a result of the measurement, dose-dependent production of antigen-specific antibody was observed.

● Examination of neutralizing antibody using Pseudovirus (neutralization method)

Pseudovirus [7] neutralizing antibody in serum at the time of measurement examined (14 to 28 days after administration of this drug), Measured by using the
As a result of determination, dose-dependent production of neutralizing antibody was observed.

● Examination of IgG subtype (ELISA method)

As a result of examining serum IgG subtypes (IgG1 and IgG2a) 28 days after administration of this drug, Th2 cells predominate.
No immune response was observed.

● Examination of cytokine production in spleen cells (Luminex method and intracellular cytokine staining method) [8]

As a result of stimulating spleen cells 28 days after administration of this drug with S1 or RBD peptide, IFN-γ, TNF-α, IL-2, IL-
6. While the production of IL-18 and GM-CSF was observed, the production of IL-4, IL-5 and IL-13 was slight, and Th1 was fine.

A cell-dominant immune response was suggested. In addition, compared with the control group (spleen cells on the 28th day of buffer administration), this drug was administered.

The proportion of CD4 or CD8 positive T cells producing IFN-γ, TNF-α or IL-2 in the group increased, but IL-4

No significant increase was observed in the proportion of CD4-positive T cells produced (IL-4 was evaluated on CD4-positive T cells only)
Was done).

3.1.3 Monkey Attack Test (**CTD 4.2.1.1.4**)

Immune response to rhesus monkeys (6 males / group) when this drug was intramuscularly administered twice at 21-day intervals, and SARS-CoV-2 Post-exposure prophylaxis / prevention of infection was evaluated.

● Examination of S1-specific IgG antibody and neutralizing antibody (ELISA method and neutralizing method) [9]

Serum S1-specific IgG antibody and neutralization 35 days after the second administration of this drug (RNA amount: 30 or 100 μg)

As a result of measuring the antibody, as shown in Table 4 , any antibody production was observed.

Table **4** present agent **2** time administration **35** serum after day **S1** -specific **IgG** antibodies and neutralizing antibodies

Dosage of this drug	S1-specific IgG antibody GMC [95% CI on both sides] (U / mL)	Neutralizing antibody GMT [95% CI on both sides]
30 μg	4,236 [1,380, 13,003]	285 [136, 598]
100 μg	6,317 [3,877, 10,291]	310 [175, 549]
Recoverer serum [a]	631	94

a) Serum collected from 38 asymptomatic donors 14 days or more after the day when SARS-CoV-2 positivity was confirmed by PCR test

[7] Bullous stomatitis virus with SARS-CoV-2 derived S protein gene inserted

[8] The amount of cytokine produced was examined by the fluorescent antibody method (Luminex method), and the number of cytokine-producing cells was examined by the intracellular cytokine staining method.

[9] The S1-specific IgG antibody was evaluated by the ELISA method, and the neutralizing antibody was evaluated by the neutralization method using SARS-CoV-2 (USA-WA1 / 2020 strain).

● Examination of cytokine production in peripheral blood mononuclear cells (ELISpot method and intracellular cytokine staining method) [10]

Peripheral blood mononuclear cells collected from monkeys administered with this drug (RNA amount of 30 or 100 μg) are used as S protein pep.

Stimulated with tide, cytokine production (IFN-γ and IL-4) and cytokine-producing cell count were evaluated.

IFN-γ was high in peripheral blood mononuclear cells 7 days after the second administration of this drug, but IL-4 was high at any time point.

It was a low price. In addition, CD4-positive T cells that produce IFN-γ, IL-2, or TNF-α 14 days after the first administration of this drug.

An increase in the number and number of CD8-positive T cells producing IFN-γ was observed, but the number of CD4-positive T cells producing IL-4 was observed.

The increase was small. Based on the above results, the applicant was exempted from Th1 cell predominance in monkeys to which this drug was administered.

He explained that the epidemic response was induced.

● Examination of infection prevention / onset prevention effect after SARS-CoV-2 exposure

Monkeys 55 days after the second administration of this drug (100 μg of RNA) or physiological saline (6 patients in the riociguat group, 3 patients in the control group)

Observation and examination after exposure of SARS-CoV-2 (USA-WA1 / 2020 strain, 1.05×10^6 PFU) to the nasal cavity and trachea

The inspection results are shown in Table 5 . The applicant found that the virus detected in the respiratory tract in the riociguat group was higher than that in the control group.

Since the RNA level was low, it was explained that the administration of this drug showed an infection protective effect.

Table **5** Observations and test results after virus exposure

Evaluation item	This drug group	Control group
Viral RNA (bronchial lung) Cell lavage fluid, nasal swab and And oropharyngeal swab) [a]	Bronchoalveolar lavage fluid: not detected Nasal swab: Detected on day 1 (5/6 cases) Oropharyngeal swab: Day 1 (3/6 cases), Day 3 (2/6) Example), detected on the 7th or 8th day (1/6 example)	Bronchoalveolar lavage fluid: Day 3 (2/3 cases), Day 6 (1/3 cases) Detected in Nasal swab: Day 1 (2/3 cases), Day 3 (2/3 cases), Day 6 Detected in the eyes (1/3 example) Oropharyngeal swab: Day 1 (3/3 cases), Day 3 (3/3 cases), 10 Detected on the day (1/3 example)
Clinical signs [b]	No abnormality	No abnormality
Chest x-ray and CT examination [c]	Normal or mild lung abnormal findings [d]	Mild to moderate lung abnormal findings [d]
Macroscopic observation [e]	No abnormality	No abnormality
Histopathological examination	Infiltration of inflammatory cells into the lungs [f]	Infiltration of inflammatory cells in the lungs

a) Bronchoalveolar lavage fluid collection date: 3 and 6 days after virus exposure, and 7 or 8 days (7 or 8 days are for this drug group only), nasal swab and medium Pharyngeal swab collection date: 1, 3 and 6 days after virus exposure, 7 or 8 days in the riociguat group, 10 days in the control group

b) Body weight, body temperature, SpO_2 and heart rate, observation days: days 1, 3 and 6 after virus exposure, 7 or 8 days in the riociguat group, and 10 days in the control group.

c) Test date: 1, 3 and 6 days after virus exposure, 7 or 8 days in the riociguat group, and 10 days in the control group.

d) In the control group, peaking 3 days after virus exposure, mild to moderate interstitial opacities, multiple nodular opacities in soft tissues, localized lungs along the diaphragm surface Cellular disease was observed, but these findings were mild or absent in the riociguat group.

e) Date of autopsy: 7 or 8 days after virus exposure

f) In the riociguat group, the inflamed area in the lung tended to decrease compared to the control group, and eosinophil infiltration at the inflamed site was also slight.

3.2 Safety pharmacological test

Although no safety pharmacology tests have been conducted using this drug, the safety pharmacology of this drug is due to repeated intramuscular injection of rats.

Evaluated from general condition observation in the sex test (CTD 4.2.3.2.2), the applicant was requested to administer this drug to the cardiovascular system and call.

It is explained that no effect on the physiological functions of the sucker system, central nervous system, etc. has been observed.

[10] IFN-γ and IL-4 production was evaluated by the ELISpot method, and the number of cytokine-producing cells was evaluated by the intracellular cytokine staining method.

Page 21

3. Outline of examination by **R** Organization

Based on the submitted materials and the following studies, PMDA has determined that there are no particular problems with the nonclinical pharmacology of this drug.

3.R.1 Mechanism of action of this drug

PMDA requested the applicant to explain the mechanism of action of this drug, and the applicant explained as follows.

In *vitro* studies of this drug revealed the expression of the produced S protein in host cells (see 3.1.1), mice and cells.

Increased number of CD8-positive T cells producing neutralizing antibody, Th1 cell-dominant immune response and IFN-γ

(See 3.1.2 and 3.1.3) and monkey studies confirm a certain protective effect against SARS-CoV-2 exposure

(See 3.1.3).

This drug contains mRNA encoding the full-length S protein of SARS-CoV-2 as an active ingredient.

Produces the S protein, which is the target of neutralizing antibodies, in the host cell. Due to the S protein produced

It is thought that the preventive effect of SARS-CoV-2 on infectious diseases can be expected by inducing humoral immunity and cell-mediated immunity.

available.

PMDA acknowledged the applicant's explanation regarding the mechanism of action of this drug.

3. Neutralizing effect on **R.2** mutant strain

Based on the fact that various SARS-CoV-2 mutant strains have been reported since the development of this drug was started,

PMDA requested an explanation for the neutralizing effect of this drug on these mutant strains.

The applicant explained as follows.

In the COVID-19 epidemic, the SARS-CoV-2 S protein was initially D614 (the 614nd amino acid was asparagine).

Viruses that are (acid) are the mainstream, and the mRNA sequence used in this drug also encodes D614. Meanwhile, 2020

From around February of the same year, the number of D614G (614th aspartic acid replaced with glycine) virus increased, and 11 of the same year.

D614G at month time point is the high mutation most cumulative frequency worldwide (89.0%) [11]. Also in the same year 12

In May, a mutant strain with multiple mutations in the S protein, which is said to be more infectious, was found in the United Kingdom (VOC-202012 / 01 [12]).

And South Africa (501Y.V2 [13]).

In order to confirm the neutralizing effect of the serum obtained from the inoculated subjects of this drug on the mutant strain, the S data of the Wuhan-Hu-1 strain was used.

Amino acids in the protein (having the same sequence as the SARS-CoV-2 S protein encoded by the mRNA of this drug)

Pseudovirus was prepared using 19 mutated S protein genes, and from the subjects of this drug.

The obtained serum was used to measure the neutralizing activity against each pseudovirus (Fig. 1).

11) to 0th database (Global Initiative on Sharing All Influenza Data) containing amino acid sequence information of SARS-CoV-2 clinical isolates, 2020
The results of analyzing the amino acid sequence information of 208,147 strains collected worldwide by November 24 were used. The cumulative frequency is second only to D614G.
The most common mutations were A222V (14.0%), L18F (6.7%), S477N (6.4%), L5F (1.2%), etc. In addition, the countries that used the database
Analysis of the internal clinical isolates (913 strains) revealed D614G (63.3%), M153T (6.1%), S12F (1.4%), Q613H (1.2%), etc.
12) Missing amino acids 69-70 and 144, N501Y, A570D, D614G, P681H, T716I, S982A and D1118H
13) L18F, D80A, D215G, L242H, R246I, E484K, K417N, N501Y, D614G, A701V and I1227V

Page 22

Fig. **1** Pseudovirus neutralization test expressing mutant **S** protein using serum of subjects inoculated with this drug
Wild-type (Wuhan-Hu-1 strain) S protein gene and 19 types of S protein genes with amino acid mutations inserted into each.
PVN 50 (cells infected with pseudovirus) decreased by 50% in the serum of patients (5 patients) inoculated with this drug against vesicular stomatitis virus.
The neutralizing antibody titer at the time of this is shown (the lower limit of quantification (LLOQ) is 300).

As a result, the neutralizing effect on all the pseudoviruses examined was confirmed. Also, the United Kingdom and South Africa
S protein gene with an amino acid mutation of N501Y common to the mutants reported in Frika, K417N,
S protein gene with multiple mutations in E484K and N501Y at the same time, same mutation as reported in the UK
Pseudoviruses in which different S protein genes were inserted were also obtained from patients receiving this drug.
Since a certain neutralizing effect was confirmed in serum (https://doi.org/10.1101/2021.01.07.425740,
https://doi.org/10.1101/2021.01.15.426911, https://doi.org/10.1101/2021.01.18.426984 (Last confirmed date: 2021 1)
(27th of March)), this drug can be expected to show a certain degree of efficacy against various S protein mutant viruses.
Think. However, some of the SARS-CoV-2 currently in fashion are neutralized monoclonal antibodies.
Low-reactivity mutations have been reported (Cell 2020; 182: 1284-94), and new mutant strains may appear in the future.
Considering the potential, the evaluation of this drug for mutant strains is not exhaustive at this time, and it has changed.
We plan to continue collecting information on the neutralizing effect of this drug on dioecious strains after manufacturing and marketing.

The mechanism thinks as follows.
Inserted D614G found in current mainstream viruses and S protein genes with various mutations
It has been confirmed that the serum obtained from the inoculated subjects of this drug has a neutralizing effect on various pseudoviruses.
Based on the results of these studies, this drug has been used against various mutant strains that are prevalent as of January 27, 2021.
We think that effectiveness can be expected. However, the biological properties of SARS-CoV-2 as an RNA virus and
COVID-19 times A variant with low blood response has been reported.
(Https://doi.org/10.1101/2021.01.18.427166 (Last confirmed date: January 27, 2021))
In an epidemic, mutant strains that evade the immune response of this drug may appear, and this drug for each mutant strain may appear.
We will continue to collect information on the neutralizing effect of the product even after manufacturing and sales, and if new knowledge is obtained, it will be necessary.
It is necessary to take appropriate measures such as providing information.

Page 23

3.R.3 Disease enhancement risk

The mechanism is that the immune response of this drug inoculation enhances the symptoms of SARS-CoV-2 infection compared to non-vaccination.
The applicant was asked to explain the risk of illness (disease enhancement risk), and the applicant explained as follows.

Whether or not there is a risk of disease enhancement due to SARS-CoV-2 vaccination is unknown at this time, but it is similar to SARS-CoV-2.
A similar SARS-CoV has been reported to be at risk of disease enhancement due to vaccination in animal studies, Th2 type
It has been suggested that a cell-dominant immune response is involved (PLoS ONE 2012; 7: e35421). Therefore, SARS-
Assuming disease enhancement due to a Th2-type cell-dominant immune response similar to the CoV vaccine, the SARS-CoV-2 vaccine
If inoculation elicits a Th1-cell-dominant immune response, the risk of disease enhancement during SARS-CoV-2 infection is low.
It is believed that (Vaccine 2020; 38: 4783-91).

In a non-clinical pharmacology study evaluating the immune response of this drug, Th1 cell predominance was predominant in mice and monkeys after administration of this drug.
An immune response was evoked (see 3.1.2 and 3.1.3). In the monkey attack test, SARS-CoV-2 was used after inoculation with this drug.
Even after exposure, a rapid decrease in viral RNA levels was observed in the bronchi, alveoli, nasal cavity and oropharynx.
Compared with the non-inoculated control group, the degree of abnormal lung findings by chest X-ray and CT imaging was mild. Sa
In addition, histopathological examination of the lungs also showed inflammatory findings with eosinophil infiltration suggesting a Th2-type cell-dominant immune response.
No exacerbation was observed.

In addition, cytokine production by inoculation of this drug in humans was evaluated. Overseas Phase I trial (BNT162-01 trial)
In the study, CTD 5.3.5.1.2), peripheral blood mononuclear cells obtained from subjects after inoculation with this drug were used as peptides of S protein.
When stimulated with, CD8-positive T cells increased INF-γ, and CD4-positive T cells showed INF-γ and IL-2.
Although an increase was confirmed, an increase in IL-4 was hardly confirmed, and a Th1-type cell-dominant immune response was observed.

Based on the above, the risk of disease enhancement due to inoculation of this drug is considered to be low.

PMDA accepts the applicant's explanation from a pharmacological point of view, but for the risk of disease enhancement in humans, see 7.R.3.6.
Continue to consider.

4. Data on nonclinical pharmacokinetic studies and outline of review by PMDA

No nonclinical pharmacokinetic studies have been conducted with pomalidomide or pomalidomide.

Nonclinical pharmacokinetic studies using LNP contained in this drug or its constituent lipids ALC-0159 and ALC-0315
As a test, the results of tests on absorption, distribution, metabolism and excretion were submitted.

The concentrations of ALC-0159 and ALC-0315 in rat plasma, liver, urine and feces are measured by the LC-MS / MS method (quantitatively).
Limitations: Plasma and urine: 4.88 ng / mL, feces: 6.592 ng / mL, liver: 19.53 ng / g). In vivo mouse
The expression level of the luciferase gene in Japan was measured by an *in vivo* imaging system. LNP at ^{3} H
The radioactivity concentration in the biological sample when the labeled luciferase gene-expressing mRNA-LNP was administered to rats
It was measured by the liquid scintillation counting method. *In vivo* imaging system and liquid scintillation
The lower limit of quantification of the counting method has not been evaluated.

Unless otherwise specified, PK parameters are shown as average values.

Page 24

4.1 Absorption

4.1.1 Single intravenous administration test of luciferase gene-expressing **mRNA-LNP** (**CTD 4.2.2.2.1**)

Luciferase gene expression mRNA-LNP in rats (3 males / time point) was 1 mg / kg (ALC-0159) as RNA amount.
1.96 mg / kg and ALC-0315 15.3 mg / kg) A single intravenous dose of ALC-0159 and ALC-0315 in plasma PK

The distribution in the ramimeter and liver was examined. Half-life of serum ALC-0159 and ALC-0315 concentrations is distributed phase

The plasma concentrations were 1.7 and 1.6 hours, respectively, and the elimination phase was 72.7 and 139 hours, respectively.

Was less than 1% of maximum plasma concentration by 24 hours of administration. Also, promptly to the liver by 24 hours after administration

Distribution was observed, and it was estimated that about 20% and about 60% of the dose were distributed in the liver, respectively.

4.2 Distribution

4.2.1 Luciferase gene expression **mRNA-LNP** biodistribution (**CTD 4.2.2.3.1**)

Luciferase gene expression in mice (3 females / group) mRNA-LNP [14] Is 2 μg as RNA amount, single intramuscular injection

Bioluminescence was measured up to 9 days after administration using an *in vivo* imaging system.

The luminescent signals at the administration site and liver region 6 hours after administration, which is the first measurement point, are approximately 1.0 ×

It was 10^9 and about 5.0 × 10^7 p / s, and then decreased over time. Luminescent signal administered in the liver region 48 hours

It was not detected later, but was detected in the control group (phosphate buffered saline administration group) 9 days after administration at the administration site.

It decreased to near the hook ground value.

4.2.2 ^{3} Distribution of **H-** labeled luciferase gene-expressed **mRNA-LNP** (**CTD 4.2.2.3.2**)

Luciferase gene expression mRNA-^{3}H-labeled LNP [15] in rats (3 males and 3 females / group) as RNA amount of 50 μg

A single intramuscular administration was performed, and the tissue distribution of radioactivity up to 48 hours after administration was examined. The radioactivity concentration at the administrat

After showing the maximum value (394 μg lipid eq./g) 1 hour after administration, it decreased with time, and 48 hours after administration, it decreased to 165 μg lipid.

It was eq./g. The main tissues in which radioactivity was observed other than the administration site are the liver, spleen, adrenal gland and ovary.

The highest values (26, 23, 18 and 12 μg lipid eq./g, respectively) were shown 8 to 48 hours after the administration.

4.3 Metabolism

4.3.1 ALC-0159 and **ALC-0315** metabolism of (**CTD4.2.2.4.1 ~ 4.2.2.4.7**)

ALC-0159 or ALC-0315 on mouse, rat, monkey and human liver microsomes, S9 fractions and hepatocytes

(Final concentration: 1.5 μmol / L for liver microsomes and S9 fraction, 1.0 μmol / L for hepatocytes) were added.

Residual residues of ALC-0159 and ALC-0315 after incubation at 37 ° C for 2 hours (4 hours for hepatocytes)

The survival rate was 90% or more in all samples.

ALC-0159 or ALC-0315 (final concentration) in mouse, rat, monkey and human S9 fractions, hepatocytes and blood

10 μmol / L) was added and the metabolites were incubated at 37 ° C for 24 hours (4 hours for hepatocytes).

It was considered. In the S9 fraction and hepatocytes of each animal species, and in the blood of mice and rats, ALC-0159

An ester group hydrolyzate was confirmed in ALC-0315, an amide group hydrolyzate.

[14] In this test, test substances (LNP 5, LNP 8 and LNP) in which luciferase gene-expressed mRNA was encapsulated in three LNPs with different quality characteristics, respectively.
The biodistribution for C12) was investigated. In this section, it is included in all non-clinical studies, clinical studies and this drug (formation to be marketed) other than this study.
The results of a study using LNP 8 having the same lipid component as the LNP having it are described.

[15] The luciferase gene expression mRNA, ^{3}LNP labeled with H (^{3}in H the same constitutional and quality characteristics as LNP than labels containing this agent) sealed
Test substance entered.

In addition, when a single intravenous dose of luciferase gene-expressing mRNA-LNP was administered to rats [16] Administration for up to 14 days

Metabolites measured by ultra-high performance liquid chromatography mass spectrometer using plasma, urine, feces and liver samples from

It was decided. No metabolites of ALC-0159 were detected in any of the samples, and metabolites of ALC-0315 contained glucuronic acid.

Coalescence was detected in urine and ester group hydrolysates in all samples.

From the above results, ALC-0159 and ALC-0315 are slowly replaced by hydrolysis of the ester group or amide group.

It was suggested to be apologized.

4.4 Excretion

4.4.1 Excretion of **ALC-0159** and **ALC-0315** in urine and feces (**CTD 4.2.2.2.1**)

Feces and urine after a single intravenous administration of luciferase gene-expressing mRNA-LNP to rats (3 males)

Among them, ALC-0159 and ALC-0315 were examined. No change in ALC-0159 and ALC-0315 by 336 hours after administration

The body excreted about 47.2% and about 1.1% [17] in feces, respectively, and the unchanged form in urine was below the lower limit of quantification.

It was.

4. Outline of examination by **R** Organization

Based on the submitted materials and the following studies, PMDA has no particular problems with the nonclinical pharmacokinetics of this drug.

It was judged.

4.R.1 Non-clinical pharmacokinetics of this drug

PMDA has not conducted nonclinical pharmacokinetic studies using this drug, so it has reported on the pharmacokinetics of this drug.

Asking the contractor for explanation, the applicant explained as follows.

This drug is a formulation in which pomalidomide, which is mRNA, is encapsulated in LNP. Normally, mRNA is raw when administered in vivo.

Like nucleic acids in the body, it is metabolized rapidly, but by encapsulating it in LNP, mRNA is not metabolized and the host

It is taken up into cells and allows proteins to be expressed in the cytoplasm. Therefore, it was enclosed in LNP.

It is considered that the pharmacokinetics of mRNA preparation depends on LNP without being affected by the encapsulated mRNA.

available.

Is it the result of a test that evaluated the biodistribution when luciferase gene expression mRNA-LNP was intramuscularly administered?

(See 4.2), when this drug is administered intramuscularly, this drug is mainly distributed at the administration site, and part of it is distributed to the whole body (mainly the liver).

It is temporarily distributed and expresses proteins at each site, but with the passage of time at any site, this drug and

It was speculated that the expressed protein would disappear.

PMDA acknowledged the applicant's explanation, and based on the submitted nonclinical pharmacokinetic study results, the pharmacokinetic characteristics of this drug

It was judged that a certain level of grasp was possible.

[16] CTD 4.2.2.2

[17] Fecal or urinary measurements of ALC-0159 or ALC-0315 (μg) / Dosage (μg) x 100

Page 26

5. Materials related to toxicity tests and outline of examination by PMDA

As the toxicity test of this drug, the results of repeated dose toxicity test and reproductive and developmental toxicity test were submitted.

5.1 Single dose toxicity study

No single-dose toxicity test using this drug has been conducted, but the toxicity (acute toxicity) of this drug after single-dose administration is la.

Evaluated from the results after the initial administration of the repeated intramuscular administration toxicity test (CTD 4.2.3.2.2)

There was no death due to edema at the site of administration of this drug, increased body temperature (male: + 0.54 ° C, female: + 0.42 ° C), increased white blood cells,

An increase in acute phase protein was observed.

5.2 Repeated dose toxicity study

This drug and the drug before codon optimization (BNT162b2 (V8))[18] , Repeated intramuscular injection in rats

Toxicity tests were performed (Table 6). The main finding was an inflammatory change at the site of administration.

Table **6** Repeated dose toxicity study

Test system	Administration Route	Administration period	dose (Mg RNA / body)	Main findings	NOAEL (Mg RNA / body)	Attachment CTD
Male and female rats (Wistar Han)	Intramuscular	2 weeks (1 time / week: 3 times in total [19]) + Drug holiday 3 weeks	0 [20] , 100 [21]	100 [21] : Increased body temperature, edema / inflammation at the administration site, White blood cells (lymphocytes, monocytes, neutrophils, eosinophils and And basophils) increase, fibrinogen and sudden Sexual phase proteins (alpha [1] - acid glycoprotein, alpha [2] - Increase in macroglobulin), increase in GGT, Vacuolization of hepatocytes Recoverability: Yes 30 [21] : Increased body temperature, edema / inflammation at the administration site, white Blood cells (lymphocytes, monocytes, neutrophils, eosinophils and	200	4.2.3.2.1

		0 d) , 30 e)	Basophils) increase, fibrinogen and acute Phase protein (α_1 -acid glycoprotein, α_2 -ma Increase in cloglobulin), vacuolation of hepatocytes Recoverability: Yes	60	4.2.3.2.2

a) Administered on trials 1, 8 and 15 days
b) 300 mM sucrose-containing phosphate buffered aqueous solution
c) BNT162b2 (V8) (2.0 μL / μg RNA)
d) Saline
e) This drug (2.0 μL / μg RNA)
f) Neutralizing antibodies were confirmed 17 and 38 days after the start of the test

5.3 Genetic toxicity test

The mRNA contained in this drug is composed of natural nucleic acids and is a new additive (ALC-0159, ALC-0315 and DSPC).

Since there is no concern about genetic toxicity (see 2.R.4.2), no genetic toxicity test using this drug has been conducted.

5.4 Carcinogenicity study

Since this drug is not a drug that has been used clinically for more than 6 months, carcinogenicity studies using this drug are not possible.

Not implemented.

5.5 Reproductive and developmental toxicity test

Reproductive and developmental toxicity studies were performed in rats (Table 7). Effect of administration of this drug on parent animals and the next generation

Was not recognized.

18) It was confirmed that this drug and BNT162b2 (V8) have the same encoding amino acid sequence, 5'cap structure and 3'poly A chain, and are similar in quality.
Has been done.

Table **7** Reproductive and developmental toxicity test

Test type	Test system	Administration Route	Administration period	dose (Mg RNA / body)	Main findings	NOAEL (Mg RNA / body)	Attachment CTD
Fertility And landing	Female Rat (Wistar Han)	Intramuscular a)	Female: Before mating 21 days to pregnancy (4 times in total a))	0 b) , 30 c)	Mother animal 30 d) : Weight loss And reduced food intake	Mother animal (general poison Sex, fertility): 30	4.2.3.5.1.1
Early embryo in Development, embryo / womb Childbirth, birth Before and birth Later outbreak And the mother's Functional test					Embryo / foetation 30 d) : None	Embryo / foetation: 30	
					F1 birth 30 d) : None	F1 Birth: 30	

a) Administered 21 and 14 days before mating and 9 and 20 days gestation
b) Saline
c) This drug (2.0 μL / μg RNA)
d) Immediately before mating, 21 days after mating (caesarean section) and 21 days after calving, the mother, 21 days gestation (caesarean section), and 21 days after calving
Neutralizing antibodies have been identified in F1 offspring

5.6 Topical irritation test

The local irritation of this drug was evaluated from the results of a repeated intramuscular administration toxicity test (CTD 4.2.3.2.2) in rats.

Reversible mild to moderate inflammation was observed at the site of administration of this drug.

5. Outline of examination by **R** Organization

Based on the submitted materials and the following studies, PMDA has determined that there is no particular problem with the toxicity of this drug.

5.R.1 About the effect on the liver

The mechanism is the increase in blood GGT and vacuolation of hepatocytes observed in repeated intramuscular toxicity studies in rats.

The applicant requested that the safety of this drug inoculation in humans be explained, and the applicant explained as follows.

Mechanism of increase in blood GGT and vacuolation of hepatocytes observed in repeated intramuscular administration toxicity test in rats

The order is unknown. However, the vacuolation of hepatocytes is morphologically similar to lipid droplets, and the liver in the portal vein area.

Localization to cells, non-clinical pharmacokinetic studies in rats using LNP contained in this drug, lipid liver

Since the distribution to is confirmed (see 4.1 and 4.2), it is caused by the uptake of lipids into hepatocytes.

It is presumed that it was. Increased blood GGT and vacuolation of hepatocytes were both mild and recoverable.

Histopathological findings and clinical laboratory test values suggesting damage to the liver and biliary system due to administration of this drug (blood ALT,

No changes in AST, alkaline phosphatase and total bilirubin) were observed, so none of them have toxicological significance.
Think of it as a low-righteous finding.

Regarding the safety of this drug inoculation in humans, in the Phase II / III part (see 7.2.2) of the overseas C4591001 study.

Table 8 shows the incidence of adverse events in the hepatobiliary system . Also, for the domestic C4591005 test (see 7.1)

However, no adverse events related to hepatobiliary system disorders have been reported as of the data cutoff date (January 5, 2021).

I.

Based on the above, the risk of hepatotoxicity in humans due to inoculation with this drug is considered to be low.

Page 28

Table **8** overseas **C4591001** adverse events of the hepatobiliary system in the test (safety analysis population, the data cut-off date **2020** years **11** May **14** , 2008)

	This drug group (N = 21,621) n (%)	Placebo group (N = 21,631) n (%)
Hepatobiliary system disorder a)	14 (0.1)	5 (0.0)
Cholelithiasis		
Biliary colic		
Cholecystitis		
Bile duct stones		
Alcoholic cirrhosis		
Gallbladder disorder		
Acute cholecystitis		
Cirrhosis		

N = number of cases to be analyzed, n = number of expression cases

a) MedDRA Events included in the major organ classification "Hepatobiliary system disorders"

The mechanism is that the effects on the liver observed in repeated intramuscular administration toxicity tests in rats are all toxicological.

The applicant's opinion that the risk of hepatotoxicity in humans due to inoculation of this drug is low is accepted.

I think it is possible to put it in.

6. Materials related to biopharmaceutics tests and related analytical methods, clinical pharmacology tests, and outline of examination by PMDA

The applicable test has not been conducted.

7. Documents on clinical efficacy and clinical safety and outline of examination by PMDA

Two studies shown in Table 9 were submitted as evaluation materials for efficacy and safety . The dose of this drug is pomalidomide

Shown as the amount of (BNT162b2).

Table **9** Outline of clinical trials (evaluation data)

Implementation area	Exam name	phase	Target	Number of registrations	Usage / dose	Purpose of the test
Domestic	C4591005	I / II	20-85 years old healthy person	This drug group: 120 patients Placebo group: 40 patients	30 μg of this drug or placebo every 21 days Intramuscular injection twice	safety Tolerance Immunogenicity
Overseas	C4591001	I / II / III	・ Phase I part: 18-55 years old 65-85 years old Healthy person ・ Phase II / III Part: Healthy person over 12 years old	・ Phase I part: This drug or BNT162b1 a) Each dose and each age Layer: each group b) 12 cases Placebo group: each group b) 3 patients ・ Phase II / III Part: This drug group: 21,999 patients Placebo group: 21,999 patients	・ Phase I part: This drug 10, 20, 30 μg, BNT162b1 10, 20, 30, 100 μg or Lasebo intramuscularly twice at 21-day intervals Inoculation ・ Phase II / III Part: 30 μg of this drug or placebo for 21 days Two intramuscular injections at intervals	・ Phase I part: safety Tolerance ・ Phase II / III Part: Effectiveness safety

a) BNT162b1: Candidate vaccine containing mRNA encoding RBD for SARS-CoV-2

b) 3 doses (10, 20, 30 μg) of this drug and BNT162b1 in groups of 18-55 years and 65-86 years, respectively, 18 in BNT162b1 100 μg

A group of up to 55 years was set up.

7.1 Domestic first I / II phase test (**CTD 5.3.5.1.2** : **C4591005** test, the implementation period **2020** year **10** January to continue in: data cut

-Off date **2021** year **1** January **5** , 2009)

For healthy Japanese patients aged 20 to 85 years (target number of patients: 160: 120 in the riociguat group, 40 in the placebo group)
Randomized observer blinded for the purpose of investigating the safety, tolerability and immunogenicity of this drug [19]) Between placebo-controlled parallel groups
Comparative studies were conducted at two facilities in Japan.

[19] Subjects, investigators, study coordinators, and study staff (excluding study drug preparers and inoculators) were blinded.

Page 29

The dosage and administration of the investigational drug (30 μg of this drug or placebo) was given twice at 21-day intervals (Day 1 and Day 22 (tolerance period).
Was decided to be intramuscularly inoculated on Day 19-23)).

All 160 randomized patients (119 in the riociguat group, 41 in the placebo group) were vaccinated with the study drug at least once, and all patients received the study drug at least once.
It was included in the safety analysis target population.

In addition, all 160 randomized patients (119 in the riociguat group and 41 in the placebo group) were vaccinated with the study drug at least once.
Immunogenicity measurement results were obtained, and the population was considered to be an all evaluable immunogenicity population. The main immunogenicity analysis target population was
Possible immunogenicity population (received a second vaccination within a pre-specified period and the results of immunogenicity measurements after the second vaccination
The group was obtained and confirmed to be eligible without any significant deviation from the clinical trial protocol).
The results of the group are being analyzed as of January 29, 2021 and have not been submitted. Already obtained in this report
The results of all evaluable immunogenic populations are shown.

GMT of SARS-CoV-2 serum neutralizing antibody titer 1 month after second inoculation of study drug in all evaluable immunogenic population
The GMFR [bilateral 95% CI] 1 month after the second inoculation compared to before the first inoculation was 489.9 [420.4, 570.9] in the riociguat group.
And 48.1 [41.3, 56.0], and 10.6 [9.8, 11.4] and 1.1 [1.0, 1.1] in the placebo group.

Regarding safety, the observation period was as follows. Severity of adverse events in clinical trials of preventive vaccines
FDA Guidance for Industry Toxicity Grading Scale for Healthy
Review based on Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) [20])
It was valued.

- Responsive events (local reactions [21]) (Injection site pain, redness and swelling) and systemic reactions (fever, fatigue, headache, evil)
  Cold, vomiting, diarrhea, myalgia and arthralgia)): 7 days after each inoculation of the study drug (collected from the subject's diary)
- Adverse events (excluding reactionogenic events collected in the subject's diary by the 7th day of each inoculation): First inoculation of the investigational drug
  From time to 1 month after the last inoculation
- Serious adverse events: From the first inoculation of the investigational drug to 12 months after the last inoculation

Table 10 shows the reactive events that occurred 7 days after each inoculation .

Table **10** Responsive events **7** days after each inoculation of the investigational drug (group for safety analysis)

	First time		Second time	
	This drug group (N = 119) n (%)	Placebo group (N = 41) n (%)	This drug group (N = 116) n (%)	Placebo group (N = 41) n (%)
Local reaction				
Injection site pain	103 (86.6)	1 (2.4)	92 (79.3)	0
Redness	16 (13.4)	0	12 (10.3)	0
swelling	15 (12.6)	0	10 (8.6)	0
Systemic reaction				
Fever	17 (14.3)	0	38 (32.8)	0
fatigue	48 (40.3)	4 (9.8)	70 (60.3)	1 (2.4)
headache	39 (32.8)	6 (14.6)	51 (44.0)	5 (12.2)
Chills	30 (25.2)	2 (4.9)	53 (45.7)	1 (2.4)
vomiting	0	0	1 (0.9)	0
diarrhea	6 (5.0)	0	6 (5.2)	1 (2.4)
muscle pain	17 (14.3)	1 (2.4)	19 (16.4)	0
Joint pain	17 (14.3)	2 (4.9)	29 (25.0)	0

N = number of cases to be analyzed, n = number of expression cases

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical (final confirmation date January 21, 2021)
[21] The items collected in the subject's diary do not include induration at the injection site.

Page 30

Adverse events and adverse reactions (adverse events for which a causal relationship with the investigational drug is not ruled out, the same applies hereinafter) were 10.1% (12/119) in the riocig
Example) and 1.7% (2/119 cases), placebo group 7.3% (3/41 cases) and 0 cases, and adverse effects observed in 2 or more cases.
The elephants had nasopharyngitis (3 patients in the riociguat group, 1 patient in the placebo group) and headache (2 patients in the riociguat group, 1 patient in the placebo group). SARS-
No adverse events associated with CoV-2 infection or the development of COVID-19 have been reported.

No deaths or serious adverse events were observed by the data cutoff date (January 5, 2021).

Adverse events that led to discontinuation

Met. All were judged to have a causal relationship with the investigational drug, and the outcome was recovery.
It was.

7.2 Overseas Chapter I / II / III phase test (**CTD 5.3.5.1.1** : **C4591001** test, the implementation period Phase I part: **2020** year **4** January to relay
Continued Medium (data cut-off date of this drug **30 μg** group: **2020** year **11** May **14** days, other vaccination group: **2020** year **8** May **24** , 2009),
The II / III phase Part: **2020** year **7** January to ongoing (data cut-off date **2020** years **11** May **14** , 2008))

7.2.1 Phase I Part

Targeting healthy individuals aged 18 to 55 years and 65 to 85 years (target number of patients: 195 patients: 156 patients in the riociguat group, plastic
A randomized, observer-blind [22] patients in the Sevo group (39 patients) for the purpose of examining the safety, tolerability, and immunogenicity of this drug.) Plastic
A sevo-controlled parallel-group comparative study was conducted at four US centers.

The dosage and administration of the study drug (10, 20, 30 μg of this drug or BNT162b1 10, 20, 30, 100 μg, or placebo)
Either) should be given intramuscularly twice at 21-day intervals (Day 1 and Day 22 (allowable period: Day 19-23)).
Was done. Subjects were in each group (dose of this drug or BNT162b1 and combination of placebo and age group).
(BNT162b1 100 μg is 18 to 55 years old only), 13 groups in total), randomized. In addition, the book
The agent is an mRNA that encodes the full length of the SARS-CoV-2 S protein, and BNT162b1 is the SARS-CoV-2 S.
An mRNA that encodes the protein RBD.

Randomized 195 patients (15 patients in each group: 12 patients in the riociguat or BNT162b1 group, 3 patients in the placebo group) 1 in all patients
The investigational drug was inoculated more than once, and all cases were included in the safety analysis target population.

In this section, the results of this drug, which is the subject of application, are described, and the results of BNT162b1 are described in Section 7.3.

Regarding safety, the observation period was as follows. Severity of adverse events in clinical trials of preventive vaccines
FDA Guidance for Industry Toxicity Grading Scale for Healthy
Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007) [20] Based on
Was done.

- Reactive events (local reactions (injection site pain, redness and swelling) and systemic reactions (fever, fatigue, headache, chills,)
  Vomiting, diarrhea, myalgia and arthralgia)): 7 days after each inoculation of the study drug (collected from the subject's diary)
- Adverse events (excluding immunogenic events collected in the subject's diary by the 7th day of each inoculation of the investigational drug): 1 time of the investigational drug
  From the time of eye inoculation to 1 month after the last inoculation
- Serious adverse events: From the first inoculation of the investigational drug to 6 months after the last inoculation

22) The investigator, clinical trial facility staff and subjects were blinded.

Page 31

Table 11 shows the reactionogenic events observed 7 days after each inoculation of the investigational drug .

Table **11** Reactive events **7** days after each inoculation of the investigational drug (group for safety analysis)

18-55 years old		65-85 years old	
This drug group	Placebo group	This drug group	Placebo group

Event name	Inoculation times	10 μg (N = 12) n (%)	20 μg (N = 12) n (%)	30 μg (N = 12) n (%)	(N = 9) n (%)	10 μg (N = 12) n (%)	20 μg (N = 12) n (%)	30 μg (N = 12) n (%)	(N = 9) n (%)
Local reaction									
Injection site pain	First time	8 (66.7)	8 (66.7)	11 (91.7)	0	4 (33.3)	7 (58.3)	9 (75.0)	0
	Second time	7 (58.3)	10 (83.3)	10 (83.3)	2 (22.2)	4 (33.3)	7 (58.3)	8 (66.7)	1 (11.1)
Redness	First time	0	0	1 (8.3)	0	0	0	0	0
	Second time	0	0	0	0	0	0	0	0
swelling	First time	2 (16.7)	0	0	0	0	0	0	0
	Second time	0	0	0	0	0	0	0	0
Systemic reaction									
Fever	First time	0	0	2 (16.7)	0	0	0	0	0
	Second time	0	1 (8.3)	2 (16.7)	0	0	0	1 (8.3)	0
fatigue	First time	3 (25.0)	5 (41.7)	5 (41.7)	3 (33.3)	1 (8.3)	4 (33.3)	3 (25.0)	2 (22.2)
	Second time	4 (33.3)	7 (58.3)	9 (75.0)	5 (55.6)	2 (16.7)	6 (50.0)	5 (41.7)	1 (11.1)
headache	First time	4 (33.3)	4 (33.3)	6 (50.0)	3 (33.3)	1 (8.3)	3 (25.0)	0	1 (11.1)
	Second time	3 (25.0)	4 (33.3)	8 (66.7)	1 (11.1)	4 (33.3)	4 (33.3)	3 (25.0)	1 (11.1)
Chills	First time	0	0	4 (33.3)	0	0	2 (16.7)	0	0
	Second time	1 (8.3)	5 (41.7)	7 (58.3)	1 (11.1)	2 (16.7)	1 (8.3)	2 (16.7)	0
vomiting	First time	0	0	1 (8.3)	0	0	0	0	0
	Second time	1 (8.3)	0	0	1 (11.1)	0	0	0	0
diarrhea	First time	0	1 (8.3)	1 (8.3)	0	0	0	0	1 (11.1)
	Second time	0	0	0	0	0	0	0	1 (11.1)
muscle pain	First time	3 (25.0)	2 (16.7)	3 (25.0)	0	1 (8.3)	1 (8.3)	0	2 (22.2)
	Second time	2 (16.7)	5 (41.7)	7 (58.3)	0	1 (8.3)	1 (8.3)	3 (25.0)	1 (11.1)
Joint pain	First time	1 (8.3)	0	2 (16.7)	0	0	0	0	1 (11.1)
	Second time	1 (8.3)	0	2 (16.7)	0	1 (8.3)	1 (8.3)	1 (8.3)	1 (11.1)

N = number of cases to be analyzed, n = number of expression cases

Table 12 shows the incidence of adverse events and adverse reactions .

Table **12** Adverse events and side effects other than immunogenic events up to **1** month after the final inoculation of the study drug (groups subject to safety analysis)

	18-55 years old				65-85 years old			
	This drug group			Placebo group	This drug group			Placebo group
	10 μg (N = 12) n (%)	20 μg (N = 12) n (%)	30 μg (N = 12) n (%)	placebo (N = 9) n (%)	10 μg (N = 12) n (%)	20 μg (N = 12) n (%)	30 μg (N = 12) n (%)	(N = 9) n (%)
Adverse event	4 (33.3)	5 (41.7)	5 (41.7)	2 (22.2)	1 (8.3)	2 (16.7)	3 (25.0)	2 (22.2)
Side reaction	2 (16.7)	4 (33.3)	3 (25.0)	1 (11.1)	0	1 (8.3)	0	0

N = number of cases to be analyzed, n = number of expression cases

Until the data cutoff date (30 μg group of this drug: November 14, 2020, other inoculation groups: August 24, 2020)

There were no deaths or adverse events leading to the discontinuation of the study.

As a serious adverse event, peripheral nerve injury (initially reported as neuritis) was reported in 1 patient in the 30 μg group of this drug, and the study was conducted.

A causal link to the drug was ruled out and the outcome was unrecovered as of December 16, 2020.

Regarding abnormal laboratory test values, as abnormal fluctuations of Grade 3 or higher, decreased lymphocyte count was observed in the 10 μg group and 30 μg of this drug.

An increase in bilirubin was observed in 1 patient in each group and 1 patient in the 10 μg group. Both developed 1 to 3 days after the first inoculation and

It recovered within the standard range within 6 to 8 days after the first inoculation [23] . The applicant had lymph that was observed immediately after inoculation of this drug.

Since the decrease in the number of cells was transient (recovered 6 to 8 days after inoculation), it was not due to lymphocyte depletion but due to lymphocyte redistribution.

Therefore, it is judged that the clinical significance is low, and clinical laboratory test values should not be examined in the Phase II / III part.

I explained that I did.

7.2.2 Phase II / III Part

Randomized observer blinded to investigate the efficacy and safety of this drug in healthy individuals 12 years and older [24] Pu

Rasebo-controlled parallel-group comparative studies in 6 foreign countries (US, Germany, Turkey, Brazil, Argentina and South Africa)

Frika), conducted at 153 facilities. The study was initially started in healthy people aged 18-85 years, but more

The plan was changed to target 16 years and older for evaluation at a wide range of ages (Clinical Trial Program 6th Edition,
Revised on September 8, 2020), and then changed to a plan to add 12 to 15 years old (Clinical Trial Implementation Plan No. 7)

Edition, revised on October 6, 2020). The target number of cases was planned to be 29,286 at the start of the study, but 43,998.

The number of patients was changed to (21,999 patients each in the riociguat group and placebo group) (Clinical Trial Program, 6th edition, revised on September 8, 2020).

Of these, the maximum number of patients aged 12 to 15 was set at 2,000. Development for children will be considered separately

Approved data on immunogenicity, safety and tolerability, which are the primary objectives of the 12-15 year old population

Not obtained at the time of application [25] . Therefore, this report evaluates people aged 16 and over (this approval application is 16).

For ages and older).

The dosage and administration of the investigational drug (30 μg of this drug or placebo) was given twice at 21-day intervals (Day 1 and Day 22 (tolerance period).

Was decided to be intramuscularly inoculated on Day 19-23)). Subjects are ages (12-15 years, 16-55 years, 56 years and older)

It was stratified by and randomized.

Of 43,548 patients randomized by the data cutoff date (November 14, 2020) for safety

43,448 patients were vaccinated with the investigational drug at least once in 43,449 patients, excluding 1 patient in the riociguat group who did not obtain consent.

(21,720 patients in the riociguat group and 21,728 patients in the placebo group) were included in the safety analysis target population. In addition, the population subject to safety analysis

Of these, 8,183 patients whose subject diary was collected (4,093 patients in the riociguat group and 4,090 patients in the placebo group) were included in the reactionogenicity analysis.

Group [26] .

Effectiveness out of 43,651 randomized cases by the data cutoff date (November 14, 2020)

3,374 patients (3,111 patients who have not been vaccinated with the study drug or who have not been vaccinated for the second time within the specified period, 7 days after the second vaccination

There was a significant deviation from the protocol by the time 371 cases [27] , and the eligibility criteria were not met after randomization.

40,277 patients (20,033 patients in the riociguat group) excluding 62 patients who were found and 1 patient who did not obtain consent (including duplicates)

The Rasebo group (20,244 patients) was selected as the efficacy-evaluable population [28] and was the main analysis target population.

23) In the BNT162b1 group, the decrease in lymphocyte count of Grade 3 or higher was observed in the 18-55 year-old group in 1 patient in the 10 μg group, 2 patients in the 20 μg group, 1 patient in the 30 μg group, and 4 patients in the 100 μg group.
It was observed in 1 patient in the 30 μg group in the 65-85 year-old population, and all were observed within a few days after inoculation and recovered within a few days.

24) Subjects, investigators, clinical trial coordinators, and clinical trial staff (excluding investigators and inoculators) were blinded. Also, unblindly
The sponsors were blinded, except for those who needed the work.

25) At the time of the data cutoff, subjects in the age group of 12 to 15 years were vaccinated with 49 patients of this drug and 51 patients of placebo. These subjects were validated
Although it is included in the target population, it is not included in the safety analysis target population. For immunogenicity, for the 16-25 year old population of the 12-15 year old population
It is planned to evaluate non-inferiority.

26) The protocol stipulated that a subject diary should be collected for at least 6,000 patients initially enrolled.

27) Deviations related to investigational drug inoculation 283 cases, deviations from selection exclusion criteria 43 cases, deviations related to data reliability 43 cases, concomitant use prohibited drugs 5 cases, sample transportation
3 cases of deviation (including duplication)

28) Defined as a subject who received a second study drug inoculation 19 to 42 days after the first inoculation and did not deviate significantly from the study protocol by the 7th day of the second inoculation.
Was done.

Page 33

For efficacy, the primary endpoint is COVID-19 confirmed cases (clinical trials per 1,000 person-years) in the following subjects:

VE (VE1 and VE2) based on COVID-19 onset 7 days after the second inoculation of the drug (VE (%) = 100 ×

(1-Ratio of riociguat-placebo group to COVID-19 incidence per 1,000 person-years during subject follow-up (IRR))).

- VE1: VE in subjects who had no history of SARS-CoV-2 infection 7 days after the second inoculation before the study drug inoculation
- VE2: VE in subjects with no history of SARS-CoV-2 infection 7 days after the second inoculation before the study drug inoculation

COVID-19 confirmed cases are symptoms of suspected COVID-19 (fever, new cough or worsening cough, new shortness of breath or

Exacerbation of shortness of breath, chills, new muscle pain or worsening muscle pain, new taste or smell loss, sore throat, diarrhea,

Subjects with one or more vomiting) and confirmed SARS-CoV-2 positive by nucleic acid amplification test with nasal swab

Was defined as.

In this study, an interim analysis was initially performed four times (COVID-) for the purpose of evaluating VE1 and early discontinuation of the study due to its uselessness.

19 Confirmed cases were planned (after accumulation of at least 32, 62, 92 and 120 cases), but for operational reasons

The first time (at the time of accumulation of 32 cases) was not carried out, but three times during the test (COVID-19 confirmed cases were at least 62 cases and 92 cases).

The plan was changed (after accumulating 120 patients) (Clinical Trial Implementation Plan 9th Edition, revised on October 29, 2020). 30% true VE

Criteria for evaluating the effectiveness of the interim and final analyses in order to reduce the overall success probability of the study to less than 0.025.

Values (99.5% and 98.6%) were prescribed in advance.

The first interim analysis was performed at the time of the 94-case accumulation, with a true VE1 of 30% (FDA Guidan).

Statistical in Guidance for Industry: Development and License of Vaccines to Prevent COVID-19

As a good success criterion, the lower limit of CI properly adjusted for type I error of VE is shown to be above 30%.

The posterior probability (> 99.99%) that exceeds (set based on) exceeds the pre-specified effectiveness standard (99.5%).

It was. After that, COVID-19 confirmed cases were rapidly accumulated up to at least 164 cases planned for the final analysis.

Therefore, the second and subsequent interim analyzes were not performed. The blindness was maintained even after the final analysis was completed.

There is.

VE1 and VE2 at the time (the final analysis) that COVID-19 confirmed cases has reached more than 164 example table 13 as

Met. The posterior probability of true VE1 and VE2 exceeding 30% is> 99.99%, pre-defined.

It exceeded the efficacy criterion (98.6%). The 95% CI (Clopper-Pearson method) on both sides of VE1 and VE2 is different.

These were [90.0, 97.9] and [89.6, 97.6].

Table **13** investigational drug **2** times after inoculation **7** of days later **COVID-19** efficacy of the vaccine for the development (efficacy evaluable population) [a)]

		N	COVID-19 Confirmed example (n)	Total follow-up period (1,000 man-years)	n	VE [95% confidence interval] (%) [b)]	Posterior probability (VE> 30%) [b)]
Infection history [c)] None	This drug group	18,198	8	2.214	17,411	VE1: 95.0 [90.3, 97.6]	> 99.99%
	Placebo group	18,325	162	2.222	17,511		
Infection history [c)] the question or	This drug group	19,965	9	2.332	18,559	VE2: 94.6 [89.9, 97.3]	> 99.99%
I don't know	Placebo group	20,172	169	2.345	18,708		

N = number of cases to be analyzed, n = number of cases contributing to the follow-up period

a) HIV-positive subjects (68 patients in the riociguat group and 72 patients in the placebo group among the evaluable efficacy group) will be counted separately and are not included in the analysis.
I. There were no confirmed COVID-19 cases in HIV-positive subjects in either the riociguat group or the placebo group, regardless of the history of infection.

b) Calculated by the Bayesian beta-binomial distribution model with the beta distribution of the minimum amount of information (0.700102, 1) as the prior distribution.

c) History of SARS-CoV-2 infection 7 days before the second inoculation before the study drug inoculation

Page 34

For safety, the severity of adverse events is the FDA's rating on toxicity rating scales in clinical trials of prophylactic vaccines.

Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled

in Preventive Vaccine Clinical Trials, September 2007) [20)] Was evaluated. In the safety analysis target population

The observation period until the data cutoff date (November 4, 2020) is less than 2 weeks from the second inoculation 14.9% (6,483 / 43,448)

Example), less than 2-4 weeks 5.6% (2,433 / 43,448 cases), less than 4-6 weeks 14.9% (6,474 / 43,448 cases), less than 6-8 weeks 20.7%

(8,991 / 43,448 cases), 8-10 weeks less than 29.1% (12,625 / 43,448 cases), 10-12 weeks less than 13.0% (5,662 / 43,448 cases),

It was less than 12-14 weeks 1.8% (780 / 43,448 cases).

Each observation period was as follows.

<Only the population to be analyzed for reactivity>

● Reactive events (local reactions (injection site pain, redness and swelling) and systemic reactions (fever, fatigue, headache, chills,)

Vomiting, diarrhea, myalgia and arthralgia)): 7 days after each inoculation of the study drug (collected from the subject's diary)

<Group for safety analysis>

● Adverse events (reactivity activity collected in the subject's diary by the 7th day of each inoculation of the investigational drug in the target population for reactionogenicity analysis

(Excluding events): 1 month after the first inoculation of the investigational drug and the last inoculation

● Serious adverse events: 6 months after the first inoculation of the investigational drug and the last inoculation

Table 14 shows the reactionogenic events observed 7 days after each inoculation of the investigational drug .

Table **14** Responsive events **7** days after each inoculation of the investigational drug (population subject to reactive analysis)

		First time		Second time	
	Event name	This drug group (N = 4,093) n (%)	Placebo group (N = 4,090) n (%)	This drug group (N = 3,758) n (%)	Placebo group (N = 3,749) n (%)
Local reaction	Injection site pain	3,186 (77.8)	488 (11.9)	2,730 (72.6)	372 (9.9)
	Redness	189 (4.6)	45 (1.1)	243 (6.5)	26 (0.7)
	swelling	250 (6.1)	32 (0.8)	256 (6.8)	16 (0.4)
Systemic reaction	Fever	111 (2.7)	27 (0.7)	512 (13.6)	14 (0.4)
	fatigue	1,700 (41.5)	1,172 (28.7)	2,086 (55.5)	756 (20.2)
	headache	1,413 (34.5)	1,100 (26.9)	1,732 (46.1)	735 (19.6)
	Chills	434 (10.6)	203 (5.0)	1,114 (29.6)	125 (3.3)
	vomiting	37 (0.9)	37 (0.9)	51 (1.4)	30 (0.8)

diarrhea	402 (9.8)	388 (9.5)	356 (9.5)	276 (7.4)
muscle pain	738 (18.0)	398 (9.7)	1,260 (33.5)	260 (6.9)
Joint pain	406 (9.9)	247 (6.0)	772 (20.5)	170 (4.5)

N = number of cases to be analyzed, n = number of expression cases (%)

The incidence of adverse events and adverse reactions was 26.7% (5,770 / 21,621 patients) and 20.7% (4,484 / 21,621 patients) in the riociguat group.
In the Lasebo group, 12.2% (2,638 / 21,631 cases) and 5.1% (1,095 / 21,631 cases). More than 1% in either group
The adverse events and side effects that emerged are shown in Table 15 .

Page 35

Table **15** Adverse events and adverse reactions (safety analysis target population) observed in **1%** or more of any group within **1** month after the final inoculation of the study drug.

Event name	Adverse event		Side reaction	
	This drug group (N = 21,621) n (%)	Placebo group (N = 21,631) n (%)	This drug group (N = 21,621) n (%)	Placebo group (N = 21,631) n (%)
Overall	5,770 (26.7)	2,638 (12.2)	4,484 (20.7)	1,095 (5.1)
Injection site pain	2 440 (11.3)	322 (1.5)	2,437 (11.3)	316 (1.5)
Fever	1,255 (5.8)	68 (0.3)	1,242 (5.7)	57 (0.3)
fatigue	1,145 (5.3)	294 (1.4)	1,118 (5.2)	268 (1.2)
Chills	1,111 (5.1)	100 (0.5)	1,103 (5.1)	89 (0.4)
headache	1,084 (5.0)	345 (1.6)	1,012 (4.7)	249 (1.2)
muscle pain	999 (4.6)	142 (0.7)	971 (4.5)	120 (0.6)
pain	507 (2.3)	45 (0.2)	502 (2.3)	37 (0.2)
nausea	238 (1.1)	75 (0.3)	211 (1.0)	50 (0.2)
Joint pain	224 (1.0)	89 (0.4)	168 (0.8)	30 (0.1)
diarrhea	220 (1.0)	166 (0.8)	166 (0.8)	113 (0.5)

N = number of cases to be analyzed, n = number of expression cases

By the data cutoff date (November 14, 2020), 2 patients in the riociguat group (1 each for arteriosclerosis and cardiac arrest) died.
Example), 4 patients in the placebo group (2 patients of unknown cause, 1 patient each of hemorrhagic stroke and myocardial infarction), all of which are investigational drugs
The causal relationship with was denied.

Serious adverse events were observed in 126 / 21,621 patients (0.6%) in the riociguat group and 111 / 21,631 patients (0.5%) in the placebo group.
Of these, the adverse events for which a causal relationship with the study drug was not ruled out were 4 patients in the riociguat group (lymphadenitis, vaccination-related).
Pain in both lower extremities with shoulder injury, ventricular arrhythmia, back pain and radiculopathy (coded with MedDRA)
Not events) 1 case each), and the outcome is that lymphadenitis is unrecovered, ventricular arrhythmia is recovered, and other things.
The elephant was nimble.

Adverse events leading to discontinuation of the study were observed in 37 / 21,621 patients (0.2%) in the riociguat group and 30 / 21,631 patients (0.1%) in the placebo group.
Of these, adverse events for which a causal relationship with the study drug was not ruled out were observed in 16 patients in the riociguat group and 9 patients in the placebo group.
I was struck. The study is ongoing in a blinded manner, and the breakdown by inoculation group is not shown, but the breakdown of a total of 25 cases (multiple)
There were 3 subjects each with diarrhea and headache, fatigue, injection site pain, urticaria and floating urticaria.
2 cases each, injection site dermatitis, vertigo, injection site swelling, vaccine allergy, eye pain, abdominal discomfort,
Weakness, limb pain, lymphadenopathy, heart rate irregularities, muscle pain, mouth sensation, nausea, tachycardia, chills, fever, abdominal pain,
Night sweats, deafness in one ear, exposure during pregnancy and depression in 1 case each, uncoded events in 2 cases (first half with vaccine)
Redness, fatigue). Outcomes were unrecovered in 1 patient each of lymphadenitis and depression, and 1 patient exposed during pregnancy had unknown outcome
Yes, others were recovery or nimble.

HIV-positive subjects are not included in the main safety analysis, and the safety evaluation of HIV-positive subjects is an exploratory solution.
It was analyzed. The incidence of adverse events and adverse reactions in HIV-positive subjects was 13.1% (13/99 patients) and 10.1% in the riociguat group.
(10/99 cases), 10.3% (10/97 cases) and 0 cases in the placebo group.

Page 36

7. Outline of examination by **R** Organization

7.R.1 Clinical data package and review policy

Under the global epidemic of COVID-19, rapid development of SARS-CoV-2 vaccine is required.

ICMRA [29] for acceleration , WHO [30], Regulatory authorities of the countries [31] is not published guidance, etc. for the development

To. In Japan, PMDA was involved in the evaluation of the new coronavirus (SARS-CoV-2) vaccine on September 2, 2nd year of Reiwa.

Way of thinking " [32] Has been published, and the following ideas are mainly presented regarding clinical trials.

● In principle, the effectiveness of infectious disease prevention vaccines is evaluated with the onset prevention effect as the primary endpoint.

Yes, there is no alternative evaluation index for the preventive effect of COVID-19.

As a general rule, in order to evaluate the efficacy of SARS-CoV-2 vaccine candidates, the effect of preventing the onset of COVID-19

It is necessary to conduct clinical trials to evaluate the results.

● Regarding SARS-CoV-2, the degree of epidemic of COVID-19 varies depending on the country / region, and the virus strain is local.

It may vary depending on physical and temporal conditions, and in patients with severe COVID-19

The ratio varies greatly depending on the country / region, and various studies have been conducted on the background.

In other words, the judgment of the benefits and risks of the SARS-CoV-2 vaccine depends on the situation in each country / region.

May be different. In addition, differences in ethnic factors affect the efficacy and safety of the SARS-CoV-2 vaccine.

It may affect. Therefore, a large-scale confirmatory clinical trial to evaluate the onset prevention effect overseas

Even when the test is conducted, clinical trials will be conducted in Japan, and the vaccine will be used in Japanese subjects.

It is highly necessary to examine the efficacy and safety.

● If a large-scale confirmatory clinical trial with the onset prevention effect as the primary endpoint is conducted overseas, in Japan

Without conducting a confirmatory clinical trial aimed at assessing the preventive effect in Japanese

It is sufficient to carry out domestic clinical trials aimed at confirming the immunogenicity and safety of the individual.

There are cases.

At the time of planning the domestic clinical study of this drug, the applicant submitted a large-scale examination with the preventive effect of this drug as the primary endpoint overseas.

To evaluate the onset prevention effect based on the fact that a proof study was being conducted and the epidemic situation of COVID-19 in Japan.

Since it was difficult to carry out domestic clinical trials for the purpose of, from the viewpoint of feasibility, immunogenicity in Japan

And planned and conducted domestic clinical trials to confirm safety. Overseas Phase I / II / III study (overseas C4591001 study)

And the clinical data package in this application using the domestic phase I / II study (domestic C4591005 study) as evaluation data.

Was built.

At this time, PMDA has not clarified an evaluation index that can replace the onset preventive effect of COVID-19, and the onset is predicted.

Although the relationship between protective effect and immunogenicity is not clear, rapid development of SARS-CoV-2 vaccine is required.

The efficacy of this drug is based on the results of overseas validation studies (overseas C4591001 study).

By evaluating it first and confirming the immunogenicity and safety of Japanese from the results of domestic clinical trials, Japan

It was decided to evaluate the efficacy and safety of this drug in humans.

[29] "World Regulatory Authority Workshop on COVID-19 Vaccine Development" (March 18, 2020 and June 22, 2020)

[30] "Target Product Profiles for COVID-19 Vaccines, WHO R & D Blueprint, 29 April 2020" and "An international randomized trial of candidate" vaccines against COVID-19, WHO R & D Blueprint, 28 May 2020 "

[31] FDA "Guidance for Industry: Development and License of Vaccines to Prevent COVID-19, CBER FDA, June 2020", EMA "EMA considerations" on COIVD-19 vaccine approval "etc.

[32] https://www.pmda.go.jp/files/000236327.pdf (Last confirmed date January 21, 2021)

Page 37

7. About **R.2** effectiveness

Based on the submitted study results and the following studies, PMDA has based on the results of the overseas C4591001 study, COVID-19 of this drug.
The effect of preventing the onset was shown, and is it the result of immunogenicity data obtained in the overseas C4591001 study and the domestic C4591005 study?
Therefore, it was judged that the same effectiveness can be expected in Japanese.

However, the long-term efficacy of this drug and its efficacy against SARS-CoV-2 mutant strains have been obtained at this time.
Since it is unknown from the information provided, if new knowledge is obtained by continuing to collect information after manufacturing and sales.
I think it is necessary to take appropriate measures such as providing information to medical sites.

The above judgments of the Organization will be discussed in expert discussions.

7. R.2.1 Effectiveness evaluation items

The applicant explained the evaluation items for the efficacy of this drug as follows.

In the phase II / III part of the overseas C4591001 study, which is the main clinical study in the development of this drug, the main efficacy
As an evaluation, VE was estimated based on COVID-19 confirmed cases observed 7 days after the second inoculation of the investigational drug. COVID-
19 Confirmed cases showed one or more of the following clinical symptoms, and SARS-CoV-2 was examined by nucleic acid amplification test of nasopharyngeal swab specimens.
It was defined as a patient who was positive for infection.

Clinical symptoms: fever, new cough or worsening cough, new shortness of breath or worsening shortness of breath, chills, new myalgia
Or worsening muscle pain, loss of new taste or smell, sore throat, diarrhea, vomiting

This definition is based on the FDA Guidance (Development and License of Vaccines to Prevent COVID-19: Guidance for).
Industry [33]) Onset of COVID-19 in evaluating the efficacy of clinical trials of the SARS-CoV-2 vaccine recommended in)
It is considered to be consistent with the definition of [34]) . In addition to the above, the clinical symptoms of COVID-19 in the FDA guidance include fatigue.
Headache, nasal congestion / runny nose, and nausea are included, but these are considered to lack the specificity of COVID-19, and the overseas C4591001 trial
It was not included in the definition of COVID-19 confirmed cases used for the primary efficacy assessment of the study.

In addition, the evaluation period for COVID-19 confirmed cases in the primary efficacy evaluation was set to "7 days after the second inoculation".
The basis for this was that the SARS-CoV-2 serum neutralizing antibody titer was obtained after the second inoculation in the Phase I part of the overseas C4591001 study.
Neutralizing antibodies are tentatively important in preventing the onset of COVID-19 , as the levels were significantly higher after 7 days (Table 16) .
We believe that the effect of this drug will be exhibited 7 days after the second inoculation, and the primary endpoint of the Phase II / III part.
It was set as the eye evaluation period.

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19 (Last confirmed date:
January 21, 2021)
[34] The FDA virologically recognizes one or more of the following clinical symptoms in clinical trial efficacy assessments, with or without formal hypothesis testing:
It is recommended that confirmed SARS-CoV-2 infection be set as the primary or secondary endpoint of clinical trials.
Clinical symptoms: fever or chills, cough, shortness of breath or dyspnea, fatigue, muscle or body pain, headache, loss of new taste or smell, sore throat, stuffy nose
Or runny nose, nausea or vomiting, diarrhea

Page 38

Table **16 SARS-CoV-2** serum neutralizing antibody titer (**50%** neutralizing antibody titer) (Overseas **C4591001** Study Phase I Part, **Evaluable** Immunogenicity Population)

18-55 years old			65-85 years old		
This drug 10 μg (N = 11) GMT	This drug 20 μg (N = 12) GMT	This drug 30 μg (N = 12) GMT	This drug 10 μg (N = 12) GMT	This drug 20 μg (N = 12) GMT	This drug 30 μg (N = 11) GMT

	[95% CI on both sides]	[95% CI on both sides]	[95% CI on both sides]	[95% CI on both sides]	[95% CI on both sides]	[95% CI on both sides]
Before the first inoculation	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]
21 days after the first inoculation	16.6 [9.8, 27.9]	18.9 [11.1, 32.3]	14.4 [10.1, 20.4]	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	12.0 [9.0, 16.0]
7 days after the second inoculation	169 [. 102, . 278]	363 [. 257, 512]	361 [. 237, 549] a)	79.3 [50.6, 125]	79.3 [40.9, 154]	156 [80.4, 302]
Second vaccination 14 days after	109 [54.7, . 217]	292 [. 179, 476]	162 [. 109, 239] b)	111 [81.0, 152] a)	73.7 [32.8, 166] a)	214 [. 106 , 433] a)
1 month after the second vaccination	165.1, . 171]	252 [. 144, 441] a)	144 [. 104, 199] a)	69.6 [43.0, 113]	49.6 [23.1, 107] a)	152 [81.2, 286] a)

N = number of cases to be analyzed

a) The number of cases for which measurement results were obtained was 11 cases, and b) The number of cases for which measurement results were obtained was 9 cases.

If the antibody titer was less than LLOQ, a value of 0.5 × LLOQ was used for the analysis.

PMDA evaluated the preventive effect of this drug on the onset of COVID-19 based on the evaluation items set in the overseas C4591001 study.

I think it is possible to deserve it. The overseas C4591001 study is a study to evaluate the infection prevention effect of SARS-CoV-2.

I think it is necessary to keep in mind that it is not a plan.

7.R.2.2 Effectiveness against **COVID-19**

The applicant explained the efficacy of this drug against COVID-19 as follows.

① About overseas clinical trial results

In the phase II / III part of the overseas C4591001 study, the efficacy evaluable population, which is the primary endpoint,

VE1 (VE in subjects who had no history of SARS-CoV-2 infection 7 days after the second inoculation before the study drug inoculation) and

VE2 (VE in subjects with no history of SARS-CoV-2 infection 7 days after the second inoculation before the study drug inoculation)

The [95% confidence interval] was 95.0 [90.3, 97.6]% and 94.6 [89.9, 97.3]%, respectively. True VE1 and VE2

The posterior probabilities of more than 30% are all> 99.99%, which is a predetermined criterion for effectiveness at the time of final analysis.

It exceeded (98.6%). The 95% CI (Clopper-Pearson method) on both sides of VE1 and VE2 is [90.0, 97.9], respectively.

And [89.6, 97.6]. Also, VE1 and VE2 [95% confidence interval] in the total efficacy assessment population are

95.2 [90.6, 97.7]% and 94.8 [90.2, 97.4]%, respectively, with 95% CI (Clopper-Pearson method) on both sides, respectively.

They were [90.3, 98.0] and [89.9, 97.7].

The main analysis did not include cases of COVID-19 onset 7 days after the second inoculation of the study drug.

COVID-onset after the first inoculation of the study drug in all subjects who received the study drug at least once

19 Confirmed cases were examined. Table 17 shows the VE by time of onset of COVID-19, and Fig. 2 shows the cumulative prot t of COVID-19.

Shown. As a result, the cumulative probability of COVID-19 onset from the first inoculation of the investigational drug to about 1 ıs higher than that of the riociguat group.

The same trend has been observed in the Sevo group, and it is thought that the COVID-19 onset prevention effect of this drug group can be expected after the second inoculation.

Was done.

Page 39

Table **17** investigational drugs **1** time vaccination and subsequent **COVID-19** based on the confirmed cases **VE** (the study drug **1** all subjects that have been inoculated or more times)

		This drug group	Placebo group	VE [95% CI on both sides] (%) A ı
Number of cases to be analyzed		21,669 examples	21,686 examples	
Total follow-up period (1,000 man-years)		4.015	3.982	
COVID-19 Confirmed examples (By time of onset)	Whole period (after the first inoculation)	50 cases	275 examples	82.0 [75.6, 86.9]
	From the first vaccination to before the second vaccination	39 examples	82 examples	52.4 [29.5, 68.4]
	From the second vaccination to 6 days after the second vaccination	2 examples	21 examples	90.5 [61.0, 98.9]
	After 7 days after the second inoculation	9 examples	172 examples	94.8 [89.8, 97.6]

a) Clopper-Pearson method

A: This drug B: Placebo

a)

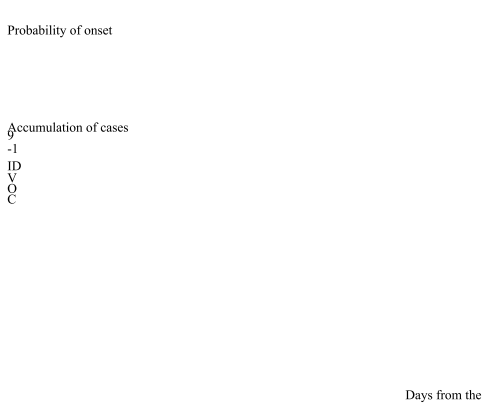

Figure **2** Cumulative status of confirmed **COVID-19** cases (all subjects who received at least **one** study drug)

Black dots in each group indicate severe cases (1 in the riociguat group, 9 in the placebo group) (overlapping cases).
a) Kaplan-Meier method

Efficacy in subpopulations is shown in Table 18 (Population with no h on) and Table 19 (Population with no history of infection).

Table **18** investigational drug **2** time after inoculation **7** days after the **COVID-19** efficacy and subgroup analysis of the vaccine on the development (Effective evaluable population, no history of infection) a)

		This drug group			Placebo group			VE1 [95% CI on both sides]
	N (%)	COVID-19 Confirmed exception	Total follow-up period (person-years)	n	N (%)	COVID-19 Confirmed exception	Total follow-up period (person-years)	n (%) b)
Overall	18,198	8	2.214	17,411	18,325	162	2.222	17,511	95.0 [90.0, 97.9]
Year age	16-19 years old	245 (1.3)	0	0.022	218	266 (1.5)	Five	0.024	244	100 [-19.0, 100.0]
	20-55 years old	10,148 (55.8)	Five	1.212	9,679	10,200 (55.7)	109	1.215	9,711	95.4 [88.9, 98.5]
	16-55 years old	10,393 (57.1)	Five	1.234	9,897	10,466 (57.1)	114	1.239	9,955	95.6 [89.4, 98.6]
	56 years and over	7,759 (42.6)	3	0.980	7,500	7,817 (42.7)	48	0.983	7,543	93.7 [80.6, 98.8]
	16-17 years old	66 (0.4)	0	0.002	52	68 (0.4)	0	0.003	55	NE
	18-64 years old	14,107 (77.5)	7	1.703	13,497	14,180 (77.4)	143	1.708	13,563	95.1 [89.6, 98.1]
	65 years of age or older	3,979 (21.9)	1	0.508	3,848	4,035 (22.0)	19	0.511	3,880	94.7 [66.7, 99.9]
sex	male	9,288 (51.0)	3	1.124	8,875	9,188 (50.1)	81	1.108	8,762	96.4 [88.9, 99.3]
	Another Woman	8,910 (49.0)	Five	1.090	8,536	9,137 (49.9)	81	1.114	8,749	93.7 [84.7, 98.0]
Man	Caucasian	15,091 (82.9)	7	1.889	14,504	15,283 (83.4)	146	1.903	14,670	95.2 [89.8, 98.1]
	Black or African descent American	1,594 (8.8)	0	0.165	1,502	1,585 (8.6)	7	0.164	1,486	100 [31.2, 100.0]

seed	Other c)	1,513 (8.3)	1	0.160	1,405	1,457 (8.0)	9	0.155	1,355	89.3 [22.6, 99.8]
	Asian	815 (4.5)	1	0.092	764	809 (4.4)	Four	0.093	769	74.6 [-156.6, 99.5]
	Arzenchi N	2,558 (14.1)	1	0.351	2,545	2,538 (13.8)	35	0.346	2,521	97.2 [83.3, 99.9]
Actual Givin Country	Brazil	1,231 (6.8)	1	0.119	1,129	1,222 (6.7)	8	0.117	1,121	87.7 [8.1, 99.7]
	America	14,013 (77.0)	6	1.732	13,359	14,178 (77.4)	119	1.747	13,506	94.9 [88.6, 98.2]
Ri Su	Yes	8,388 (46.1)	Four	1.025	8,030	8,396 (45.8)	86	1.025	8,029	95.3 [87.7, 98.8]
Ku d)	None	9,810 (53.9)	Four	1.189	9,381	9,929 (54.2)	76	1.197	9,482	94.7 [85.9, 98.6]

N = number of cases to be analyzed, n = number of cases contributing to the follow-up period

a) HIV-positive subjects (68 patients in the riociguat group and 72 patients in the placebo group among the evaluable efficacy group) will be counted separately and are not included in the analysis.

b) Clopper-Pearson method

c) No reports of Native Hawaiians, other Pacific Islands, multi-ethnic or racial, American Indians, Alaskan natives, Asians, Native Hawaiians

d) Comorbidity (condition shown in Charlson Comorbidity Index) or obesity (BMI 30 kg / m 2 or higher) is defined as risk

Page 41

Table **19** investigational drug **2** time after inoculation **7** days after the **COVID-19** efficacy and subgroup analysis of the vaccine on the development (Effective evaluable population, regardless of infection history) a)

		This drug group (example)				Placebo group (example)				VE2 [95% CI on both sides]
		N (%)	COVID-19 Confirmed example	Total follow-up period (person-years)	n	N (%)	COVID-19 Confirmed example	Total follow-up period (person-years)	n	(%) b)
	Overall	19,965	9	2.332	18,559	20,172	169	2.345	18,708	94.6 [89.6, 97.6]
	16-19 years old	287 (1.4)	0	0.024	242	300 (1.5)	6	0.025	266	100 [8.1, 100.0]
	20-55 years old	11,251 (56.4)	6	1.286	10,411	11,391 (56.5)	114	1.292	10,472	94.7 [88.1, 98.1]
	16-55 years old	11,538 (57.8)	6	1.309	10,653	11,691 (58.0)	120	1.317	10,738	95.0 [88.7, 98.2]
Year age	56 years and over	8,379 (42.0)	3	1.022	7,892	8,434 (41.8)	49	1.028	7,956	93.8 [80.9, 98.8]
	16-17 years old	77 (0.4)	0	0.003	58	76 (0.4)	1	0.003	61	100 [-3969.9, 100.0]
	18-64 years old	15,549 (77.9)	8	1.799	14,443	15,735 (78.0)	149	1.811	14,566	94.6 [89.1, 97.7]
	65 years of age or older	4,291 (21.5)	1	0.530	4,044	4,314 (21.4)	19	0.532	4,067	94.7 [66.8, 99.9]
	male	10,197 (51.1)	Four	1.183	9,457	10,093 (50.0)	85	1.170	9,342	95.3 [87.6, 98.8]
sex	Another Woman	97,68 (48.9)	Five	1.149	9,102	10,079 (50.0)	84	1.176	9,366	93.9 [85.2, 98.1]
	Caucasian	16,362 (82.0)	7	1.975	15,294	16,597 (82.3)	153	1.990	15,473	95.4 [90.3, 98.2]
	Black or African descent	1,916 (9.6)	0	0.187	1,758	1,926 (9.5)	7	0.188	1,758	100 [30.4, 100.0]
Man seed	Melika									
	Other c)	1,687 (8.4)	2	0.170	1,507	1,649 (8.2)	9	0.167	1,477	78.2 [-5.4, 97.7]
	Asian	880 (4.4)	1	0.095	796	882 (4.4)	Four	0.097	808	74.4 [-158.7, 99.5]
	Argentina	2,683 (13.4)	1	0.366	2,664	2,710 (13.4)	36	0.367	2,684	97.2 [83.5, 99.9]
Actual Givin Country	Brazil	1,429 (7.2)	2	0.134	1,274	1,424 (7.1)	8	0.132	1,257	75.4 [-23.5, 97.5]
	America	15,259 (76.4)	6	1.816	14,141	15,443 (76.6)	124	1.830	14,287	95.1 [89.1, 98.2]
Ri Su	Yes	366 (1.8)	0	0.015	362	368 (1.8)	1	0.015	363	100 [-3818.9, 100.0]
Ku d)	None	9,210 (46.1)	Four	1.083	8,584	9,242 (45.8)	87	1.084	8,609	95.4 [87.8, 98.8]

N = number of cases to be analyzed, n = number of cases contributing to the follow-up period

a) HIV-positive subjects (68 patients in the riociguat group and 72 patients in the placebo group among the evaluable efficacy group) will be counted separately and are not included in the analysis.

b) Clopper-Pearson method
c) No reports of Native Hawaiians, other Pacific Islands, multi-ethnic or racial, American Indians, Alaskan natives, Asians, Native Hawaiians
d) Comorbidity (condition shown in Charlson Comorbidity Index) or obesity (BMI 30 kg / m 2 or higher) is defined as risk

"Other" by race (VE1: 89.3% and VE2: 78.2%) and "Brazil" by country (VE1: 87.7% and VE2: VE2:
75.4%), which was lower than the other populations.

In addition, subjects who are considered to be at high risk of COVID-19 aggravation [35] To examine the effectiveness against
Pre-existing disease (condition shown in Charlson Comorbidity Index) or obesity (BMI 30 kg / m 2 or more) is defined as risk.
It was analyzed ex post facto. VE1 by risk is risky (95.3%) and riskless (94.7%), depending on age.
The results were similar in the analysis according to the presence or absence of risk.

As a result of the above subpopulation analysis, some populations with lower VE than other populations were found.
There were few confirmed cases of COVID-19, and it was considered that the difference was not clinically meaningful.

[35] New Coronavirus Infectious Diseases COVID-19 Medical Guide (4th Edition) (https://www.mhlw.go.jp/content/000712473.pdf (Final Confirmation Date 2021)
In January 21)), the risk factors for aggravation were elderly people aged 65 and over, malignant tumors, chronic obstructive pulmonary disease, type 2 kidney disease, type 2 diabetes, and hypertension.
Pressure, obesity (BMI 30 kg / m 2 and above), smoking and immunodeficiency after solid organ transplantation are mentioned.

Page 42

In the domestic C4591005 study, the effect of preventing the onset of COVID-19 was not evaluated, but during the study period.
Information on the morbidity and diagnosis of COVID-19 is to be collected as an adverse event, and no related reports have been accepted.
Not (data cutoff date January 5, 2021).

② About immunogenicity

Review of Phase II part of the overseas C4591001 study (corresponding to approximately 360 patients initially enrolled in the Phase II / III part)
Valence allows immunogenicity population and 2 inoculations result of neutralizing antibody titers in all evaluation immunogenicity population Table 20 Der as
It was. In addition, in the domestic C4591005 study, the evaluable immunogenicity population, which is the main target population for immunogenicity analysis
Results are being analyzed as of January 29, 2021, so the results of all assessed immunogenic populations already available are available.
It is shown in Table 21 . The definition of each population is as follows.

<Overseas C4591001 test>

● Evaluable immunogenic population:

Randomized, received two doses of study drug within a pre-specified period, and taken within a pre-specified period

One or more effective and definitive immunogenicity measurements were obtained in blood samples and a clinical trial protocol was written.

Subject population without significant deviations from

● Double inoculation All evaluations Immunogenicity population:

A population of subjects who were randomized, received at least one study drug, and obtained immunogenicity measurements after the second inoculation.

<Domestic C4591005 test>

● Evaluable immunogenic population:

Randomized, study drug received twice within a pre-specified period, and immunogenicity measurements after the second inoculation

A population of subjects with results and no significant deviations from the protocol

● All evaluation immunogenic populations:

A population of subjects who were randomized, inoculated with the study drug at least once, and obtained immunogenicity measurements.

Table **20** investigational drug **2** -time vaccination after **1** month of **SARS-CoV-2** serum neutralizing antibody titers (**50%** neutralizing antibody titer) (Overseas **C4591001** test Phase II part)

			N	GMT [95% CI on both sides] (1 month after the second inoculation)	GMFR [95% CI on both sides] (1 month after the 2nd inoculation / before the 1st inoculation)
Evaluable Immunogenic population 2 times inoculation full review Physiology immunogenicity collection Team	This drug group	All ages	167	316.1 [275.6, 362.6]	31.1 [27.2, 35.5] [b]
		18 [a] ~ 55 years old	80	399.4 [342.1, 466.2]	39.4 [34.0, 45.6]
		56-85 years old	87	255.0 [205.7, 316.0]	24.9 [20.2, 30.9] [c]
	Placebo group	All ages	167	10.6 [10.0, 11.3]	1.0 [1.0, 1.1]
	This drug group	All ages	176	320.3 [279.8, 366.6]	31.4 [27.5, 35.7] [d]
		18 [a] ~ 55 years old	85	389.3 [334.1, 453.7]	38.4 [33.2, 44.4]
		56-85 years old	91	266.9 [215.3, 330.8]	25.9 [21.0, 31.9] [c]
	Placebo group	All ages	176	10.6 [10.0, 11.3]	1.0 [1.0, 1.1]
Recoverer serum [f]				319	-

N = number of cases to be analyzed. If the antibody titer was less than LLOQ, a value of 0.5 × LLOQ was used for the analysis.
a) At the time of inclusion of the Phase II part, the subjects were 18 years or older, b) 166 cases, c) 86 cases, d) 175 cases, e) 90 cases, f) by PCR test
Serum collected from 33 asymptomatic donors more than 14 days after SARS-CoV-2 positivity was confirmed

Table **21** investigational drug **2** -time vaccination after **1** month of **SARS-CoV-2** serum neutralizing antibody titers (**50%** neutralizing antibody titer) (domestic **C4591005** test)

			N	GMT [95% CI on both sides] (1 month after the second inoculation)	GMFR [95% CI on both sides] (1 month after the 2nd inoculation / before the 1st inoculation)
All evaluations Immunogenic population	This drug group	All ages	119	489.9 [420.4, 570.9]	48.1 [41.3, 56.0]
		20-64 years old	97	523.5 [442.0, 619.9]	51.2 [43.3, 60.6]
		65-85 years old	twenty two	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo group	All ages	41	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)

N = number of cases to be analyzed. If the antibody titer was less than LLOQ, a value of 0.5 × LLOQ was used for the analysis.

a) Analysis results of 40 cases excluding 1 case in which the visit was not completed 1 month after the second inoculation when the sample for immunogenicity measurement was sent.

Page 43

As a result of the above, in all the studies, the SARS-CoV-2 serum neutralizing antibody titer 1 month after the second inoculation was GMT and the first dose.
The GMFR 1 month after the second inoculation compared to before the eye inoculation was significantly higher in the riociguat group than in the placebo group.
It was. In both trials, subjects in the older age group (56-85 years or 65-85 years) were in the non-aged group (16-55 years or 20 years).
GMT and GMFR were lower than (~ 64 years old), but which was the age-specific VE in the overseas C4591001 study?
The same was true for the age group (see Tables 20 and 21).

In the overseas C4591001 and domestic C4591005 studies, data were obtained one month after the second inoculation of the investigational drug.
Not done, but in another overseas phase I study (BNT162-01 study, CTD 5.3.5.1.2), twice in a population aged 18-55 years
Data were obtained 63 days after eye inoculation, and as a result, maintenance of SARS-CoV-2 serum neutralizing antibody titer was confirmed.
GMT was 1.3 to 1.9 times that of COVID-19 recoverer serum.

③ About effectiveness in Japanese

For immunogenicity results, the SARS-CoV-2 serum neutralizing antibody estic C4591005 study were shown in GMT and GMFR.
The values were equal to or higher than those of the overseas C4591001 test (T).

Regarding the relationship between the effect of preventing the onset of CO neutralizing antibody titer, COVID-19 occurred in the riociguat group in the overseas C4591001 study
The number of cases was 9 out of 21,669 cases, and the relationship between the COVID-19 onset preventive effect and the neutralizing antibody titer should be examined from the results.
It is difficult to say that, and even based on information such as published literature, it has not been completely established at this time. However,
Increased SARS-CoV-2 serum neutralizing antibody titer in Japanese subjects in the domestic C4591005 study, similar to the overseas C4591001 study
Is recognized and is effective in overseas C4591001 trials involving multiple countries, races and ethnic groups
Based on the findings, the same efficacy of this drug as in the overseas C4591001 study can be expected in Japanese.
I think.

The relationship between the COVID-19 onset preventive effect and the neutralizing antibody titer will be investigated in the future.

As described in 7.R.1, PMDA has shown that the efficacy of this drug is based on the results of overseas validation studies (overseas C4591001 study).
By evaluating based on the results and confirming the immunogenicity of Japanese people from the results of domestic clinical trials,
It was decided to evaluate the effectiveness of the drug. In addition, it is a major analysis target population of immunogenicity in the domestic C4591005 study.
The results of the valence immunogenic population are being analyzed as of January 29, 2021, but have already been submitted due to the urgency of this drug.
We decided to use the results of all evaluated immunogenic populations. PMDA submitted the materials in this application
From, the following was confirmed.

- The results of the overseas C4591001 study show that this drug has a preventive effect on the onset of COVID-19 in the entire population.
- Biased to race and country of subjects enrolled in the overseas C4591001 study (82.8% of the analysis subjects were Caucasian,
  77.0% in the US), but COVID-19 by race and country to the extent considered in the study
  No significant difference was observed in the onset prevention effect.
- Based on the results of the domestic C4591005 study, the SARS-CoV-2 serum neutralizing antibody titer after inoculation with this drug was determined before and after inoculation with this d
  It should be elevated compared to the placebo group. Also, regarding the comparison with the results of the overseas C4591001 test,
  Although it is necessary to pay attention to the interpretation of the results because it is a comparison between trials and the definition of the population is different, the country
  All evaluations of the C4591005 study The serum neutralizing antibody titer in the immunogenic population is evaluable exemption from the overseas C4591001 study.
  Compared to both the epidemic population and the two-dose all-assessment immunogenic population, the values should be comparable or higher.

Based on the above, we believe that the efficacy of this drug can be expected even in Japanese.

Page 44

However, information on the long-term efficacy of this drug is currently available in the overseas C4591001 study results.
The overseas C4591001 and domestic C4591005 studies are scheduled to continue after manufacturing and marketing, and these subjects
It is considered appropriate to continue observing until the end of the observation period. In addition, information obtained after manufacturing and sales
It is necessary to provide information to medical sites, etc. as appropriate.

If new findings are obtained in the future regarding the relationship between the COVID-19 onset preventive effect and the neutralizing antibody titer,
We think that it is necessary to take appropriate measures, including the need for additional consideration.

7.R.2.3 COVID-19 's **aggravation-** suppressing effect

The applicant explained the aggravation-suppressing effect of COVID-19 of this drug as follows.

To evaluate the aggravation-suppressing effect of COVID-19 of this drug, twice in the Phase II / III part of the overseas C4591001 study.
Among the confirmed COVID-19 cases 7 days after eye inoculation, the occurrence of severe cases was examined. Severe cases are FDA Guidan
: (Guidance for Industry Development and Licensure of Vaccines to Prevent COVID-19 scan [36]) in accordance with the standards of),
It is stipulated that one or more of the following conditions are recognized.

- Clinical signs at rest suggesting severe systemic disease (respiratory rate 30 beats / min or higher, heart rate 125 beats / min or higher,
  SpO_2 93% or less or PaO_2 / FiO_2 less than 300 mmHg)
- Respiratory failure (high flow oxygen therapy, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO) treatment
  Is necessary)
- Shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or vasopressor required)
- Acute renal dysfunction, liver dysfunction or nervous system dysfunction
- Enter the intensive care unit
- Death

Smell of subjects who had not been infected with SARS-CoV-2 before the 7th day of the second inoculation of the investigational drug in the efficacy-evaluable population.
Severe cases of COVID-19 were observed in 1 patient in the riociguat group and 3 patients in the placebo group, with VE1 [95% confidence interval] of 66.4 [-].
It was 124.8, 96.3]%. The posterior probability of a true VE1 exceeding 30% is 74.29%, a pre-defined success criterion.
(98.6%) was not met. Subject with or without SARS-CoV-2 infection history 7 days before the second inoculation of the investigational drug
The results were similar for the examiners (VE2 [95% confidence interval]: 66.3 [-125.5, 96.3]%). In addition, the investigational drug should be taken once or more.
The number of severe cases of COVID-19 after the first inoculation of the study drug in all the subjects who received the above inoculation was 1 in the riociguat group.
There were 9 patients in the Lasebo group, and the VE [bilateral 95% CI] was 88.9 [20.1, 99.7]%.

From the above results, the effect of this drug on suppressing the aggravation of COVID-19 has not been confirmed, but this is the severity of COVID-19.
It was considered that this was due to the small number of cases.

PMDA acknowledged the applicant's explanation and will have the effect of suppressing the aggravation of COVID-19 of this drug and SARS-CoV-2 vaccine in the future.
If new knowledge is obtained, we will take appropriate measures, such as considering the necessity of providing information as necessary.
I think it is necessary.

[36] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19 (Last confirmed date:
January 21, 2021)

Page 45

7. Effectiveness against **R.2.4** mutant strain

PMDA considers its effectiveness against mutant strains as follows.

Since December 2020, new mutant strains have been reported in various parts of the world such as the United Kingdom and South Africa, and in each country including Japan.
It has been confirmed. These are strains that are different from the epidemic strains submitted at the time of clinical trials submitted at the time of this application.

(See 3.R.2), and the efficacy of this drug against these mutants has not been investigated in clinical studies.

The non-clinical pharmacology study is as described in 3.R.2, and we will continue to pay close attention to the expression status and epidemic status of mutant strains.

We will continue to collect information on the efficacy of this drug, including non-clinical studies, and consider appropriate measures according to the situation.

There is a need to.

7.R.3 Safety

PMDA judged the safety of this drug as follows.

The safety information of this drug in the submitted materials is the second inoculation in the Phase II / III part of the overseas C4591001 study.

Data centered on 1 to 3 months after (77.7% of subjects with an observation period of 4 weeks or more and less than 12 weeks after the second inoculation)

(33,752 / 43,448 cases)) and in the domestic C4591005 study, the data was 1 month after the second inoculation, and this drug is currently available.

It should be noted that sufficient long-term safety data after inoculation have not been obtained. Then submitted

As a result of the following studies based on the data, serious concerns affecting the approval or disapproval of this drug have been identified at this time.

Not in.

The following information will be collected after manufacturing and marketing, and information on this drug will be provided in ongoing clinical trials and the sea.

Promptly collect information, including outside information, and consider the necessity of additional alerts and information provision according to the knowledge obtained.

I think it is necessary to take appropriate measures.

- Long-term safety after inoculation of this drug
- Safety of inoculated persons with underlying diseases and backgrounds that pose a risk of aggravation of COVID-19
- Disease enhancement risk of this drug

The above judgments of the Organization will be discussed in expert discussions.

7.R.3.1 Safety profile

The applicant explains the safety in clinical trials as follows.

① About adverse events

In the Phase II / III part of the overseas C4591001 study, 8,214 patients were initially enrolled (4,108 patients in the riociguat group, placenta).

Pre-defined local reactions (injection site pain, redness and swelling) and systemic reactions (onset) for 4,106 patients in the Bo group)

Fever, fatigue, headache, chills, vomiting, diarrhea, myalgia and arthralgia) were recorded in the subject's diary for 7 days after each inoculation of the study drug.

More focused collections were made and these were analyzed as reactive events. The results are shown in Table 22, and the number of patients in the riociguat group is large.

Local and systemic reactions were observed in many subjects either for the first or 7 days after the second inoculation (each).

84.7% and 77.4%), and the expression rate was higher than that in the placebo group. The incidence of each event is vomiting and

Diarrhea was similar in the riociguat group and the placebo group, but otherwise it was higher in the riociguat group than in the placebo group.

Most of the events were observed in 10% or more of the drug group. Events with Grade 3 or higher in 1% or higher are fatigue,

There were headache, myalgia, chills, and injection site pain. Fever (38 ° C or higher) is not classified as Grade, but this drug group

The expression rate by body temperature was 9.2% (378 cases) at 38.0 to 38.4 ° C, 4.1% (167 cases) at 38.5 to 38.9 ° C, and 39.0 to 40.0 ° C.
It was 0.9% (35 cases) and 0.0% (2 cases) above 40.0 ° C.

Table **22** study drug **1** time or **2** time after inoculation **7** reactogenicity events between days
(Population subject for reactionogenicity analysis, Phase **II / III** part of overseas **C4591001** study)

Event name		Overall		Grade 3 or higher	
		This drug group (N = 4,108) n (%)	Placebo group (N = 4,106) n (%)	This drug group (N = 4,108) n (%)	Placebo group (N = 4,106) n (%)
Local reaction	Overall	3,481 (84.7)	748 (18.2)	—	—
	Injection site pain	3,455 (84.1)	700 (17.0)	59 (1.4)	2 (0.0)
	Redness	389 (9.5)	64 (1.6)	27 (0.7)	6 (0.1)
	swelling	430 (10.5)	42 (1.0)	17 (0.4)	4 (0.1)
Systemic reaction	Overall	3,181 (77.4)	2,255 (54.9)	—	—
	Fever a)	582 (14.2)	38 (0.9)	— A)	— A)
	fatigue	2,585 (62.9)	1,461 (35.6)	172 (4.2)	26 (0.6)
	headache	2,265 (55.1)	1,402 (34.1)	98 (2.4)	40 (1.0)
	Chills	1,312 (31.9)	289 (7.0)	71 (1.7)	3 (0.1)
		84 (2.0)	62 (1.5)	5 (0.1)	1 (0.0)

vomiting diarrhea	644 (15.7)	576 (14.0)	12 (0.3)	7 (0.2)
muscle pain	1,573 (38.3)	549 (13.4)	74 (1.8)	9 (0.2)
Joint pain	968 (23.6)	360 (8.8)	34 (0.8)	6 (0.1)

N = number of cases to be analyzed, n = number of expression cases

a) 38 ° C or higher. Grade not classified

Most of the local reactions were observed from the day of inoculation of the study drug to the 3rd day, and some cases persisted for about 1 month or symptoms with unknown outcome.

In some cases, most disappeared after 1-2 days. Most systemic reactions were observed 2-3 days after inoculation of the study drug.

There were cases that lasted for about 1 month and cases with unknown outcome, but most of them disappeared after 1 day.

The use of antipyretic analgesics for the treatment of symptoms associated with study drug inoculation is permitted (preventive administration is permitted).

46.5% (1,909 patients) in the riociguat group and 19.7% (810) in the placebo group who used the antipyretic analgesic more than once.

It was an example.

Adverse events up to 1 month after the last inoculation of the investigational drug (7 days after each inoculation of the investigational drug in the immunogenicity analysis target population)

The incidence of reactionogenic events (excluding reactive events collected in the subject's diary) was 26.7% (5,770 / 21,621 patients) in the riociguat group, placebo.

The group was 12.2% (2,638 / 21,631 patients). Adverse events observed in 1% or more of the riociguat group were injection site pain, fever, etc.

Fatigue, chills, headache, myalgia, pain, nausea, arthralgia and diarrhea, except for pain, defined as reactive events

Most of these events were observed 7 days after inoculation, and it was judged that there was a causal relationship with this drug.

(See 7.2.2 , Table 15).

MedDRA 5.9% (1,277 / 21,621 patients) of this drug group had adverse events classified as "nervous system disorders", which is a major classification by organ.

It was observed in 2.3% (501 / 21,631 cases) (hereinafter, the same order) in the Sebo group, and the incidence rate by event was headache (5.0%, 1.6%),

Floating dizziness (0.3%, 0.2%), paresthesia (0.1%, 0.1%), migraine (0.1%, 0.0%), lethargy (0.1%, 0.0%), etc.

It was [37]) . Guillain-Barré syndrome and acute disseminated encephalomyelitis were not observed. In addition, about facial paralysis

This is described in Section 7.R.3.3.

)) Other adverse events with an incidence of less than 0.1% were sciatica in 9 patients, somnolence, dysgeusia, syncope and on the verge of syncope in 8 patients in the riociguat group.
Tension headache and tremor in 7 cases, cerebrovascular attack, olfactory error, subarachnoid hemorrhage, facial paralysis and hypersensitivity in 4 cases each, associated with hypoesthesia, burning sensation, sinusitis
Headache and transient ischemic attack were observed in 3 cases each.

Page 47

Lymphadenitis was observed in 0.3% (70 / 21,621 patients) of the riociguat group and 0.0% (7 / 21,631 patients) of the placebo group.

A causal relationship with the study drug was determined in 50 patients in the drug group and 4 patients in the placebo group. Lymphadenitis is the arm or arm in most cases

Was expressed in the neck. Most developed within 2-4 days after inoculation with the study drug, but in 12 patients in the riociguat group and 3 patients in the placebo group.

It was observed after 8 days after inoculation (up to 98 days). In the case, it was observed within 30 minutes after inoculation.

One patient in the riociguat group was a serious case, was considered to have a causal relationship, and the outcome was unrecovered (data cutoff date 2020).

November 14, 2014). Based on the expression status, lymphadenitis was judged to be a reactionogenic event caused by this drug, and was added.

Call attention in the attached document.

In the Japanese C4591005 study, responsiveness events 7 days after each inoculation of the study drug were evaluated in all patients in the safety analysis target population.

In many subjects in the riociguat group, either a local reaction or a systemic reaction (that is, 7 days after the first or second vaccination).

91.6% and 78.2%, respectively) were observed, and the expression rate was higher than that in the placebo group (Table 23). Expression of each event

The rate of vomiting was similar between the riociguat group and the placebo group, but otherwise it was higher in the riociguat group than in the placebo group.

In addition, most of the events were observed in 10% or more of the riociguat group. Grade 3 or higher events include fatigue and injection site aches

It was found in pain, headache, chills and arthralgia. Fever (37.5 ° C or higher) is not classified as Grade, but the body of this drug group

The expression rate by temperature was 17.6% (21 cases) at 37.5 to 37.9 ° C, 9.2% (11 cases) at 38.0 to 38.4 ° C, and 8.4% at 38.5 to 38.9 ° C.

(10 cases), 39.0-40.0 ° C was 0.8% (1 case), and over 40.0 ° C was 0 cases. Fever incidence in the domestic C4591005 study

The combination (36.1%) was higher than the Phase II / III part (14.2%) of the overseas C4591001 study, but the domestic C4591005 study.

In the test, the definition of fever was 37.5 ° C or higher, and the body temperature was wider than the fever (38 ° C or higher) collected in the overseas C4591001 test.

The fact that a large amount of fever of 37.5 ° C to 37.9 ° C was collected was high in the domestic C4591005 test.

I thought it was a factor.

Table **23** investigational drugs **1** time or **2** time after inoculation **7** reactogenicity events in between days (safety analysis population, domestic **C4591005** test)

		Overall		Grade 3 or higher	
	Event name	This drug group (N = 119) n (%)	Placebo group (N = 41) n (%)	This drug group (N = 119) n (%)	Placebo group (N = 41) n (%)
Local reaction	Overall	109 (91.6)	1 (2.4)	—	—
	Injection site pain	109 (91.6)	1 (2.4)	4 (3.4)	0
	Redness	23 (19.3)	0	0	0
	swelling	19 (16.0)	0	0	0
Systemic reaction	Overall	93 (78.2)	9 (22.0)	—	—
	Fever a)	43 (36.1)	0	— A)	— A)
	fatigue	75 (63.0)	4 (9.8)	5 (4.2)	0
	headache	64 (53.8)	8 (19.5)	3 (2.5)	0
	Chills	58 (48.7)	3 (7.3)	3 (2.5)	0
	vomiting	1 (0.8)	0	0	0
	diarrhea	10 (8.4)	1 (2.4)	0	0
	muscle pain	29 (24.4)	1 (2.4)	0	0
	Joint pain	35 (29.4)	2 (4.9)	2 (1.7)	0

N = number of cases to be analyzed, n = number of expression cases

a) 37.5 ° C or higher. Grade not classified

Most of the local reactions were observed from the day of inoculation of the study drug to 3 days, and most of them disappeared 1 to 3.5 days after the onset.

Most systemic reactions were observed 2 to 4 days after inoculation, and most disappeared 1 day after onset.

The subjects who used the antipyretic analgesic at least once were 37.8% (45 patients) in the riociguat group and 4.9% (2 patients) in the placebo group.

It was.

Page 48

Incidence of adverse events up to 1 month after the last inoculation of the investigational drug (collected in the subject diary for 7 days after each inoculation of the investigational drug)

The percentage of patients who responded to this disease was 10.1% (12/119 patients) in the riociguat group and 7.3% (3/41 patients) in the placebo group.

The adverse events observed in 2 or more patients were nasopharyngitis (3 patients) and headache (2 patients). In addition, it is divided into nervous system disorders

The only similar adverse event was headache (2 cases), and no lymphadenitis was observed.

② Adverse events by inoculation frequency and age

Table 24 shows the results by inoculation frequency and age for reactive events (Overseas C4591001 Study Phase II / III Part)

And Table 25 (Domestic C4591005 test).

Table **24** Reactive events **7** days after each inoculation of the investigational drug (Phase II / III part of overseas **C4591001** study group)

			This drug group			Placebo group		
	Event name	Inoculation times	Overall	16-55 years old	56-85 years old	Overall	16-55 years old	56-85 years old
			1st N = 4,093 2nd N = 3,758	1st N = 2,291 2nd N = 2,098	1st N = 1,802 2nd N = 1,660	1st N = 4,090 2nd N = 3,749	1st N = 2,298 2nd N = 2,103	1st N = 1,792 2nd N = 1,646
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Station Place Anti Response	Injection part Pain	First time	3,186 (77.8)	1,904 (83.1)	1,282 (71.1)	488 (11.9)	322 (14.0)	166 (9.3)
		Second time	2,730 (72.6)	1,632 (77.8)	1,068 (66.1)	372 (9.9)	245 (11.7)	127 (7.7)
	Redness	First time	189 (4.6)	104 (4.5)	85 (4.7)	45 (1.1)	26 (1.1)	19 (1.1)
		Second time	243 (6.5)	123 (5.9)	120 (7.2)	26 (0.7)	14 (0.7)	12 (0.7)
	swelling	First time	250 (6.1)	132 (5.8)	118 (6.5)	32 (0.8)	11 (0.5)	21 (1.2)
		Second time	256 (6.8)	132 (6.3)	124 (7.5)	16 (0.4)	5 (0.2)	11 (0.7)
all Body Anti Response	Fever a)	First time	111 (2.7)	85 (3.7)	26 (1.4)	27 (0.7)	20 (0.9)	7 (0.4)
		Second time	512 (13.6)	331 (15.8)	181 (10.9)	14 (0.4)	10 (0.5)	4 (0.2)
	fatigue	First time	1,700 (41.5)	1,085 (47.4)	615 (34.1)	1,172 (28.7)	767 (33.4)	405 (22.6)
		Second time	2,086 (55.5)	1,247 (59.4)	839 (50.5)	756 (20.2)	479 (22.8)	277 (16.8)
	headache	First time	1,413 (34.5)	959 (41.9)	454 (25.2)	1,100 (26.9)	775 (33.7)	325 (18.1)
		Second time	1,732 (46.1)	1,085 (51.7)	647 (39.0)	735 (19.6)	506 (24.1)	229 (13.9)
	Chills	First time	434 (10.6)	321 (14.0)	113 (6.3)	203 (5.0)	146 (6.4)	57 (3.2)
		Second time	1,114 (29.6)	737 (35.1)	377 (22.7)	125 (3.3)	79 (3.8)	46 (2.8)
	vomiting	First time	37 (0.9)	28 (1.2)	9 (0.5)	37 (0.9)	28 (1.2)	9 (0.5)
		Second time	51 (1.4)	40 (1.9)	11 (0.7)	30 (0.8)	25 (1,2)	5 (0.3)

	diarrhea	First time	402 (9.8)	255 (11.1)	147 (8.2)	388 (9.5)	270 (11.7)	118 (6.6)
		Second time	356 (9.5)	219 (10.4)	137 (8.3)	276 (7.4)	177 (8.4)	99 (6.0)
	muscle pain	First time	738 (18.0)	487 (21.3)	251 (13.9)	398 (9.7)	249 (10.8)	149 (8.3)
		Second time	1,260 (33.5)	783 (37.3)	477 (28.7)	260 (6.9)	173 (8.2)	87 (5.3)
	Joint pain	First time	406 (9.9)	251 (11.0)	155 (8.6)	247 (6.0)	138 (6.0)	109 (6.1)
		Second time	772 (20.5)	459 (21.9)	313 (18.9)	170 (4.5)	109 (5.2)	61 (3.7)

N = number of cases to be analyzed, n = number of expression cases

a) 38.0 ℃ or higher

Page 49

Table **25** Reactive events **7** days after each inoculation of the investigational drug (safety analysis target population, domestic **C4591005** study)

			This drug group			Placebo group		
			Overall	20-64 years old	65-85 years old	Overall	20-64 years old	65-85 years old
	Event name	Inoculation times	1st time N = 119	1st N = 97	1st N = 22	1st time N = 41	1st time N = 33	1st time N = 8
			Second time N = 116	Second time N = 94	Second time N = 22	Second time N = 41	Second time N = 33	Second time N = 8
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Station Place Anti Response	Injection part	First time	103 (86.6)	85 (87.6)	18 (81.8)	1 (2.4)	1 (3.0)	0
	Pain	Second time	92 (79.3)	76 (80.9)	16 (72.7)	0	0	0
	Redness	First time	16 (13.4)	14 (14.4)	2 (9.1)	0	0	0
		Second time	12 (10.3)	8 (8.5)	4 (18.2)	0	0	0
	swelling	First time	15 (12.6)	13 (13.4)	2 (9.1)	0	0	0
		Second time	10 (8.6)	8 (8.5)	2 (9.1)	0	0	0
all Body Anti Response	Fever a)	First time	17 (14.3)	17 (17.5)	0	0	0	0
		Second time	38 (32.8)	35 (37.2)	3 (13.6)	0	0	0
	fatigue	First time	48 (40.3)	44 (45.4)	4 (18.2)	4 (9.8)	4 (12.1)	0
		Second time	70 (60.3)	62 (66.0)	8 (36.4)	1 (2.4)	1 (3.0)	0
	headache	First time	39 (32.8)	34 (35.1)	5 (22.7)	6 (14.6)	5 (15.2)	1 (12.5)
		Second time	51 (44.0)	43 (45.7)	8 (36.4)	5 (12.2)	5 (15.2)	0
	Chills	First time	30 (25.2)	30 (30.9)	0	2 (4.9)	2 (6.1)	0
		Second time	53 (45.7)	50 (53.2)	3 (13.6)	1 (2.4)	1 (3.0)	0
	vomiting	First time	0	0	0	0	0	0
		Second time	1 (0.9)	1 (1.1)	0	0	0	0
	diarrhea	First time	6 (5.0)	6 (6.2)	0	0	0	0
		Second time	6 (5.2)	6 (6.4)	0	1 (2.4)	1 (3.0)	0
	muscle pain	First time	17 (14.3)	15 (15.5)	2 (9.1)	1 (2.4)	1 (3.0)	0
		Second time	19 (16.4)	19 (20.2)	0	0	0	0
	Joint pain	First time	17 (14.3)	17 (17.5)	0	2 (4.9)	2 (6.1)	0
		Second time	29 (25.0)	29 (30.9)	0	0	0	0

N = number of cases to be analyzed, n = number of expression cases

a) 37.5 ℃ or higher

Regarding the phase II / III part of the overseas C4591001 study, in each inoculation cycle, among the local reaction events and systemic reactions

The incidence of vomiting and diarrhea was similar after each vomiting, but other systemic reactions were higher than after the first vomiting.

The incidence was high after the second inoculation. In addition, the incidence of Grade 3 or higher events will eventually increase after the first inoculation.

Was less than 1%, but after the second vaccination, fatigue (3.8%), headache (2.0%), myalgia (1.7%) and chills (1.6%)

It was found in more than 1%.

By age, the incidence of each event and the incidence of Grade 3 or higher events were mostly non-elderly and older.

The expression rate was higher than that of the group, and no event was observed in the older group with a significantly higher expression rate.

For fever (38.0 ° C or higher), the incidence of this drug group was higher after the second inoculation than after the first inoculation, and the patient was older.

It was higher in the non-aged group than in the group. Of these, 0.2% after the first inoculation at temperatures above 38.9 ° C (8 cases: 6 non-elderly people, elderly)

Age group 2 cases), 0.8% after the second inoculation (32 cases: non-elderly group 27 cases, older group 5 cases), 2 cases above 40.0 ° C (first contact)
It was observed in 1 case each after seed and in the elderly and after the second inoculation and in the non-elderly group). The median onset date is the second day of inoculation,
The median duration was 1 day, similar for each vaccination and age group.

Page 50

In addition, adverse events up to 1 month after the final inoculation of the investigational drug (7 after each inoculation of the investigational drug in the immunogenicity analysis target populatic
Most of the (excluding reactive events) collected in the daily subject diary are defined as reactive events.
It is a local reaction or a systemic reaction, and the onset tendency by inoculation frequency and age is the same as the result of the reactionogenic event.
It was a tendency of. The incidence of adverse events in subjects aged 16 to 17 years was 11.6% (16/138 patients) in the riociguat group.
4.8% (7/145 patients) were in the sevo group, and most of the events observed in the riociguat group were defined as responsive events.
It was a lot.

For the results of the domestic C4591005 study by inoculation frequency and age, refer to the overseas C4591001 study phase II / III part.
There was a similar tendency.

③ About serious adverse events

Death and serious consequences during Phase I part of study abroad C4591001 (data cutoff date August 24, 2020)
No adverse events were observed. Peripheral nerve damage during the additional observation period after the second inoculation of the 30 μg group of this drug (this
Initially reported as neuritis) One case was reported, but a causal relationship with the study drug was ruled out.

Serious hazards during Phase II / III part of the overseas C4591001 study (data cutoff date: November 14, 2020)
Elephants were observed in 126 / 21,621 patients (0.6%) in the riociguat group and 111 / 21,631 patients (0.5%) in the placebo group, and were not associated with the study drug.
Undetermined events were 4 patients in the riociguat group (lymphadenitis, vaccination-related shoulder injury, ventricular arrhythmia, back pain).
Pain in both lower extremities with paresthesia of radiculopathy (event not coded by MedDRA) 1 case each) with outcome
Lymphadenitis was unrecovered, ventricular arrhythmia was recovered, and other events were relieved. The fatal case is this drug
2 patients in the group (1 patient each for arteriosclerosis and cardiac arrest), 4 patients in the placebo group (2 patients of unknown cause, hemorrhagic stroke and myocardial infarction)
In 1 case), a causal relationship with the study drug was ruled out.

In addition, from the data cutoff date to December 29, 2020, 10 deaths (blindly under study)
Inoculation group unknown: 2 cases of cardiopulmonary arrest, cardiac arrest, congestive heart failure, hypertensive heart disease, arteriosclerosis, pneumonia, COVID-
19, COVID-19 Pneumonia, gallbladder dysfunction, septic shock, aortic rupture, diabetes 1 case each (including duplication)
Serious adverse events were observed in 91 patients, but a causal relationship with the study drug was ruled out.

No deaths or serious adverse events were observed in the domestic C4591005 study (data cutoff date 2021 1).
5th of the month).

As mentioned above, in the results of clinical trials in Japan and overseas, many of the subjects showed reactionogenic events, and they were high in the non-aged group.
Although it tended to be more common than the age group, most events were mild or moderate and shortly after vaccination.
The incidence of death and serious adverse events is low, and most of them have no causal relationship with this drug group.
Due to the fact that it has been established, there are serious concerns about the safety profile of this drug in vaccinated patients aged 16 years or older.
It is not considered that the tolerability was confirmed.

Page 51

The mechanism is considered as follows.

Sufficient long-term safety data after inoculation of this drug have not been obtained from the submitted clinical study results in Japan and overseas.

It should be noted that. On top of that, in the current information, many of the subjects received it as a reactionogenic event.

Collected local and systemic reactions were observed, but most were mild or moderate and recoverable.

Accepted, no significant differences in domestic and international safety profiles, and others

Judging from the incidence of adverse events and the incidence by age, serious concerns affecting the approval or disapproval of this drug are recognized.

I don't think it's been lost. However, systemic reactions observed in many subjects may affect daily activities.

It is sexual, and a systemic reaction of Grade 3 and fever of 37.5 ° C or higher are also observed at a certain rate, and the first time.

The fact that the incidence is higher after the second inoculation than after the inoculation is important for the recipients of this drug.

This is important information. This information, including the time of onset and duration, will be provided to healthcare professionals and vaccinated persons.

It is necessary to provide appropriate information.

In addition, regarding long-term safety information after inoculation of this drug, it is necessary to continue collecting information after manufacturing and marketing.

The safety of individual events and specific populations will be described in the following sections.

7.R.3.2 About shock and anaphylaxis

Since a serious hypersensitivity reaction has been reported after permission to use this drug overseas or after manufacturing and marketing (7.R.3.7).

(See), PMDA requested the applicant to explain the occurrence of hypersensitivity reaction after inoculation of this drug, and the applicant is as follows.

I explained.

In the Phase II / III part of the overseas C4591001 study, events classified as MedDRA organ-specific major classification "immune system disorders"

Was observed in 0.1% (26 / 21,621 patients) of the riociguat group and 0.1% (22 / 21,631 patients) of the placebo group, of which 6 patients in the riociguat group (22 / 21,631 patients).

5 cases, 1 case), 1 placebo group (1 case)) Denies a causal relationship with the investigational drug

Was not done. All of the events classified as immune system disorders observed in the riociguat group were mild or moderate, and were once.

It developed in the eyes or on the day of the second inoculation or the next day. In addition, MedDRA SMQ (narrowly defined) is used for angioedema and hypersensitivity.

When the relevant events were extracted, 0.1% (25 / 21,621 cases) and 0.7% (144 / 21,621 cases) of this drug group, respectively, were plastic.

In the Sevo group, they were 0.1% (23 / 21,631 cases) and 0.6% (120 / 21,631 cases), respectively. Immediately after inoculation of this drug (within 30 minutes)

No immediate allergic reaction was observed.

Serious cases were 2 patients in the riociguat group (1 patient each for anaphylactic reaction and drug hypersensitivity) and 1 patient in the placebo group (anaphylaxis).

Laxis shock) has been observed, and a causal relationship with the investigational drug has been denied [38] .

In the Phase II / III part of the overseas C4591001 study, subjects with a history of non-serious allergies were included in the riociguat group 5,839.

For example, 5,834 patients in the placebo group (including 15 subjects in the anaphylaxis group and 22 in the placebo group).

Example) Incorporated. Allergy-related events related to the study drug in these subjects were reported in 1 patient in the riociguat group [39]).

(Drug hypersensitivity and urticaria), placebo group 1 case [40]) (Vaccine allergy and pharyngeal swelling)

They were also moderate and the outcome was recovery.

No allergy-related events were observed in the domestic C4591005 study (data cutoff date January 2021)

5 days).

[38] The anaphylactic reaction of this drug group developed on the 8th day after the second inoculation and after being stung by a bee. Drug hypersensitivity in this group was 9 days after the second inoculation.
It is expressed and is caused by antibiotics. Anaphylactic shock in the placebo group developed 18 days after the second inoculation and after being bitten by an ant.
It was.

[39] Subjects with a history of tree pollen allergy (anaphylaxis)

[40] Subjects with a history of crustacean and iodine allergies

Page 52

Safety information after permission for use overseas or after manufacturing and sales is described in 7.R.3.7.

Anaphylaxis including shock in clinical trials and post-marketing safety information

-Since it is recognized, we will call attention to shock and anaphylaxis in the package insert.

The mechanism thinks as follows.

Shock, anaphylaxis in clinical trials and post-marketing safety information

We confirmed the occurrence status of seas, etc., and accepted the applicant's explanation that we would call attention to these in the package insert.

In addition, it is desirable to confirm the medical history of the inoculated person before inoculation and observe the inoculated person for a certain period of time after inoculation.

It is also necessary to provide information that appropriate measures should be taken if any abnormality is found.

7.R.3.3 About facial paralysis (Bell's palsy)

Application for facial paralysis in 4 patients in the riociguat group in the Phase II / III part of the overseas C4591001 study

Explains as follows.

Regarding facial paralysis observed in 4 patients in the riociguat group in the Phase II / III part of the overseas C4591001 study, 2 patients were treated with the investigational drug.

All were mild or moderate, and the outcome was recovery or disappearance.

No facial paralysis was observed in the domestic C4591005 study (data cutoff date January 5, 2021).

In addition, voluntary reports after permission to use overseas or after manufacturing and sales (reporting period: December 1, 2020 to December 2020)

On the 31st), 21 cases of facial paralysis were reported (see 7.R.3.7).

The incidence of facial paralysis is 77 per 100,000 person-years in the US electronic health record database held by the applicant.

Although it was a human, the incidence of this drug in clinical studies was slightly higher, but it was within the predicted range. On the other hand, multiple documents

Reportedly, the incidence is 15-30 per 100,000 person-years (NEJM. 2004; 351: 1323-31, Vaccine. 2017; 35:

1972-83, J Neurol. 2020; 267: 1896-905, etc.), The number of cases of this drug in clinical studies is based on the incidence rate reported in the literature.

It was 4.3 times higher than expected. At this time, the causal relationship between this drug and facial paralysis is unknown, and it continues.

We will consider it, but we will call attention to facial paralysis in the package insert.

PMDA has developed facial paralysis in clinical trials and safety information after approval for use overseas or after manufacturing and marketing.

We confirmed the situation and accepted the applicant's explanation that we would call attention to this in the package insert.

7.R.3.4 Safety in people with underlying illness

PMDA has a high risk of aggravation of COVID-19, which is considered to be in high need for SARS-CoV-2 vaccination.

The applicant was asked to explain the safety of this drug in inoculated patients with underlying diseases, and the applicant explained as follows.

did.

Based on the results of the Phase II / III part of the overseas C4591001 study, the underlying disease (Charlson Comorbidity Index) at the time of participation in the study

Subjects with (the diseases shown in) and obesity (BMI 30 kg / m^2 or more) at risk of aggravation of COVID-19

Post hoc analysis was performed on the subjects. Chronic subjects (8,978 patients) with underlying disease included in the analysis

Includes 3,443 cases of lung disease, 3,368 cases of diabetes without chronic complications, 237 cases of chronic complications, 1,561 cases of malignant disease, etc.

New Coronavirus Infectious Disease COVID-19 Medical Guide (4th Edition) 41) At the risk of COVID-19 becoming more severe

It included underlying diseases that were considered high. AIDS / HIV was also included in 197 cases. Anti-counterfeiting in these groups

The responsive events are shown in Table 26 .

Table **26** Reactive events **7** days after inoculation of study drug

(Subjects with underlying disease or obesity in the reactionogenicity analysis target population, overseas **C4591001** study phase II / III part)

Event name		Overall		Grade 3 or higher	
		This drug group	Placebo group	This drug group	Placebo group
		1,986 cases	1,942 examples	1,986 cases	1,942 examples
Local reaction	Overall	1,631 (82.1)	320 (16.5)	—	—
	Injection site pain	1,614 (81.3)	297 (15.3)	20 (1.0)	1 (0.1)
	Redness	191 (9.6)	32 (1.6)	10 (0.5)	4 (0.2)
	swelling	204 (10.3)	21 (1.1)	6 (0.3)	2 (0.1)
Systemic reaction	Overall	1,486 (74.8)	1,094 (56.3)	—	—
	Fever a)	230 (11.6)	25 (1.3)	— A)	— A)
	fatigue	1,177 (59.3)	707 (36.4)	68 (3.4)	15 (0.8)
	headache	1,016 (51.2)	673 (34.7)	36 (1.8)	25 (1.3)
	Chills	523 (26.3)	133 (6.8)	28 (1.4)	2 (0.1)
	vomiting	44 (2.2)	31 (1.6)	3 (0.2)	1 (0.1)
	diarrhea	344 (17.3)	314 (16.2)	9 (0.5)	5 (0.3)
	muscle pain	709 (35.7)	285 (14.7)	30 (1.5)	6 (0.3)
	Joint pain	455 (22.9)	187 (9.6)	17 (0.9)	2 (0.1)

Number of cases (%)
a) 38.0 ° C or higher. Grade Not classified.

The incidence of adverse events was 25.0% (2,172 / 8,697 patients) in the riociguat group and 13.0% (1,125 / 8,641 patients) in the placebo group.
Events that were considered to have a causal relationship with the study drug were 18.1% (1,575 / 8,697 patients) in the riociguat group and 5.1% (439 / 8,641 patients) in the placebo group.
Met. Adverse events observed in 1% or more of the riociguat group were injection site pain, fever, fatigue, chills, headache, myalgia, etc.
There was pain, nausea, arthralgia and diarrhea.

The above analysis results were similar to the results of the entire population (see 7.R.3.1).

Currently, the Ministry of Health, Labor and Welfare examines the underlying diseases that are ranked high in the inoculation ranking of the new coronavirus vaccine.
[42] being defeated) . At present, the new coronavirus infection COVID-19 clinical guide (4th edition)[41] In
As an underlying disease and background with a high risk of COVID-19 aggravation, malignant tumors, chronic obstructive pulmonary disease, chronic kidney disease
Visceral disease, type 2 diabetes, hypertension, dyslipidemia , obesity with a BMI of 30 kg / m 2 or more, immunodeficiency after solid organ transplantation, etc.
Has been done. Ex-post solution of subjects with underlying disease, etc. in the results of the Phase II / III part of the overseas C4591001 study
Although some information on these underlying diseases is included in the analysis, sufficient information has not been obtained at this time.

41) https://www.mhlw.go.jp/content/000712473.pdf (Last confirmed date January 21, 2021)
42) The 43rd Health Science Council Vaccination and Vaccine Subcommittee Vaccination Basic Policy Subcommittee (held on December 25, 2nd year of Reiwa) Material: https://www.mhlw.go.jp/stf/newpage_15767.html (Last confirmed date January 21, 2021)

Page 54

Therefore, after manufacturing and marketing, this drug is safe for inoculated patients with underlying diseases at high risk of COVID-19 aggravation.
We plan to collect information about integrity.

The mechanism thinks as follows.

Based on the results of the Phase II / III part of the overseas C4591001 study, safety in subjects with underlying disease or obesity
It was confirmed that the sex was similar to that of the whole population. However, the underlying diseases incorporated in clinical trials are relatively cheap.
It is in a fixed state and is expected to be inoculated to people with underlying diseases in various states after manufacture and sale. That
Therefore, since it is important to collect information under the actual conditions of use, the need for this drug is high after manufacturing and marketing.
Regarding the safety of this drug in inoculated patients with underlying diseases at high risk of COVID-19 aggravation
I accepted the applicant's explanation to collect information.

7.R.3.5 Safety for pregnant women

Regarding the safety for pregnant women, the applicant explained as follows.

In the clinical study of this drug, pregnant women were stipulated in the exclusion criteria, but in the Phase II / III part of the overseas C4591001 study,
Twenty-three cases were reported to be pregnant, nine of whom were discontinued due to pregnancy. In the pregnancy outcome of these subjects
No information is available at this time and we will continue to track it.

Spontaneous reporting after permission to use overseas or after manufacturing and sales (reporting period: December 1, 2020-December 31, 2020)

Administration to pregnant women was confirmed in 28 cases, and no particular concern was observed (see 7.R.3.7).
In addition, since no particular concern was found in the reproductive / developmental toxicity test (see 5.5), it is expected for pregnant women.

It is possible to inoculate when the benefits of vaccination outweigh the risks.

PMDA accepted the applicant's explanation. Pregnancy outcomes and post-marketing information for pregnant women inoculated with this drug in clinical trials

Therefore, when new findings are obtained, it is necessary to take appropriate measures such as considering the necessity of additional alerts.

I think.

7.R.3.6 Risk of disease enhancement

The applicant explained the risk of disease enhancement after inoculation with this drug as follows.

In the pharmacological study, we decided to inoculate this drug from the study of cytokine production after inoculation of this drug in animals and humans.

The risk of disease enhancement was considered low (see 3.R.3).

In clinical trials, the number of patients with COVID-19 is low, and the risk of disease enhancement is long.

Although it may be necessary to observe the period, the information available at this time is up to 1 to 3 months after the second inoculation of the investigational drug.

77.7% (33,752 / 43,448) of subjects whose observation period was 4 to 12 weeks after the second inoculation of the study drug.

Example)), it is difficult to evaluate the risk of disease enhancement by this drug.

At this time, the risk of this drug for enhancing disease in humans is unknown, so we will continue to collect information after manufacturing and marketing.

PMDA accepted the applicant's explanation. The risk of increasing disease in humans of this drug will continue after manufacturing and marketing.

It is appropriate to collect information including overseas information and provide information promptly when new knowledge is obtained.

I think.

Page 55

7.R.3.7 Safety information after permission for use overseas or after manufacturing and sales

The applicant explains the safety information after permission for use overseas or after manufacturing and sales as follows.

To. As of December 31, 2020, the drug has received conditional marketing approval in 32 countries and is provisionally supplied in 19 countries.

It is estimated that approval was obtained and approximately 26,079,300 inoculations had been shipped by December 31 of the same year. Main shipping destinations (countries)

The ratio of (or region) to total shipments was 39.3% in the United States, 22.4% in the United Kingdom, 18.4% in the EU, and 17.9% in Asia.

Reportable period (2020) in the 1st Summary Monthly Safety Report (January 13, 2021) of this drug

From December 1st to December 31st of the same year, 3,615 cases were spontaneously reported, with 12 valid safety signals (anaphylaxis).

Kissy, injection site redness, injection site swelling, malaise, nausea, vomiting, diarrhea, irritability, insomnia, injection site pruritus

Feeling, limb pain, facial paralysis) was detected. Anaphylaxis is an important identified risk, injection site redness,

Injection site swelling, malaise and nausea are identified risks (not significant risks), vomiting and diarrhea are risks

It was judged that this was not the case, and the rest was to be evaluated continuously. As a result of the evaluation, during the reporting period

The benefit / risk profile of this drug is judged to be good.

The outline of the main voluntary reports is shown below.

● Death

There were 10 deaths reported (including 7 medically confirmed). Reported event names are 5 deaths, cardiac arrest

There were 3 cases of cessation, 1 case each of heart failure, diarrhea and myocardial infarction. Ages range from 41 to 95 years, with 7 patients aged 65 and over

It was. 4 out of 10 patients with frailty syndrome with underlying disease [43] , 1 patient with immunodeficiency, 1 patient with hypertension, remaining 4

The example was lack of information.

● Anaphylaxis

There were 824 reports of anaphylactic reactions in MedDRA SMQ (wide and narrow areas) (of which medically confirmed)

There were 613 cases), and the number of reports was 1,245, of which 314 were serious. Outcome is death

There were 3 deaths, 259 unrecovered cases, 31 cases of recovery but sequelae, 603 cases of recovery or improvement, and 350 cases of unknown. Outcome

Of the 3 deaths (3 cases), 2 (reported event name: cardiac arrest) all suffered from frailty syndrome with multiple underlying diseases.

One case was lacking in information.
In addition, events corresponding to anaphylactic reaction (narrow range) in MedDRA SMQ were reported in 43 cases, and anaphylaxis.

Raksi reaction 32 cases, anaphylactic reaction 5 cases, anaphylactic shock 4 cases, circulatory collapse and sho

There was one symptomatology each. Thirteen of the 43 had a history of asthma, anaphylaxis or hypersensitivity.

● Immune-mediated / autoimmune disorders

There were 91 reports of immune-mediated / autoimmune disorders (of which 68 were medically confirmed). Report

The number was 92, of which 27 were serious. Two or more reported events were hypersensitivity 42 cases, anosmia 31 cases,

There were 2 cases each of autoimmune disorder, facial paresis and pericarditis. Outcomes were 24 unrecovered cases, recovered but with sequelae

There were 2 cases, recovery or improvement 31 cases, and unknown 35 cases.

43) Q & A regarding "Guidelines for clinical evaluation of drugs used for the elderly" (ICH E7 Q & A: 2010)
In QA3, vulnerable elderly patients (so-called "frail" geriatric patients (mental)) who are likely to have adverse events
Elderly patients who are physically and physically vulnerable or who are in a state of social care or long-term care, or elderly patients who are at high risk of them).

Page 56

● Facial paralysis

Facial paralysis was reported in 21 cases (of which 11 were medically confirmed). The number of reports is 21

Of these, 14 were serious. Outcomes were 7 unrecovered, 1 recovered but with sequelae, 4 recovered or relieved, unknown

There were 9 cases.

● Nervous system events

There were 18 reports of nervous system events (including 13 medically confirmed reports). The number of reports is 22

Of these, 18 were serious. Two or more reported events were seizures 6 cases, cerebrovascular attacks 5 cases, epilepsy,

There were 2 cases each of systemic tonic-clonic seizures and Guillain-Barré syndrome. Outcomes were 4 unrecovered, but recovered

There were 3 cases with sequelae, 7 cases of recovery or improvement, and 8 cases of unknown.

● Disease enhancement

There is no unified definition for disease enhancement at this time, but among spontaneous reports, disease enhancement is possible under the following conditions.

Searched for possible reports.

<Search conditions>
Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammation syndrome in children;

As a result, 4 cases were searched, and respiratory events (4 cases of dyspnea, 1 case of hypoxia) were reported in all cases.

A gastrointestinal event (diarrhea) was also reported in one case. Symptoms developed in a short period of time (7 hours to 1 week) after inoculation.

In 3 cases, the symptoms were mild, but in 1 case, severe symptoms were observed. However, this case was 24 after the first inoculation.

Given that it is expressed within hours and that disease enhancement is thought to develop by an immunological mechanism,

It was not determined to be evidence of disease enhancement.

● Frailty patients with underlying illness 43) Inoculation

Of the spontaneous reports, 274 patients with frailty syndrome with underlying illness were included. 1,182 cases in these populations

Events were reported, with 77 major headaches, 59 fatigue, 46 fever, chills and nausea, and vaccination site aches.

There were 35 cases of pain and 32 cases of dizziness. Outcomes were 4 deaths, 92 unrecovered, recovered but with sequelae 6 and times

There were 130 cases of recovery or improvement and 42 cases of unknown. Of the 4 deaths (4), 1 was a patient with severe heart and lung disease

Death due to cardiac arrest (reported event name), 1 patient with a history of heart attack, active heart disease and malignant tumor

Patients who died of heart failure and cardiac arrest (reported event name), 2 elderly people with a history of dementia (84 years old)

He was 91 years old) and died of unknown cause.

● Inoculation for pregnant and lactating women

Of the spontaneous reports, 28 pregnant women and 39 lactating women were confirmed.

Of the 28 pregnant women, 26 reported vaccination exposure during pregnancy, 9 of which were non-serious with clinical symptoms
(4 vaccination site pains, 2 headaches and 2 limb pains, bloody secretions, myalgia, pain and rhinorrhea)
Was reported.

Page 57

Of 39 lactating babies, 4 had non-serious events (abdominal discomfort, loss of appetite, hypersensitivity, illness, infant vomiting,
Infant irritability, insomnia, irritability, drowsiness, fever, redness and vomiting were reported (1 each).

In addition, anaphylaxis will be examined in detail from the applicant's safety database.
An algorithmic MedDRA SMQ for reports of this drug received by January 4, 2021.
We searched for reports corresponding to anaphylactic reactions in (region and narrow region). As a result, 81 cases were applicable, of which 53 cases were applicable.
Was a serious case. Of 81 cases, Brighton Collaboration Case Definition Criteria (Vaccine. 2007; 25: 5675-84) [44]
18 cases met Level 1, 26 cases met Level 2, and none met Level 3.
There were 21 cases with insufficient evidence and 16 cases that did not meet any of the conditions. 81 outcomes died
There were 1 case, 14 cases that had not recovered, 44 cases that had recovered / improved or recovered but had sequelae, and 22 cases that were unknown. Allergies in the past
There were 27 cases with a history of hypersensitivity, anaphylactic reaction, etc.

Based on the above information, the benefit / risk profile of this drug is good based on the information obtained so far.
I decided. For anaphylaxis and facial paralysis, please refer to the package inserts in 7.R.3.2 and 7.R.3.3.
Call attention with.

PMDA has confirmed the safety information after permission for use overseas or after manufacturing and sales. Also, anaphylaxis
We have confirmed the following reports regarding serious allergic reactions including kissy.
In the United States, from December 14, 2020 to December 23, 2020, when inoculation of this drug was started under an emergency use authorization,
The first dose of this drug was given to 1,893,360 patients, and 4,393 adverse events (0.2%) were Vaccine Adverse Event Reporting.
Reported to System (VAERS) (MMWR Morb Mortal Wkly Rep 2021; 70: 46-51). Serious allergic anti
There were 175 possible reports, of which 21 were anaphylactic and non-anaphylactic alleles.
There were 86 ghee reactions. Of the 21 patients with anaphylaxis, 19 received epinephrine.
In addition, 17 cases had a history of allergies (drugs, food, insect bites), of which 7 cases were anaphylaxis.
I had a history. Of 86 cases of non-anaphylactic allergic reaction, 56 cases have a history of allergy
It was.
In the UK, from December 8, 2020 to December 11, 2020, when vaccination with this drug was started under temporary approval, 3
An example of a serious allergic reaction was reported. Two of these had a history of food or drug allergies.

PMDA started inoculation of this drug in December 2020, and although serious events including fatal cases have been reported,
At this point, the causal relationship is not clear, and safety information overseas will be accumulated in the future.
Based on the obtained information, the safety of this drug will be continuously evaluated, and the necessity of additional alerts and information provision will be examined.
I think it is necessary to take appropriate measures such as debating.

[40] Level 1: One or more major skin symptoms and one or more major cardiovascular symptoms (and / or one or more major respiratory symptoms)
Level 2: ① One or more major cardiovascular symptoms and one or more major respiratory symptoms
② One or more major cardiovascular symptoms (or one or more major respiratory symptoms) and one or more Minor in one or more different organs
Symptoms
③ One or more major skin symptoms and one or more Minor cardiovascular symptoms (and / or one or more Minor respiratory symptoms)
Level 3: One or more Minor cardiovascular (or respiratory) symptoms and one or more Minor symptoms in two or more different organs

Page 58

7.R.4 Clinical position

The mechanism considers the clinical position of this drug as follows.

As of January 20, 2021, the cumulative number of SARS-CoV-2 infected persons (the number of PCR test positive persons) in Japan is 332,231.

Of these, 71,129 were severe cases and 4,547 died. [45] . Asymptomatic infected person cannot grasp everything, so no

It is estimated that the number of infected people, including those with symptoms, is even higher. The number of infections by age group is highest in the 20s, followed by those in their 30s.

40s, but many in the order of the 50s, the number of deaths and severe and the number of persons greater than 60 generations [46] .

The incubation period from SARS-CoV-2 exposure to onset is 1 to 14 days, and it usually develops in about 5 [days47] .

In addition, the cause of community-acquired infections is that they are infectious even before the onset of symptoms and are highly infectious shortly after the onset of symptoms.

Caused (New Coronavirus Infectious Disease COVID-19 Medical Guide (Version 4.1)[41]).

In Japan, on May 7, 2020, Remdesivir is an antiviral drug for the indication of SARS-CoV-2 infection.

Bill was approved as a treatment. In addition, dexamethasone can be used within the range of approved indications.

In addition, various therapeutic agents are used in the medical field according to the severity and symptoms (new coronavirus infection).

COVID-19 Medical Guide (Version 4.1)[41]) However, even with these treatments, the number of infected people, severe cases and deaths

It has increased. In addition, although the causal relationship with COVID-19 has not been clarified, it is a virus in some infected persons.

It has been reported that symptoms such as olfactory dysfunction, dysgeusia, dyspnea, and hair loss persist even after disappearance (Open Forum Infect).

Dis. 2020; 7: 0faa507.doi: 10.1093 / ofid / ofaa507). As of January 2021, the number of infected people has continued to increase in Japan.

When the medical system is tight and the onset of COVID-19 results in aggravation or death.

Given that there are some cases, prevention of the onset of COVID-19 is extremely important. "New Coronavirus Infection vs.

Discussions in the policy subcommittee and interim report as a government "[48] says, "Death from a new coronavirus infection.

We will reduce the number of dead and severely ill as much as possible, and as a result, prevent the spread of the new coronavirus infection. "

Is the purpose of vaccination, but it is approved in Japan for the purpose of preventing COVID-19.

There is no chin.

The results of the Phase II / III part of the overseas C4591001 study showed the preventive effect of this drug on the onset of COVID-19 in Japan.

In the C4591005 study, an increase in serum neutralizing antibody titer was confirmed to be equal to or higher than that in the overseas C4591001 study.

It is thought that a similar effect of preventing the onset of COVID-19 can be expected for humans (see 7.R.2), and it is safe and tolerable.

It was considered that there was no concern about sex, which would affect the approval or disapproval (see 7.R.3). Long-term efficacy after inoculation with this drug

The safety and aggravation-suppressing effect of this drug on mutant strains are unknown at this time (see 7.R.2 and 7.R.3).

Although there is uncertainty about its efficacy (see 3.R.2), inoculation of this drug is expected to prevent the onset of COVID-19.

As of January 2021, the number of infected people will increase and medical treatment will be expected to lead to a reduction in the number of cases in Japan.

Given the current situation where the system is tight, this drug was used as the first preventive vaccine against COVID-19 in Japan.

I think it is meaningful to make it possible to seed.

[45] https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html#h2_1 (Last confirmed date January 21, 2021)
[46] https://www.mhlw.go.jp/content/10906000/000716059.pdf (Last confirmed date January 21, 2021)
[47] https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
Final confirmation date: January 21, 2021)
[48] https://www.cas.go.jp/jp/seisaku/ful/bunkakai/corona_vaccine_2.pdf (Last confirmed date January 21, 2021)

Page 59

7.R.5 Efficacy / Effects

PMDA considers the efficacy and effects of this drug as follows.

The results of the Phase II / III part of the overseas C4591001 study showed the preventive effect of this drug on the onset of COVID-19 in Japan.
In the C4591005 study, an increase in serum neutralizing antibody titer was confirmed to be equal to or higher than that in the overseas C4591001 study.
It was judged that the same effect of preventing the onset of COVID-19 can be expected for humans (see 7.R.2). "New Coronau
Concept of Evaluation of Illus (SARS-CoV-2) Vaccine "[32] , Indications of approved vaccines, etc.
Based on this, the indication of this drug is "prevention of infectious diseases by SARS-CoV-2" according to the indication at the time of application.
It was judged that it was appropriate.

The above judgments of the Organization will be discussed in expert discussions.

7. About **R.6** usage and dosage

The applicant explained the basis for setting the dosage and administration of this drug as follows.

In the Phase I part of the overseas C4591001 study conducted as a dose-ranging study, riociguat 10, 20 or 30 μg was administered for 21 days.
The safety, tolerability and immunogenicity of two inoculations at intervals were examined, and the results were as follows.

- Regarding SARS-CoV-2 serum neutralizing antibody titer after inoculation of this drug, 21 days after the first inoculation at any dose
  The increase was slight, but a marked increase was observed after 7 days after the second inoculation (7.R.2.1, see Table 16).
- Neutralizing antibody titers are higher than those in the 20 μg group in the elderly population, which is considered to be at high risk of COVID-19 aggravation.
  Was also high in the 30 μg group (see 7.R.2.1 , Table 16).
- There were no concerns about safety at any dose.

Based on the above results, the dosage and administration of this drug to be examined in the Phase II / III part is 30 μg at a time at 21-day intervals (allowable period).
Was set to be intramuscularly inoculated twice in 19 to 23 days), and the test was conducted. As a result, the effectiveness of this drug was confirmed.
(See 7.R.2), and judged to be acceptable in terms of safety and tolerability (see 7.R.3).

The estimation result of the cumulative probability of COVID-19 after the first inoculation of the investigational drug in the Phase II / III part is 1
Until the 14th day after the second vaccination, the same transition occurred in the riociguat group and the placebo group, after which the placebo group increased while the pills
There was almost no increase in the drug group, and a large difference was observed between the riociguat group and the placebo group after the second inoculation (see 7.R.2.2).
Teru). Although the effectiveness of a single inoculation has not been investigated, it is 2 for the induction of neutralizing antibodies in the Phase I part.
Considering that a single vaccination was necessary, we think that a single vaccination alone is not sufficient from the viewpoint of sustainability of the effect.

Regarding the interval between the first and second vaccinations, the phase II / III part has a 21-day interval (allowable period is 19 to 23).
However, the efficacy analysis was performed for subjects who received the second dose 19 to 42 days after the first dose.
It is stipulated in advance that the analysis should be performed in the population including the drug, and the preventive effect of this drug on the onset of COVID-19 was shown in the population.
(See 7.R.2). Subjects in the evaluable population who received the second dose 24-42 days after the first dose
616 of 18,198 patients in the riociguat group and 659 of 18,325 patients in the placebo group were included [49] . To these groups
COVID-19 was confirmed in 1 patient in the riociguat group and 4 patients in the placebo group on and after 7 days after the second inoculation.
95% CI] (subjects without a history of SARS-CoV-2 infection 7 days after the second inoculation before the study drug inoculation) was 73.3 [-170,
It was 99.5]%.

[49] The breakdown of the inoculation interval was as follows. 24 to 25 days: 212 patients in the riociguat group, 242 patients in the placebo group, 26 to 30 days: 264 patients in the riociguat group, 273 in the placebo group
Examples, 31-35 days: 88 patients in the drug group, 91 patients in the placebo group, 36-40 days: 32 patients in the drug group, 41 patients in the placebo group, 40-42 days: 20 patients in the drug group, placebo group
12 cases

Although the number of cases is small and definitive evaluation is difficult, efficacy is expected even in the population with inoculation intervals of 24-42 days.
I think it can be done.

Also, in the domestic C4591005 study, the same dosage and administration as the phase II / III part of the overseas C4591001 study was set and tested.
Based on the results of immunogenicity, the effect of preventing the onset of COVID-19 can be expected even in Japanese (see 7.R.2.2), and it is safe.
No Japanese-specific concerns were found regarding sexuality and tolerability (see 7.R.3).

Based on the above, it was considered possible to set the dosage and administration of this drug based on the results of these clinical studies. This drug
When 1 vial is diluted with 1.8 mL of Japanese Pharmacopoeia physiological saline, is the volume equivalent to 30 μg of this drug 0.3 mL?
Therefore, the application dosage and administration should be "dilute with 1.8 mL of Japanese Pharmacopoeia physiological saline, and usually 0.3 mL once for a total of 2 times for 3 weeks.
Inoculate intramuscularly at intervals. "

Based on the results of studies on the efficacy (see 7.R.2) and safety (see 7.R.3) of this drug, PMDA decided on the dosage and administration.
Therefore, after diluting with 1.8 mL of physiological saline, which is equivalent to 30 μg of this drug, 0.3 mL is taken as one dose, for a total of 2 times for 3 weeks.
It was judged that it was possible to set intramuscular injection at intervals. In addition, the effectiveness of only one inoculation and the inoculation interval
Based on clinical trial settings, the efficacy of the extension over 24 days has not been fully established.
It is considered appropriate to inoculate twice at 3-week intervals.

7.R.6.1 About the target age for inoculation

The applicant explained the target age for inoculation of this drug as follows.

The domestic C4591005 study was conducted in 20-85 years of age to determine safety, tolerability and immunogenicity in Japanese.
evaluated. On the other hand, in the Phase II / III part of the overseas C4591001 study, efficacy and safety in subjects 16 years and older
Was the wholeness confirmed, and was there any clinically concerned result in the analysis by age group?
Therefore, in Japan as well, it is possible to inoculate people aged 16 and over.

In the Phase II / III part of the overseas C4591001 study, immunogens for children aged 12 to 15 years during the study were conducted.
Added plans to consider sex, safety and tolerability. Subjects in these age groups in the efficacy analysis
Although some data is included, sufficient results have not been obtained at this time. Therefore, for children
The development plan will be examined based on the results.

PMDA is targeting 20-85 years old in the domestic C4591005 study, and in Japanese, it is a day at 16-19 years old.
Although no data has been obtained, the above explanation of the applicant, 20 in the domestic C4591005 test and the overseas C4591001 test
No significant differences in immunogenicity and safety profiles over the age of age were observed in Japan at this time.
Considering the epidemic situation of SARS-CoV-2, it is possible that the target age for inoculation of this drug is 16 years or older.

Page 61

7. R.7 Matters to be considered after manufacturing and sales

The applicant plans to conduct a post-marketing surveillance of this drug as follows.

Limited information is available by the time of marketing approval for Japanese safety, including long-term data on this drug.
(See 7.R.3), SARS-CoV-2 infection after inoculation with this drug may theoretically cause disease enhancement.
Therefore (see 3.R.3), the safety of this drug for 12 months after the second inoculation, including the risk of disease enhancement, etc., will be examined.
Use-results survey for the purpose of (preliminary inoculator health status survey for medical professionals)
Inoculation at (https://www.mhlw.go.jp/content/10906000/ 000721004.pdf (Last confirmed date: January 21, 2021))
Of those who agree to follow-up for 12 months after the second inoculation of this drug)
Is.

In addition, it is considered that there is a high risk of aggravation of COVID-19, for which sufficient safety information has not been obtained in clinical studies of this drug.
Basic disease for the purpose of examining the safety after inoculation of this drug for persons with the underlying disease (see 7.R.3.4).
A specific drug use-results survey (observation period: 1 month from the date of the first inoculation to 1 month after the second inoculation) was conducted for persons with the disease.
Will be given.

For the domestic C4591005 study, after approval of this drug, switch to post-marketing clinical studies to check long-term safety, etc.
I will discuss it.

In addition, in order to promote the proper use of this drug and ensure safety, as an additional risk minimization activity, this drug is a side effect.
We plan to create a list of responses at regular intervals and provide it to medical professionals.

PMDA considers that the applicant's policy regarding plans such as post-marketing surveillance is acceptable. Also, of domestic information
Not only overseas information (ongoing overseas C4591001 test, information after overseas license or manufacturing and marketing approval)
Based on the information obtained, the safety of this drug is continuously evaluated, and additional warnings and information are given.
We think that it is necessary to take appropriate measures such as considering the necessity of providing information.

The above judgments of the Organization will be discussed in expert discussions.

Page 62

7.3 Adverse events observed in clinical studies other than this drug (**BNT162b1**)

The safety of the Phase I part of the overseas C4591001 study (see 7.2.1) in the BNT162b1 group is shown below.
Su. The 100 µg group received the first inoculation because the second inoculation at the same dose was discontinued after the first inoculation [50] .
Only time data is shown.

Table 27 shows the reactionogenic events observed 7 days after each inoculation .

Table **27** Responsive events **7** days after each inoculation of the investigational drug (group for safety analysis)

		18-55 years old					65-85 years old			
		BNT162b1				Placebo a)	BNT162b1			placebo
Event name	Inoculation times	10 µg (N = 12)	20 µg (N = 12)	30 µg (N = 12)	100 µg a) (N = 12)	(N = 12) b)	10 µg (N = 12)	20 µg (N = 12)	30 µg (N = 12)	(N = 9)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local reaction										
Injection site pain	1st time	7 (58.3)	9 (75.0)	12 (100)	12 (100) [1]	2 (16.7)	7 (58.3)	11 (91.7)	11 (91.7)	1 (11.1)
	Second time	10 (83.3)	11 (91.7)	12 (100)	-	2 (22.2)	8 (66.7)	9 (75.0)	9 (75.0)	0
Redness	First time	0	0	2 (16.7)	4 (33.3)	0	0	0	0	0
	Second time	0	0	2 (16.7)	-	0	0	1 (8.3)	1 (8.3)	0
swelling	First time	0	3 (25.0)	2 (16.7)	5 (41.7)	0	1 (8.3)	1 (8.3)	2 (16.7)	0
	Second time	0	1 (8.3)	3 (25.0)	-	0	1 (8.3)	2 (16.7)	3 (25.0)	0
Systemic reaction										
Fever	1st time	1 (8.3)	0	1 (8.3)	6 (50.0)	0	0	0	3 (25.0)	0
	Second time	1 (8.3)	2 (16.7)	9 (75.0)	-	0	0	6 (50.0)	4 (33.3) [1]	0
fatigue	1st time	4 (33.3)	8 (66.7)	6 (50.0)	10 (83.3) [2]	3 (25.0)	2 (16.7)	7 (58.3)	6 (50.0) [1]	4 (44.4)
	Second time	8 (66.7) [1]	10 (83.3) [1]	Ten (83.3)	-	2 (22.0)	3 (25.0)	7 (58.3) [1]	8 (66.7) [1]	2 (22.2)
headache	1st time	5 (41.7)	6 (50.0)	6 (50.0)	9 (75.0) [1]	3 (25.0)	3 (25.0)	4 (33.3)	6 (50.0)	0
	Second time	10 (83.3)	8 (66.7)	12 (100)	-	0	5 (41.7)	9 (75.0) [1]	9 (75.0)	1 (11.1)
	First time	1 (8.3)	3 (25.0)	7 (58.3) [1]	10 (83.3) [1]	0	1 (8.3)	1 (8.3)	2 (16.7)	2 (22.2)

Chills	Second time	3 (25.0)	6 (50.0)	8 (66.7)	-	0	3 (25.0)	7 (58.3)	4 (33.3)		0
vomiting	First time	0	0	0	0	0	0	0	0	0	0
	Second time	0	0	0	-	0	0	0	1 (8.3)		0
diarrhea	1st time	2 (16.7)	0	1 (8.3)	4 (33.3)	0	1 (8.3)	1 (8.3)	0		0
	Second time	0	1 (8.3)	1 (8.3)	-	0	0	1 (8.3)	2 (16.7)		0
muscle pain	1st time	1 (8.3)	4 (33.3)	3 (25.0)	7 (58.3) [1]	0	2 (16.7)	2 (16.7) [1]	5 (41.7)	1 (11.1)	
	Second time	5 (41.7)	9 (75.0)	7 (58.3)	-	0	4 (33.3)	4 (33.3)	4 (33.3)		0
Joint pain	1st time	2 (16.7)	1 (8.3)	0	3 (25.0) [1]	1 (11.1)	2 (16.7)	1 (8.3)	1 (8.3)		0
	2nd time	4 (33.3)	6 (50.0)	3 (25.0)	-	0	3 (25.0)	3 (25.0)	2 (16.7)		0

N = number of cases to be analyzed, n = number of expression cases

Numbers in [] are Grade 3 (fever over 38.9 ° C) (Grade 4 (fever over 40 ° C) is not recognized)
a) BNT162b1 100 μg and the corresponding placebo are only the results after the first inoculation.
b) Second time N = 9

50) Severe injection site pain was observed after the first inoculation in the 18-55 year old population, and the frequency of fatigue, headache, chills, and fever was higher than in the 30 μg group.
The second dose was discontinued and replaced with BNT162b1 10 μg or the corresponding placebo.

Page 63

Table 28 shows the incidence of adverse events and side effects other than immunogenic events .

Table **28** Rate of adverse events and adverse reactions up to **1** month after the final inoculation of the study drug (population subject to safety analysis)

	18-55 years old						65-85 years old				
Event name	BNT162b1			placebo	BNT162b1	placebo	BNT162b1			placebo	
	10 μg	20 μg	30 μg		100 μg once a)	Once a)	10 μg	20 μg	30 μg		
	(N = 12)	(N = 12)	(N = 12)	(N = 9)	(N = 12)	(N = 3)	(N = 12)	(N = 12)	(N = 12)	(N = 9)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Adverse event	6 (50.0)	5 (41.7)	6 (50.0)	2 (22.2)	6 (50.0)	1 (33.3)	6 (50.0)	7 (58.3)	3 (25.0)	4 (44.4)	
Side reaction	3 (25.0)	4 (33.3)	6 (50.0)	1 (11.1)	6 (50.0)	1 (33.3)	3 (25.0)	4 (33.3)	2 (16.7)	1 (11.1)	

N = number of cases to be analyzed, n = number of expression cases
a) Observation period is up to 3 weeks after the first inoculation

There were no deaths, serious adverse events or adverse events leading to the discontinuation of the study.

Regarding abnormal laboratory test values, as abnormal fluctuations of Grade 3 or higher, 1 patient in the BNT162b1 10 μg group in the 18-55 year-old group,
It was observed in 2 patients in the 20 μg group, 1 patient in the 30 μg group, 4 patients in the 100 μg group, and 1 patient in the 10 μg group and 1 patient in the 30 μg group in the 65-85 year-old g
It was. Both were observed within a few days after inoculation, and recovered within the standard range within a few days.

8. Conformity survey results and JQA's judgment regarding the materials to be attached to the approval application by JQA

8.1 Judgment by PMDA on the results of the conformity document survey

The investigation is currently underway, and the results and JQA's judgment will be reported in Report (2).

8.2 Judgment of PMDA on **GCP** field survey results

The investigation is currently underway, and the results and JQA's judgment will be reported in Report (2).

9. Comprehensive evaluation at the time of preparation of the report on special approval (**1**)

From the submitted materials, the effectiveness of this product for the prevention of infectious diseases caused by SARS-CoV-2 was shown and confirmed.
We think that safety is acceptable in light of the benefits. This drug was the first application for manufacturing and marketing approval in Japan.
It is a vaccine aimed at preventing infections caused by SARS-CoV-2, and it is clinically possible to inoculate this drug.
I think it is meaningful.

If it can be determined that there are no particular problems based on the examination in the expert consultation, this drug may be approved.
Think.

Page 64

Report on special approval (**2**)

February 8, 3rd year of Reiwa

Application item

[Sales name]	Community intramuscular injection
[common name]	Coronavirus-modified uridine RNA vaccine (SARS-CoV-2)
	(Active ingredient name: Tojinameran)
[Applicant]	Pfizer Japan Inc
[Application date]	December 18, 2nd year of Reiwa

[List of abbreviations, etc.]

As stated separately.

1. Examination contents

The outline of the expert consultation and the subsequent examination by the Organization is as follows. In addition, the expert committee of this expert consultation Based on the proposals from the expert advisors regarding this item, the members will be asked to "specialize in the Pharmaceuticals and Medical Devices Agency. Nominated in accordance with the provisions of "Notice Concerning Implementation of Meetings, etc." (No. 8 of 20th dated December 25, 2008).

In the expert consultation, is the expert advisor's judgment regarding the quality, efficacy, safety, etc. of this drug described in report (1)? In support of the above, additional opinions were given on the following points.

PMDA examined the following points additionally and took necessary measures.

1.1 Effectiveness and efficacy / effect

At the expert consultation, the expert advisors will discuss the "7.R.2 efficacy" and "7.R.5 efficacy / effect" of the report (1). In addition to the opinions supporting the judgment of the Organization, the following opinions were given.

● No long-term efficacy data have been obtained for the overseas C4591001 study, and VE results are short after the second vaccination.

It is necessary to provide information to the medical field that it is period data. Also, long-term efficacy data is subtracted.

Continue to collect, and if the duration of efficacy becomes clear, check for the need for booster vaccination

Need to defeat.

● The *in vitro* data currently available for the SARS-CoV-2 mutant strain was confirmed in the overseas C4591001 study.

It does not deny the efficacy of this drug. On the other hand, it is expected that new mutant strains will appear in the future.

Therefore, the appearance status and epidemic situation of mutant strains will be continuously followed up, and *in vitro* neutralization using mutant strains will be carried out.

If new findings are obtained by conducting tests, etc., we will provide information to the medical field and take measures according to the situation.

It is necessary to consider the placement.

● Sufficient information has not been obtained from the results of clinical studies regarding the COVID-19 aggravation-suppressing effect of this drug. However

However, the COVID-19 preventive effect of this drug reduces the number of cases, resulting in the number of severe cases and death.

It is expected that it will lead to a reduction in the number of deaths.

Page 65

● The SARS-CoV-2 infection preventive effect of this drug has not been evaluated in clinical studies. When this drug is inoculated
However, in order to prevent the spread of infection, basic infections such as congestion, avoidance of close contact and sealing, hand washing and cough etiquette
Preventive measures need to be continued and this should be communicated to health care workers and vaccinated persons.
● The relationship between immunogenicity and the preventive effect of onset needs to be examined in the future.

PMDA communicates the opinions of the expert advisors to the applicant, who is responsible for long-term post-marketing efficacy and mutant strains.
Appropriate measures will be taken regarding examination and provision of information to medical staff and vaccinated persons regarding the implementation of infection prevention measures.
Answered.

In addition, the results of the evaluable immunogenic population, which is the main analysis of the domestic C4591005 study, were presented after expert consultation.
The results are shown in Table 29. The mechanism should be similar to the results of all assessed immunogenic populations already submitted.
(Results of all evaluated immunogenic populations are reported (1) 7.R.2.2 Table 21 is reprinted), and results of overseas C4591001 study (report)
It was confirmed that the level was similar to that of Notification (1) 7.R.2.2 Table 20). Report the confirmation results to the expert advisors, no additional opinions
won.

Table **29** investigational drug **2** -time vaccination after **1** month of **SARS-CoV-2** serum neutralizing antibody titers (**50%** neutralizing antibody titer) (domestic **C4591005** test)

			N	GMT [95% CI on both sides] (1 month after the second inoculation)	GMFR [95% CI on both sides] (1 month after the 2nd inoculation / before the 1st inoculation)
Evaluable Immunogenic population	This drug group	All ages	116	524.5 [459.7, 598.4]	51.5 [45.2, 58.7]
		20-64 years old	94	570.7 [497.6, 654.5]	55.8 [48.7, 63.9]
		65-85 years old	twenty two	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo group	All ages	40	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)
All evaluations Immunogenic population	This drug group	All ages	119	489.9 [420.4, 570.9]	48.1 [41.3, 56.0]
		20-64 years old	97	523.5 [442.0, 619.9]	51.2 [43.3, 60.6]
		65-85 years old	twenty two	365.6 [254.6, 525.0]	36.6 [25.5, 52.5]
	Placebo group	All ages	41	10.6 [9.8, 11.4] a)	1.1 [1.0, 1.1] a)

N = number of cases to be analyzed. If the antibody titer was less than LLOQ, a value of 0.5 × LLOQ was used for the analysis.
a) Analysis results (evaluable) excluding one case in which the visit was not completed one month after the second inoculation when the sample for immunogenicity measurement was sent.
Immunogenic population: 39 cases, all evaluation immunogenic population: 40 cases)

1.2 About safety

In the expert consultation, the expert advisors gave an opinion supporting the decision of the Organization in "7.R.3 Safety" in Report (1).
In addition, the following opinions were expressed. Regarding the risk of disease enhancement, see "1.4 Drug Risk Management Plan (Draft)".
About ".

● In clinical studies in Japan and overseas, most of the adverse events observed after inoculation with this drug were mild or moderate.
It does not overturn the benefits of. However, in some subjects, the extent to which it affects daily life
Physical reactions were observed, and the incidence of adverse events was higher at the second inoculation than at the first inoculation.
The fact that it was higher in the non-aged group than in the age group is important information for healthcare professionals and vaccinated persons of this drug.
Therefore, it is necessary to provide safety information on this drug including this information. Also, a side reaction tool
Physical symptoms, time of onset after inoculation, duration, response to symptoms onset and duration (use of antipyretic analgesics,
It is also necessary to provide information on symptoms that require consultation with a medical institution).
● For allergic reactions such as anaphylaxis, serious reactions after permission for overseas use or after manufacturing and sales
Is also recognized, and special attention is required. In addition to calling attention in the package insert, medical staff and recipients
It is important for the inoculators to provide information including the time of onset and initial symptoms. In addition, medical history when inoculating

Page 66

Etc., observe for a certain period of time after inoculation, and take appropriate measures and treatments when symptoms appear.

It is necessary to take measures including the establishment of a system at the time of inoculation.

● For people with a history of hypersensitivity, doctors may be at a loss as to whether or not to inoculate. Can be inoculated by a doctor

It is necessary to provide specific information so that it can be judged whether or not it is.

● In the information in the safety database held by the applicant, the information after permission for overseas use or after manufacturing and sales is announced.

Of 81 reports corresponding to illaxy reaction, 57 were female, allergic, hypersensitivity, anaphylactic anti-anaphylactic reaction

It is stated that 27 cases with a history of response, etc. and 4 cases with a history of COVID-19 were included.

It was. Regarding anaphylaxis, etc., background factors that pose a risk of expression based on the information collected in the future, etc.

When analysis is performed and important findings are obtained, it is necessary to appropriately call attention.

● For Frail patients with underlying disease, the causal relationship is unknown after overseas license or manufacturing and sales.

However, adverse events including death have been reported after inoculation with this drug. Safety information for the patient is currently available

Although not sufficiently accumulated in terms of points, COVID-19 may be at high risk of aggravation, SARS-CoV-2 Wakuchi

Since it is assumed that the need for vaccination is high, doctors say that the benefits of vaccination with this drug outweigh the risks.

Judgment was made, and the inoculated person or his / her surrogate agreed to the inoculation after understanding the effects and side reactions of this drug.

In that case, it is possible to inoculate this drug. Continue to collect and collect safety information for the patient

It is necessary to promptly publish the information provided and to update the information as appropriate thereafter.

PMDA communicates the opinions of the above expert advisors to the applicant, and the applicant collects safety information after manufacturing and sales.
He also replied that he would take appropriate measures to provide information to medical staff and vaccinated persons.

1.3 Usage / Dose

In the expert consultation, the expert advisors will support the judgment of the mechanism of "7.R.6 Usage / Dose" in Report (1).
In addition to the observations, the following opinions were expressed.

● It is necessary to provide information on how to deal with people who did not receive the second dose every 3 weeks after the first dose of this drug.

is there.

PMDA examined the following points.

As described in "7.R.6 Usage / Dose" of Report (1), the inoculation interval in the overseas C4591001 study is
It is set to 19 to 23 days, and some subjects have been inoculated at intervals of up to 42 days, but the inoculation interval has been increased to 24 days or more.
The effectiveness of the extension has not been fully established. In addition, the efficacy of a single inoculation of this drug has not been established.
Therefore, it is considered appropriate to inoculate this drug twice at 3-week intervals. On the other hand, under actual usage, 3 weeks
In some cases, it may not be possible to inoculate at intervals, in which case the second inoculation should be given as soon as possible.
Need to urge.

The PMDA will inform the applicant of the opinions of the above expert advisors and the results of the PMDA's examination, and the applicant will conduct clinical trials.
About providing information on the interval between vaccinations and the need for a second vaccination to healthcare professionals and recipients
He answered that he would respond appropriately.

Page 67

1.4 About drug risk management plan (draft)

In the expert consultation, the following PMDA's decisions regarding post-marketing disease enhancement risk assessment are supported by the expert advisors.
Was done.

Disease-enhancing risk assessment is an important issue, but its standard assessment method is well established internationally.
Zu [51] , It is difficult to judge the presence or absence of disease enhancement only from the clinical situation of individual patients, in the overseas C4591001 study
There are few cases of COVID-19 onset and severe cases after inoculation of this drug, and the onset status of COVID-19 in the long term after inoculation is also
Since it is unknown, the risk of disease enhancement is sufficient in conventional drug use-results surveys conducted under daily medical care.
I think that there is a limit to the evaluation. Therefore, after manufacturing and sales, for the time being, the follower of the overseas C4591001 test
-Up, through the drug use-results survey conducted by the applicant, long-term COVID-19 onset status and severe illness after inoculation

By analyzing the information of the cases, we will find out how to evaluate the risk of disease enhancement and the disease enhancement of SARS-CoV-2 vaccine in the future.
If new risk findings are obtained, the number of diseases of this drug will increase based on long-term data after inoculation of this drug.
It is necessary to reconsider the evaluation of strong risk.

In addition, at the expert consultation, the expert advisors of the mechanism of the report (1) "7.R.7 Post-marketing considerations"
In addition to the opinions supporting the judgment, the following opinions were given.

● After manufacturing and marketing, this drug is used by a large number of people, and when a large amount of post-marketing safety information is collected.
is assumed. High level regarding collection of safety information of this drug, evaluation and publication of benefit risk balance
It is important that it be done quickly with good transparency.

Based on the opinions of the above expert advisors, PMDA will collect safety information after manufacturing and sales, and benefit risk balun.
The applicant requested the applicant to respond promptly to evaluate and publish the information, and the applicant agreed.

Based on the above discussions, PMDA has listed the current drug risk management plan (draft) for this drug in Table 30.
Set up the safety considerations shown, as well as the additional pharmacovigilance monitoring activities shown in Tables 31, 32 and 33.
We have determined that it is appropriate to carry out additional risk minimization activities.

Table **30** Safety considerations and efficacy considerations in the drug risk management plan (draft)

Safety considerations		
Significant identified risks	Significant potential risks	Important missing information
• Shock, anaphylaxis	• Disease enhancement associated with vaccination (Vaccine-associated enhanced disease (VAED)) and Cutin-related respiratory disease enhancement (Vaccine-associated enhanced respiratory disease (VAERD))	• When inoculated to pregnant or lactating women safety
Effectiveness considerations		
• Not applicable		

51) Regarding disease enhancement, Brighton Standardized Case Definition "Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection," Analysis, and Presentation of Immunization Safety Data "(https://brightoncollaboration.us/vaed/ (final confirmation date: February 3, 2021))
No specific case definition is given.

Page 68

Table **31** Summary of additional drug safety monitoring activities and additional risk minimization activities in the draft drug risk management plan

Additional Pharmacovigilance Monitoring Activities	Additional risk minimization activities
• Immediately after marketing survey	• Providing information through a survey immediately after marketing
• Post-marketing clinical trial (C4591005 study: domestic phase I / II study)	• Creation and provision of materials (proper use guide) for healthcare professionals
• For inoculated persons (medical workers) who are inoculated early after approval General use results survey (follow-up survey)	• Creation and provision of materials for vaccinated persons (inoculated person guidance sheet)
• Have an underlying disease that is considered to be at high risk of COVID-19 aggravation Specific use-results survey targeting people	• Regular publication of adverse reaction occurrence status
• Overseas clinical trials (C4591001 trials: overseas phase II / III trials, and C4591015 Study: Overseas Phase II / III study for pregnant women)	

Table **32** Outline of general drug use-results survey plan for healthcare professionals (draft)

Purpose	Confirmation of long-term safety up to 12 months after the second inoculation of this drug (preliminary inoculator health status survey for healthcare professionals) (Conducted as a follow-up survey after the end of the observation period (about 1 month after the second inoculation))
Target person	Those who have consented to participate in this survey among the subjects of the pre-inoculator health status survey for medical professionals
Observation period	From the day after the end of the observation period (about 1 month after the second inoculation) of the health status survey of the prior inoculators to 12 months after the second inoculation of this drug. so
Scheduled number of cases	All patients who consented to participate in this survey among the subjects of the prior inoculator health status survey for medical professionals
Main survey items	Background of the recipient (history, complications, allergy history, female only: pregnancy / lactation, etc.), inoculation status of this drug, etc. Cutin inoculation information, concomitant medications, serious adverse events, COVID-19 information (SARS-CoV-2 test information, pathogen test positive person Presence / absence of onset, date of diagnosis, presence / absence of response / treatment), etc.

Table **33 Outline of the specific drug** use-results survey plan for those who are considered to be at high risk of **COVID-19** (draft)

Purpose	Confirmation of safety in patients receiving this drug, which is considered to have a high risk of COVID-19 aggravation

Survey method	Central registration method
Target person	Patients receiving this drug who are considered to be at high risk of COVID-19 aggravation
Observation period	28 days after the first inoculation and 28 days after the second inoculation (about 7 weeks)
Scheduled number of cases	1,000 cases
Main survey items	Background of the recipient (history, complications, allergy history, female only: pregnancy / lactation, etc.), inoculation status of this drug, etc. Cutin inoculation information, concomitant medications, adverse events, COVID-19 information (SARS-CoV-2 test information, pathogen test positive: onset No, date of diagnosis, presence / absence of response / treatment), etc.

1.5 About quality

1.5.1 About process validation

Regarding the process validation of the drug, which was said to be underway in Report (1), the applicant submitted the request in January 2021.
He explained that he was planning to get grades.

The mechanism thinks as follows.

3 lots of formulations manufactured overseas on an actual manufacturing scale and used under an emergency use authorization
Although it was confirmed that the above lot analysis results conformed to all standards, it was originally final.
This product can be constantly manufactured with process validation results of 3 consecutive lots based on the manufacturing method.
And need to be confirmed. However, due to the current COVID-19 epidemic and the social need for this drug, it is constant.
It was judged that it was unavoidable that the confirmation that it could be manufactured on a regular basis would be ex post facto. However, the process of formulation
As soon as the validation results are obtained, it is necessary to submit them to the Organization immediately.

Page 69

1.5.2 Number of inoculations that can be collected from **one** vial

During the review, an additional test was conducted to confirm that 6 doses could be collected from 1 vial, and the results were submitted.

Of the injection syringes (1 mL) and needles that are or will be distributed in Japan, they were available.
Physiology using normal or small dead space injection syringes (10 products in total) and needles (6 products in total)
It was examined whether it was possible to collect 0.3 mL each 6 times from a vial containing 2.17 mL of saline solution. As a result, a specific series
With the combination of syringe and injection needle, it was possible to collect 6 times.

PMDA can confirm the submitted test results and collect 6 doses from 1 vial for the applicant.
Regarding information on syringes and needles, we instructed medical practice to provide appropriate information.

2. Corrections to the report (**1**) **regarding** special approval

Report (1) was corrected as follows. The conclusion of report (1) will not be affected even after this correction.

page	line	Before correction	Edited
16	3	mRNA-LNP [14]	mRNA-LNP [14]
27	13 ~ 14	Breakdown of 27 cases in total	Breakdown of 25 cases in total (some subjects had multiple events)
31 Table 17		Number of cases to be analyzed: This drug group 21,699 examples, Placebo group 21,686 examples COVID-19 Confirmed example (Time of onset Separate): Second inoculation 2 examples, Twice from After eye inoculation 6 Until the day 121 examples	Number of cases to be analyzed: This drug group 21,669 examples, Placebo group 21,686 examples COVID-19 Confirmed example (Time of onset Separate): Second inoculation 2 examples, Twice from After eye inoculation 6 Until the day 21 examples
34 Table 20		2 inoculation all evaluation Immunogenic population, Placebo group all year age: GMFR 1.2 [1.0, 1.3]	2 inoculation all evaluation Immunogenic population, Placebo group All year age: GMFR 1.0 [1.0, 1.1]
34 Table 21		All evaluation immunity Primary population, Placebo group all year age: GMT 10.6 [9.8, 11.4]	All evaluation immunity Primary population, Placebo group all year age: GMT 10.6 [9.8, 11.4] [a]
35	15	9 out of 21,699 cases	9 out of 21,669 cases

41 Table 25			Placebo group 20-64 years old n (%)			Placebo group 20-64 years old n (%)	
	fatigue	Second time	5 (15.2)		fatigue	Second time	1 (3.0)

(Addition / change of underlined part, deletion of canceled line part)

3. Conformity survey results and JQA's judgment regarding the materials to be attached to the approval application form by JQA

3.1 Judgment by PMDA on the results of the conformity document survey

A conformity document survey was conducted on the materials to be attached to the approval application based on the provisions of the Pharmaceuticals and Medical Devices Act.
As a result, PMDA has determined that there is no problem in conducting the examination based on the submitted approval application materials.
It was.

3.2 Judgment of PMDA on **GCP** field survey results

For materials (CTD 5.3.5.1.1, CTD 5.3.5.1.2) that should be attached to the approval application based on the provisions of the Pharmaceuticals and Medical Devices Act
Then, a GCP field survey was conducted. As a result, about conducting the examination based on the submitted approval application materials
The mechanism determined that there would be no problem.

Page 70

4. Comprehensive evaluation

Based on the above examination of the submitted materials, PMDA applied for approval with the following approval conditions.
It is judged that the indications / effects and dosage / administration may be prepared and approved as follows. This item is new
Since it is a drug containing active ingredients, the reexamination period is 8 years, and it can be used for both biological products and specified biological products.
Not applicable, and both the drug substance and the drug are judged to be powerful drugs.

[Efficacy / Effect]

Prevention of infectious diseases with SARS-CoV-2

[Dosage and administration]

Dilute with 1.8 mL of Japanese Pharmacopoeia saline and inoculate 0.3 mL once intramuscularly twice, usually at intervals of 3 weeks.

[Approval conditions]

1. Upon approval, this drug is a pharmaceutical medical device based on the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
It was decided to impose the following obligations listed in each item of Article 28, Paragraph 3 of the Ordinance for Enforcement of the Act.

(1) No. 1 relationship

This drug is a specially approved item approved based on the provisions of Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act.
Yes, information on long-term stability, etc. is limited at the time of approval, so it will continue after manufacturing and sales.
Collect and report information.

(2) No. 2 relationship

If you become aware of the occurrence of a disease, disorder or death suspected to be due to the use of this drug, report it promptly.
To do.

(3) No. 3 relationship

The fact that this drug has received special approval and the purpose of the approval are medical personnel who use this drug.
Take necessary measures to be understood and properly explained to the inoculated person or the surrogate.

(4) No. 4 relationship

Report the sales volume or award quantity of this drug as necessary.

2. Upon approval, this drug is subject to the following conditions based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act.
When.

(1) Formulate a drug risk management plan and implement it appropriately.

(2) Since the current knowledge is limited, it is related to the safety of this drug such as side effect information after manufacturing and marketing.

Data will be collected at an early stage based on a predetermined plan, and pharmaceutical products will be collected.
Submit to the Pharmaceuticals and Medical Devices Agency and take necessary measures for proper use of this drug. At that time, the country implements

Appropriately reflect the information obtained from health surveys.

(3) When the results of clinical trials currently being conducted or planned in Japan and overseas are obtained, the results will be promptly published in Germany.

Submit it to the Pharmaceuticals and Medical Devices Agency, and consider the efficacy and safety of this drug.

Take necessary steps to make new information readily available to health care workers and vaccinated persons.

In addition, we will appropriately cooperate with the government regarding the dissemination of information on the efficacy and safety of this drug.

Page 71

(4) When inoculating this drug, we will continue to collect information on the efficacy and safety of this drug.

Eh, in advance, the inoculated person or the surrogate will be provided with the latest information on efficacy and safety in writing.

Properly explain to the doctor that the patient will be inoculated after being explained and obtaining written consent on the medical examination slip, etc.

To do.

(5) The grace period for submitting materials based on Article 41 of the Pharmaceutical and Medical Devices Act Enforcement Regulations is calculated from the acquisition of approval.

It will be 6 months. For materials submitted based on 1.- (1), 2.- (2) or 2.- (3) above

If it is deemed necessary to change the approval items, Article 74-2, Paragraph 2 of the Pharmaceuticals and Medical Devices Act

May order changes to approval items based on paragraph 3.

3. Since this drug is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, the provisions of Article 75-3 of the same Act

When it is found that it no longer falls under any of the items of Article 14-3, Paragraph 1 of the same law, or Health Guard

Obtain these approvals when we deem it necessary to prevent the occurrence or spread of life-threatening harm

It may be erased.

that's all

Page 72

Separate note

[List of abbreviations, etc.]

Abbreviation	English language	Japanese
ALC-0159	2-[(polyethylene glycol)-2000]-N, N-ditetradecyclacetamide	2-[(Polyethylene glycol) -2000] -N, N-di Tetradecylacetamide
ALC-0315	[(4-hydroxybutyl) azanediyl] bis (hexane-6,1-diyl) bis (2-hexyldecanoate)	[(4-Hydroxybutyl) Azandiyl] Bis (F) Xan-6,1-diyl) bis (2-hexyldecanoic acid) Steal)
ALT	Alanin aminotransferase	Alanine aminotransferase
AST	Aspartate aminotransferase	Aspartate aminotransferase
ATP	Adenosine triphosphate	Adenosine triphosphate
BMI	Body mass index	Anthropometric index
BNT162b1	-	Encodes RBD for SARS-CoV-2 S protein MRNA
BNT162b2	-	Codes the full length of the SARS-CoV-2 S protein MRNA
CI	Confidence interval	Confidence interval
COVID-19	Coronavirus disease	Infectious diseases caused by SARS-CoV-2
CTD	Common technical document	Common technical document
CTP	Cytidine triphosphate	Cytidine triphosphate
CQA	Critical quality attribute	Important quality characteristics
ddPCR	Droplet digital polymerase chain reaction	Droplet Digital Polymerase Chain Reaction
DNA	Deoxyribonucleic acid	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero- 3-phosphocholine	1,2- distearoyl -sn - glycero-3-phosphocholine
EMA	European Medicines Agency	European Medicines Agency
ELISA	Enzyme-linked immunosorbent assay	Enzyme immunoassay
ELISpot	Enzyme-linked immunospot	Enzyme immunity spot
ESI MS	ElectroSpray ionization-mass spectrometry	Electrospray ionization-mass spectrometry
EU	European Union	European Union
FDA	Food and Drug Administration	US Food and Drug Administration
GMC	Geometric mean concentration	Geometric mean antibody concentration
GM-CSF	Granulocyte macrophage colony-stimulating factor	Granulocyte macrophage colony stimulating factor
GMFR	Geometric mean fold rise	Geometric mean rise factor
GMT	Geometric mean titer	Geometric mean antibody titer
GTP	Guanosine triphosphate	Guanosine triphosphate
GGT	γ-glutamyltransferase	γ- Glutamyl transferase
HEK293T cells	Human embryonic kidney 293 T cells	Human fetal-derived kidney cells
HIV	Human immunodeficiency virus	Human immunodeficiency virus
HPLC	High performance liquid chromatography	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	International Council for Harmonization of Pharmaceutical Regulations
ICMRA	International Coalition of Medicines Regulatory Authorities	International cooperation organization of regulatory authorities
IFN-γ	Interferon-gamma	Interferon gamma
IgG	Immunoglobulin G	Immunoglobulin G
IL-2 / 4/5/6/13/18	Interleukin 2/4/5/6/13/18	Interleukin 2/4/5/6/13/18
IP-RP-HPLC	Ion pair reversed phase-high performance liquid chromatography	Ion vs. Reverse Phase High Performance Liquid Chromatography

Page 73

Abbreviation	English language	Japanese
IRR	Incidence rate ratio	Disease incidence ratio
LNP	Lipid nanoparticle	Lipid nanoparticles
LLOQ	lower limit of quantitation	Lower limit of quantification
$_{m1}\Psi$TP	N_1-methylpseudouridine triphosphate	N_1-Methyl Pseudouridine Triphosphate
MCB	Master cell bank	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities ICH International Pharmaceutical Glossary	
mRNA	Messenger RNA	Messenger RNA
PaO_2 / FiO_2	Partial pressure of arterial oxygen / Fraction of inspiratory oxygen	Arterial oxygen partial pressure / inhaled oxygen concentration
p / s	Photons per second	A unit of luminosity of a light source
PCR	Polymerase chain reaction	Polymerase chain reaction
PK	Pharmacokinetics	Pharmacokinetics
QbD	Quality by design	Quality by design
qPCR	Quantitive polymerase chain reaction	Quantitative polymerase chain reaction
RBD	Receptor binding domain	Receptor binding domain
RNA	Ribonucleic acid	Ribonucleic acid
RT-PCR	Reverse transcription PCR	Reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome	Severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus	SARS coronavirus
S protein	Spike protein	Spike protein
S1	-	Carboxy-terminal region of S protein containing RBD Area
S2	-	Amino-terminal side of S protein containing transmembrane region region
SMQ	Standardised MedDRA queries	MedDRA standard search formula
SpO_2	Oxygen saturation of peripheral artery	Peripheral arterial oxygen saturation
Th1 / 2	T helper cell type 1/2	1/2 type helper T cell
TNF-α	Tumor necrosis factor --alpha	Tumor necrosis factor α
UTP	Uridine triphosphate	Uridine triphosphate
UV	Ultraviolet	Ultraviolet rays
VE	Vaccine efficacy	Vaccine effect
WCB	Working cell bank	Working cell bank
WHO	World Health Organization	who
Pharmaceuticals and medical devices Equal law	-(Not applicable)	Quality, effectiveness and safety of pharmaceuticals, medical devices, etc. Law Concerning Securing, etc. (Law of August 10, 1960) No. 145)
Pharmaceuticals and medical devices Equal Law Enforcement Regulations	-(Not applicable)	Quality, effectiveness and safety of pharmaceuticals, medical devices, etc. Law Enforcement Regulations on Securing, etc. (February 1958 1) Ministry of Health and Welfare Ordinance No. 1)
Pharmaceuticals and medical devices Etc. Law Enforcement Ordinance	-(Not applicable)	Quality, effectiveness and safety of pharmaceuticals, medical devices, etc. Ordinance for Enforcement of Law Concerning Security (February 1, 1958) Cabinet Order No. 11)
mechanism	-(Not applicable)	Pharmaceuticals and Medical Devices Agency
Report (1) / (2)	-(Not applicable)	Report on special approval (1) / (2)
This drug	-(Not applicable)	For intramuscular injection of community, LNP enclosed BNT162b2
Tolvaptan	-(Not applicable)	BNT162b2, Tojinameran