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Briefing Session on COVID-19 Vaccine “S-268019”

March 4, 2022

Presentation

Kyokawa: Thank you for joining us today. We are now holding a briefing session on the domestic Phase 2/3 booster trial of S-268019, a vaccine for the novel coronavirus.

I am Kyokawa from Shionogi, and I will be moderating today's session. Thank you.

Let me begin by introducing today's speakers.

Dr. Masaharu Shinkai, Vice President and Director of the Clinical Trial Development and Research Center at Tokyo Shinagawa Hospital, is the principal investigator for the Phase 2/3 booster trial in Japan for the development of S-268019.

Next, Isao Teshirogi, President and CEO.

Teshirogi: Thank you very much.

Kyokawa: Next, Toshinobu Iwasaki, Senior Executive Officer, Vice President of Pharmaceutical Development.

Iwasaki: Thank you very much.

Kyokawa: Lastly, Masashi Deguchi, Vice President of Project Management.

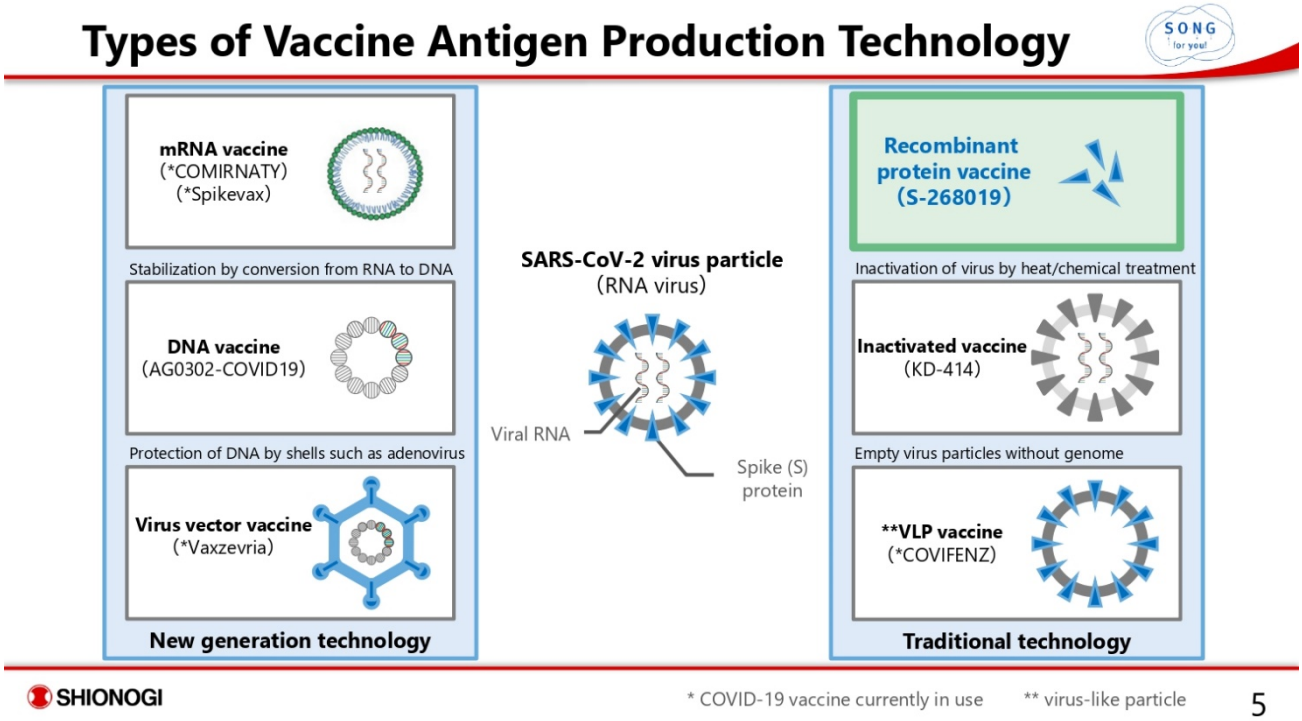
Deguchi: Thank you very much.

Kyokawa: As for today's schedule, after Mr. Deguchi first talks about the development status of S-268019 and Dr. Shinkai will present the preliminary results of the S-268019 trial. After that, Dr. Teshirogi will make a few remarks, and then, we will have time for a question-and-answer session. The event is scheduled to end at 5:30 PM. Thank you.

We will now get started. I will hand over to Mr. Deguchi. Thank you.

Deguchi: This is Deguchi, Project Management. I will start with a presentation.

I will first give an overview of our SARS-CoV-2 vaccine, S-268019, and the overall status of the clinical trial. We will then hear about the details of the Phase 2/3 additional immunization comparative trial, for which an interim report has just been released from Dr. Shinkai of Shinagawa Hospital.

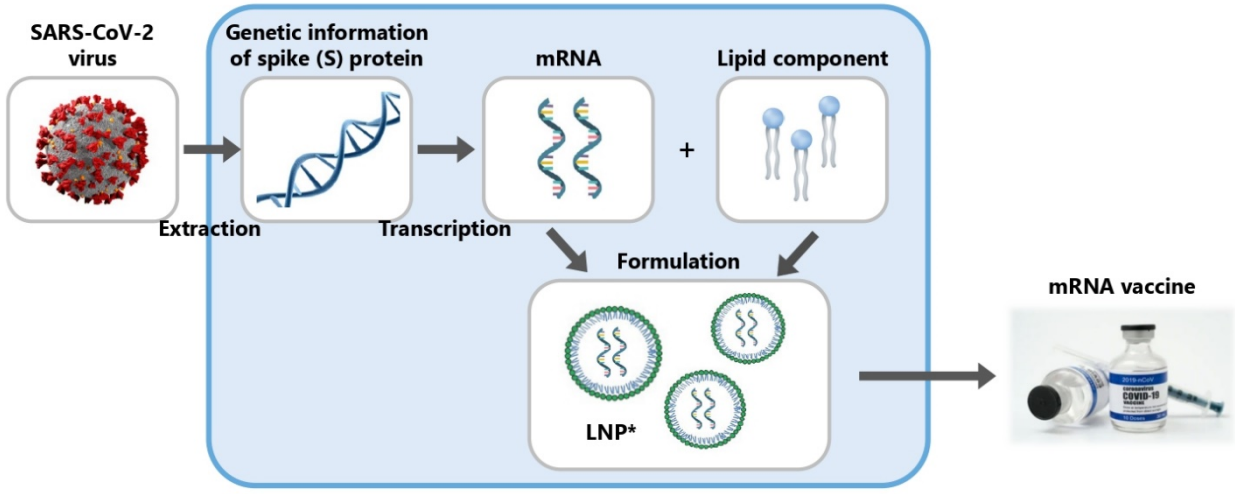


Thank you.

This slid shows a classification chart for SARS-CoV-2 vaccines. Vaccines can be classified into various difference types, depending on the technology used.

In the SARS-CoV-2 vaccine, the antigen of interest is generally the spike protein, which is a hook that the virus uses to attach itself to cells. The method of introduction and presentation varies.

Manufacturing Process of mRNA Vaccine



mRNA is encapsulated in LNP so that it is not degraded in the body

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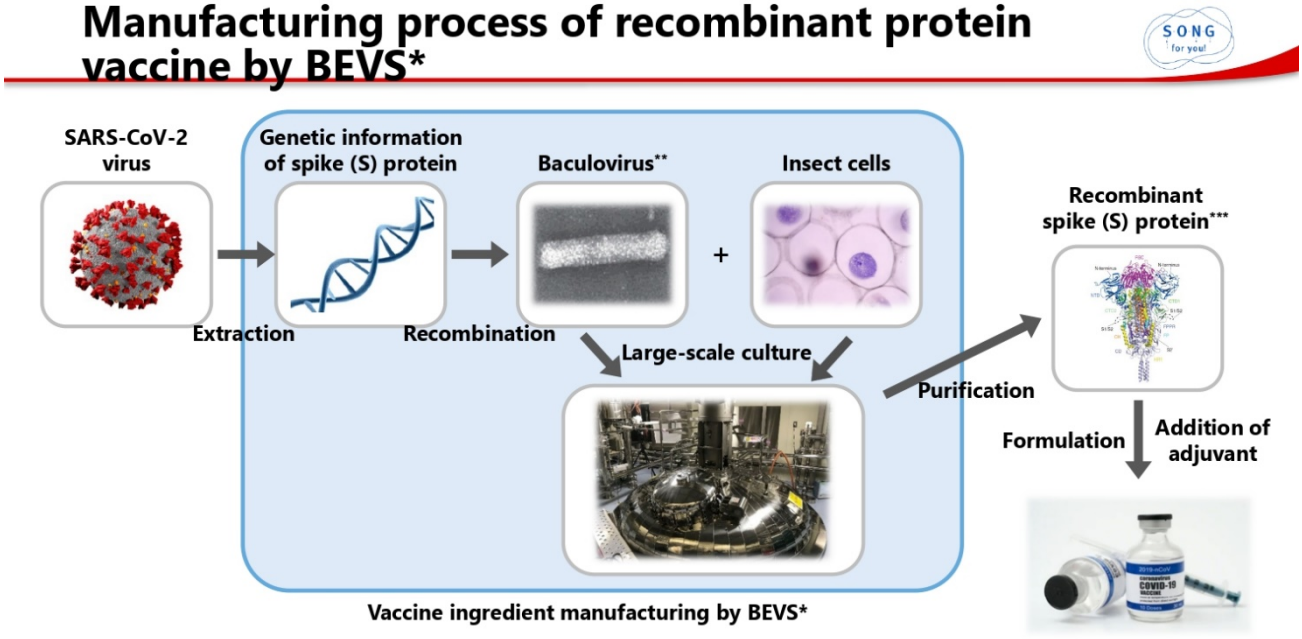
* lipid nanoparticle

For example, the mRNA category at the top left includes COMIRNATY, the intramuscular injection.

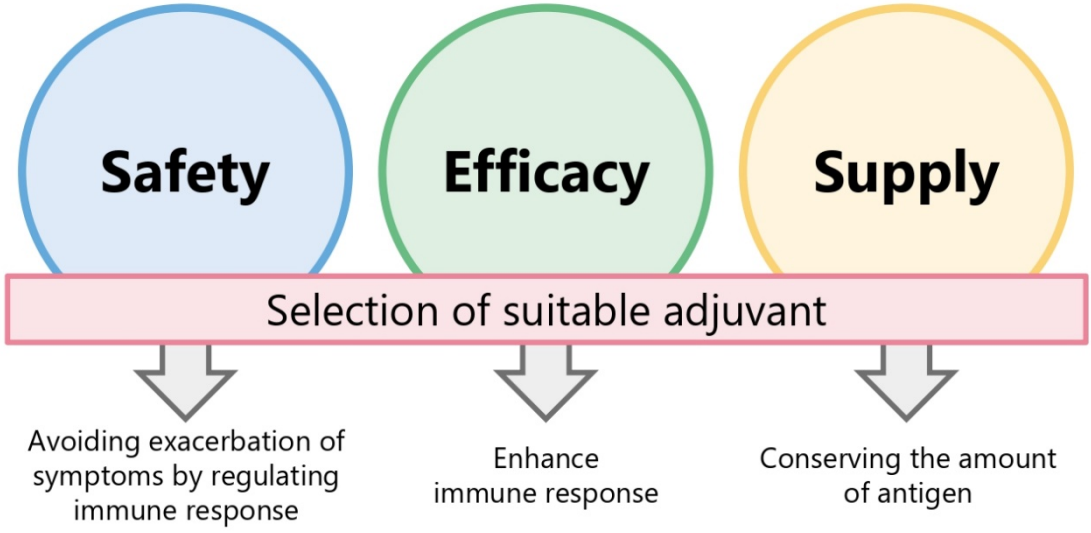
This vaccine contains mRNA, which holds genetic information about the spike protein. To prevent degradation in the body, they are encapsulated in lipid nanoparticles. The body then produces a spike protein from the mRNA, which is then presented to the human immune system.



On the other hand, our vaccine, S-268019, uses a recombinant protein production technology named BEVS. Using a production clock system, we recombine the genetic information of the spike protein into a baculovirus, which is then infected into insect cells and cultured in large quantities. Recombinant spike protein is generated, combined with an immune-enhancing adjuvant, formulated, and administered to humans.

This method, using recombinant protein vaccines, is what could be called a conventional method. To put it another way, it is a type of vaccine technology for which a great deal of information has already been accumulated. We know a lot about safety and efficacy.

Importance of Suitable Adjuvant Selection



There are three important points to consider when creating a recombinant protein vaccine in terms of how to properly select the adjuvant.

The first of these is safety. The adjuvant itself is safe is important, of course. But depending on the combination of antigen and adjuvant, there is a risk that a vaccine does not support the immune response on the contrary may exacerbate disease. Therefore, to create a combination of elements that avoids exacerbation of the condition is important.

The next, efficacy, is the ability to sufficiently enhance the immune response.

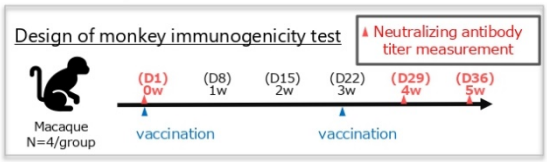
And finally, supply. The SARS-CoV-2 vaccine program requires widespread, large-scale vaccination to prevent the spread of infection. In other words, the situation calls for an adequate supply of vaccine. If the addition of adjuvant can induce sufficient immunity even at reduced antigen levels, it will lead to an increase in the supply of the vaccine.

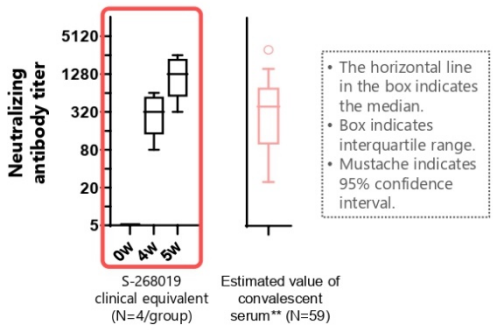
Overview of S-268019

Antigen manufacturing technology	BEVS*
Product characteristics	Full-length spike (S) protein + adjuvant
Adjuvant	A-910823
Expected dosage	• Priming vaccine; 0.5 mL twice, usually every 4 weeks, intramuscular injection • Booster vaccine; 0.5 mL once, intramuscular injection

Previous nonclinical results

- Monkey immunogenicity test
  - 2 vaccinations (3 weeks intervals)
  - Measure neutralizing antibody titers 29 and 36 days after vaccination





S-268019 showed neutralizing antibody titers similar to or exceeding recovered patient serum

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* Baculovirus Expression Vector System
** Estimate from measurements in another test

With these points in mind, here is an overview of S-268019.

As shown in the table above, S-268019 is formulated by using BEVS to combine a full-length spike protein produced with recombinant protein synthesis technology, and A-910823, an adjuvant created by our company. For priming vaccine, we assume a total of two intramuscular inoculations of 0.5 mL per dose at four-week intervals. For booster vaccine, one intramuscular inoculation of 0.5 mL per dose is assumed.

Bottom of slid is a representative example of our nonclinical results to date. We administered two doses of S-268019 to crab-eating macaques and measured neutralizing antibody titers in their blood four and five weeks later. As shown in the red box on the right graph shows neutralizing antibody titers in humans are almost equal to or exceed the level of neutralizing antibodies in recovered patient sera of infected patients.

Positioning of S-268019

Significance of domestic vaccine

- Domestic vaccines are extremely important from a national security perspective
  - Building a system that can rapidly provide vaccines at the required timing in Japan
  - Response to new variants that may occur originally in Japan

Environment surrounding booster vaccine

- Since the prevention of onset/the exacerbation prevention effect by the priming vaccination decreases with the passage of time, the third booster vaccination is urgent
- Many people have experienced side effects with the priming vaccination and the booster vaccination, and the 3rd vaccination has not progressed in Japan

Domestic vaccine that can be boosted with a good balance between efficacy and safety

The addition of new vaccine options will increase the rate of booster vaccinations, leading to prevention of the spread of infection and suppression of exacerbations

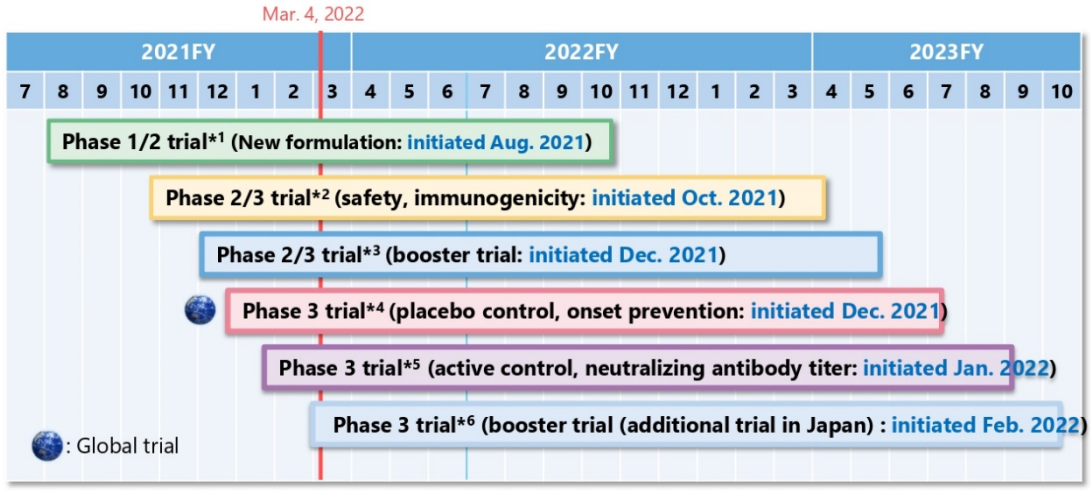
The following is a summary of the positioning of S-268019. There are two main points here.

The one point is its significance as a domestically produced vaccine. We aim to ensure vaccine availability in the required quantities at the required times in the country. In order to respond quickly to new mutant strains that may occur in Japan in the future, it is highly significant to have an integrated domestic vaccine value chain from the research stage to development, manufacturing, and supply in Japan.

The second point is as follows. It relates to the environment surrounding booster vaccines. It is well known that after initial vaccination, the effectiveness of the vaccine in preventing the onset and severity of disease and the vaccine effect fades with the passage of time. As a result, booster vaccine will be necessary. On the other hand, many people experienced adverse reactions during the priming vaccine. Another issue is how to accelerate booster vaccination in such an environment.

We aim to add S-268019 to the list of new vaccine options, as a domestic vaccine that can be administered as an booster vaccination with a good balance of efficacy and safety, and achieving a good balance between efficacy and safety. We hope to increase the rate of additional vaccination in the third dose and beyond to prevent the spread of infection and curb the severity of illness in society as a whole.

S-268019 : List of Ongoing Clinical Trials



*1 jRCT2031210269, *2 jRCT2031210383, *3 jRCT2031210470, *4 NCT05212948, *5 jRCT2051210151, *6 jRCT2031210613

Phase 1/2 Clinical Trial was supported by Japan Agency for Medical Research and Development (AMED)

This is an overall summary of the clinical trial of S-268019.

We are running six clinical trials. I will not go into too many details about each one, but I will explain very briefly how each trial is positioned.

S-268019 : Overview of Ongoing Clinical Trials 1/2

	Phase 1/2 trial	Phase 2/3 trial	Active control, neutralizing antibody titer trial	Placebo control, onset prevention trial
Priming/Booster	Priming	Priming	Priming	Priming
Subjects	Healthy adults between the ages of 20 and 64	Adults over 20 years old, elderly over 65 years old (including subjects with COVID-19 history, vaccinated subjects)	Adults over 18 years old, elderly	Adults over 18 years old
Study design	Randomized, observer-blind	Multicenter, open-label	Multicenter, randomized, active control, parallel-group, observer-blind	Placebo-controlled cross-over
Primary endpoints	AEs, treatment-related AEs, SAEs, solicited AEs, vital signs, laboratory tests, ECG	Safety at the end of the evaluation period (at 28 days following the second vaccination)	SARS-CoV-2 neutralizing antibody titer at 28 days following the second vaccination	Number of participants with occurrence of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19
Target sample size	60 subjects in 3 groups (S-268019: 24 subjects x 2 groups, placebo: 12 subjects)	3,100 subjects (naïve: over 2,000 subjects, subjects with COVID-19 history: over 30 subjects, vaccinated subjects: over 30 subjects, elderly: 100 subjects)	1,000 subjects (500 subjects: VAXZEVRIA intramuscular injection, 500 subjects: S-268019)	54,915 subjects (S-268019: 36,610, placebo: 18,305)
Dosing regimen	Intramuscular injection, two dose (Day1, Day22)	Intramuscular injection, two dose (Day1, Day29)	Intramuscular injection, two dose (Day1, Day29)	1st period Intramuscular injection, two dose (Day1, Day29) 2nd period Intramuscular injection, two dose (Day225, Day253)
Status	• Disclosed at the Japan Society for Vaccinology (December 4, 2021) • Follow-up evaluation for 1 year after inoculation of each index is ongoing • Additional vaccination for subjects in active drug group who wish to receive the third vaccination is ongoing	• Completed the 2nd inoculation of all subjects • Completed observation through Day 57 with no major safety concerns • Topline results including GMT of neutralizing antibody will be presented at Annual Meeting of Japanese Association for Infectious Diseases in April 2022	• Superiority trial to compare GMT of neutralizing antibody to a licensed vaccine (VAXZEVRIA intramuscular injection) • Completed the 1st inoculation of all subjects	• Initiated in Vietnam from December 2021 • Subject registration is progressing smoothly

Phase 1/2 Clinical Trial was supported by Japan Agency for Medical Research and Development (AMED)

On the left of slid is the Phase 1/2 trial, which was conducted in a small number of patients, to establish safety and dosage. In the next Phase 2/3 trial to the right, we accumulated safety and immunogenicity data on approximately 3,000 cases. In addition, we have active control neutralizing antibody titers trial and placebo control onset prevention trial, which are pivotal trial assessing initial immunity.

S-268019 : Overview of Ongoing Clinical Trials 2/2

	Phase 2/3 booster trial	Phase 3 booster trial
Priming/Booster	Booster	Booster
Subjects	Adults over 20 years old who at least 6 months have passed after completion of the second vaccination with COMIRNATY	Participant who have received 2 doses of SARS-CoV-2 vaccine (Adults between the ages of 20 and 64: only SPIKEVAX, elderly over 65 years old: COMIRNATY or SPIKEVAX) and 6 months or more and 8 months or less after second dose
Study design	Randomized, observer-blind, active-controlled	Single center, open-label
Primary endpoints	Geometric mean titer (GMT) of SARS-CoV-2 neutralizing antibody on Day 29 Seroresponse rate of SARS-CoV-2 neutralizing antibody on Day 29	Safety
Target number of participants	204 participants (S-268019 group: 102 participants, COMIRNATY group: 102 participants)	150 participants (100 adults, 50 elderly)
Dosing regimen	Intramuscular injection, one dose	Intramuscular injection, one dose
Status	• Completed the 1st inoculation of all subjects • **Disclosed top-line results** (Mar. 4, 2022)	• Initiated subject registration (Feb. 28, 2022)

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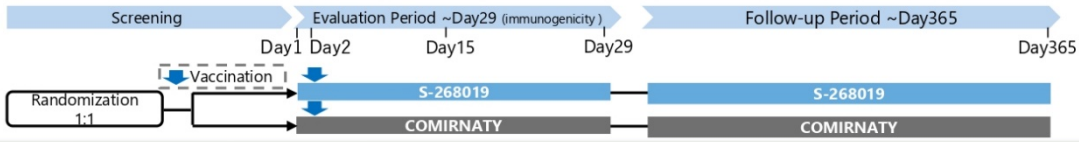
About booster vaccine, two trials are underway.

One is a Phase 2/3 booster trial, which is a comparative trial with COMIRNATY. The Phase 3 booster trial on the right is intended for those who 6 months or more and 8 months or less after second vaccination with SPIKEVAX, and the elderly are also included in the trial.

Dr. Shinkai will explain about the Phase 2/3 booster trial on the left, for which an interim report has been published.

Overview of the Phase 2/3 Booster Trial

Objectives	To evaluate if the immunogenicity of S-268019 demonstrates noninferiority compared to COMIRNATY and safety as a booster dose after completion of vaccination with two doses of COMIRNATY
Subjects	Adults over 20 years old who at least 6 months have passed after completion of the second vaccination with COMIRNATY
Study design	Randomized, observer-blind, active-controlled
Endpoints	• Primary: GMT of SARS-CoV-2 neutralizing antibody titer and seroresponse rate on Day 29 • Secondary: immunogenicity other than the primary endpoint (GMT of neutralizing antibody titer and IgG antibody titer, GMFR, seroresponse rate), safety (AEs/treatment-related AEs/SAEs and others), clinical efficacy (number of SARS-CoV-2-positive participants) • Exploratory: Immunological indices (cellular immunity, Th1/Th2 balance, assessment of immunity after booster vaccination (analysis of functions and characteristics of antibody to SARS-CoV-2 and immune cells))
Target number of participants	204 participants
Dosing regimen	Intramuscular injection, one dose
Dose	S-268019 group: A solution in which 10 mg of antigen is dissolved in a 50% v/v oil in water emulsion containing an adjuvant COMIRNATY group: 0.3mL tozinameran (30μg, diluted with physiological saline)
Duration	Nov. 2021~Jan. 2023
Study site	Tokyo Shinagawa Hospital



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This will be the last slide from me. This is a brief description of the Phase2/3 booster trial.

The objective was to trial the non-inferiority of S-268019 immunogenicity as a booster vaccination in comparison to COMIRNATY and to evaluate its safety. Subjects were 20 years of age and older and were at least six months post completion of two doses of COMIRNATY.

The trial design is randomized, observer-blind, and real drug-controlled. The primary endpoints were the geometric mean of SARS-CoV-2 neutralizing antibody titer and antibody response rate on Day 29 after booster vaccine. Secondary endpoints are other immune response, safety, and clinical efficacy. Also, for exploratory purposes, we are collecting data on cellular immunity.

The target number of cases is 204. The dosage and treatment groups consist of S-268019 and COMIRNATY and the trial was started at Tokyo Shinagawa Hospital in November 2021.

Dr. Shinkai will now give us an overview of the results of this trial and present the interim results.

Shinkai: This is Shinkai, Deputy Director of Tokyo Shinagawa Hospital. I would like to give a interim report on the Phase 2/3 booster trial of the S-268019 COVID-19 vaccine, for which I submitted a paper last night.

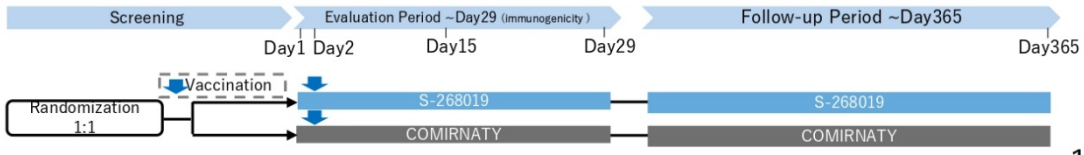
First of all, more than 90% of people have already received two doses of the vaccine at this time, so we participated in this trial because we believe that the third dose of vaccine is very important.

First of all, I would like to thank all the subjects who participated, recognizing the importance of this trial, as well as Mis. Kabasawa of Tokyo Shinagawa Hospital, who sacrificed his own time to conduct the trial in such a short period of time. I would like to express my deepest gratitude to the CRC (Clinical Research Coordinators) and to the Director of Tokyo Shinagawa Hospital, Dr. Kamachi, and all the staff of Tokyo Shinagawa Hospital, who provided their full support while also performing their normal hospital duties. This support included taking blood samples, conducting tests, administering injections, and so on. Thank you.

About COI Tokyo Shinagawa Hospital was commissioned to conduct this trial, but I have no conflicts of interest to declare.

Overview of the Phase 2/3 Booster Trial

Objectives	To evaluate if the immunogenicity of S-268019 demonstrates noninferiority compared to COMIRNATY and safety as a booster dose after completion of vaccination with two doses of COMIRNATY
Subjects	Adults over 20 years old who at least 6 months have passed after completion of the second vaccination with COMIRNATY
Study design	Randomized, observer-blind, active-controlled
Endpoints	• Primary: SARS-CoV-2 neutralizing antibody titer on Day 29 • Secondary: immunogenicity other than the primary endpoint (GMT of neutralizing antibody titer and IgG antibody titer, GMFR, seroresponse rate), safety (AEs/treatment-related AEs/SAEs and others), clinical efficacy (number of SARS-CoV-2-positive participants) • Exploratory: Immunological indices (cellular immunity, Th1/Th2 balance, assessment of immunity after booster vaccination (analysis of functions and characteristics of antibody to SARS-CoV-2 and immune cells))
Target number of participants	204 participants
Dosing regimen	Intramuscular injection, one dose
Dose	S-268019 group: A solution in which 10 mg of antigen is dissolved in a 50% v/v oil in water emulsion containing an adjuvant COMIRNATY group: 0.3mL tozinameran (30 μg, diluted with physiological saline)
Duration	Nov. 2021~Jan. 2023
Study site	Tokyo Shinagawa Hospital



As mentioned earlier, we gave this third injection to those over 20 years old who had been inoculated twice and more than six months prior. As you can see bottom of slide, the allocation was one-to-one, so our medical staff did not know which injection was given to which person. We were also able to conduct an extremely bias-free, high-quality, observer-blind clinical trial. The subjects were not aware which vaccine they had received.

In addition, since the trial took place at the end of December, most of the subjects were healthcare workers. There were two groups of subjects, those who had received S-268019, and those who had received COMIRNATY. Per-group results become available in the analysis.

Key Demographics of Participants

Immunogenicity Subset

		S-268019 N=103	COMIRNATY N=102*
Sex	Male	72	73
	Female	31	29
Age (years)	Min	21	21
	Max	59	60
BMI	Min	16.1kg/m^2	16.4kg/m^2
	Max	54.4kg/m^2	41.8kg/m^2

- Randomized：206 (S-268019: 103, COMIRNATY: 103)
- Safety analysis population：206 (S-268019: 103, COMIRNATY: 103)
- Immunogenicity subset：205 Analyzed at Baseline (S-268019: 103, COMIRNATY: 102*)
  Analyzed at Day15、29 (S-268019: 103, COMIRNATY: 101*, **)

* at screening: Exclude from analysis (n=1); Confirmed positive anti-SARS-CoV-2 N-protein antibody test after the booster dose
** at Day15 and Day29: Exclude from analysis (n=1); Confirmed positive anti-SARS-CoV-2 N-protein antibody test at Day15

First of all, in terms of participants background, there were 103 participants in the S-268019 group and 102 in the COMIRNATY group. There was no difference in gender, with 72 and 73 male patients, and 31 and 29 female patients.

There was no difference in age between the two groups, with a minimum age of 21 years and a maximum of 59 years in the S-268019 group and 60 years in the COMIRNATY group.

Regarding BMI, the minimum for the S-268019 group was 16.1kg/m^2, and that for the COMIRNATY group was 16.4 kg/m^2. The maximum values were 54.4 kg/m^2 and 41.8 kg/m^2, respectively.

One subject was excluded from the 206 subjects who cooperated in this trial because although he had no recollection of infection, he was positive for anti-N-protein antibody at screening, suggesting he had already been infected.

Also, one person tested positive for anti-N-protein antibody on Day 15, probably having become infected during the New Year's holidays. Although the individual did not recall becoming infected, they were deemed to have been infected and excluded from analysis.

Immunogenicity

< Statistical Hypothesis Testing >

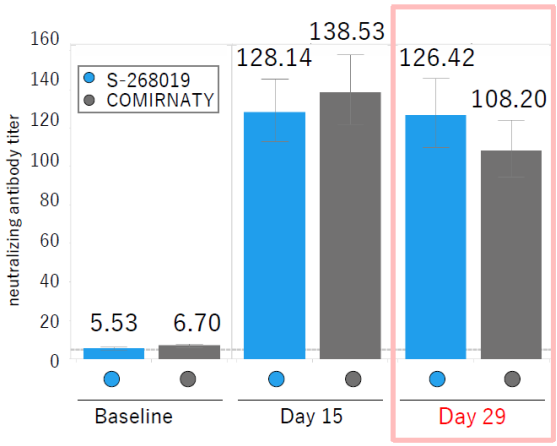
If both the lower limit of the 95% confidence interval (CI) for the GMTR (S-268019 to COMIRNATY) of SARS-CoV-2 neutralizing antibody is greater than 0.67 and the lower limit of the 95% CI for the difference in seroresponse rate (S-268019 minus COMIRNATY) of SARS-CoV-2 neutralizing antibody is greater than −10%, the noninferiority is confirmed.

Next, the Primary endpoints, immunogenicity.

As you can see on the slide, the statistical hypothesis testing here is that the lower limit of the 95% confidence interval of the geometric mean antibody titer ratio of S-268019 against COMIRNATY is greater than 0.67. In other words, if the 95% confidence interval of the geometric mean is greater than 0.67, we know that this S-268019 group was noninferior.

The seroresponse rate of neutralizing antibody titer is also judged to be noninferior to COMIRNATY in terms of immunogenicity if the lower limit of the 95% confidence interval is greater than minus 10%. With that in mind, I would like to move on to the next slide.

GMT of SARS-CoV-2 neutralizing antibody titer



GMT of SARS-CoV-2 neutralizing antibody on Day 29 (primary endpoints)

	S-268019 N=103	COMIRNATY N=101
GMT	126.42	108.20
95% confidence interval	109.76, 145.62	94.57, 123.80
GMT ratio*1	1.17	---
95% confidence interval *1	0.96, 1.42 (0.67 < 0.96)	---
One-sided P-value for non-inferiority *2	<.0001	---

Titer values reported as below the LLOQ are replaced by 0.5 x LLOQ., LLOQ (5.0)
*1 The GMT, GMT ratio with corresponding 95% CI are estimated by back transformation of the adjusted mean, the intervention difference and its 95% CI which are obtained using analysis of covariance (ANCOVA) model fitted on the log-transformed titers. The model includes intervention group as fixed effect as well as age (continuous) and sex as covariates.
*2 The non-inferiority margin is 0.67.

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This slide shows GMT of SARS-CoV-2 neutralizing antibody titer.

The vertical axis on the left side shows the neutralizing antibody titer. The two baselines, before the first dose, are the S-268019 group in blue and the COMIRNATY group in gray. I personally feel 5.53 and 6.70 these initial neutralizing antibody titers, after two COMIRNATY vaccinations, are very low.

Day 15 neutralizing antibody titer is the bar in the middle. The S-268019 value is 128.14, while that of COMIRNATY is 138.53. These are essentially comparable.

Next to that is the primary endpoint in this case, which is, in essence, what we rank as most important in assessing noninferiority before conducting a clinical trial. The rightmost bar is the value on Day 29. Here, the value for the S-268019 group was 126.42 and that for COMIRNATY was 108.20. The table on the right shows that if the lower limit of the 95% confidence interval is greater than 0.67, noninferiority is verified. The value is 0.96, confirming that noninferiority was found.

Seroresponse Rate of SARS-CoV-2 neutralizing antibody titer on Day 29

Seroresponse Rate on Day 29*1 (primary endpoints)

*1 Seroresponse rate is defined as the proportion of participants with a ≥4-fold increase in post-vaccination antibody titer from baseline.

	S-268019 N=103	COMIRNATY N=101
Number of Seroresponse	103	101
Seroresponse Rate	100.0%	100.0%
Difference in proportion of seroresponse	0.0%	---
95% confidence interval	-5.8, 5.8 -10<-5.8	---
One-sided P-value for non-inferiority*2	0.0004	---

*2 The non-inferiority margin is -10%.

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Next is the other primary endpoint. This time, there are co-primary endpoints, both of which had to be met to be considered validated.

Seroresponse rate is defined as the proportion of participants with a ≥4-fold increase in post-vaccination antibody titer from baseline. If you look here, the S-268019 group is 100% and the COMIRNATY group is 100%. Just by looking at the numbers, you can see that there is noninferiority, but the 95% confidence interval I mentioned earlier is greater than minus 10%, so noninferiority was verified for this as well. The p-value was 0.0004, which also statistically verified noninferiority.

Result of Primary Endpoints

Interim results showed noninferiority of S-268019 to COMIRNATY in co-primary endpoints: GMT and seroresponse rate for neutralizing antibodies on day 29

In the interim report, this trial met its primary endpoint.

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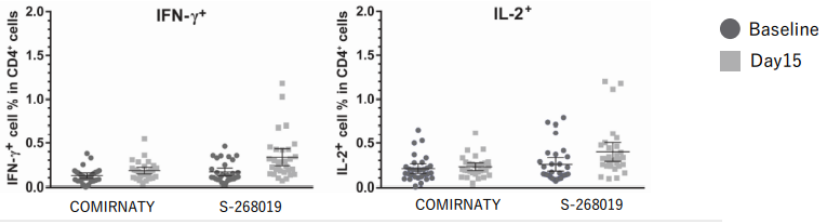
The two results we had now are the primary endpoints of this trial, we could prove noninferiority. Since noninferiority was demonstrated in both the GMT of neutralizing antibody titer and the antibody response rate, we were able to demonstrate the immunogenicity of S-268019 against COMIRNATY. This means that noninferiority has been verified. The so-called primary endpoints have been achieved.

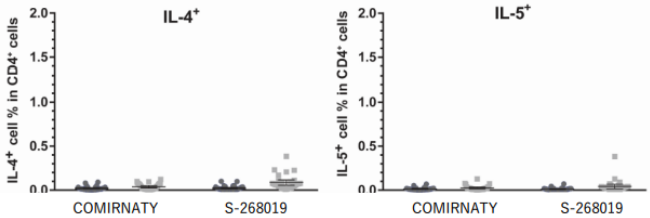
Immunologic Assays by Flow Cytometry (ICS-FCM)*

CD4⁺T Cell

T-helper type 1



T-helper type 2



A strong bias toward the T-helper type 1 phenotype was noted

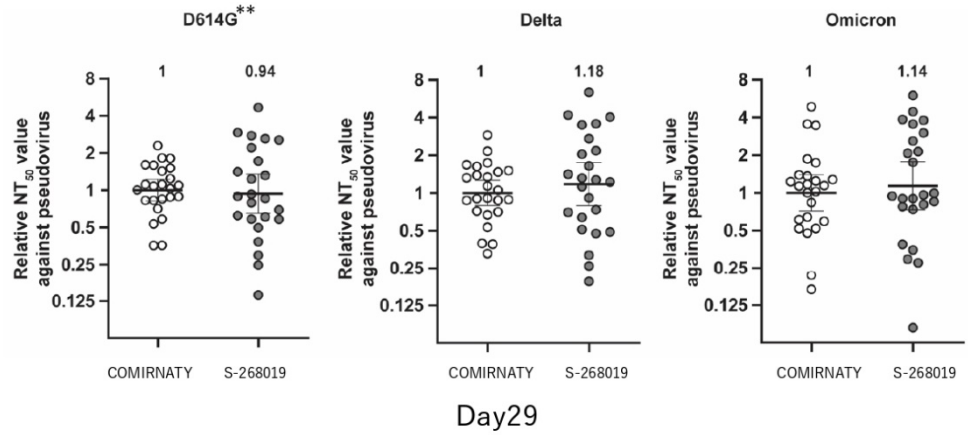
* T-cell responses were assessed for a subgroup (n=30/group) sampled from participants who gave consent to assess cellular immunity. 24

Next, we look at types of T-cells. Using a machine called a flow cytometry, we can distinguish between cells of different types.

The top one is the Th1 type and the bottom one is the Th2 type. The Th1 type is said to be involved in the elimination of viruses, and the Th2 type is said to be involved in allergies. It is extremely important that a good balance between Th1 and Th2 cell types following vaccination. If you look at the IFN-γ^+ above, you can see that there is a slight rise in both the COMIRNATY and S-268019 groups in the Day 15 square on the right side. You can also see that it says IL-2^+-positive cells. The right side of Day 15 is slightly higher.

On the other hand, as for the lower side, where it says Th2-type, IL-4^+, and IL-5^+, I personally felt that it was a rather good vaccine because these figures hardly changed. This means that it promoted the Th1 response and did not predominantly promote the Th2 response.

Neutralizing Antibody Titer against Pseudotyped Virus with SARS-CoV-2 Mutation Spike Protein*



Serum samples from both vaccine groups neutralized pseudovirus variants including Omicron variants with similar potency as indicated by NT50 values relative to COMIRNATY

* Before reassessment, a subgroup (n=24/group) sampled from participants were extracted from groups with the same distribution of neutralizing antibody titers and ages, and the neutralizing antibody titers were assessed using Pseudotyped virus.
** European strain with D614G mutation introduced into spikes of WK-521 strain

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There is public health concern because of the spread of the Omicron variant strain. Following the strain of the 5th wave, we saw the Delta variant strain, and now, we have the Omicron variant strain.

A live virus, is very infectious, so it is difficult to verify, but pseudoviruses are very commonly used to measure neutralizing antibody titers. The Omicron variant strain on the far right is the pseudovirus but this time we are looking at the neutralizing antibody titer against the pseudovirus.

Under the Omicron variant, the value for S-268019 is 1.14, and the value is 1 for COMIRNATY. Since this one also went up almost equally, this analysis indicates that S-268019 showed neutralizing antibody titer against various SARS-CoV-2 mutant strains, including the Omicron variant strain, equivalent to that of COMIRNATY.

So far, I've spoken mostly about effectiveness. In my personal opinion, the virus is very effective: more so than I expected before starting this trial.

Secondly, although we currently administer vaccines and provide outpatient services, we still see a large number of patients with adverse reactions. These include things like a fever or numbness in the hands. Therefore, we still consider adverse reactions and safety to be very important.

Treatment-related AEs (Treatment-related AEs will be defined as AEs considered to be "related" to the study intervention)

<* Any systemic solicited TRAEs>

- The following AEs were collected as solicited systemic AEs within 7 days after study intervention (Day1 to Day8)
  - Fever, Nausea/vomiting, Diarrhea, Headache, Fatigue, Myalgia, Arthralgia, Chills

<** Any local solicited TRAEs>

- The following AEs were collected as solicited local AEs within 7 days after study intervention (Day1 to Day8)
  - Pain ,Erythema/redness ,Induration ,Swelling

		S-268019 N=103	COMIRTY N=103
Treatment-related AEs (TRAEs)	Participants	99	101
	(%) of participants	96.1%	98.1%
Any systemic solicited TRAEs*	Participants	72	81
	(%) of participants	69.9%	78.6%
Any local solicited TRAEs**	Participants	70	75
	(%) of participants	68.0%	72.8%

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In general, adverse reactions to vaccines include fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and other systemic adverse reactions, as well as local adverse reactions that occur at the site of administration. It could be localized pain, redness, induration, swelling, and so on.

The pertinent results are below. Looking at the S-268019 group and the COMIRNATY group, we see that the adverse reactions themselves occur in 96.1% and 98.1% of participants, respectively. The figures are 69.9% and 78.6% for the any systemic solicited TRAEs, and 68% and 72.8% for any local solicited TRAEs effects.

Treatment-related AEs (TRAEs) (Incidents, 5% or more)

		S-268019 N=103	COMIRNATY N=103
participants ((%) of participants)	**Participants with any Treatment-related AEs**	**99 (96.1%)**	**101 (98.1%)**
	Headache	26 (25.2%)	43 (41.7%)
	Diarrhea	4 (3.9%)	6 (5.8%)
	Myalgia	42 (40.8%)	49 (47.6%)
	Arthralgia	8 (7.8%)	11 (10.7%)
	Vaccination site pain	69 (67.0%)	75 (72.8%)
	Fatigue	45 (43.7%)	55 (53.4%)
	Pyrexia	40 (38.8%)	61 (59.2%)
	Vaccination site erythema	6 (5.8%)	9 (8.7%)
	Chills	4 (3.9%)	7 (6.8%)
	Neutrophil percentage increased	78 (75.7%)	81 (78.6%)
	C-reactive protein increased	34 (33.0%)	46 (44.7%)
	White blood cell count increased	9 (8.7%)	11 (10.7%)

Looking from the top, headaches accounted for 26 and 43 cases, or 25.2% and 41.7%, respectively. In the S-268019 group, 40.8%, or 42 participants, had myalgia. The figure was 47.6%, or 49 participants, in the COMIRNATY group. Below that, vaccination site pain was reported in 69 cases in the S-268019 group and 75 participants in the COMIRNATY group. Fatigue and lethargy were reported in 45 and 55 cases, respectively. Pyrexia was reported in 40 and 61 cases, respectively.

Several blood samples were taken, and these showed raised neutrophil count in 78 and 81 cases, respectively.

So-called markers of inflammation were raised in more than 5% of participants, with the phenomenon seen in 34 and 46 cases, respectively.

Solicited Systemic AEs and Solicited Local TRAEs (Incidents)

			S-268019 N=103	COMIRNATY N=103
Any systemic solicited TRAEs	participants ((%) of participants)	Participants with any systemic solicited TRAEs	72 (69.9%)	81 (78.6%)
		Fever	40 (38.8%)	61 (59.2%)
		Nausea/Vomiting	5 (4.9%)	5 (4.9%)
		Diarrhea	4 (3.9%)	6 (5.8%)
		Headache	26 (25.2%)	43 (41.7%)
		Fatigue	45 (43.7%)	55 (53.4%)
		Myalgia	42 (40.8%)	49 (47.6%)
		Arthralgia	8 (7.8%)	12 (11.7%)
		Chills	4 (3.9%)	7 (6.8%)
Any local solicited TRAEs	participants ((%) of participants)	Participants with any local solicited TRAEs	70 (68.0%)	75 (72.8%)
		Pain	68 (66.0%)	75 (72.8%)
		Erythema/Redness	7 (6.8%)	9 (8.7%)
		Induration	0 (0.0%)	0 (0.0%)
		Swelling	1 (1.0%)	1 (1.0%)

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The next slide summarizes any systemic solicited TRAEs at the top and any local solicited TRAEs at the bottom.

As before, the S-268019 group is on the left and the COMIRNATY on the right. The percentages are as I told you earlier.

Solicited Systemic AEs and Solicited Local TRAEs (Severity)

- Grade 5 : Death related to AE.
- Grade 4 : Life-threatening consequences; urgent intervention indicated.
- Grade 3 : Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL.
- Grade 2 : Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 1 : Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

A semicolon (;) indicates "or" within the description of grade.

				S-268019 N=103	COMIRNATY N=103
Any systemic solicited TRAEs	participants ((%) of participants)	Severity	**Total**	**72 (69.9%)**	**81 (78.6%)**
			Grade 5	0 (0.0%)	0 (0.0%)
			Grade 4	0 (0.0%)	0 (0.0%)
			Grade 3	1 (1.0%)	4 (3.9%)
			Grade 2	15 (14.6%)	31 (30.1%)
			Grade 1	56 (54.4%)	46 (44.7%)
Any local solicited TRAEs	participants ((%) of participants)	Severity	**Total**	**70 (68.0%)**	**75 (72.8%)**
			Grade 5	0 (0.0%)	0 (0.0%)
			Grade 4	0 (0.0%)	0 (0.0%)
			Grade 3	0 (0.0%)	0 (0.0%)
			Grade 2	2 (1.9%)	5 (4.9%)
			Grade 1	68 (66.0%)	70 (68.0%)

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What is important about adverse reactions is if someone experiences a very severe reaction after receiving the vaccine. In the adverse reaction grading, Grade 5 is life-threatening, and Grade 4 is very serious. Fortunately, there were no Grade 4 or 5 cases in the S-268019 group or the COMIRNATY group, so there were no life-threatening adverse reactions.

Grade 3 is a degree of adverse reaction that limits daily activities. Grade 2 is defined as anything that restricts daily activities other than personal activities. Grade 1 is mild. I think it's okay if it's Grade 1. If events are controlled down to Grade 2 or so, we as physicians can give injections with peace of mind.

Grade 3 was the highest grade of specific systemic adverse reactions, with one case in the S-268019 group and four cases in the COMIRNATY group. Grade 2 events occurred in 15 and 31 cases, respectively. There were and 56 and 46 cases, respectively, of Grade 1 events.

As for the lower part, there were no Grade 3, 4, or 5 cases, and 1.9%, 4.9%, 66%, and 68% of cases were Grade 1 or 2, which are almost the same those of the S-268019 group. The great thing is that there were no Grade 4 or 5 events. I personally feel that it is very good that there were so few Grade 3 events.

Solicited Systemic AEs and Solicited Local TRAEs (Timing of Onset)

				S-268019 N=103	COMIRNATY N=103
Any systemic solicited TRAEs	participants ((%) of participants)	Timing of Onset (Day)	1	36 (35.0%)	44 (42.7%)
			2	50 (48.5%)	61 (59.2%)
			3	2 (1.9%)	2 (1.9%)
			4	0 (0.0%)	0 (0.0%)
			5	0 (0.0%)	0 (0.0%)
			6	0 (0.0%)	2 (1.9%)
			>=7	0 (0.0%)	0 (0.0%)
Any local solicited TRAEs	participants ((%) of participants)	Timing of Onset (Day)	1	37 (35.9%)	43 (41.7%)
			2	35 (34.0%)	36 (35.0%)
			3	0 (0.0%)	1 (1.0%)
			>=4	0 (0.0%)	0 (0.0%)

Next, since you have probably all been vaccinated, of course, you can probably guess roughly when the adverse reactions will occur, but the timeline for the S-268019 group is on the left and that of the COMIRNATY group is on the right.

I think this is the typical pattern, and I'll go through these sequentially. There were roughly 36 and 44 cases, respectively, on the day of vaccination. There were 50 and 61 cases the next day. Next, there are two and two cases, respectively, on the third day. Adverse reactions generally develop within 48 hours of vaccination.

There were two events in the COMIRNATY group on the sixth day, but in general, systemic adverse reactions occurred by about 48 hours post-vaccination. I feel that as physicians, we should take appropriate measures during that early period.

Below that, there are specific local adverse reactions. Participants with localized events numbered 37 and 43 on the day of vaccination, and 35 and 36 on the second day. This indicates that adverse reactions generally occur on the same day or by the next day.

Solicited Systemic AEs and Solicited Local TRAEs (Incidents, Severity) 1/3

			S-268019 N=103	COMIRNATY N=103
Fever participants ((%) of participants)	Severity	Total	40 (38.8%)	61 (59.2%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	1 (1.0%)	2 (1.9%)
		Grade 2	2 (1.9%)	7 (6.8%)
		Grade 1	37 (35.9%)	52 (50.5%)
Nausea/ Vomiting participants ((%) of participants)	Severity	Total	5 (4.9%)	5 (4.9%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	1 (1.0%)	0 (0.0%)
		Grade 1	4 (3.9%)	5 (4.9%)

			S-268019 N=103	COMIRNATY N=103
Diarrhea participants ((%) of participants)	Severity	合計	4 (3.9%)	6 (5.8%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	1 (1.0%)
		Grade 2	1 (1.0%)	1 (1.0%)
		Grade 1	3 (2.9%)	4 (3.9%)
Headache participants ((%) of participants)	Severity	合計	26 (25.2%)	43 (41.7%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	7 (6.8%)	12 (11.7%)
		Grade 1	19 (18.4%)	31 (30.1%)

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Let us now look at the seriousness of each of these events separately.

First, fever is as I said, with the S-268019 group on the left and the COMIRNATY group on the right. It occurred at Grade 3 in 1 and 2 cases, Grade 2 in 2 and 7 cases, and Grade 1 in 37 and 52 cases, so I think the results are comparable or slightly lower.

As for nausea/vomiting, 1 and 0 cases were Grade 2, and 4 and 5 cases were Grade 1.

As for diarrhea, one and one cases were Grade 2, and three and four cases were Grade 1.

Headaches often occur, and although headaches are difficult, there were 7 and 12 cases with Grade 2 and 19 and 31 cases with Grade 1.

Grade 3 fever is a fever between 39 and 40 degrees Celsius. There were 1 and 2 cases, respectively.

Solicited Systemic AEs and Solicited Local TRAEs (Incidents, Severity) 2/3

			S-268019 N=103	COMIRNATY N=103
Fatigue participants ((%) of participants)	Severity	Total	45 (43.7%)	55 (53.4%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	1 (1.0%)
		Grade 2	9 (8.7%)	22 (21.4%)
		Grade 1	36 (35.0%)	32 (31.1%)
Myalgia participants ((%) of participants)	Severity	Total	42 (40.8%)	49 (47.6%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	1 (1.0%)	7 (6.8%)
		Grade 1	41 (39.8%)	42 (40.8%)

			S-268019 N=103	COMIRNATY N=103
Arthralgia participants ((%) of participants)	Severity	Total	8 (7.8%)	12 (11.7%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	2 (1.9%)	5 (4.9%)
		Grade 1	6 (5.8%)	7 (6.8%)
Chills participants ((%) of participants)	Severity	Total	4 (3.9%)	7 (6.8%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	2 (1.9%)	4 (3.9%)
		Grade 1	2 (1.9%)	3 (2.9%)

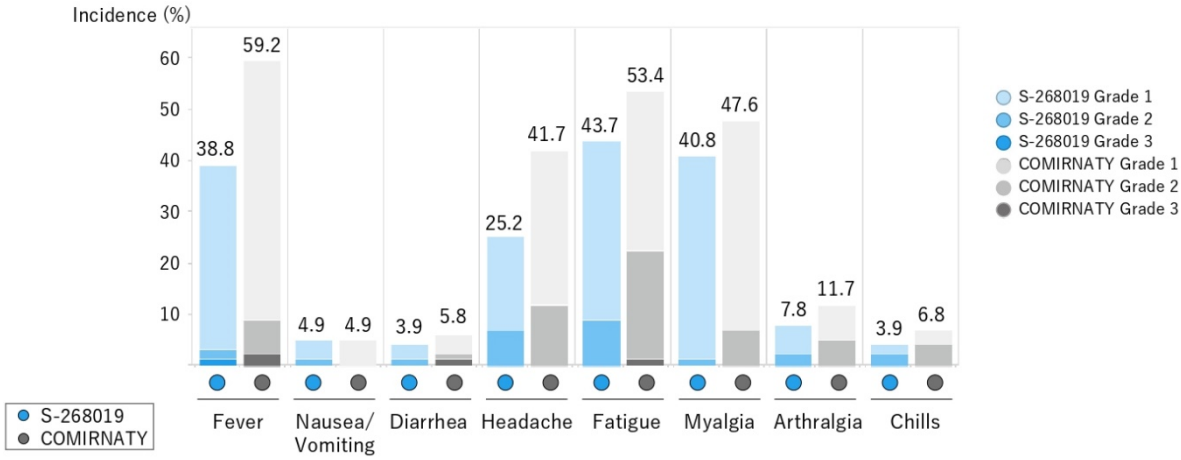
Next, as for lethargy and fatigue, 9 and 22 cases were Grade 2, and 36 and 32 cases were Grade 1.

Also, myalgia were 1 and 7 cases with Grade 2, and 41 and 42 cases with Grade 1.

Arthralgia was Grade 2 in 2 and 5 cases, and Grade 1 in 6 and 7 cases.

Chills were Grade 2 in 2 and 4 cases, and Grade 1 in 2 and 3 cases.

Solicited Systemic AEs and Solicited Local TRAEs (Incidents, Severity) 3/3



Here is a table that summarizes these figures. You can see that the blue is S-268019, and the COMIRNATY group is on the right.

The vertical axis is the incidence of adverse reactions. We can see that the results for S-268019 are equivalent or lower. The dark blue and dark gray are Grade 3 events. We can see that the two groups are almost the same for Grade 1 and Grade 2, and I think it is easy for us as physicians to management these milder adverse reactions. I am very pleased with the results.

Solicited Local TRAEs (Incidents, Severity) 1/2

			S-268019 N=103	COMIRNATY N=103
Pain participants ((%) of participants)	Severity	Total	68 (66.0%)	75 (72.8%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	0 (0.0%)	5 (4.9%)
		Grade 1	68 (66.0%)	70 (68.0%)
Erythema /Redness participants ((%) of participants)	Severity	Total	7 (6.8%)	9 (8.7%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	1 (1.0%)	0 (0.0%)
		Grade 1	6 (5.8%)	9 (8.7%)

			S-268019 N=103	COMIRNATY N=103
Induration participants ((%) of participants)	Severity	Total	0 (0.0%)	0 (0.0%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	0 (0.0%)	0 (0.0%)
		Grade 1	0 (0.0%)	0 (0.0%)
Swelling participants ((%) of participants)	Severity	Total	1 (1.0%)	1 (1.0%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	1 (1.0%)	0 (0.0%)
		Grade 1	0 (0.0%)	1 (1.0%)

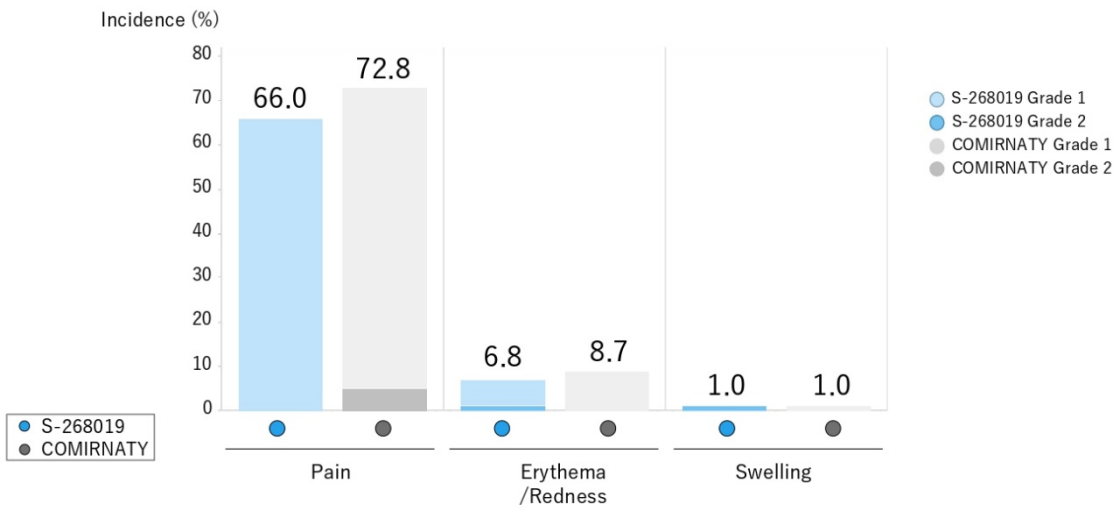
Next, solicited Local TRAEs. In the case of pain, Grade 2 events were seen in 0 and 5 cases, and Grade 1 in 68 and 70 cases.

Erythema, or rash, was Grade 2 in 1 and 0 cases, and Grade 1 in 6 and 9 cases.

There were no cases of induration.

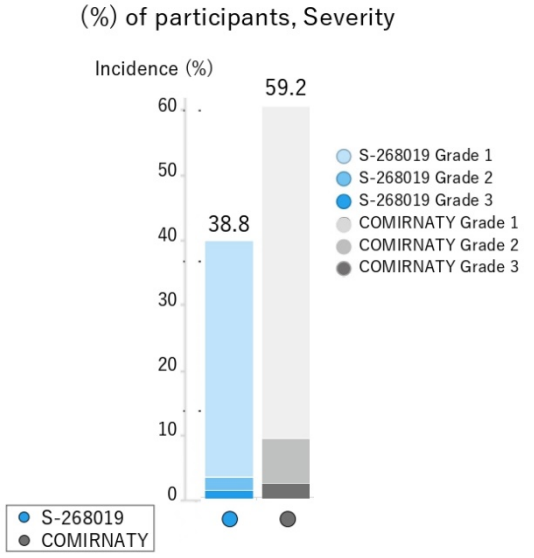
The number of participants with swelling was also 1 and 0 for Grade 2 and 0 and 1 for Grade 1.

Solicited Local TRAEs (Incidents, Severity) 2/2



If you look here, with the vertical axis as incidence, you can also see that the S-268019 group is almost equal or lower than the COMIRNATY group. In the local area, there were no events of Grade 3 or higher, which is reassuring in terms of management as a physician.

Solicited Systemic AEs ：Fever ((%) of participants, Severity, Timing of Onset)



			S-268019 N=103	COMIRNATY N=103
Fever participants ((%) of participants)	Severity	Total	40 (38.8%)	61 (59.2%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	1 (1.0%)	2 (1.9%)
		Grade 2	2 (1.9%)	7 (6.8%)
		Grade 1	37 (35.9%)	52 (50.5%)
	Timing of Onset	1	9 (8.7%)	19 (18.4%)
		2	30 (29.1%)	42 (40.8%)
		3	1 (1.0%)	0 (0.0%)
		>=4	0 (0.0%)	0 (0.0%)

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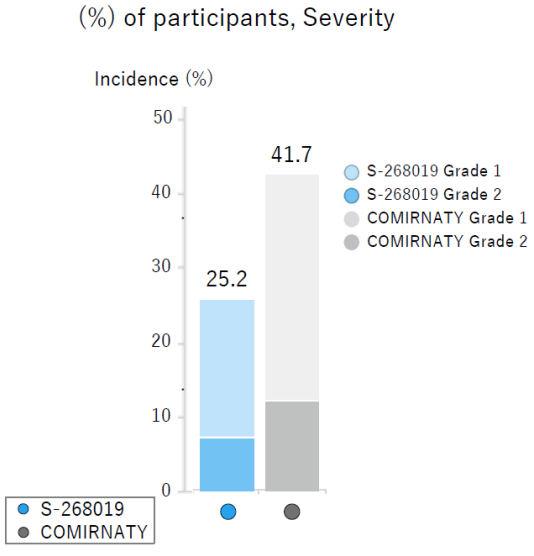
As for adverse reactions, we are concerned about major reactions such as fever, so let's take a look at these again. The figure is 37 and 52 cases.

The onset of events is usually by the third day. As a result, I felt that it was necessary to pay attention to this and provide medication to lower a fever in advance.

Solicited Systemic AEs ：Headache ((%) of participants, Severity, Timing of Onset)



			S-268019 N=103	COMIRNATY N=103
Headache participants ((%) of participants	Severity	Total	26 (25.2%)	43 (41.7%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	0 (0.0%)
		Grade 2	7 (6.8%)	12 (11.7%)
		Grade 1	19 (18.4%)	31 (30.1%)
	Timing of Onset	1	5 (4.9%)	16 (15.5%)
		2	20 (19.4%)	25 (24.3%)
		3	1 (1.0%)	1 (1.0%)
		4	0 (0.0%)	0 (0.0%)
		5	0 (0.0%)	0 (0.0%)
		6	0 (0.0%)	1 (1.0%)
		>=7	0 (0.0%)	0 (0.0%)

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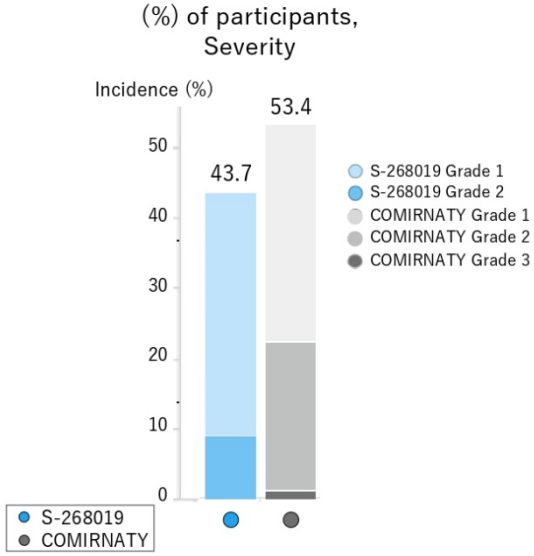
Next is headache.

Headache is also an effect we see quite a lot. Here, the incidence was 25.2% for the left and 41.7% for the right. Here, too, there were 7 and 12 Grade 2 cases, and 19 and 31 Grade 1 cases. The point is that the headache did not become so severe that the patient was unable to take care of himself, so we prescribe headache medication as soon as possible to deal with the problem.

In terms of the time of occurrence, all of these events generally occur within 48 hours of vaccination, so we would like to pay attention to this and respond accordingly.

Solicited Systemic AEs ：Fatigue ((%) of participants, Severity, Timing of Onset)

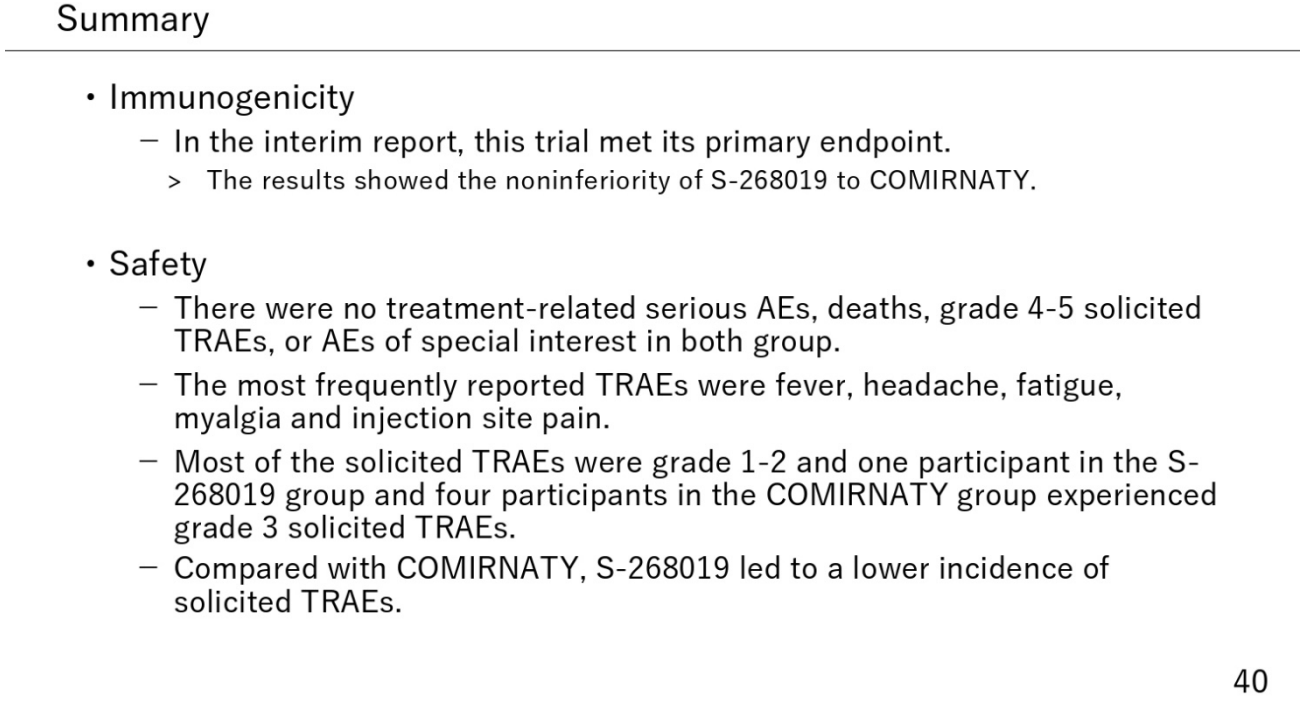


			S-268019 N=103	COMIRNATY N=103
Fatigue participants ((%) of participants	Severity	Total	45 (43.7%)	55 (53.4%)
		Grade 5	0 (0.0%)	0 (0.0%)
		Grade 4	0 (0.0%)	0 (0.0%)
		Grade 3	0 (0.0%)	1 (1.0%)
		Grade 2	9 (8.7%)	22 (21.4%)
		Grade 1	36 (35.0%)	32 (31.1%)
	Timing of Onset	1	24 (23.3%)	16 (15.5%)
		2	21 (20.4%)	39 (37.9%)
		>=3	0 (0.0%)	0 (0.0%)

Finally, fatigue.

We see many participants who are sluggish after receiving the vaccine. The same trend is seen here, with incidence of 43.7% and 53.4%. Grade 3 is 0 and 1, Grade 2 is 9 and 22, and Grade 1 is 36 and 32, so I think that S-268019 is lower with respect to fatigue as well.

We know that occurrence is usually observed within two days, or in other words, by the next day after vaccination.



Let me summarize the information so far.

The interim report on immunogenicity, which is the efficacy of the Phase 2/3 trial, showed that the trial met its primary endpoint, which means that the trial vaccine is expected to be effective. Noninferiority to COMIRNATY was verified in GMT of neutralizing antibody titers and antibody response rate on Day 29.

Next, safety. Regarding safety, there were no serious adverse reactions, deaths, or adverse reactions of particular note in either group.

The most frequent adverse reactions were fever, headache, fatigue, myalgia, and pain at the injection site.

Most specific systemic/local adverse reactions in both groups were Grade 1 or Grade 2. An event of Grade 3 was observed in one case in S-268019 and four cases in the COMIRNATY group.

Compared to the COMIRNATY group, the S-268019 group had a similar or lower incidence of specific systemic/local adverse reactions.

This concludes my presentation. Thank you very much.

Kyokawa: Thank you very much, Dr. Shinkai.

Now, before the Q&A session, we will hear a few words from Dr. Teshirogi. Thank you.

Teshirogi: Thank you all for joining us today. Now that we've heard from Dr. Shinkai, I would like to begin by expressing my deepest gratitude to him for conducting such an extensive trial in such a short period of time. I would like to thank Dr. Kabachi, the Director of Tokyo Shinagawa Hospital, Mis. Kabasawa, and all the other wonderful CRC members who have supported this trial, as well as all the medical professionals who have dedicated their time to this trial. Thank you very much.

Today, Dr. Shinkai will be assisting us in the Q&A. In particular, I believe that the results of the third noninferiority trial, which is one of the Phase 2/3 trials and is known as a booster trial, are very good. I would like to use these results to further promote product development.

We don't really intend to talk about the future schedule today, or about what other trials are going on. We plan to hold a separate session on those topics. Today, we would welcome questions regarding this noninferiority trial, including questions you have for Dr. Shinkai.

Dr. Shinkai has stern words about the number and quality of clinical papers in our country. He has said that good clinical trial results should be delivered in a timelier manner.

It would be natural for me to say so, but Dr. Shinkai and Mis. Kabasawa have been looking at almost all of the data together. We were not able to touch the data at all, and it was only after we were informed that the database had been locked that we were finally able to participate and perform statistical analysis. We, on the Company side, could not see anything, so we were very nervous until the very end, but the results were good and we are happy about it.

Also, Dr. Shinkai has put all this together and submitted a paper with incredible speed. It is not good to disclose in this way what has not been submitted for publication, so I would like to thank you for the speed with which you were able to submit your paper in the course of your own research. I hope that Japanese clinical papers will continue to be disseminated to the world with the same speed and quality as Dr. Shinkai's. As a manufacturer, we would like to cooperate with such activities to the best of our ability.

I would like to thank all of you for coming here today, and I would like to hear about our vaccine from medical professionals, including about how it has been administered to the subjects. Thank you for your cooperation today.

Kyokawa: Thank you very much.

Question & Answer

Kyokawa : We will now move on to the Q&A session.

We will now begin by taking questions from the investor analysts in the audience. Please raise your hand if you have a question.

Mr. Yamaguchi from Citigroup Global Markets, please.

Yamaguchi : My name is Yamaguchi from Citigroup. Thank you very much for your time today. I would like to ask you a few questions.

First of all, I think I understand that this trial was performed to investigate non-inferiority, but just looking at the numbers, I don't know if this is statistically sound or not, but some of the major items are numerically superior. Does that mean that as a result, you can say that the results were superior? In other words, I thought there were some areas where you could potentially beat COMIRNATY.

Deguchi : Thank you. I will answer this question.

We still believe that statistical analysis is the most important factor in interpreting data, and therefore, statistically speaking, what we see here is non-inferiority. I think this is the first thing I should reiterate.

Numerically, in fact, the GMT of neutralizing antibody titer on Day 29 of the primary endpoint is higher for S-268019.However, what kind of significance this has, or whether it can be replicated, or what kind of significance it could have, is something that we will have to look at in the future, for example, when we follow up with longer-term data. We would like to clarify the position of the other trial groups by examining them as well, but we would like to refrain from commenting solely on the numerical value of this data.

Yamaguchi : Also, I think the balance between Th1 and Th2 was very important from the initial concept of S-268019. I know this is the same story again, but at a glance, S-268019 seems to raise interferon and interleukin 2 more than the COMIRNATY. In other words, it seems to raise Th1 more strongly. Would you say that it might look that way? Or are you not able to comment on that? I'd be grateful if you could let us know.

Deguchi : I'm sorry. It is the same answer again.

Yamaguchi : I understand.

Finally, you mentioned at the beginning that many of the subjects were medical workers. I don't think this question is directly related to, say, efficacy, but I'm wondering about the possibility of bias. Given the patient demographics, is there a possibility of bias in the frequency or level of reporting of adverse reactions?

Shinkai : Thank you.

The booster trial was started in December. At that time, those who at least 6 months have passed after completion of the vaccination with COMIRNATY were limited to healthcare workers.

As you said, this demographic does not represent Japan as a whole, but at least, there was no bias between groups in this trial. As a result, we don't have any problem interpreting the result as showing non-inferiority.

Yamaguchi : In terms of side effects, I think that overall there were fewer side effects, although of course this is also non-inferiority. I think there were very few considering grade. I don't think there were any effects where the figure was higher than in the COMIRNATY group.

So can you say that there was a trend here, and that side-effects were lower overall?

Deguchi : Again, I think the answer is the same as the answer I gave earlier.

Shinkai : Regarding adverse reactions in participants, my impression is that, although we see a great number of patients at our hospital for vaccines, my impression of the COMIRNATY group is about the same as what I see in general clinical practice. This is just my impression.

During the trial I was not able to tell who was injected the S-268019, so I had no idea which one was which. But when I summarized the results, I feel that the S-268019 group had the same or lower adverse reactions.

Yamaguchi : I understand.

Kyokawa : Thank you very much.

Next, Mr. Sakai from Credit Suisse, please go ahead.

Sakai : My name is Sakai from Credit Suisse.

I'm afraid I have to start from the beginning, but I was wondering why you chose COMIRNATY this time and not SPIKEVAX. I think one reason for this is probably that it was easier to gather subjects for clinical trials, but I would like to hear your rationale for this.

Also, this is really a hypothetical question, but I would like to know if you have any thoughts on what would happen if SPIKEVAX had been used. This is my first question.

Deguchi : I will answer your question.

I think the background that COMIRNATY is being selected in this trial is the timing of the past booster vaccination. This trial began last November.

We had to ask ourselves which vaccines would have been given over six months previously. At that time, COMIRNATY was the most popular vaccine in Japan at that time. Therefore, COMIRNATY was selected for this trial.

As I mentioned earlier in my slide, we are considering two trials for booster immunization. Because it's time for people who have been vaccinated with SPIKEVAX to pass 6 months, we are also envisioning the trial with SPIKEVAX.

I would like to explain the booster trial on page 15 again. On the left, eligible subjects in this trial that was presented today were those who have been given two doses of the COMIRNATY vaccine. The third booster vaccination is used S-268019 or COMIRNATY as a comparative trial.

On the right side, the composition of the clinical trial is slightly different and is open label. In this trial, no comparison of control drugs is set. The subjects are those who have already been vaccinated twice with SPIKEVAX. This open label trial will show how well the immunogenicity increases and how much safety data can be obtained when S-268019 is given to subjects who have already been given SPIKEVAX.

Sakai : So all 150 subjects are receiving your vaccine?

Deguchi : Yes, that's what I mean.

Sakai : Understood.

Also, I understand that you have submitted a paper, but this time it is written only as top-line results (interim report). I'm sorry, I haven't had a chance to read the paper yet, but if there are any more details about its contents that I should know, I would be very interested in hearing about them.

Shinkai : The content of today's presentation is exactly the content of the paper. Of course, before publication, any paper requires thorough verification.

Even though top-line results, we should firmly disseminate what is of a quality that can be published in a dissertation, so we have summarized it as a dissertation as soon as possible. The information should be of sufficient quality to be published as a paper, so we have compiled it into a paper. As for the content, it is as I presented today.

Sakai : Thank you very much.

I guess this will be my last question. In a sense, I think that the results show that the primary endpoints have been met and safety has also been cleared, but what is the next step?

I know that there are several additional trials going on right now, and I think that the Phase 2/3 booster trial will increase the expectations of this vaccine considerably. What are your thoughts about these other trials, including the probability of success?

Shinkai : This trial is a noninferiority study, so I don't know if I should say more than that, but personally, as a physician examining people who have been vaccinated twice, I think it would be better for us. if there were a variety of vaccines available, it is very helpful.

There are many people who cannot receive this vaccine because of TRAEs to it, so from a physician's point of view, I would just like to say that it would be very helpful if the number of types of vaccines could be increased.

Sakai : Thank you very much.

Kyokawa : Another analyst would like to ask a question. Mr. Tanaka of Mizuho, please go ahead.

Tanaka : Tanaka, Mizuho Securities. Thank you for your time today.

I think it was a very good result, but I think you mentioned that you were happier with the outcome than when you first took on the project. Perhaps you might have thought that the efficacy of the recombinant protein vaccine might be slightly inferior to that of the mRNA vaccine at first, since it is said that the mRNA vaccine is dosed higher. I think you may have initially thought that there would be good results in TRAEs, but is that not correct?

Shinkai : I am really sorry. Personally, as I said before, I was very happy to undertake this trial, but I think that we have been thinking about the COVID-19 since February 2020, and now that the current vaccine has been released, things are going in a very positive direction. Without these vaccines, it's a bit frightening to think about.

This has been a comparison of non-inferiority against a very effective vaccine. While I didn't know which was which since it was a blind trial, I did have that feeling.

Tanaka : Thank you very much.

One more thing, I was told not to ask about other trials, but the neutralizing antibody titer and other data this time may indicate that there is a possibility that the data for highly effective prophylaxis about 55,000 cases now in the global trial. Is there a feeling that this is the case?

Deguchi : We have high expectations. Therefore, we are of course eager to focus our efforts on this area, and our expectations are also growing. Of course, since it is data, we would like to evaluate it carefully.

Tanaka : One more point, the adjuvant was changed in the middle of the process to a new formulation. I don't know about this adjuvant, but would it be correct to say that this adjuvant is very good for Th1 and Th2 balance?

Deguchi : We have selected the adjuvant after a lot of consideration from that point of view, and we believe that the results reflect that.

Tanaka : Thank you very much.

Kyokawa: Thank you very much.

Let me now move on to the next question from the media. Please raise your hand if you have any questions.

Reporter A: There are three points I would like to ask Dr. Shinkai.

The clinical trial started in November, and you were able to perform the interim report without waiting six months. Were there any techniques that you used to make progress so quickly?

Shinkai: One was the support of the entire hospital, including Dr Kabachi.

Clinical trials involve a lot of processes, such as taking blood samples, processing specimens, mailing them, entering data, and so on. I think it was a bit difficult with the original number of members. The speed of the project was made possible by the support we received from the entire hospital while doing actual clinical work with the COVID-19 patients.

After all, there were many subjects who thought about vaccines in the future. I think these two points.

Reporter A: Also, regarding the number of subjects this time, I think there were 200 subjects, but on the other hand, Daiichi Sankyo is conducting clinical trials with 5,000 subjects. How should we evaluate the scale of hundreds of cases as an evaluation of immunogenicity?

Deguchi: This question is about the protocol, so I will answer.

In that sense, we believe that this number is sufficient for comparison of immunogenicity and statistical verification for that purpose. So this result is unwavering.

As for the number of cases, it is still quite meaningful to accumulate safety data. We believe it is significant. In that sense, although we are talking about a slightly different trial, we have already accumulated safety data on 3,000 cases of vaccination with this vaccine, so our stance is that we should try to collect such comprehensive data and then consider the matter.

Reporter A: One more question, I would like to ask for your perspective on the trend of difficulty in lowering antibody titers. When I looked at the data after 15 days and 29 days, I saw that it didn't seem to drop that much, but could you tell me about the outlook for titer reduction, and the need for analysis? How does your company plan to collect data on this?

Deguchi: I think it is very important to know how this will be sustained in the long term, and we will continue to track this data. In the design of this trial, we are also following up for one year, during which time we will provide appropriate long-term follow-up as needed.

Incidentally, as for the data in the literature, we can also take it as a fact that the level of immunity and neutralizing antibody titers are low at four or six months after initial vaccination. We have observed this in our data. Therefore, we will keep a very close watch on the extent to which levels from the booster vaccine is maintained, and we will continue to collect data.

Reporter A: In your view, Dr. Shinkai, do you have any comments on the expectations of the data, or in terms of expectations based on the fact that it is a recombinant protein vaccine?

Shinkai: Exactly the same, we took it at Day 69 and then after that, so we believe that we should look closely at that data to make a decision. We have high expectations.

Kyokawa: Okay then, next person please.

Reporter B: Thank you very much for your time today.

I would like to ask Dr. Shinkai about boosters. I have heard that the third round of inoculation is now underway in Japan, and that the adverse reactions are quite severe. When considering the booster in the real world, I think it will be very important to consider what sort of adverse reactions will occur.

First of all, you explained that Grade 4 fever is between 39 and 40 degrees Celsius, but could you please tell us how you draw the line for Grades 1, 2 and 3?

Shinkai: Regarding fever, Grade 3 is 39 to 40 degrees Celsius, Grade 2 is 38.5 to 39, and Grade 1 is 38 to 38.4 degrees Celsius.

Reporter B: Thank you very much. I wanted to ask you what you think of the adverse reaction results that came out this time. I think that in all the results, the reactions are not more intense for Shionogi's investigational vaccine. Please tell us whether it can be said that the adverse reactions are generally milder or less burdensome for the patient when Shionogi's products are used compared to three inoculations with COMIRNATY.

Shinkai: Since we are not considering the data from that statistical perspective, I can only say that the adverse reactions were less than or equivalent to the control.

Reporter B: Thank you very much.

Today, you mentioned that the future is another matter, but looking at the results of this project, I think that the world's concern is when this will become available. With these results, what are your thoughts on the timing of the application for approval? Are you considering of applying first with the indication of booster vaccination?

Iwasaki Based on the results of this trial, and from future studies, we will have more data on the two priming inoculations. As Mr. Deguchi mentioned earlier, we would like to discuss the safety package and how much is needed with the authorities as such data becomes available in the future.

Naturally, we are very confident in the results of this trial, and we would like to consider it in the future with a view to acquiring the efficacy of booster vaccine in the future.

Reporter B: Thank you very much.

Reporter C: Thank you for your presentation.

Now that Mr. Iwasaki has mentioned that booster vaccine is being considered as the first indication, I would like to ask one question. What is the time frame for this, what kind of system are you looking at, what kind of demographic are you targeting, and are you thinking of this as a fourth inoculation while the third inoculation is still in progress, or as a third inoculation? Thank you.

Iwasaki: We have not yet discussed this at all with the MHLW or PMDA. This is the first time we have received these results, and we would like to discuss these issues based on the data. I hope you will understand if I refrain from giving specifics for the future at this time.

Naturally, we would like to continue to disclose such data and communicate our views as soon as we are able.

Reporter C: I understand that the initial immunization trial is now underway, but specifically how many subjects have been gathered and what is the status? Obviously, not all of the data is available right now, but could you let us know what data you can see?

Deguchi: The second yellow line from the left shows the results of Phase 2/3. We have finished registering about 3,000 patients here. The next trial to compare neutralizing antibody titers with VAXZEVRIA as the first immunization is also progressing well. Once we have the results, we will disclose them as well, and we will consider our future policy based on that data. We are steadily registering cases.

Prevention of the onset of disease in the rightmost area, this is a global trial. We have been promoting and enrolling subjects mainly in Vietnam, and the enrollment of subjects is progressing smoothly in line with our expectations.

Iwasaki: I would like to add that we have already completed the second dose of inoculation in approximately 1,000 cases, and we are now looking at the intermediate analysis of neutralizing antibodies around Day 36 and 50. We are now looking at efficacy as a priming inoculation. We are considering evaluating this on the basis of immunogenicity.

Reporter C: Is there any particular reason why you chose VAXZEBRIA?

Deguchi: We discussed this with the MHLW, and at this point, we agreed that VAXZEVRIA should be used as a control drug. That is how we arrived at this point.

I think that should answer the question.

Kyokawa: Okay, one more person, please.

Reporter D: Thank you for your time today.

I am afraid this is a very rudimentary question, but I think it is a little difficult for the general public to understand why the non-inferiority test was conducted in the first place. Why can you only say it was non-inferiority even if the results were better? Can you explain a bit more about non-inferiority? It would be helpful if you could explain in some easy-to-understand way whether you can say that they were equal or possibly more than equal or something like that. That's my first question.

Deguchi: This is a difficult question to answer.

In a general sense, the word means there is no difference, and if we convert it into everyday speech, I think the most appropriate phrase would be "no difference".

We use the term non-inferiority in this way in thinking about this trial.

Reporter D: What is Shionogi's evaluation of the result that there was no difference, or what might be your understanding of the result?

Deguchi: We are aware that COMIRNATY has been proven to be highly effective in initial immunization as well as in booster vaccinations. That is the kind of data we have.

Therefore, in terms of immunogenicity, we are very encouraged by the fact that the results show that our vaccine is non-inferior to the COMIRNATY under the environment of booster vaccination.

Reporter D: Second question. In terms of adverse reactions, as mentioned in the previous question, I got the impression that the overall adverse reactions were less than or equal to the same level, or mild. Could you tell us if you would like to add some of these points to the evaluation axis in the future, or if it will be useful?

Iwasaki: As Dr. Shinkai mentioned at the beginning, there are people who are very reluctant to receive the vaccine because of adverse reactions. We would like to add the impression of the safety of our vaccine in the

long term by looking at, for example, the degree to which patients return to their normal activities, as well as analyzing regular data in the future.

We believe that only then can we say that the vaccine is truly safe.

Reporter D: If that's the case, the results this time do not show that it is statistically superior or anything like that, but that's something to be worked on in the future.

Iwasaki : Yes.

Reporter D: Thank you very much.

Lastly, I think you talked about 100 million times of supply capacity, but please let us know if there are any updates.

Teshirogi : Regarding that, as a rough outline, we are making preparations to start commercial supply in May or later. Of course, we will be working not only on this data but also on a comprehensive program of clinical trials. As Mr. Iwasaki said, we believe that this data is of very strong value. So how should we think about this?

Mr. Deguchi did not mention this earlier, but again, COMIRNATY is an established vaccine that has been approved for booster vaccination. In this respect, the fact that this result was achieved in comparison with a product that is not in clinical trials but has already been approved is very encouraging. The Company is committed to supplying the product for commercial production as scheduled. We will continue to work with this in mind.

Reporter D: Thank you very much.

Kyokawa : Next, we would like to move on to the analysts who are participating from the Web. Mr. Kotani from Nomura Securities, please go ahead.

Kohtani : First of all, I would like to ask about the definition of fever. I believe it is still defined as 38 degrees or higher in the US and Europe, but looking at the US label for Pfizer's COMIRNATY, the frequency of fever is listed as 16% after the second vaccination. In your trial, it is 59% for COMIRNATY. Is it very likely to get a fever the third time, or is the definition different? There seems to be a big difference in the numbers.

The incidence was very low frequency in an NEJM article on the Novavax vaccine, so I wonder why the difference in fever is showing up like this.

Also, I don't know if you can answer this, but I'm thinking about what causes fever after COMIRNATY vaccination. The substances that are likely to cause fever are probably the lipids ALC-0315 and ALC-0159. If that is the case, then I am wondering if it is inevitable due to the structure of the mRNA vaccines that they will tend to cause fever. I wonder that would make it difficult to make them as safe as recombinant protein vaccines, and how do you think?

Shinkai : Thank you for your question.

As a physician, I have administered the second and third rounds of the COMIRNATY to many people, and it is difficult to give concrete details about the fever. However, my impression is that the fever is a little more frequent following the third vaccine.

However, as you can see here, the fever was Grade 2 in 1.9% of cases, and 6.8% in the case of COMIRNATY. That is the frequency of fever of 38.5 to 39 degrees Celsius. Of course, this is only the result of this trial, so we

can't extrapolate outside that. We can only say that this was one of the results of the analysis of unbiased data following the third vaccination of just over 100 participants.

Grade 1 includes the fact that some subjects entered their symptoms electronically, and Grade 1 also includes the fact that they themselves felt fever. So I think, in that sense, the two and seven Grade 2 cases would be more objectively correct. However, there is a fact that this trial resulted in such a result.

Kohtani : What do you think is the cause of the fever?

Shinkai : I believe that the fever is caused by cytokines abnormalities, such as IL-6, due to the presence of a foreign substance in the body.

Kohtani : Understood.

The second point is as follows. I probably have to ask someone from Shionogi about this, but I believe that the choice of adjuvant was also behind the success of this vaccine. Some adjuvants can inevitably cause fever. The code A-910823 is written on page 10, which I'm assuming is an internal Company code. So of course, we don't know what it is.

Novavax vaccine has quite a lot of adjuvants because it uses a 5 microgram antigen and a 50 microgram matrix M, but your company has quite a few. Is it correct to understand that your vaccine contains less adjuvant?

Deguchi : It is difficult to answer about the quantity. We use a different type of adjuvant than Novavax uses. Therefore, it is difficult to say how large or small the quantity is.

Kohtani : I will go to the third question.

Regarding production, this is the first time your company has showed the amount of antigen is 10 microgram. In the past, UMN Pharma's influenza vaccine was 4-valent vaccine with a 1-valent 45 microgram, so it was about 180 microgram in total of antigens. In comparison, 10 microgram is very small. So, if I check this now, I find UNIGEN and your company are building a factory in Gifu Prefecture. I believe the construction started in May and the plant has two tanks of 21,000 liters, when will this be operational?

I believe you mentioned that these two tanks will be able to supply enough for 30 million people. Can you tell us about the current status of the plant and how it meshes with production? This is the last question.

Teshirogi : I will answer your question.

At present, our first production line is operational, and if it runs at full capacity, it will logically be able to produce up to 60 million doses. We originally said to be for 30 million people because we thought it was two doses, but the construction of the second line has been completed and we are now doing IQ, PQ, and OQ. It will be in full operation by the end of the year. Then, we should be able to make up to 120 million doses.

However, we are not sure if we will be able to logically achieve all of the production in this way from the beginning. I know this may sound a bit repetitive, but the first line is already in operation, and we are accumulating a variety of data in preparation for commercial production that will start in May.

Kohtani : As a supplement, the yield between the previous BEVS influenza vaccine and the current COVID-19 vaccine has not changed, have they? I would be interested to know if there is a decline, increase, or anything else.

Teshirogi : It's hard to make any kind of comparison because things are different, but I think the correct way to put it is that they are not that far off.

Of course, this one is a little trickier in terms of refinement, since there are a lot of complications such as a trimer. both Novavax and Sanofi will probably have a very hard time with the purification process. I think this is probably has a slightly higher yield because the influenza one is probably more established.

Kohtani : Understood. Thank you.

Kyokawa : We will take one more question from the web. Mr. Ueda of Goldman Sachs Securities, please go ahead.

Ueda : My name is Ueda from Goldman Sachs Securities. Thank you very much for your explanation today.

I would first like to ask you to tell me about the data on page 21. In our earlier discussion, you mentioned that there might be a possibility that neutralizing antibody titers might be maintained over a longer period of time. If so, if you have any thoughts at this time as to what mechanisms might be involved in that case, could you please share them with us?

Deguchi : I assume you are asking what would happen if it were to persist for a long period of time.

It is not easy to speculate on this at this point in time. It would be great to have that sort of data. That's why it's been so useful to work with Dr. Shinkai this time, to get various data in this trial. We are also spreading the net in other trials in an exploratory manner. We believe that it would be a legitimate scientific approach to find something that leads to that mechanism.

If the decline curve is different from ours, it could be because the way COMIRNATY antigen is presented is different from ours. One hypothetical point is whether this could affect the time period over which it is presented, or the intensity of the effect.

The second point is regarding our adjuvant, and whether it triggers a long-term memory immunity, like long-term B-cell-mediated memory immunity, or not. So, this is the second hypothetical point to consider.

We would like to follow up on how such hypotheses are working with actual data on possible candidates. This is a point that I would very much like to work on as a researcher.

Ueda : Thank you very much.

One last point, I would like to know your thoughts on what is clinically important in selecting a booster vaccine. Just in terms of neutralizing antibody titers, I think it was mentioned that with the SPIKEVAX, cross vaccination would increase neutralizing antibody titers more than a third dose of COMIRNATY. I think Shionogi's vaccine has a very good safety profile. And I would say that we should not place too much emphasis on the absolute value of neutralizing antibody titers, so this vaccine is very promising. Am I correct in my understanding? Thank you.

Shinkai : When I give a vaccine as a physician, the most desirable thing is still that there should be no TRAEs, so I think that the absence of Grade 4 or 5 adverse reactions is important.

Grade 3 events also interfere with peoples' everyday lives, so fewer Grade 3 reactions would be ideal.

In terms of Grade 1, when we consider safety and efficacy, we must consider that some TRAEs are inevitable, and I do not give much weight to Grade 1 TRAEs in actual clinical practice. I still think it is clinically important that there are few events of Grade 3 or above.

Next, I have been treating many patients with the COVID-19 since February 2020, and those who have not been vaccinated are more likely to become seriously ill. Considering that there are many cases, I think it is very important to control the severity of the disease.

It is difficult to control infection, so I personally think that a vaccine that has few adverse reactions and can control severe infections is important. That's all.

Ueda : Thank you. That's all from me. Thank you very much.

Kyokawa : Thank you very much.

I would like to ask just one media person from the web.

Reporter E: Thank you.

Dr. Shinkai mentioned earlier that it would be helpful to have a variety of vaccines, but I would like to hear some more specifics about that.

Shinkai : This is just my personal opinion, but subjects have various adverse reactions. Patients may get reactions such as pain in the soles of the feet, numbness in the hands, Guillain-Barre reactions, and so on. And as I just mentioned, it is important to avoid Grade 3, 4, or 5 reactions. We hope to see more and more combinations and timing of vaccines, such as various recombinant protein vaccines, inactivated vaccines, viral vector vaccines, mRNA vaccines, and so on, that can be administered at various times, with fewer adverse reactions, and with effectiveness in reducing the severity of the disease. This is very helpful for us.

Reporter E : Thank you very much.

Kyokawa : Thank you very much.

Apologies for going a little over time. We will wrap up the briefing there. Thank you very much.

Teshirogi : Thank you very much.

[END]