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Safety and immunogenicity of NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: Interim report of a phase I/II randomized controlled trial

Taisei Masuda [a,*], Kyoko Murakami [b], Kenkichi Sugiura [c], Sho Sakui [c], Ron P Schuring [d], Mitsuhiro Mori [a]

[a] Japan Development, Global Vaccine Business Unit, Takeda Pharmaceutical Company Ltd, Japan
[b] Japan Medical and Policy Affairs, Medical Affairs Office, Global Vaccine Business Unit, Takeda Pharmaceutical Company Ltd, Japan
[c] Statistical and Quantitative Sciences, Data Sciences Institute, Takeda Pharmaceutical Company Ltd, Japan
[d] Clinical Development, Global Vaccine Business Unit, Takeda Pharmaceuticals International AG, Switzerland

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ABSTRACT

Background: We evaluated the safety and immunogenicity of NVX-CoV2373, a recombinant SARS-CoV-2 nanoparticle vaccine, in healthy Japanese participants.

Methods: This phase 1/2, randomized, observer-blind, placebo-controlled trial conducted in Japan (two sites), enrolled healthy Japanese adults aged ≥ 20 years with no history/risk of SARS-CoV-2 infection and no prior exposure to other approved/investigational SARS-CoV-2 vaccines or treatments. Participants were stratified by age (< 65 or ≥ 65 years) and randomized to receive two doses of either NVX-CoV2373 (5 μg SARS-CoV-2 rS; 50 μg Matrix-M1) or placebo, 21 days apart. Primary outcomes were safety and immunogenicity assessed by serum IgG antibody levels against SARS-CoV-2 rS protein on day 36. Herein, we report the primary data analysis at 4 weeks after the second dose, ahead of 12-month follow-up completion (data cut-off: 8 May 2021).

Results: Between 12 February 2021 and 17 March 2021, 326 subjects were screened, and 200 participants enrolled and randomized: NVX-CoV2373, n = 150; placebo, n = 50. Solicited adverse events (AEs) through 7 days after each injection occurred in 121/150 (80.7%) and 11/50 (22.0%) participants in the NVX-CoV2373 and placebo arms, respectively. In the NVX-CoV2373 arm, tenderness and injection site pain were the most frequently reported solicited AEs after each vaccination, irrespective of age. Robust immune responses occurred with NVX-CoV2373 (n = 150) by day 36: IgG geometric mean fold rise (95% confidence interval) 259 (219, 306); seroconversion rate 100% (97.6, 100). No such response occurred with placebo (n = 49).

Conclusion: Two doses of NVX-CoV2373 given with a 21-day interval demonstrated acceptable safety and induced robust anti-SARS-CoV-2 immune responses in healthy Japanese adults. Funding: Takeda Pharmaceutical Company Limited and Japan Agency for Medical Research and Development (AMED). ClinicalTrials.gov identifier: NCT04712110.

1. Introduction

Vaccination remains the most appropriate strategy to bring the novel coronavirus disease 2019 (COVID-19) pandemic under control, with currently available vaccines primarily targeting spike glycoprotein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prototype strain [1].

NVX-CoV2373 is in development as a recombinant SARS-CoV-2 nanoparticle vaccine, consisting of 5 μg of a recombinant nanoparticle spike protein (SARS-CoV-2 rS) plus 50 μg of Matrix-M1 adjuvant (NVX-CoV2373, Novavax) [2]. Clinical data have shown that a two-dose regimen administered 21 days apart is well tolerated and associated with robust immune responses in healthy adults [2–5].

Abbreviations: AE, adverse event; AMED, Japan Agency for Medical Research and Development; CI, confidence interval; COVID-19, coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; FAS, full analysis set; GMFR, geometric mean fold rise; GMT, geometric mean titer; ICH, International Conference on Harmonisation; LLOQ, lower limit of quantitation; MAAE, medically attended adverse event; MN, microneutralization; nAb, neutralizing antibody; PMDA, Pharmaceuticals and Medical Devices Agency; PPS, per protocol set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAE, serious adverse event; SAS, safety analysis set; SCR, seroconversion rate; ULOQ, upper limit of quantification.

* Corresponding author at: Takeda Pharmaceutical Company Limited, 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka 540-8645, Japan.

E-mail addresses: taisei.masuda@takeda.com (T. Masuda), kyoko.murakami@takeda.com (K. Murakami), kenkichi.sugiura@takeda.com (K. Sugiura), sho.sakui@takeda.com (S. Sakui), ron.schuring@takeda.com (R.P Schuring), mitsuhiro.mori@takeda.com (M. Mori).

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In a UK-based phase 3 trial of 14,039 volunteers, two intramuscular 5-μg doses of NVX-CoV2373 administered 21 days apart were associated with overall efficacy against mild, moderate and severe disease of 89.7% (95% confidence interval [CI]: 80.2 to 94.6) for all circulating strains and 96.4% (95% CI: 73.8 to 99.4) for non-B1.1.7 COVID-19 strains [3]. Similar efficacy has been reported in a preprint publication of a US and Mexico-based randomized phase 3 trial of 29,949 volunteers, with an overall vaccine efficacy of 90.4% (95% CI: 82.9 to 94.6, P < 0.001) and efficacy against moderate-to-severe disease of 100% (95% CI: 87.0 to 100) vs placebo [5]. To date, no studies have specifically investigated the safety and immunogenicity of NVX-CoV2373 in an Asian population.

This phase 1/2 study of NVX-CoV2373 (development code: TAK-019) in healthy Japanese adults (aged ≥ 20 years) is undertaken to evaluate the safety and immunogenicity of two doses of NVX-CoV2373 given 21 days apart, as a requirement for vaccine registration in Japan.

Here, we present first assessment of safety and immunogenicity of NVX-CoV2373 in healthy Japanese adults, with the primary data analysis at 4 weeks after the second dose, ahead of 12-month follow-up completion.

2. Methods

2.1. Study design and participants

This phase 1/2 randomized, observer-blind, placebo-controlled trial, conducted at two centers in Japan evaluates the safety and immunogenicity of NVX-CoV2373 (TAK-019) administered as two doses 21 days apart, in Japanese adults. The trial design was developed in accordance with the guidance from the Pharmaceuticals and Medical Devices Agency (PMDA) [6]. The study was conducted in accordance with all applicable regulations, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP and the Declaration of Helsinki ethical principles. The study protocol was approved by an institutional review board, which covered both centers, and all patients provided written informed consent in advance of participation. This study is registered on ClinicalTrials.gov (NCT04712110).

Participants were healthy Japanese adults aged ≥ 20 years, based on medical history, physical examination and the investigator's judgement. Exclusion criteria included the receipt of any other SARS-CoV-2 vaccine or experimental novel coronavirus vaccine, a positive SARS-CoV-2 test result during pre-trial assessment or close contact with a confirmed COVID-19 case within 30 days prior to NVX-CoV2373 vaccination.

2.2. Randomization and blinding

Randomization tables were used by unblinded designees or sponsor personnel to assign the randomization to NVX-CoV2373 or placebo. To prepare and administer the vaccines, designated site personnel were unblinded to the assigned groups, and had no further involvement in data collection or post-injection evaluation. The investigators (data collectors), participants, and data evaluators were blinded to trial-group assignment.

The trial planned to enroll 200 participants: n = 150, NVX-CoV2373 arm; n = 50, placebo arm. Participants were stratified by age: ≥ 20 years to < 65 years (NVX-CoV2373, n = 100; placebo, n = 40); ≥ 65 years (NVX-CoV2373, n = 50; placebo, n = 10). The primary analysis of safety and immunogenicity was performed after all participants had completed the day 50 visit (28 days post-second dose). After database lock (day 50 data), the trial was unblinded and became an open-label study. Participants were informed of their group assignment (NVX-CoV2373 or placebo) and were required to provide additional consent to continue the study. Participants were removed from the trial if they had received an approved SARS-CoV-2 vaccine during the trial, both before and after database lock, including open-label phase.

2.3. Trial procedures

Participants were randomized (3:1) to receive deltoid intramuscular injection (injection volume, 0.5 mL; needle diameter, 25G; needle length, 1 in. [2.54 cm]) of either two doses of NVX-CoV2373 vaccine (5 μg of SARS-CoV-2 rS and 50 μg of Matrix-M1) or two doses of saline placebo on day 1 and day 22 (21 days after the first injection; Fig. 1). In-person visits with all participants were taken for safety and immunogenicity follow-ups on day 1 (first dose), day 8 (7 + 3 days post-first dose), day 22 (21 + 3 days post-first dose), day 36 (14 + 3 days post-second dose), day 50 (28 + 3 days post-second dose), day 202 (180 ± 7 days post-second dose) and day 387 (365 ± 14 days post-second dose). Herein we report the data obtained up to day 50.

2.4. Safety assessments

Participants self-reported oral body temperature and solicited local and systemic adverse events (AEs) in an eDiary for 7 days after each injection (including the day of injection). Solicited local AEs included injection site pain, tenderness, erythema/redness, induration and swelling; solicited systemic AEs were fever, fatigue, malaise, myalgia, arthralgia, nausea/vomiting and headache. Unsolicited AEs were collected for 49 days following the first injection and for 28 days following the second injection. All participants were followed for serious AEs (SAEs), medically attended AEs (MAAEs), and AEs leading to trial withdrawal or discontinuation from day 1, continuing to day 387. Solicited AEs were assessed in accordance with The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [7], with minor modifications. The relationship (causality) of AEs to the NVX-CoV2373 vaccine was assessed by the investigator. AEs were considered related to treatment where there was a suspicion or a reasonable possibility that the vaccine contributed to the AE. Blood hematology and chemistry tested were performed on samples taken on days 1, 8, 22, 36 and 50. Participants were tested for SARS-CoV-2 infection by polymerase chain reaction test at days 1, 22, and 50 and at any occasions when clinical symptoms were suspected.

2.5. Immunogenicity assessments

Immunogenicity was assessed in blood samples collected on days 1 (before injection), 22 (before injection), 36, 50, 202 and 387, using previously described methodology that is briefly summarized [4,8]: the total anti-SARS-CoV-2 rS protein IgG antibody levels (serum IgG Ab) were measured by an enzyme-linked immunosorbent assay (ELISA) specific for SARS-CoV-2 rS protein (performed at Novavax Clinical Immune Laboratory [Gaithersburg, Maryland, USA]). The total anti-SARS-CoV-2 rS protein IgG antibody level in a serum sample was quantitated in ELISA unit, EU/mL, by comparison to a reference standard curve (2-fold dilution series of 12 dilutions starting 1:1000). The results were analyzed in singleton by SoftMax Pro software (Molecular Devices, San Jose, USA) using 4-PL curve fit.

Serum neutralizing antibody (nAb) titers against SARS-CoV-2 were measured using a live virus microneutralization (MN) assay developed and validated for Novavax by 360Biolabs (Melbourne, Australia). The residual non-neutralized virus was detected via cytopathic effect by microscopic scoring by an experienced subject

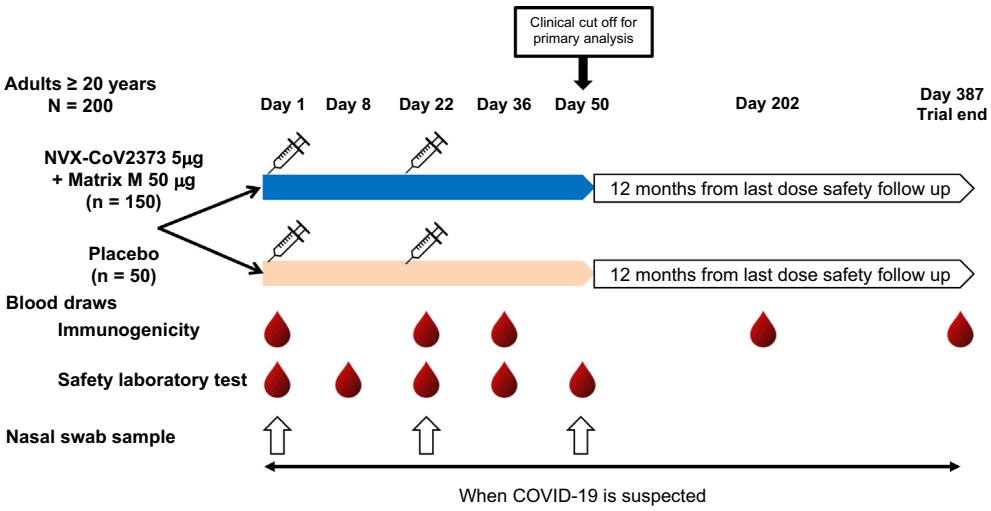

Fig. 1. Schematic of trial design. COVID-19 = coronavirus disease 2019; N/n = number of participants.

matter expert. Two replicate wells per dilution were scored as either positive (SARS-CoV-2 cytopathology is present) or negative (healthy Vero E6 monolayer). The neutralization titer was expressed as the reciprocal of the highest dilution at which ≥ 50% of the replicate wells were protected from infection (MN_{50}).

Both the IgG Ab and nAb assays were fully validated at initiation for this study.

2.6. Outcomes

The primary safety endpoints were (i) solicited AEs for 7 days after each injection; (ii) unsolicited AEs for 49 days after the first injection (i.e., 21 days following first injection [day of injection + 20 subsequent days] and 28 days following second injection [day of second injection + 27 subsequent days]); (iii) MAAEs, SAEs, AEs leading to injection discontinuation and (iv) AEs leading to withdrawal from the trial up to and including day 50; and (v) the proportion of participants with SARS-CoV-2 infection through day 50.

The primary immunogenicity endpoint was Serum IgG Ab levels against SARS-CoV-2 rS protein on day 36. Secondary immunogenicity endpoints monitored throughout the follow-up period (except day 36, which was the primary endpoint), were serum IgG Ab levels to SARS-CoV-2 rS protein and serum nAb titers to wild-type virus.

2.7. Statistical analysis

The sample size for the trial was considered sufficient with a 95% probability of observing at least one AE with a 2% event rate in the NVX-CoV2373 arm and the sample size was not determined by formal statistical power calculations. The data presented herein are from the primary analysis of safety and immunogenicity, after all participants completed the day 50 visit (data cut-off date: 8 May 2021). The full analysis set (FAS) and safety analysis set (SAS) included all randomized participants who received ≥ 1 injection and, the SAS having ≥ 1 safety assessment. The per protocol set (PPS) included the FAS participants who had received injections at both time points, no significant protocol deviations and evaluable immunogenicity data. Unsolicited AEs were assessed and coded according to Medical Dictionary for Regulatory Activities version 24.0.

The immunogenicity endpoints and their respective 95% CIs were reported for the PPS and included the geometric mean titer (GMT), geometric mean fold rises (GMFR), and seroconversion rate (SCR; defined as percentage of participants with a change from below the lower limit of quantification (LLOQ) to equal to or above LLOQ, or a ≥ 2 [if seropositive at baseline] or 4-fold [if seronegative at baseline] rise from baseline). The LLOQ was 200 EU/mL for serum IgG Ab and 20 for nAb. If antibody values fell below LLOQ, these were replaced by a value 0.5 × LLOQ. Values higher than the upper limit of quantification (ULOQ) were recorded as the ULOQ values (206,767 EU/mL for serum IgG Ab and 10,240 MN_{50} for nAb).

Sub-group analyses of solicited AEs and immunogenicity were stratified by age group (≥ 20 years to < 65 years, and ≥ 65 years), and made using SAS version 9.4 (SAS Institute Inc., Cary, USA).

3. Results

3.1. Participants

Between 12 February 2021 and 17 March 2021, 326 subjects were screened, and 200 participants enrolled and randomized (150 participants in the NVX-CoV2373 arm; 50 participants in the placebo arm; Fig. 2). In the NVX-CoV2373 arm, 150/150 (100.0%) participants received both doses of the vaccine. In the placebo arm, 49/50 (98.0%) participants received both doses; one participant did not receive a second dose of placebo due to an AE of tinnitus of mild severity occurring 5 days after the first dose.

The SAS and FAS both included all 200 participants; and 150/150 (100.0%) participants were included in the PPS of the NVX-CoV2373 arm and 49 of 50 (98.0%) of the participants receiving placebo. The participant who was excluded from the PPS was the participant detailed above who withdrew from treatment due to the AE of tinnitus.

Baseline characteristics of participants in the NVX-CoV2373 and placebo arms were generally balanced across and within these groups (Table 1). The mean age in the NVX-CoV2373 arm was 52.6 (range: 20–77) and 50.8 (range: 20–76) years in the placebo group; 85/150 (56.7%) and 29/50 (58.0%) of participants were male, and all participants were Japanese. Overall, 60 participants (30.0%) were aged ≥ 65 years (50/150 [33.3%] in the NVX-CoV2373 arm; 10/50 [20.0%] in the placebo arm).

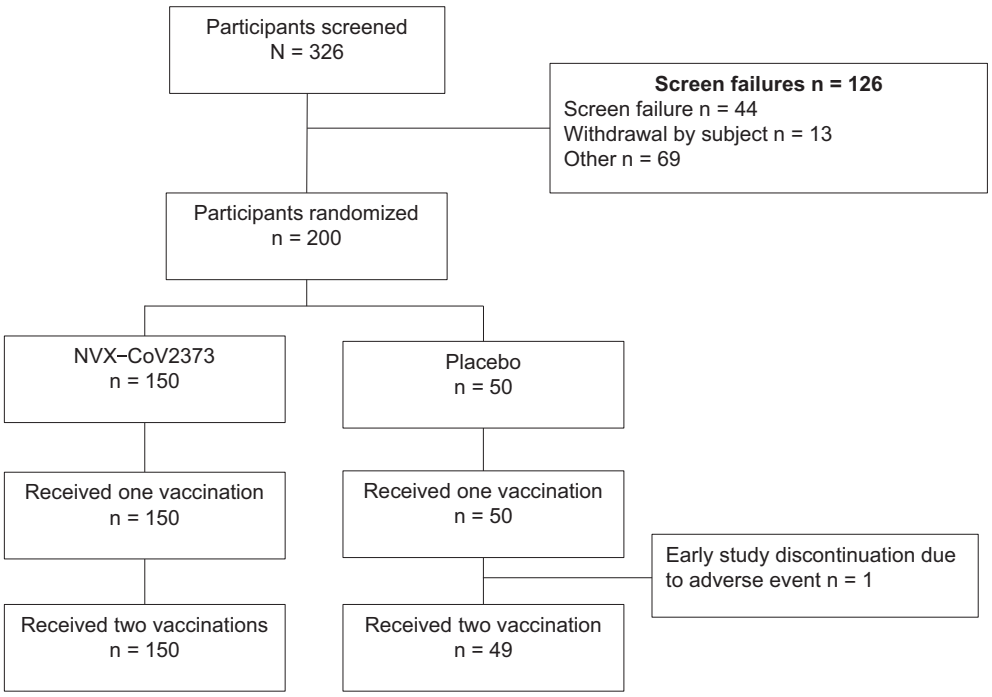

Fig. 2. Participant disposition.

Table 1
Patient demographics.

	NVX-CoV2373			Placebo		
	Total (N = 150)	≥ 20 to < 65 years (N = 100)	≥ 65 years (N = 50)	Total (N = 50)	≥ 20 to < 65 years (N = 40)	≥ 65 years (N = 10)
Age years, mean (range)	52.6 (20–77)	44.0 (20–64)	69.8 (65–77)	50.8 (20–76)	45.7 (20–64)	71.1 (66–76)
Sex, n (%)						
Male	85 (56.7)	54 (54.0)	31 (62.0)	29 (58.0)	23 (57.5)	6 (60.0)
Female	65 (43.3)	46 (46.0)	19 (38.0)	21 (42.0)	17 (42.5)	4 (40.0)
Race, n (%)						
Asian	150 (100.0)	100 (100.0)	50 (100.0)	50 (100.0)	40 (100.0)	10 (100.0)
Other	0	0	0	0	0	0
BMI kg/m^2, mean (SD)	23.3 (2.85)	23.0 (2.83)	23.9 (2.82)	22.8 (2.87)	22.7 (3.15)	23.1 (1.28)

BMI = body mass index, SD = standard deviation.
Percentages are based on the number of vaccinated participants.

3.2. Safety

3.2.1. Solicited AEs

For the 7 days following any injection, solicited local and systemic AEs occurred in a higher proportion of participants who received NVX-CoV2373 than placebo (overall incidences after any injection, 121/150 [80.7%] vs 11/50 [22.0%] participants, respectively; Table 2), and these increased after the second doses in both treatment groups.

In the NVX-CoV2373 arm, the most frequently reported solicited systemic AEs across all age groups and after the first and second vaccination were myalgia (26/150 [17.3%] and 49/150 [32.7%], respectively), malaise (15/150 [10.0%] and 44/150 [29.3%], respectively) and headache (16/150 [10.7%] and 32/150 [21.3%], respec-

Table 2
Solicited adverse events within 7 days after injection (safety analysis set).

	First injection		Second injection		Any injection	
n (%)	NVX-CoV2373 (N = 150)	Placebo (N = 50)	NVX-CoV2373 (N = 150)	Placebo (N = 49)	NVX-CoV2373 (N = 150)	Placebo (N = 50)
Any solicited adverse event	90 (60.0)	6 (12.0)	112 (74.7)	6 (12.2)	121 (80.7)	11 (22.0)
Maximum severity						
Grade 1	67 (44.7)	5 (10.0)	48 (32.0)	4 (8.2)	53 (35.3)	8 (16.0)
Grade 2	22 (14.7)	1 (2.0)	44 (29.3)	2 (4.1)	48 (32.0)	3 (6.0)
Grade 3	1 (0.7)	0	19 (12.7)	0	19 (12.7)	0
Grade 4	0	0	1 (0.7)	0	1 (0.7)	0

Subjects with more than one event are counted only once for the maximum severity.

tively). In all age groups, the most frequently reported solicited local AEs after the first and second vaccination were tenderness (65/150 [43.3%] and 94/150 [62.7%], respectively) and injection site pain (44/150 [29.3%] and 75/150 [50.0%], respectively; Fig. 3).

Solicited local and systemic AEs through day 7, following first and second injections were mostly grade ≤ 2 severity (mild or moderate) in both arms (Fig. 3; Table 2). The incidence of grade ≥ 3 solicited AEs increased after the second injection, particularly for systemic AEs (Fig. 3). In the NVX-CoV2373 arm, the incidence of grade 3 or 4 solicited AEs after the second vaccination was 13.3% (20/150 participants) vs 0.7% (1/150 participants) after the first vaccination. Grade 4 fatigue, malaise, and headache were reported in one (0.07%) participant after the second injection in the NVX-CoV2373 arm. After the first and second vaccination, solicited systemic AEs were resolved after a median duration of 2.0 days (range, 1–13) and 1.0 day (range, 1–13), respectively; solicited local AEs were resolved within a median of 2.0 days (range, 1–7) and 3.0 days (range, 1–10), respectively, following first and second injections in the NVX-CoV2373 arm.

In the subgroup analyses of age, the incidence of both solicited systemic and local AEs in the NVX-CoV2373 arm was higher among participants aged < 65 years versus participants ages > 65 years (Fig. 3 and Supplementary Information).

3.2.2. Unsolicited AEs

A higher proportion of participants receiving NVX-CoV2373 reported unsolicited AEs than in the placebo arm (54/150 [36.0%] compared with 9/50 [18.0%], respectively; Table 3). Of the unsolicited AEs, these were assessed as treatment-related in 39/150 (26.0%) and 3/50 (6.0%) participants, respectively (Table 3). The most frequent unsolicited AEs occurring in the 50 days after the first vaccination in the NVX-CoV2373 arm were injection site pruritus (26/150 [17.3%] participants), followed by diarrhea and chills (each, 5/150 [3.3%] participants); in the placebo arm, no unsolicited AEs were experienced by > 1 participant. No unsolicited AEs grade ≥ 3 were reported in either treatment group. MAAEs were reported in 4/150 (2.7%) participants receiving NVX-CoV2373 (the only event reported by ≥ 2 participants was dental caries) and in 2/50 (4.0%) of the placebo arm. All MAAEs occurred in the ≥ 20 to < 65 years age group in the NVX-CoV2373 arm.

There were no deaths or AEs leading to withdrawal from the study reported. No unsolicited SAEs or SARS-CoV-2 infections were reported for participants through day 50 after the first injection in either treatment arm. By the clinical cut-off date for primary analysis (8 May 2021), one SAE of SARS-CoV-2 infection requiring hospitalization was reported in the placebo arm (this event was subsequently resolved) and no SAE was reported in the NVX-CoV2373 arm. There were no clinically meaningful changes in vital signs or clinical laboratory safety tests for any participants, irrespective of treatment group.

3.2.3. Immunogenicity

Following two doses of NVX-CoV2373 vaccine, given 21 days apart, induction of serum IgG Ab levels to SARS-CoV-2 rS protein

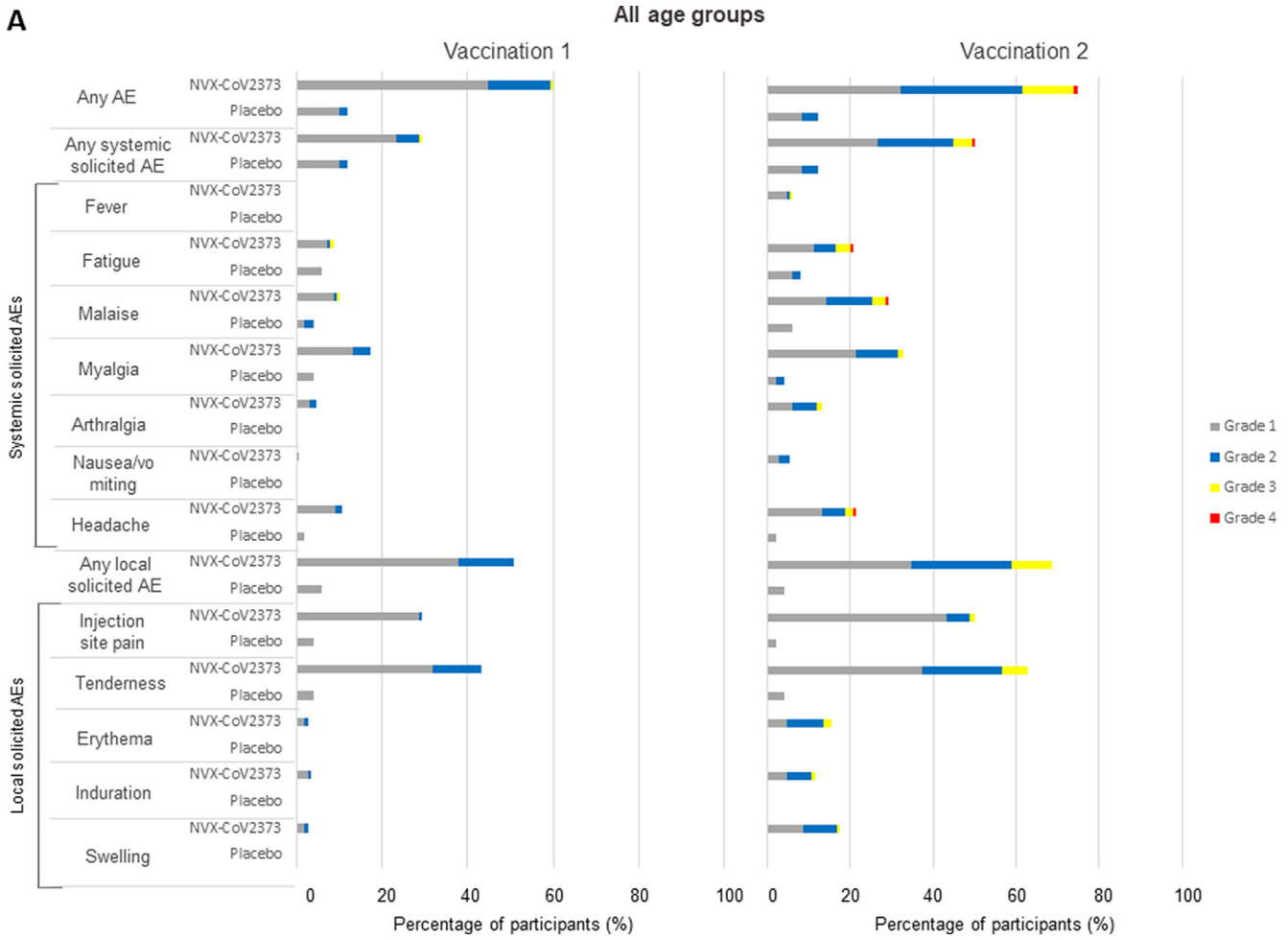

Fig. 3. Local and systemic solicited adverse events within 7 days after injections in A) all age groups and B) by age group. AE = adverse event.

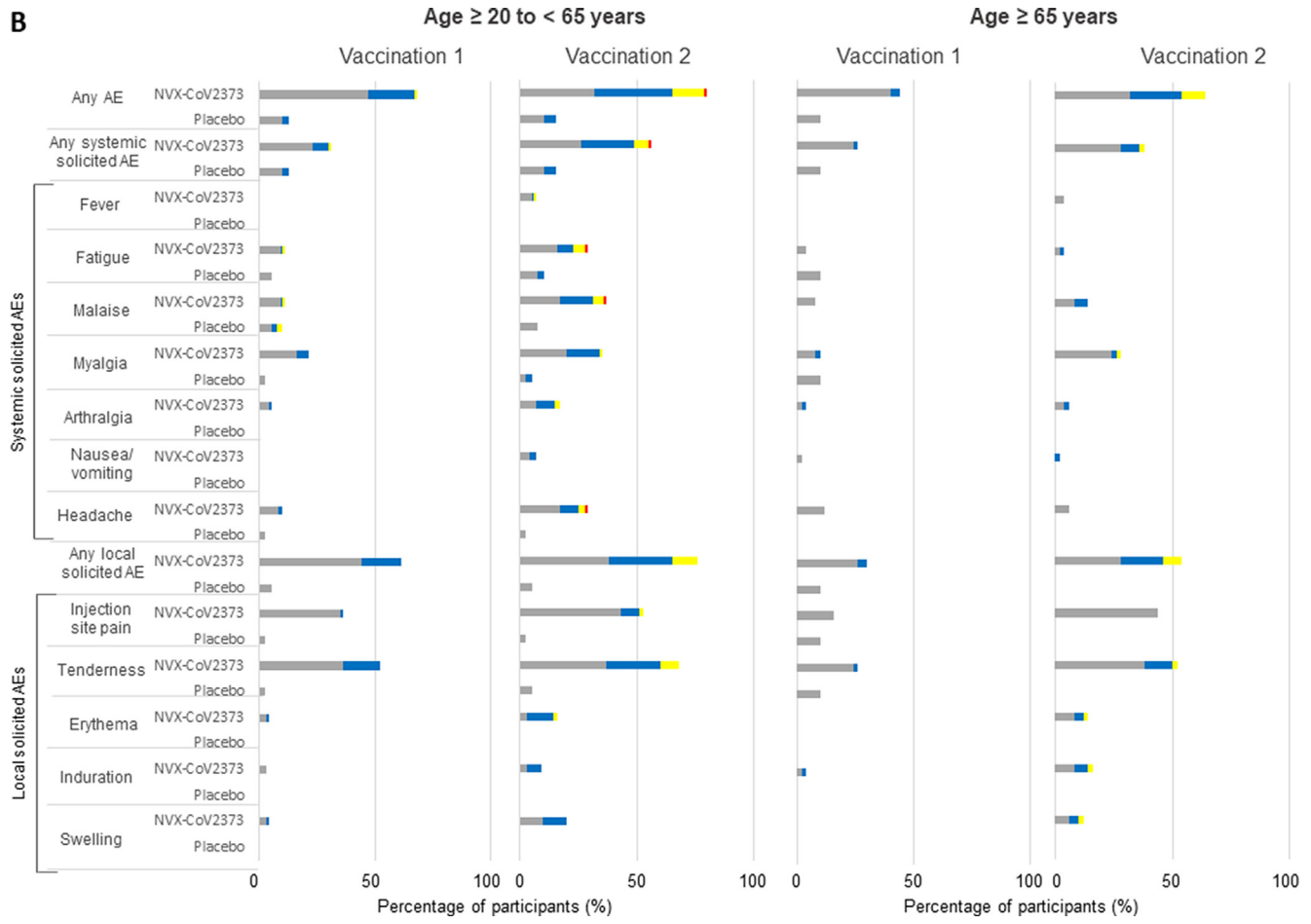

Fig. 3 (*continued*)

Table 3
Summary of unsolicited adverse events by treatment arm and injection (safety analysis set).

n (%)	First injection		Second injection		Any injection	
	NVX-CoV2373 N = 150	Placebo N = 50	NVX-CoV2373 N = 150	Placebo N = 49	NVX-CoV2373 N = 150	Placebo N = 50
Any unsolicited adverse event	15 (10.0)	4 (8.0)	44 (29.3)	6 (12.2)	54 (36.0)	9 (18.0)
Maximum severity						
Grade 1	12 (8.0)	4 (8.0)	40 (26.7)	6 (12.2)	47 (31.3)	9 (18.0)
Grade 2	3 (2.0)	0 (0.0)	4 (2.7)	0	7 (4.7)	0
Grade ≥ 3	0	0	0	0	0	0
Relationship to intervention						
Not related	8 (5.3)	2 (4.0)	10 (6.7)	5 (10.2)	15 (10.0)	6 (12.0)
Related	7 (4.7)	2 (4.0)	34 (22.7)	1 (2.0)	39 (26.0)	3 (6.0)

Subjects with more than one event are counted only once for the maximum severity. Only events that started on and after first injection are included. AEs after injection 1 is 21 days following first injection and AEs after injection 2 is 28 days following second injection. AEs after any injection is until day 50 from first injection.

was recorded for all participants in the NVX-CoV2373 arm from baseline by day 36 (Table 4). Induction of serum IgG Ab levels was not observed in the placebo group (Table 4).

The GMT of serum IgG Ab level in the NVX-CoV2373 arm was 120 EU/mL (95% CI: 111, 130) at baseline and 31,037 EU/mL (95% CI: 26837, 35894) on day 36 (14 days post-second dose); GMFR and SCR on day 36 were 259 (95% CI: 219, 306) and 100% (95% CI: 97.6, 100), respectively. In the NVX-CoV2373 arm, serum IgG Ab levels to SARS-CoV-2 rS protein increased by day 22 (21 days after first vaccination; GMT 1390 EU/mL [95% CI: 1141, 1694]) and then further increased by day 36 (31,037 EU/mL [95% CI: 26837, 35894]); thereafter, Ab levels remained elevated through day 50 (Table 4). The increase in serum IgG Ab levels was considerably greater after the second vaccination than after the first vaccination. No increase of serum IgG Ab level was observed with placebo.

Neutralizing activity by nAb for wild-type virus was equal to or below LLOQ in all participants at baseline (one each in the NVX-CoV2373 and placebo arms had nAb values equal to LLOQ [i.e., 20] at baseline); after the second vaccination (day 36; 14 days post-second dose) participants had a GMT of 884 (95% CI: 749, 1044), GMFR (calculated by imputing baseline values as 0.5 × LLOQ) of 88 (95% CI: 75, 104) and SCR of 99% (95% CI: 96, 100) in the NVX-CoV2373 arm. Placebo treatment resulted in no increases of nAb. In the NVX-CoV2373 arm, nAb titer values increased by day 22 (21 days after the first vaccination; GMT 50

Table 4
Geometric mean humoral immunogenicity responses to NVX-CoV2373 by age group (per protocol data set).

	NVX-CoV2373			Placebo		
	Total (N = 150)	≥ 20 to < 65 years (N = 100)	≥ 65 years (N = 50)	Total (N = 49)	≥ 20 to < 65 years (N = 39)	≥ 65 years (N = 10)
SARS-CoV-2 IgG antibody titers,[a] *EU/mL*						
Baseline						
GMT (95% CI)	120 (111, 130)	111 (103, 119)	140 (116, 169)	128 (107, 154)	129 (104, 160)	127 (88, 183)
Day 22						
GMT (95% CI)	1390 (1141, 1694)	1798 (1443, 2239)	831 (575, 1201)	145 (115, 182)	147 (112, 193)	137 (84, 223)
GMFR (95% CI)	11.6 (9.4, 14.2)	16.2 (13.0, 20.1)	5.9 (4.0, 8.7)	1.1 (1.0, 1.2)	1.1 (1.0, 1.3)	1.1 (0.9, 1.3)
Seroconversion, n (%)	124 (82.7)	89 (89.0)	35 (70)	3 (6.1)	2 (5.1)	1 (10)
SCR (95% CI[b])	82.7 (75.6, 88.4)	89.0 (81.2, 94.4)	70 (55.4, 82.1)	6.1 (1.3, 16.9)	5.1 (0.6, 17.3)	10 (0.3, 44.5)
Day 36						
GMT (95% CI)	31,037 (26837, 35894)	36,083 (30816, 42251)	22,963 (17156, 30735)	132 (110, 160)	132 (106, 164)	132 (86, 205)
GMFR (95% CI)	259 (219, 306)	325 (275, 384)	164 (115, 234)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (0.9, 1.2)
Seroconversion, n (%)	150 (100)	100 (100)	50 (100)	0	0	0
SCR (95% CI[b])	100 (97.6, 100)	100 (96.4, 100)	100 (92.9, 100)	0 (0.0, 7.3)	0 (0.0, 9.0)	0 (0.0, 30.8)
Day 50						
GMT (95% CI)	23,911 (20737, 27570)	27,087 (23319, 31464)	18,679 (13835, 25218)	135 (109, 166)	137 (106, 176)	128 (88, 187)
GMFR (95% CI)	199 (169, 234)	244 (208, 286)	133 (94, 190)	1.0 (1.0, 1.1)	1.1 (1.0, 1.1)	1.0 (0.9, 1.1)
Seroconversion, n (%)	149 (100)[c]	99 (100)	50 (100)	1 (2.0)	1 (2.6)	0
SCR (95% CI[b])	100 (97.6, 100)	100 (96.3, 100.0)	100 (92.9, 100)	2.0 (0.1, 10.9)	2.6 (0.1, 13.5)	0 (0.0, 30.8)
Neutralizing antibody titers,[d] *MN_{50}*						
Baseline						
GMT (95% CI)	10.0 (10.0, 10.1)	10.1 (9.9, 10.2)	10.0 (10.0, 10.0)[e]	10.1 (9.9, 10.4)	10.2 (9.8, 10.6)	10.0 (10.0, 10.0)[e]
Day 22						
GMT (95% CI)	50 (41, 61)	68 (54, 86)	27 (20, 37)	10.4 (9.9, 10.9)	10.5 (9.9, 11.2)	10.0 (10.0, 10.0)
GMFR (95% CI)	5.0 (4.1, 6.1)	6.8 (5.3, 8.6)	2.7 (2.0, 3.6)	1.0 (2.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)
Seroconversion, n (%)	101 (67)	77 (77)	24 (48)	0	0	0
SCR (95% CI[b])	67 (59, 75)	77 (68, 85)	48 (34, 63)	0 (0.0, 7.3)	0 (0.0, 9.0)	0 (0.0, 30.8)
Day 36						
GMT (95% CI)	884 (749, 1044)	1062 (899, 1253)	614 (428, 881)	10.4 (9.9, 10.9)	10.4 (9.9, 10.9)	10.7 (9.2, 12.5)
GMFR (95% CI)	88 (75, 104)	105 (89, 125)	61 (43, 88)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.1 (0.9, 1.3)
Seroconversion, n (%)	149 (99)	100 (100)	49 (98)	0	0	0
SCR (95% CI[b])	99 (96, 100)	100 (96, 100)	98 (89, 100)	0 (0.0, 7.3)	0 (0.0, 9.0)	0 (0.0, 30.8)
Day 50						
GMT (95% CI)	510 (423, 615)	580 (471, 715)	394 (270, 575)	10.4 (9.9, 10.9)	10.5 (9.9, 11.2)	10.0 (10.0, 10.0)
GMFR (95% CI)	51 (42, 61)	58 (47, 71)	39 (27, 58)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)
Seroconversion, n (%)	146 (98.0)	98 (99.0)	48 (96.0)	0	0	0
SCR (95% CI[b])	98 (94, 100)	99 (95, 100)	96 (86, 100)	0 (0.0, 7.3)	0 (0.0, 9.0)	0 (0.0, 30.8)

CI = confidence interval, GMFR = geometric mean fold rise, GMT = geometric mean titer, LLOQ = lower limit of quantification, nAb = neutralizing antibody, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, SCR = seroconversion rate, ULOQ = upper limit of quantification.
Titer values measured as below LLOQ (20 MN_{50}) are imputed to a value that is half of the LLOQ. Titer values measured as above ULOQ (10,240 MN_{50}) are imputed at the ULOQ value. Subjects with fold-rise ≥ 2 and 4 from baseline are justified using the imputed values. The fold rise is calculated as the ratio of the post-injection titer level to the baseline titer level (where baseline is defined as the last measurement taken before the first dose of study intervention).
[a] SARS-CoV-2 IgG antibody titers as measured by enzyme-linked immunosorbent assay (LLOQ: 200 EU/mL, ULOQ: 206,767 EU/mL).
[b] Two-sided 95% Clopper-Pearson CI for proportions within each treatment group.
[c] n = 149.
[d] The neutralizing antibody titer was expressed as the reciprocal of the highest dilution at which ≥ 50% of the replicate wells were protected from infection (MN_{50}).
[e] Less than LLOQ.

[95% CI: 41, 61]) and then further increased by day 36 (884 [95% CI: 749, 1044]); thereafter, nAb titer values remained elevated through day 50 (510 [95% CI: 423, 615]).

Serum IgG Ab levels to SARS-CoV-2 rS protein and neutralizing antibody to wild type virus increased in all age groups with similar patterns of response, but the magnitude of the increase was slightly attenuated in participants aged 65 years old and above, compared with participants aged ≥ 20 years to < 65 years old (Table 4 and Supplementary Information). No significant differences in results were observed between the FAS and PPS (data not shown).

4. Discussion

This was the first assessment of the safety and immunogenicity of NVX-CoV2373 in a healthy Asian population aged ≥ 20 years, in a phase 1/2 study. Two NVX-CoV2373 vaccine doses (5 μg of SARS-CoV-2 rS and 50 μg of Matrix-M1) given 21 days apart were well tolerated by healthy Japanese participants and resulted in a robust anti-SARS-CoV-2 immune response. There were no clinically relevant differences in safety profile relative to published study data from non-Asian populations [2–4].

Solicited AEs were reported in the NVX-CoV2373 vaccine arm with higher frequency than placebo and increased after the second dose. Systemic and local AEs were predominantly of grade 1 or 2 severity and generally resolved within 3 days. Where AEs of grade ≥ 3 occurred, they occurred more frequently after the second vaccine dose than after the first dose.

In the present study, the frequency of solicited AEs after each dose of NVX-CoV2373 vaccine (dose 1, 60.0%; dose 2, 74.7%) and profile of AEs reported were in line with the UK-based phase 3 study (dose 1, 57.6%; dose 2, 79.6%) [3]. There was a trend in the present study towards a lower incidence of some solicited AEs, notably fatigue, malaise, tenderness and injection site pain, among

older adults (≥ 65 years vs < 65 years). A similar trend was seen in the UK phase 3 study [3].

Interestingly, the incidence of fever in the present study after the second vaccination (all grade, 9/150 [6.0%]; grade ≥ 3, 1/150 [0.7%]) appeared to be lower than that of mRNA vaccines, tested in Asian populations [9,10]. In a phase 1/2 study conducted in Japan, the SARS-CoV-2 BNT162b2 mRNA vaccine administered at the recommended dose of 30 μg was associated with fever after the second dose in ∼ 37% of adult participants (aged 20–64 years) and in ∼ 14% of older participants (aged 65–85 years), with grade 3 events occurring in 1% of the younger and 0% of the older participants [10]. No new safety concerns were identified in the present study.

In healthy Japanese participants aged ≥ 20 years, two doses of NVX-CoV2373 administered 21 days apart resulted in a robust immune response, peaking two weeks after the second vaccination (day 36). At day 36 the GMFRs of serum IgG Ab levels to SARS-CoV-2 rS protein and nAb titers to wild-type virus were > 258-fold (serum IgG Ab) and > 88-fold (nAb), respectively and SCRs were 100% and 99%, respectively. By day 50 (4 weeks after the second dose), GMFR was slightly decreased to 199.1 for serum IgG Ab and 50.7 for nAb in the NVX-CoV2373 arm; however, SCR remained at 100% for IgG and at 98% for nAb. Linear correlations between log-transformed IgG Ab levels and log-transformed nAb titers on day 36 (Pearson's r = 0.77 [95% CI: 0.70, 0.83]) and day 50 (Pearson's r = 0.73 [95% CI: 0.65, 0.80]) were observed in the NVX-CoV2373 arm.

While making direct comparisons between studies is difficult due to different methodologies, a similar response pattern and time course was reported in a phase 1 study of NVX-CoV2373 in healthy adults in Australia [2]. Hence, we would anticipate that NVX-CoV2373 would achieve similar vaccine efficacy in a Japanese population as has been demonstrated in global study populations.

Our study had several limitations. Given the precautionary approach of phase 1/2 studies, our study was restricted by its small sample size. The study only included healthy adults aged ≥ 20 years and did not assess the vaccine in a pediatric population or in individuals with comorbidities. Finally, we did not assess the efficacy of the vaccine as prophylaxis for COVID-19.

5. Conclusion

Two doses of NVX-CoV2373 vaccine (5 μg of SARS-CoV-2 rS and 50 μg of Matrix-M1) administered with a 21-day interval resulted in a robust anti-SARS-CoV-2 immune response and indicated an acceptable safety profile in healthy Japanese adults (≥ 20 years).

Authors' contribution

All authors attest they meet the International Committee for Medical Journal Editors (ICMJE) criteria for authorship. Taisei Masuda: study conception and design, acquisition of data, data analysis and interpretation, and drafting and revision of manuscript; Kyoko Murakami: study conception and design, data analysis and interpretation, and drafting and revision of manuscript; Kenkichi Sugiura: study conception and design, data analysis and interpretation, and drafting and revision of manuscript; Sho Sakui: data analysis and interpretation, and revision of manuscript; Ron P. Schuring: acquisition of data, data analysis and interpretation, and drafting of manuscript; Mitsuhiro Mori: study conception and design, data analysis and interpretation, and revision of manuscript. All authors have read and approved the final manuscript and agree for it to be published.

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Data sharing statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results of the completed study, will be made available after the publication of the final study results within three months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

Declaration of competing interest

TM, KM, KS, SS, and MM are employees of Takeda Pharmaceutical Company Ltd. RPS is an employee of Takeda Pharmaceuticals International AG. KM holds stocks in Takeda Pharmaceutical Company Ltd.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.035.

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