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Safety, Immunogenicity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered With Seasonal Influenza Vaccines Within a Randomised Controlled Trial

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Corresponding Author:	Paul T Heath St George's University of London London, UNITED KINGDOM
First Author:	Paul T Heath
Order of Authors:	Paul T Heath
	Seth Toback
	Eva Galiza
	Catherine Cosgrove
	James Galloway
	Anna L Goodman
	Pauline A. Swift
	Sankarasubramanian Rajaram
	Alison Graves-Jones
	Jonathan Edelman
	Fiona Burns
	Angela Minassian
	Iksung Cho
	Lakshmi Kumar
	Joyce Plested
	Joy Rivers
	Andreana Robertson
	Filip Dubovsky
	Greg Glenn
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Summary [word count 250/250-word limit] Background Safety and immunogenicity of COVID-19 vaccines when co-administered with influenza vaccines have not yet been reported. Methods A sub-study on influenza vaccine co-administration was conducted as part of the phase 3 randomised trial of NVX-CoV2373's safety and efficacy; ~400 participants meeting main study entry criteria, with no contraindications to influenza vaccination, were enroled. After randomisation to receive NVX-CoV2373 or placebo, sub-study participants received an open-label influenza vaccine at the same time as the first dose of NVX-CoV2373. Reactogenicity was evaluated for 7 days post-vaccination plus monitoring for unsolicited adverse events (AEs), medically-attended AEs (MAAEs), and serious AEs (SAEs). Vaccine efficacy against COVID-19 was assessed. Findings Sub-study participants were younger (median age 39; 6.7 % ≥65 years), more racially diverse, and had fewer comorbid conditions than main study participants. Reactogenicity events more common in co-administration group included tenderness

	(70.1% vs 57.6%) or pain (39.7% vs 29.3%) at injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and balanced between the two groups. Co-administration resulted in no change to influenza vaccine immune response, while a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. Vaccine efficacy against COVID-19 was 87.5% (95% CI: -0.2, 98.4) in those 18-<65 years in the sub-study while efficacy in the main study was 89.8% (95% CI: 79.7, 95.5). Interpretation This is the first study to demonstrate safety, immunogenicity, and efficacy of a COVID-19 vaccine when co-administered with influenza vaccines. Funding Funded by Novavax, Inc. Registry Numbers: EudraCT No. 2020-004123-16; ClinicalTrials.gov Identifier: NCT04583995

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Safety, Immunogenicity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered With Seasonal Influenza Vaccines Within a Randomised Controlled Trial

Seth Toback, M.D.[1], Eva Galiza, M.B., B.S.,[2], Catherine Cosgrove, Ph.D.[2], James Galloway, Ph.D.[3], Anna L. Goodman, D.Phil.,[4], Pauline A. Swift, Ph.D[5], Sankarasubramanian Rajaram[6], Alison Graves-Jones[7], Jonathan Edelman[8], Fiona Burns, Ph.D.,[9], Angela M. Minassian, D.Phil.,[10], Iksung Cho, M.S.,[1], Lakshmi Kumar[1], Joyce S. Plested[1], E. Joy Rivers, Ph.D.,[1], Andreana Robertson, M.S.[1], Filip Dubovsky, M.D.[1], Greg Glenn M.D.[1], Prof Paul T. Heath, FRCPCH[2] ; on behalf of the 2019nCoV-302 Study Group*

[1]Novavax, Inc., Gaithersburg, MD, USA; [2]Vaccine Institute, St. George's, University of London and St. Georges University Hospitals NHS Foundation Trust, London, UK; [3]Centre for Rheumatic Disease, King's College London, London, UK; [4]Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, and MRC Clinical Trials Unit at University College London, London, UK; [5]Department of Nephrology, Epsom and St. Helier University Hospitals NHS Trust, London, UK; [6]Seqirus UK Limited, Maidenhead, UK; [7]Seqirus Australia Pty. Ltd., Melbourne, Australia; [8]Seqirus USA Inc., Summit, NJ, USA; [9]Institute for Global Health, University College London, and Royal Free London NHS Foundation Trust; [10]Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford, and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

*Listed in the Supplemental Material.

Correspondence to:

Prof. Paul T. Heath, FRCPCH, Vaccine Institute, St. George's, University of London and St. Georges University Hospitals NHS Foundation Trust, London, UK; Email: pheath@sgul.ac.uk

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Summary [word count 250/250-word limit]

Background Safety and immunogenicity of COVID-19 vaccines when co-administered with influenza vaccines have not yet been reported.

Methods A sub-study on influenza vaccine co-administration was conducted as part of the phase 3 randomised trial of NVX-CoV2373's safety and efficacy; ~400 participants meeting main study entry criteria, with no contraindications to influenza vaccination, were enroled. After randomisation to receive NVX-CoV2373 or placebo, sub-study participants received an open-label influenza vaccine at the same time as the first dose of NVX-CoV2373. Reactogenicity was evaluated for 7 days post-vaccination plus monitoring for unsolicited adverse events (AEs), medically-attended AEs (MAAEs), and serious AEs (SAEs). Vaccine efficacy against COVID-19 was assessed.

Findings Sub-study participants were younger (median age 39; 6.7 % ≥65 years), more racially diverse, and had fewer comorbid conditions than main study participants. Reactogenicity events more common in co-administration group included tenderness (70.1% vs 57.6%) or pain (39.7% vs 29.3%) at injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and balanced between the two groups. Co-administration resulted in no change to influenza vaccine immune response, while a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. Vaccine efficacy against COVID-19 was 87.5% (95% CI: -0.2, 98.4) in those 18-<65 years in the sub-study while efficacy in the main study was 89.8% (95% CI: 79.7, 95.5).

Interpretation This is the first study to demonstrate safety, immunogenicity, and efficacy of a COVID-19 vaccine when co-administered with influenza vaccines.

Funding Funded by Novavax, Inc.

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Version 2: Preferred Summary for Publication

Summary [word count 298/250-word limit]

Background The safety and immunogenicity profile of COVID-19 vaccines when administered concomitantly with seasonal influenza vaccines have not yet been reported.

Methods A sub-study on influenza vaccine co-administration was conducted as part of the phase 3 randomised trial of the safety and efficacy of NVX-CoV2373. The first ~400 participants meeting main study entry criteria and with no contraindications to influenza vaccination were invited to join the sub-study. After randomisation in a 1:1 ratio to receive NVX-CoV2373 (n=217) or placebo (n=214), sub-study participants received an age-appropriate, licensed, open-label influenza vaccine with dose 1 of NVX-CoV2373. Reactogenicity was evaluated via electronic diary for 7 days post-vaccination in addition to monitoring for unsolicited adverse events (AEs), medically-attended AEs (MAAEs), and serious AEs (SAEs). Influenza haemagglutination inhibition and SARS-CoV-2 anti-spike IgG assays were performed. Vaccine efficacy against PCR-confirmed, symptomatic COVID-19 was assessed. Comparisons were made between sub-study and main study participants.

Findings Sub-study participants were younger, more racially diverse, and had fewer comorbid conditions than main study participants. Reactogenicity events more common in the co-administration group included tenderness (70.1% vs 57.6%) or pain (39.7% vs 29.3%) at injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and balanced between the two groups. Co-administration resulted in no change to influenza vaccine immune response, while a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. Vaccine efficacy in the sub-study was 87.5% (95% CI: -0.2, 98.4) while efficacy in the main study was 89.8% (95% CI: 79.7, 95.5).

Interpretation This is the first study to demonstrate the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with seasonal influenza vaccines. The results suggest concomitant vaccination may be a viable immunisation strategy.

Funding This study was funded by Novavax, Inc.

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Research in Context

Evidence before this study

We searched PubMed for research articles published from December 2019 until 1 April 2021 with no language restrictions for the terms “SARS-CoV-2”, “COVID-19”, “vaccine”, “co-administration”, and “immunogenicity”. There were no peer-reviewed publications describing the simultaneous use of any SARS-CoV-2 vaccine and another vaccine. Several vaccine manufacturers had recent publications on phase 3 trials results (Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, and the Gamaleya Research Institute of Epidemiology and Microbiology). Neither these publications nor their clinical trials’ protocols (when publicly available) described co-administration and they often had trial criteria specifically excluding those with recent or planned vaccination with any licenced vaccine near or at the time of any study injection.

Added value of this study

Immune interference and safety are always a concern when two vaccines are administered at the same time. This is the first study to demonstrate the safety and immunogenicity profile and clinical vaccine efficacy of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine.

Implications of all the available evidence

This study provides much needed information to help guide national immunisation policy decision making on the critical issue of concomitant use of COVID-19 vaccines with influenza vaccines.

INTRODUCTION

It has been over a year since the start of the pandemic due to coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); a devastating disease with more than 209 million cases and 4.3 million deaths reported as of 19 August 2021.[1] Seasonal influenza epidemics also occur globally and the World Health Organization (WHO) estimates that 290,000–650,000 individuals die from influenza each year, with the highest rates of death occurring in older adults and children younger than 2 years of age.[2] Public health recommendations in many countries include yearly influenza vaccination as a key preventative strategy.[3]

Global COVID-19 vaccination efforts are now well underway with over 4.5 billion vaccine doses administered as of 18 August 2021.[1] This continued mass COVID-19 vaccination programme will certainly coincide with influenza vaccination programmes. While the need for booster doses of COVID-19 vaccines has not yet been determined, the timing of such doses would likely overlap with the 2021–2022 influenza season in many settings. In addition, most countries will be still administering primary COVID-19 vaccine doses to the population when the need for influenza vaccines arises. Currently, there are no data regarding the co-administration of COVID-19 vaccines with other vaccines as most phase 3 trials of COVID-19 vaccines either excluded participants with recent or planned receipt of other licensed vaccines or required an interval of at least 1 week between them. In particular, knowledge of the effects of co-administration on immune responses and safety is needed to formulate public health policy in light of simultaneous vaccination programmes. This is particularly important as immunosenescence may leave older adults more vulnerable to influenza infection, complications, and mortality, as well as reduce their immune responses to standard influenza vaccines.[4] Current guidance in the United Kingdom (UK) is to separate the administration of any deployed COVID-19 and influenza vaccines by at least 7 days to avoid incorrect attribution of potential adverse events (AEs).[3] The Centers for Disease Control in the United States recommends a 14-day interval between these vaccines.[5] However, the need for multiple clinic visits may lead to reduced compliance and hence reduced vaccination rates. To ensure

adequate vaccine uptake of both COVID-19 and influenza vaccines, co-administration would encourage the public to take up these vaccines in one visit rather than returning 7 or more days later.

Herein we report the results of a sub-study of a phase 3 UK trial that assessed the safety and efficacy of two doses of NVX-CoV2373 compared with placebo.[6] In the main trial, a total of 15,187 participants underwent randomisation, and 14,039 were included in the per-protocol (PP) efficacy population. Of the participants, 27.9% were 65 years of age or older, and 44.6% had coexisting illnesses. A vaccine efficacy of 89.7% (95% confidence interval [CI], 80.2 to 94.6) against symptomatic PCR-proven COVID-19 was demonstrated. The reactogenicity was generally mild and transient and the incidence of serious adverse events (SAEs) was low and similar in the two groups. [6]

This sub-study aimed to evaluate the safety, immunogenicity, and efficacy of NVX-CoV2373 when co-administered with a licensed seasonal influenza vaccine.

METHODS

Trial Design and Participants

This influenza and COVID-19 vaccine co-administration study was a planned sub-study of a phase 3, randomised, observer-blinded, placebo-controlled trial to evaluate the efficacy and safety of two 5-µg doses of NVX-CoV2373, administered intramuscularly 21 days apart, compared with placebo.[6] Briefly, this study enroled 15,139 participants at 33 sites in the UK beginning in September 2020. Eligible participants for the main trial were men and non-pregnant women 18 to 84 years of age (inclusive) who were healthy or had stable chronic medical conditions. Health status was assessed at screening and based on medical history, vital signs, and physical examination. Key exclusion criteria included a history of documented COVID-19, treatment with immunosuppressive therapy, or diagnosis with an unstable medical condition. Full details on the methods and design of the main trial are reported elsewhere.[6] The protocol is available with the full text of this article at xxxx.org.

The first approximately 400 participants who met additional sub-study criteria were invited to participate in the influenza co-administration sub-study (Figure 1). Additional specific inclusion criteria included having not already received a 2020/2021 seasonal, licensed influenza vaccine and having no prior history of allergy or severe reaction to influenza vaccines. All participants were excluded from receipt of any live vaccine within 4 weeks or any vaccine within 2 weeks of the first dose of study vaccine or placebo co-administered with the influenza vaccine. Sub-study enrolment was not randomised or stratified by age.

All participants provided written informed consent before enrolment in the trial. The trial was designed and funded by Novavax. The trial protocol was approved by the North West—Greater Manchester Central Research Ethics Committee (Ref 20/NW/03/99) and was performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines.

Safety oversight was performed by an independent safety monitoring committee.

Procedures

Seasonal influenza vaccine co-administration sub-study participants were selected prior to study vaccine randomisation. Approximately 400 consecutive, non-randomised, eligible participants from four study hospitals in the main study were enroled. Participants were then randomly assigned in a 1:1 ratio via block randomisation to receive two intramuscular injections (0.5 mL) of NVX-CoV2373 or placebo (normal saline), 21 days apart. Randomisation was stratified by site and by age ≥65 years. Participants in the seasonal influenza vaccine co-administration sub-study then received a concomitant dose of seasonal influenza vaccine with the first study injection only. This comprised a single intramuscular injection (0.5 mL) of a licensed influenza vaccine in the opposite deltoid to that of the study vaccine or placebo and was given at the same time. Although the main study was observer-blinded, the influenza vaccine was administered in an open-label manner.

The study vaccine NVX-CoV2373 consisted of 5-µg SARS-CoV-2 rS with 50-µg Matrix-M adjuvant. Two different influenza vaccines were utilised in the study to comply with national influenza vaccination recommendations[7]:

- Influenza vaccine quadrivalent, cellular (QIVc) (Flucelvax® Quadrivalent, Seqirus UK Limited, Maidenhead, UK) for those 18 to 64 years of age
- Adjuvanted trivalent influenza vaccine (aTIV) (Fluad®, Seqirus UK Limited, Maidenhead, UK) for those ≥65 years of age

Immunogenicity Assessments

Blood was collected from all trial participants at baseline and at Day 21 for those in the influenza sub-study and for all trial participants at baseline and Day 35 (14 days after the second dose of study vaccine). A haemagglutination inhibition (HAI) assay antibody was performed in all influenza sub-study participants at baseline and at Day 21. An enzyme-linked immunosorbent assay (ELISA) for SARS-CoV-2 anti-Spike (anti-S) protein immunoglobulin G (IgG) was performed at baseline and on Day 35 in approximately 900 non-randomised participants from two study sites in the main study (as part of an immunogenicity cohort) as well as in those in the influenza sub-study (see Supplemental Material for additional assay details).

Safety

After each study vaccination, participants remained under observation at the study site for at least 30 minutes to monitor for the presence of any acute reactions. Solicited local and systemic AEs were collected via an electronic diary for 7 days after each injection for approximately 2000 non-randomised participants from four study sites in the main study (as part of a reactogenicity cohort) as well as those in the influenza sub-study. Participants in the influenza sub-study were instructed to record local reactogenicity for the study vaccine (NVX-CoV2373 or placebo) injection site only. All participants were assessed for unsolicited AEs from the first injection or injections through 21 days; SAEs, AEs of special interest (AESIs) [including AESIs relevant to COVID and potentially-immune-mediated medical conditions (PIMMCs) – see

Supplemental Tables S1 and S2)] and medically-attended AEs (MAAEs) were assessed from the first injection(s) through the end of the study period while only treatment-related MAAEs were analysed from the first injection(s) through Day 35. Unsolicited AEs and other safety events were reported for all participants who provided informed consent and received at least one injection in the main study and a co-administered influenza vaccine in the sub-study. Data from this ongoing phase 3 trial for the purpose of this analysis were assessed at a median of approximately 4 months after the first study injection (i.e. the dose with which influenza vaccine was co-administered). The safety follow-up period was the same for both the main study and sub-study. Participants in the influenza vaccine co-administration sub-study, the main study immunogenicity cohort, and main study reactogenicity cohort were all enroled at separate, distinct locations.

Efficacy

The primary efficacy endpoint was the first occurrence of virologically-confirmed symptomatic mild, moderate, or severe Covid-19, with onset at least 7 days after the second vaccination in participants who were seronegative at baseline. Symptomatic Covid-19 was defined according to US Food and Drug Administration (FDA) criteria.[6] Symptoms of possible Covid-19 were assessed throughout the trial and collected using an electronic symptom diary for at least 10 days from symptom onset. At the onset of suspected Covid-19 symptoms, participants called their study site and when instructed, mucosal specimens from the nose and throat were collected daily over a 3-day period to assess for SARS-CoV-2 infection. Virological confirmation was performed using polymerase chain reaction testing. Daily temperature self-measurements were recorded at home for at least 10 days and participants were evaluated for an initial clinical assessment (in 1–3 days). A follow-up assessment was conducted (in 7–10 days) where physical examinations were performed and vital signs were collected.

Statistical Analysis

Safety Analysis

Unsolicited AEs, SAEs, MAAEs, and AESIs were analysed in all participants who received at least one dose of NVX-CoV2373 or placebo for the main study and one dose of NVX-CoV2373 or placebo plus one dose of influenza vaccine for the sub-study. Safety events were summarised descriptively. Solicited local and systemic AEs after the first injection(s) were also summarised by FDA toxicity grading criteria and duration after each injection (see **Supplementary Table S3**). Unsolicited AEs were coded by preferred term and system organ class using Version 23.1 of the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarised by severity and relationship to study vaccine. Participants in the sub-study were then compared with participants in the main study, by study vaccine and influenza vaccine received (NVX-CoV2373 plus influenza vaccine; NVX-CoV2373 alone; placebo plus influenza vaccine; placebo alone).

Immunogenicity Analysis

For participants who received the influenza vaccine, strain-specific immune responses to influenza vaccine were assessed, as measured by HAI and reported as geometric mean titres (GMTs), geometric man fold-rise (GMFR) comparing at Day 0 (baseline) and at Day 21, and seroconversion rates (SCRs) (defined as the proportion of subjects with either a baseline reciprocal titre of <10 and a post-vaccination reciprocal titre ≥40, or a baseline titre of ≥10 and a post-vaccination titre ≥4-fold higher). For influenza strain-specific GMTs according to group (influenza vaccine concomitantly administered with NVX-CoV2373 or with placebo), titres reported below the lower limit of quantitation (LLOQ; i.e. below the starting dilution of assay reported as "<10") were set to half that limit (i.e. 10 / 2 = 5).

For the SARS-CoV-2 anti-S protein IgG antibody levels measured by the ELISA assay, geometric mean ELISA units (GMEUs) at each study visit (Day 0 and Day 35), the geometric mean fold rises (GMFRs) comparing at Day 0 and at Day 35, along with 95% CI, were summarised by vaccine group (NVX-CoV2373 plus influenza vaccine; NVX-CoV2373 alone; placebo plus influenza vaccine; placebo alone). Data were also assessed by age group (18 to <65, ≥65 to 84) and corresponding influenza vaccine types (QIVc and aTIV, respectively). The SCR for the IgG antibody was defined as a proportion of participants with ≥4-fold rises. ELISA units (EUs)

reported below the lower limit of quantitation (LLOQ; i.e. below the starting dilution of assay reported as "<200") were set to half that limit (i.e. 200 / 2 = 100).

For both HAI and IgG antibody measured by treatment group, the 95% CIs were calculated based on the t distribution of the log-transformed values, then back transformed to the original scale for presentation as GMTs/GMEUs and GMFRs. The SCRs, along with 95% CIs based on the Clopper-Pearson method, were summarised by vaccine group. The PP immunogenicity analysis set was defined as those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2 infection prior to any visit where serology was measured.

Non-randomised comparisons of the Day 35 anti-S EUs were performed using a geometric mean ratio (GMR) defined as the ratio of two GMEUs. An analysis of covariance on log transformed values with group, age, and baseline EUs was performed. The ratios of geometric least square means and 95% CIs for the ratios were calculated by back transforming the mean differences and 95% confidence limits for the differences of log (base 10) transformed EUs between the two groups. The two-sided 95% CIs for the absolute rate difference between two groups were constructed using the Newcombe method.

Efficacy Analysis

The main trial was designed and driven by the total number of events expected to achieve statistical significance for the primary endpoint – a target of 100 mild, moderate, or severe Covid-19 cases for the main study. The target number of 100 cases for the final analysis provides >95% power for 70% or higher vaccine efficacy. The main (hypothesis testing) event-driven analysis for the final analyses of the primary objective was carried out at an overall one-sided type I error rate of 0.025 for the primary endpoint. The primary endpoint (PP population) was analysed in participants who were seronegative at baseline, received both doses of study vaccine or placebo, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic Covid-19 from the first dose until 6 days after the second

dose (PP efficacy population). Vaccine efficacy was defined as VE (%) = (1 – RR) × 100, where RR = relative risk of incidence rates between the two study groups (NVX-CoV2373 or placebo). The estimated RR and its CI for the main study were derived using Poisson regression with robust error variance.[8] Hypothesis testing of the primary endpoint was carried out against the null hypothesis: H0: vaccine efficacy ≤30%. The study met success criterion by rejecting of the null hypothesis to demonstrate a statistically significant vaccine efficacy. As the influenza co-administration sub-study was an exploratory objective, no formal power calculation was performed to assess any specific endpoint.

Role of the Funding Source

The study was funded by Novavax, and the sponsor had primary responsibility for the study design, study vaccines, protocol development, study monitoring, data management, and statistical analyses. All data were gathered by the non-Novavax authors (representing trial sites) and their teams. Data interpretation, writing of the manuscript, and the decision to submit were undertaken by the first (ST, representing the Sponsor) and last (PTH, representing the trial sites) authors. All authors reviewed and approved the manuscript before submission.

RESULTS

Participants

Between 28 September and 28 November 2020, a total of 15,187 participants were randomised into the main phase 3 trial of which 431 were co-vaccinated with a seasonal influenza vaccine (QIVc or aTIV, depending on participant age); 217 sub-study participants received NVX-CoV2373 + QIVc / aTIV and 214 received placebo + QIVc / aTIV. In the influenza sub-study group, 43.3 % were female, 75.1% were White, 22.7% were from ethnic minorities or reported multiple races, 27.1% had at least one comorbid condition (based on Centers for Disease Control and Prevention definitions[5]). The median age of sub-study participants was 39 years, 32.9% were 50 years of age or older, and 6.7 % were 65 years of age or older (see **Supplementary Table S4**). Within the sub-study, there were 29 aTIV recipients with a median age of 66 years (n=16 in the NVX-CoV2373 arm) and 69 years (n=13 in the placebo arm) and

402 QIVc recipients with a median age of 38 years (n=201 in the NVX-CoV2372 arm) and 37 years (n=201 in the placebo arm) (**Table 1**). A total of 431 participants were assessed for unsolicited AEs, SAEs, MAAEs, and AESIs, while 404 participated in the assessment of reactogenicity. All 431 participants were part of the evaluable immunogenicity population for both HAI and anti-S IgG assays. The sub-study group overall was younger, more racially diverse, and had fewer comorbid conditions than participants in the main study and the main study reactogenicity and immunogenicity cohorts (**Table 1, Supplementary Tables S4 and S5**). The main study immunogenicity cohort for the anti-S IgG assay included 999 participants in the intention-to-treat population who had received either the NVX-CoV2373 vaccine or placebo alone. The main study reactogenicity cohort included 2310 from the safety population who had received at least one dose of the NVX-CoV2373 vaccine or placebo alone.

Safety and Reactogenicity

Overall local reactogenicity (assessed only at the non-influenza vaccine injection site) was largely absent or mild in the co-administration group, NVX-CoV2373 alone group, and placebo plus influenza vaccine group (**Figure 2**). Any local reaction was reported in 70.1% of those co-vaccinated (1.7% severe), 57.6% in the NVX-CoV2373 alone group (1.0% severe), 39.4% (0% severe) in the placebo plus influenza vaccine group, and 17.9% (0.2% severe) in the placebo alone group. The most commonly reported local reactions were injection site tenderness and injection site pain, occurring in 64.9% and 39.7% of those co-vaccinated and 53.3% and 29.3% of those given NVX-CoV2373 alone, respectively.

Any systemic reaction was reported in 60.1% of those co-vaccinated (2.9% severe), 45.7% in the NVX-CoV2373 alone group (1.3% severe), 47.2% in the placebo plus influenza vaccine group (2.8% severe), and 36.3% (1.1% severe) in the placebo alone group. In general, the incidence of specific systemic reactogenicity events was similar within all of these groups (**Figure 2**). The most commonly reported systemic events were muscle pain and fatigue, occurring in 28.3% and 27.7% of those co-vaccinated and 21.4% and 19.4% of those given NVX-CoV2373 alone, respectively, with muscle pain (28.3%) also occurring more frequently in the co-administration

group than the placebo plus influenza vaccine group (20.0%). Notably, fever (temperature ≥38°C) was reported in 4.3%, 2.0%, 1.7%, and 1.5% in the co-vaccinated, NVX-CoV2373 alone, placebo plus influenza vaccine, and placebo alone groups, respectively (see **Supplementary Tables S6–S9**).

When assessed by specific influenza vaccine type, QIVc in those <65 years of age and aTIV in those ≥65 years of age, among those administered concomitantly with NVX-CoV2373, there was a trend towards lower rates of local and systemic reactogenicity in the older group who received the aTIV. Of note, the median duration of reactogenicity events was generally 1–2 days for local events and approximately 1 day for systemic events in both the co-vaccinated group and the NVX-CoV2373 alone group. When assessed by specific influenza vaccine type, there was a general trend for a shorter duration of reactogenicity among those ≥65 years of age (aTIV recipients) (data not shown).

Unsolicited AEs reported up to 21 days after first vaccination were predominantly mild in severity and were similarly distributed across the co-vaccinated and NVX-CoV2373 alone groups (**Table 2**). The frequency of all and severe AEs in the co-vaccinated group (18.4% and 0.5%, respectively) was similar to those in the NVX-CoV2373 alone group (17.6% and 0.4%, respectively). These rates were also similar to the rates of all and severe AEs in the placebo plus influenza vaccine group (14.5% and 0.0%, respectively) and placebo alone group (14.0% and 0.4%, respectively). The unsolicited AEs occurring in >1% of the co-vaccinated group included headache (2.3%), fatigue (1.8%), and oropharyngeal pain (1.4%). Rates of all MAAEs were 7.8% and 3.8% in those co-vaccinated and those who received NVX-CoV2373 alone, respectively, while rates of MAAEs in the placebo plus influenza vaccine group and placebo group alone were 8.4% and 3.9%, respectively. Rates of treatment-related MAAEs were lower and balanced in all groups (**Table 2**). The rate of SAEs was also low and balanced among the sub-study participants and those not involved in the sub-study. No treatment-related SAEs were reported in sub-study participants. No PIMMCs and/or AESIs relevant to COVID-19 were seen in the influenza co-

administration sub-study, with resulting event rates similar to those not involved in the sub-study. There were no episodes of anaphylaxis or deaths within the sub-study.

Immunogenicity

Response to influenza vaccine

There were no statistically significant differences in baseline HAI GMT titres between those in the sub-study co-vaccinated with NVX-CoV2373 plus influenza vaccine group and those in the placebo plus influenza vaccine group (**Figure 3A&B**). In the QIVc groups, HAI GMTs were significantly higher after vaccination on Day 21 while in the much smaller aTIV groups, there was overlap in GMT CIs before and after vaccination. No difference in Day 21 HAI GMTs was seen between the NVX-CoV2373 plus influenza vaccine group and the placebo plus influenza vaccine group for any individual influenza strain (A/H1N1, A/H3N2, B/Victoria, or B/Yamagata) for either influenza vaccine. GMFR values followed the same pattern (see specific strain information in **Supplementary Table S10** and **Table S11**). For both QIVc and aTIV, HAI SCRs were generally high for the influenza A strains but lower for the influenza B strains (**Figure 4A&B**).

Response to NVX-CoV2373

Baseline anti-S EUs were similar in participants in the sub-study co-vaccinated with NVX-CoV2373 and influenza vaccine and those who received placebo plus influenza vaccine as well as in those vaccinated in the main study immunogenicity cohort with NVX-CoV2373 alone (data for the immunogenicity PP population are in **Table 3**). In both groups vaccinated with NVX-CoV2373 plus influenza vaccine or with NVX-CoV2373 alone, the Day 35 GMEUs were significantly higher than those at baseline. A difference in GMEUs was observed between the two PP groups (NVX-CoV2373 plus influenza vaccine [n=178]: 31,236.1 [95% CI: 26,295.51, 37,104.9] vs. NVX-CoV2373 alone [n=414]: 46,678.3 [95% CI: 40,352.2, 49,468.2]). A post hoc assessment of the ratio between the two geometric means when adjusted for baseline EUs, age, and treatment group was 0.57 (95% CI: 0.47, 0.70). This difference was also reflected in the GMFRs, but not in the SCRs, which were 97.8% and 99.0% in the two groups, respectively. The Day 35 GMEUs were numerically lower in the ≥65-year-old (aTIV) concomitant vaccination

group compared with the 18- to <65-year-old (QIVc) concomitant vaccination group, although the number of participants in the concomitant aTIV group was small. However, the GMFRs were large, >200, and the SCRs were both >97%. This diminution in immunogenicity with increasing age was also seen in the main study immunogenicity cohort. The subgroup of participants receiving concomitant NVX-CoV2373 and any influenza vaccine who were seropositive (n=19) at baseline achieved Day 35 GMEUs that were significantly greater than those in similar participants who were seronegative (n=198) at baseline (71,115.6 [95% CI: 46,813.8, 108,032.8] vs. 30,439.1 [95% CI: 25,713.4, 36,033.5], respectively) (see **Supplementary Table S12A**).

Efficacy

Among 386 participants in the influenza sub-study who were also in the efficacy PP population, there were two cases of virologically-confirmed, symptomatic Covid-19 with onset at least 7 days after the second dose among vaccine recipients and eight cases among placebo recipients. A post hoc analysis of the primary endpoint demonstrated a vaccine efficacy of 74.8% (95% CI, -19.7 to 94.7) Among those 18 to <65 years of age (n=360), there was one case of virologically-confirmed, symptomatic Covid-19 with onset at least 7 days after the second dose among vaccine recipients and eight cases among placebo recipients; vaccine efficacy of 87.5% (95% CI, -0.2 to 98.4) (**Supplementary Table S13**. There were too few cases among those in the PP population who were ≥65 years to calculate a vaccine efficacy. All influenza sub-study cases in the PP group were due to the Alpha (B.1.1.7) variant. Among 431 participants in the influenza sub-study ITT population, vaccine efficacy was 80.6% (95% CI, 13.3 to 95.7) (**Supplementary Table S13**). Vaccine efficacy in the entire main study PP population 18 to <65 years of age was 89.8% (95% CI, 79.7 to 95.5) while vaccine efficacy against the Alpha variant alone in the main study PP population was 86.3% (95% CI, 71.3 to 93.5).

DISCUSSION

This study is the first to demonstrate the safety, immunogenicity, and efficacy of any COVID-19 vaccine when co-administered with a seasonal influenza vaccine or any other vaccination. Most COVID-19 vaccine trials have excluded participants receiving other vaccinations at the time or

near the time of injection with study vaccine and therefore have no interaction studies addressed in their labels.[9–11] Although no specific comparative immunogenicity endpoints were pre-specified in this exploratory sub-study, we found no evidence for interference of the COVID-19 vaccine with the QIVc influenza vaccine. Definitive conclusions about aTIV were not possible because of the small number of participants older than 65 years of age. We did, however, observe an impact of concomitant administration of an influenza vaccine on the absolute magnitude of the anti-S antibody response. This impact did not seem to be clinically meaningful as vaccine efficacy appeared to be preserved. Co-administration also appeared to have no clinically meaningful effect on systemic or local reactogenicity and no additional safety concerns were found to be associated with co-vaccination. Solicited local and systemic reactogenicity events after co-administration were generally similar to the incidence and severity of those for each vaccine when administered separately. The incidence of more subjective local reactogenicity (pain and tenderness) was elevated in the co-vaccinated group above the level of either the NVX-CoV2373 alone or placebo plus influenza vaccine groups, but the rates for more objective local events (erythema and swelling) were low and indistinguishable between all groups. These increased rates were largely driven by an increase in mild symptoms. It is unclear if subjects were biased in their assessment of pain and tenderness at the study injection site having received two co-administered vaccinations; the fact that placebo injections were assessed as causing more local pain/tenderness when given concomitantly with an influenza vaccine (in the opposite arm) compared with placebo injections, when given alone, would suggest this is likely to be the case. Another explanation is that participants recorded local symptoms from the influenza injection site despite being instructed to consider symptoms at the injection site of the study vaccine only. The rate for any systemic reactogenicity event in those co-vaccinated was modestly elevated over the rate for either NVX-CoV2373 or influenza vaccine alone, consistent with an overall higher vaccine immunogen load and the relatively younger participant population in the sub-study. This was seen mainly for the events of muscle pain and fever, yet despite the relative increase in the rate of fever, the absolute fever rate in those who received two co-administered vaccinations was modest (4.3%). Rates of severe events were low in all groups and showed no clinically

meaningful pattern of increased reactogenicity. The elevation in some reactogenicity events may, in part, have been due to the overall younger age of the influenza vaccine sub-study participants compared with the main study reactogenicity cohort (median age 39.0 years [93.3% 18 to <65 years] vs. a median age of 52.0 years [80.1% 18 to <65 years]). Those ≥65 years of age who received two adjuvanted vaccines compared with those <65 years of age who received the adjuvanted NVX-CoV2373 and unadjuvanted QIVc had lower rates of reactogenicity; this effect of age was also seen in the NVX-CoV2373 alone group and in prior NVX-CoV2373 studies[6,12,13] and is consistent with immunosenescence.

The rates of AEs, SAEs, and AESIs were low and balanced between those given NVX-CoV2373, influenza vaccine, or both. The rate of any MAAE was higher in sub-study participants compared with non-sub-study participants. This difference was less apparent when assessing treatment-related MAAEs only. The increased rate of all MAAEs in the sub-study may represent a health-care seeking bias in those desiring an influenza vaccine rather than a true increase in medical visits due to AEs related to co-vaccination or receipt of the influenza vaccine plus placebo; an assessment of these excess medical visits revealed that most were general practice visits associated with health maintenance concerns (data not shown).

The magnitude of the humoral response to either influenza vaccine was not affected by co-administration with NVX-CoV2372 when assessed at 21 days after dosing, although care should be used in generalising this observation to aTIV because of the small sample size. The post-vaccination rise in GMTs and SCRs for each strain were high when either influenza vaccine was administered with placebo or NVX-CoV2373, although there was a generally lower response to the influenza B strains found in all influenza vaccine recipients. The humoral immune response to influenza B strains is dependent upon numerous factors, including age and prior influenza vaccine exposure.[14] Low influenza B SCRs[15] and lower SCRs relative to influenza A strains[16,17] have been seen with prior immunogenicity studies of quadrivalent inactivated influenza vaccines.

In contrast, there was a modest reduction in the anti-S EUs observed with the co-administration of NVX-CoV2373 and an influenza vaccine. It is unclear if this reduction was due to vaccine

interference or due to the non-randomised nature of the studied groups. In the absence of a correlate of protection, it is difficult to interpret the significance of this finding. The post hoc assessment of vaccine efficacy in this sub-study in those 18 to <65 years of age was 87.5% compared with the vaccine efficacy of 89.8% in the same age group from the PP efficacy populations in the main study, although given the small number of endpoint cases in the sub-study the lower bound of the CI was just below zero. The similar vaccine efficacy within the influenza vaccine co-administration group would suggest that the reduction in the anti-S EUs as a result of co-administration may not be clinically meaningful. In fact, the levels of anti-S EUs in those receiving both vaccines (in either those 18 to <65 or ≥65 years of age) was still over 3-fold greater than the anti-S EUs found in convalescent serum, suggesting that EUs in this range found in sub-study participants may be protective.[18,19] It should be also noted that no difference in the rates of SCRs were seen between those co-vaccinated and those who received NVX-CoV2373 alone.

It is also apparent that the extent of the reduction in anti-S EUs may be less relevant in participants who are seropositive at baseline, as they achieved high values post-vaccination with co-administration of influenza vaccine with a mean of 71,115 EUs in co-vaccinated seropositive participants of all ages compared with a mean of 44,678 EUs in PP NVX-CoV2373 alone recipients of all ages (yet this was not as large as the mean of 125,490 EUs in seropositive NVX-CoV2372 alone recipients) (**Table 3** and **Supplementary Table S12A**). One possible explanation for this finding is that seropositive individuals have pre-existing T-cell and B-cell populations with immune memory against the SARS-CoV2 spike protein minimizing any possible effect of immune interference. Therefore, it is possible that influenza vaccine co-administration may impact priming but have no impact on the immune response in previously primed individuals. An implication of this is that influenza vaccine co-administration with the second dose of any two-dose COVID-19 vaccine schedule, or with a subsequent booster dose of COVID-19 vaccine, may overcome any potential immune interference. This should be assessed further as it has important implications for public health vaccination strategies.

Although this is the first study to show the co-administration of a COVID-19 with a seasonal influenza vaccine, influenza vaccine co-administration has been well studied. Our study utilised two different influenza vaccines for different age groups in compliance with UK influenza vaccination guidelines.[20] For those <65 years of age, a cell culture–derived, inactivated quadrivalent influenza vaccine was used. QIVc was approved in the UK in December 2018 for individuals 9 years and older and extended to 2 years and older in 2020. For the older cohort, a MF59 squalene-based, oil-in-water aTIV was administered. This aTIV was approved in the UK in August 2017. In two studies of the MF59 aTIV given concomitantly with a pneumococcal vaccine, antibody responses to either vaccine were not affected and the safety data were consistent with expected rates of AEs for both vaccines.[21,22] No interference or safety concerns have been reported with a QIV co-administered with pneumococcal and herpes zoster vaccines.[23,24]

The strengths of this sub-study include the placebo-controlled design and its alignment with national influenza vaccine policy in the use of both adjuvanted and unadjuvanted influenza vaccines in different age groups. Study limitations include the small overall sub-study size (with few participants ≥65 years of age owing to the high rate of routine influenza vaccination among participants in this age group at study start), small number of sub-study efficacy endpoints, lack of formal pre-specified non-inferiority statistical assessment of immunogenicity, and the lack of randomisation in recruiting the influenza sub-study, immunogenicity, and reactogenicity cohorts. A stronger design could have been four randomised arms consisting of NVX-CoV2373 plus influenza vaccine, NVX-CoV2373 plus placebo, influenza vaccine plus placebo, and placebo plus placebo. Another limitation was the open-label design in administering the influenza vaccine, but this was required to order to allow participants to consider only the study vaccine injection site for assessment of local symptoms. Finally, the assessment of neutralising antibody titres may have benefitted the immunogenicity investigation, yet prior studies with NVX-CoV2373 have shown a strong correlation between the anti-S and wild-type microneutralizations results.[18]

This is the first study to demonstrate the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine. These data

demonstrate no early safety concerns with the concomitant administration of NVX-CoV2373 with an influenza vaccine. Immunogenicity of the influenza vaccine was preserved with concomitant administration while a modest decrease in the immunogenicity of the NVX-CoV2373 vaccine was found. Vaccine efficacy in those 18 to <65 years appeared to be preserved in those receiving both vaccines compared with those vaccinated with NVX-CoV2373 alone. Future clinical trials and post-licensure studies of COVID-19 vaccines should include safety and immunogenicity data on co-administration with common adult and paediatric vaccines. More research on the concomitant vaccination of COVID-19 and influenza vaccines is needed, especially in those >65 years of age, to help guide national immunisation policy on this critical issue.

Contributors

ST, JSP, LK, FD, GG, IC, AR, and EJR are Novavax employees. PTH is the chief investigator. ST, PTH, JP, LK, FD, GG, IC, and AR contributed to the protocol and design of the study. EG, CG, ALG, JG, FB, AMM and PAS are study site principal investigators. SR, JE, and AG are Seqirus employees. EG, CG, ALG, JG, FB, AMM and PS contributed to the study or data collection. IC and AR verified the data and reviewed the statistical analysis. All authors reviewed, commented on, and approved this manuscript prior to submission for publication.

Declaration of interest

ST, JSP, LK, FD, GG, IC, AR, and EJR are Novavax employees and SR, JE, and AG are Seqirus employees as they receive a salary for their work. All other authors (PTH, FB, EG, CC, JG, ALG, AMM, PAS) declare no competing interest.

Data sharing

The protocol for this phase 3 study is publicly available from Novavax.

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[TABLES]

Table 1: Demographics and baseline characteristics of participants in the influenza vaccine co-administration sub-study and entire study populations (ITT population)

	NVX-CoV2373 + aTIV (n=16)	NVX-CoV2373 + QIVc (n=201)	Placebo + aTIV (n=13)	Placebo + QIVc (n=201)	Total Study, ITT Population (n=15139)
Age, yr (SD)	66.9 (1.86)	40.3 (12.72)	69.3 (3.73)	40.2 (11.57)	53.1 (14.91)
Median	66.0	38.0	69.0	37.0	55.0
Range	65, 71	20, 64	65, 77	23, 64	18, 84
Age group, n (%)					
18-64 yr	0 (0)	201 (100)	0 (0)	201 (100)	11014 (72.8)
≥65 yr	16 (100)	0 (0)	13 (100)	0 (0)	4125 (27.2)
Sex, n (%)					
Male	6 (37.5)	117 (58.2)	4 (30.8)	114 (56.7)	7808 (51.6)
Female	10 (62.5)	84 (41.8)	9 (69.2)	87(43.3)	7331 (48.4)
Race or ethnic group, n (%)					
White	12 (75.0)	151 (75.1)	11 (84.6)	153 (76.1)	14280 (94.3)
Black or African American	0 (0)	4 (2.0)	0	2 (1.0)	60 (0.4)
Asian	0 (0)	14 (7.0)	1 (7.7)	22 (10.9)	462 (3.1)
Multiple	4 (25.0)	25 (12.4)	0 (0)	23 (11.4)	136 (0.9)
Not reported	0 (0)	3 (1.5)	1 (7.7)	1 (0.5)	176 (1.2)
Other	0 (0)	3 (1.5)	0 (0)	0 (0)	17 (<0.1)
Missing	0 (0)	1 (0.5)	0 (0)	0 (0)	8
Hispanic or Latinx quadrivalent	1 (6.3)	9 (4.5)	1 (7.7)	4 (2.0)	125 (0.8)
SARS-CoV-2 serostatus, n (%)	15 (93.8)	183 (91.0)	12 (92.3)	184 (91.5)	14362 (94.9)
Negative	1 (6.3)	18 (9.0)	0 (0.0)	13 (6.5)	643 (4.2)
Positive	0 (0)	0 (0)	1 (0.7)	4 (2.0)	134 (0.9)
Missing					
Comorbidity status*					
Yes	5 (31.3)	50 (24.9)	7 (53.8)	55 (27.4)	6767 (44.7)
No	11 (68.8)	151 (75.1)	6 (46.2)	146 (72.6)	8372 (55.3)

*Comorbid subjects are those identified who have at least one of the comorbid conditions reported as a medical history or have a screening body mass index value greater than 30 kg/m^2.

Percentages are based on the intention-to-treat data set within the seasonal influenza vaccine sub-study (by vaccine type; aTIV for those ≥65 years of age and QIVc for those <65 years of age) and overall.

Abbreviations: aTIV=adjuvanted trivalent influenza vaccine; ITT=intention-to-treat; QIVc=influenza vaccine quadrivalent, cellular; SD=standard deviation.

Table 2: Safety data from participants in the influenza vaccine co-administration sub-study and participants in the entire study population (without sub-study participants)

	NVX-CoV2373 + Influenza Vaccine	Placebo + Influenza Vaccine	NVX-CoV2372 Alone	Placebo Alone
	n=217	n=214	n=7352	n=7356
Any AE	40 (18.4%)	31 (14.5%)	1297 (17.6%)	1030 (14.0%)
Any severe AE	1 (0.5%)	0 (0%)	33 (0.4%)	33 (0.4%)
SAE	1 (0.5%)	0 (0%)	43 (0.6%)	44 (0.6%)
MAAE	17 (7.8%)	18 (8.4%)	279 (3.8%)	288 (3.9%)
Treatment-related MAAE	3 (1.4%)	0 (0%)	34 (0.5%)	17 (0.2%)
PIMMC	0 (0%)	0 (0%)	5 (<0.1%)	8 (0.1%)
AESI related to COVID	0 (0%)	0 (0%)	8 (0.1%)	22 (0.3%)

Influenza vaccine co-administration sub-study participants compared with the entire ITT study population, excluding the co-vaccination sub-study group. Adverse events and severe adverse events are those within 21 days of study dose 1 (with or without co-administration of influenza vaccine). SAEs, MAAEs, AESIs, and PIMMCs are assessed for the entire study period.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ITT, intention-to-treat; MAAE=medically-attend adverse event; PIMMC= potentially-immune-mediated medical condition; SAE=serious adverse event.

Table 3: Anti-S IgG on Day 0 and Day 35 in the influenza vaccination sub-study and immunogenicity cohort, in the PP population, by age group

		NVX-CoV2373 + Influenza Vaccine					Placebo + Influenza Vaccine			
		Day 0		Day 35			Day 0		Day 35	
	n	Point estimate	(95% CI)	Point estimate	(95% CI)	n	Point estimate	(95% CI)	Point estimate	(95% CI)
GMEU										
IIV + NVX-CoV2372 or placebo, all ages	n=178	116.3	(107.7, 125.6)	31236.1	(26295.5, 37104.9)	n=181	111.4	(105.1, 118.1)	115.7	(106.1, 126.1)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168	115.8	(107.2, 125.0)	31516.9	(26316.2, 37745.3)	n=170	112.2	(105.4, 119.3)	116.8	(106.5, 128.0)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10	125.6	(75.0, 210.3)	26876.1	(15374.6, 46981.5)	n=11	100.0	(100.0, 100.0)	100.0	(100.0, 100.0)
GMFR										
IIV + NVX-CoV2372 or placebo, all ages	n=178			268.6	(221.0, 326.4)	n=181			1.0	(1.0, 1.1)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168			272.3	(222.3, 333.5)	n=170			1.0	(1.0, 1.1)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10			214.0	(96.5, 474.6)	n=11			1.0	(1.0, 1.0)
SCR										
IIV + NVX-CoV2372 or placebo, all ages	n=178			97.8	(94.3, 99.4)	n=181			0.6	(0.0, 3.0)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168			97.6	(94.0, 99.3)	n=170			0.6	(0.0,3.2)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10			100.0	(69.2, 100.0)	n=11			0.0	(0.0, 28.5)

Table 3: Anti-S IgG on Day 0 and Day 35 in the influenza vaccination sub-study and immunogenicity cohort, in the PP population, by age group (cont'd)

		NVX-CoV2373 Alone					Placebo Alone			
		Day 0		Day 35			Day 0		Day 35	
	n	Point estimate	(95% CI)	Point estimate	(95% CI)	n	Point estimate	(95% CI)	Point estimate	(95% CI)
GMEU										
NVX-CoV2373 or placebo alone, all ages	n=414	112.2	(107.5, 117.0)	44678.3	(40352.2, 49468.2)	n=417	110.3	(106.3, 114.5)	113.2	(106.8, 120.0)
NVX-CoV2373 or placebo alone, 18 to <65	n=300	111.9	(106.2, 117.9)	47564.3	(42327.3, 53449.4)	n=310	109.7	(105.2, 114.4)	113.5	(105.6, 122.0)
NVX-CoV2373 or placebo alone, ≥65	n=114	112.8	(105.0, 121.2)	37892.8	(30833.3, 46568.5)	n=107	112.1	(103.4, 121.4)	112.3	(103.1, 122.3)
GMFR										
NVX-CoV2373 or placebo alone, all ages	n=414			398.4	(358.6, 442.6)	n=417			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, 18 to <65	n=300			425.0	(375.7, 480.8)	n=310			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, ≥65	n=114			335.9	(274.4, 411.1)	n=107			1.0	(1.0, 1.0)
SCR										
NVX-CoV2373 or placebo alone, all ages	n=414			99.0	(97.5, 99.7)	n=417			0.7	(0.1, 2.1)
NVX-CoV2373 or placebo alone, 18 to <65	n=300			99.0	(97.1, 99.8)	n=310			1.0	(0.2, 2.8)
NVX-CoV2373 or placebo alone, ≥65	n=114			99.1	(95.2, 100.0)	n=107			0.0	(0.0, 3.4)

Influenza vaccine co-administration sub-study participants compared with the PP immunogenicity population (data are shown for participants who consented to have IgG levels assessed; data by all ages, those <65 and those ≥65). Comparison of the anti-S IgG GMEUs at baseline (Day 0) and 35 days and Day 35 GMRF and SCR after vaccination with NVX-CoV2373 or placebo with either aTIV, QIVc, or alone.

Abbreviations: aTIV=adjuvanted trivalent influenza vaccine; GMFR=geometric mean fold rise; GMEU=geometric mean ELISA unit; IgG=immunoglobulin G; IIV= inactivated influenza vaccine (both aTIV and QIVc); PP=per-protocol; QIVc=influenza vaccine quadrivalent, cellular; S=spike; SCR=seroconversion rate.

[FIGURE LEGENDS AND FIGURES]

Figure 1: Main study, influenza vaccine sub-study, and study cohorts. The main study intention-to-treat (ITT) population (n=15,139) were all participants who received at least one dose of NVX-CoV2373 or placebo. Those who were enroled in the influenza sub-study were then removed to create the main study safety population (n=14,708) used to make safety comparisons with the sub-study. The main study per-protocol (PP) efficacy population included all participants who were seronegative at baseline, received both doses of study vaccine, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic Covid-19 from the first dose until 6 days after the second dose. The influenza sub-study total ITT population included all those received at least one dose of NVX-CoV2373 or placebo and any influenza vaccine (n=431). This entire group was assessed for immunogenicity (haemagglutination inhibition assay and ELISA testing for anti-S IgG). Of these, 404 recorded data into the 7-day reactogenicity diary (influenza sub-study reactogenicity population). Those who did not record data included those who were unable to download the e-dairy or were non-compliant with its use. Of the 431 sub-study participants, 386 also met the PP efficacy definition as defined above. The immunogenicity cohort ITT population included all subjects from the main study who received at least one dose of NVX-CoV2373 or placebo and underwent ELISA testing for anti-S IgG. The per-PP immunogenicity subset were those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2 infection prior to any visit where serology was measured. The reactogenicity cohort ITT population included all subjects from the main study who received at least one dose of NVX-CoV2373 or placebo and recorded data into the e-diary. The influenza sub-study, immunogenicity cohort, and reactogenicity cohort were enroled at four, four, and two unique study hospitals, respectively, who had the resources to manage the additional study requirements.

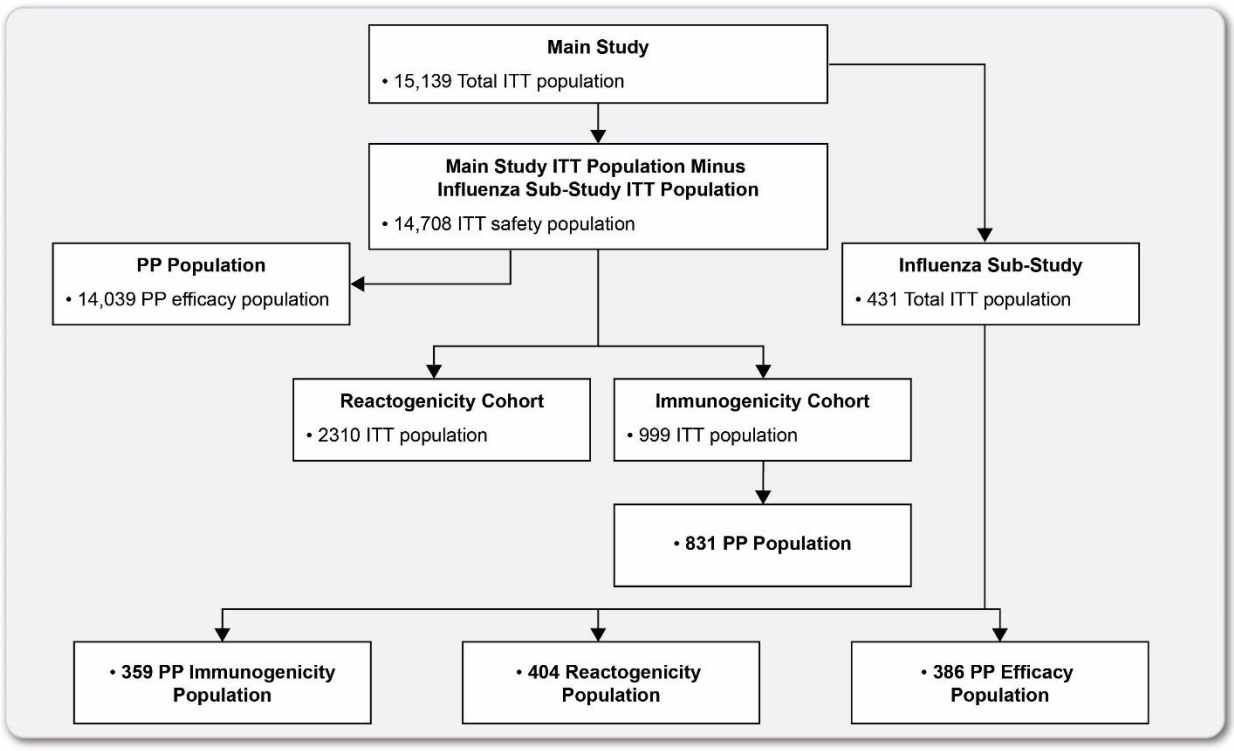

Main Study
• 15,139 Total ITT population
Main Study ITT Population Minus Influenza Sub-Study ITT Population
• 14,708 ITT safety population
PP Population
• 14,039 PP efficacy population
Influenza Sub-Study
• 431 Total ITT population
Reactogenicity Cohort
• 2310 ITT population
Immunogenicity Cohort
• 999 ITT population
• 831 PP Population
• 359 PP Immunogenicity Population
• 404 Reactogenicity Population
• 386 PP Efficacy Population

Figure 2: Reactogenicity data from participants in the influenza vaccine co-administration sub-study and participants in the reactogenicity cohort population after dose 1: local and systemic. The percentage of participants in each treatment group with solicited local and systemic adverse events during the 7 days after each vaccination is plotted according to the maximum toxicity grade (mild, moderate, severe, or potentially life-threatening) in participants included in the seasonal influenza vaccine sub-study and those included in the reactogenicity cohort.

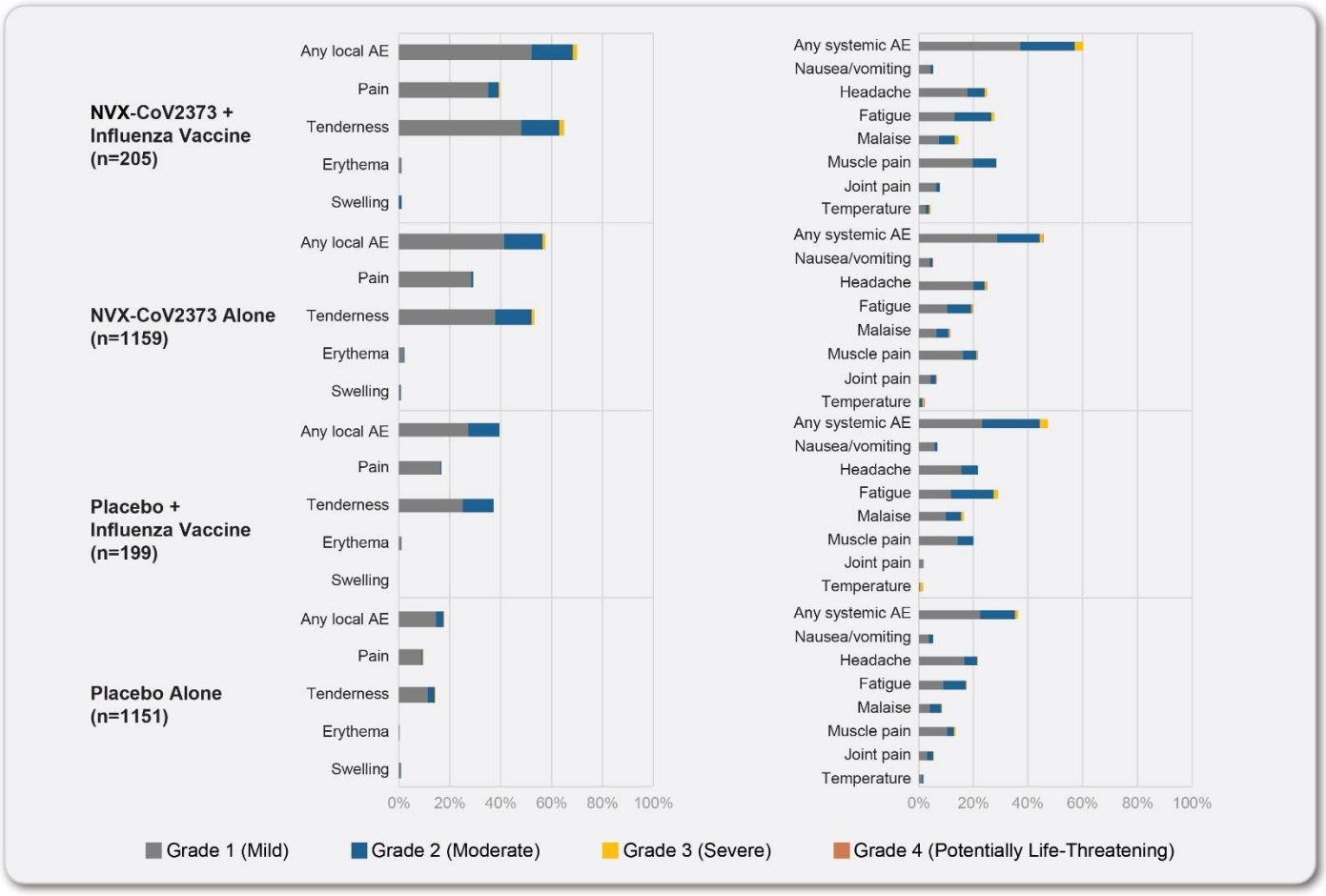
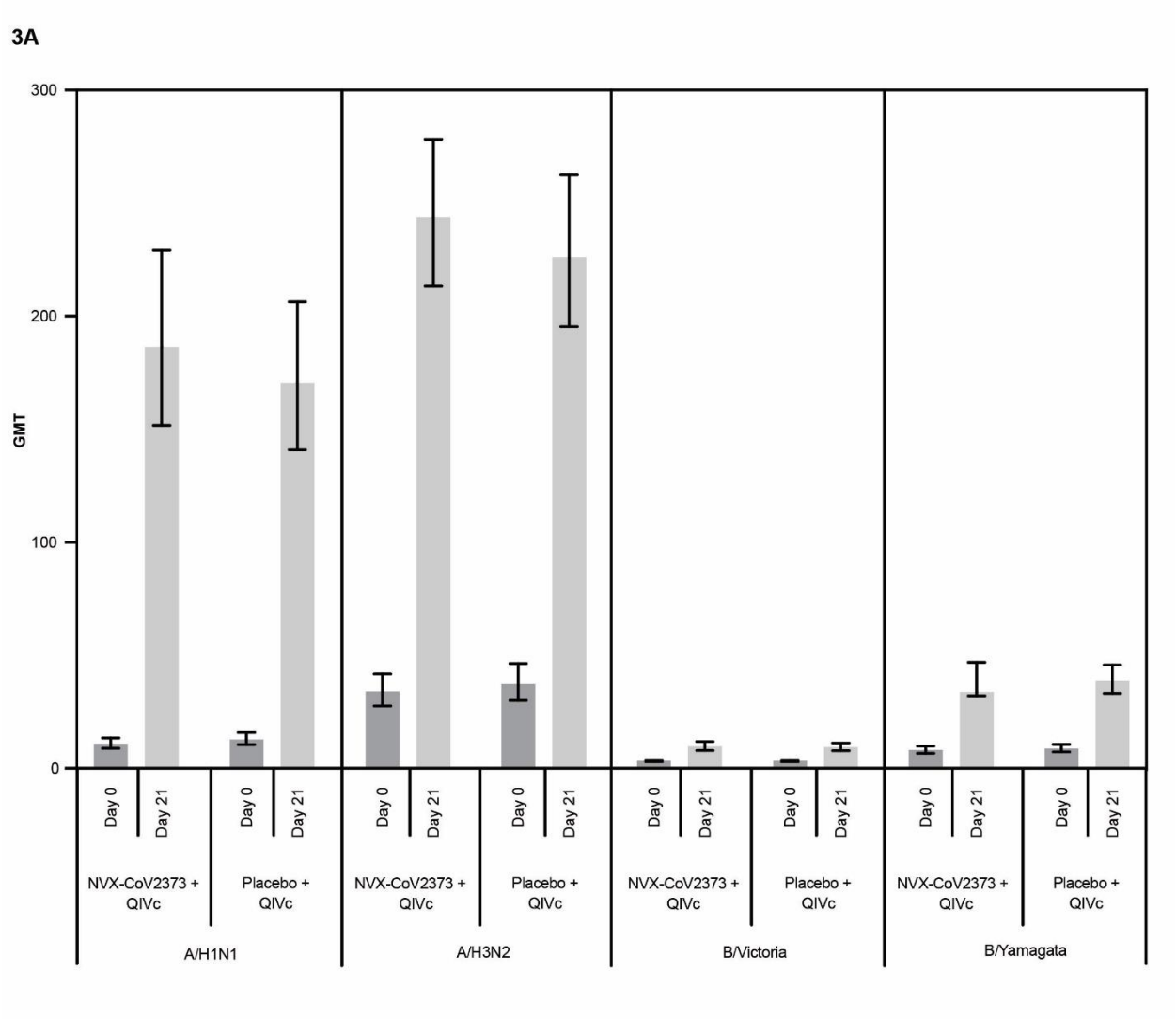


Figure 3: A) HAI GMTs on Day 0 and Day 21 in the QIVc Group; B) HAI GMTs on Day 0 and Day 21 in the aTIV Group.

Comparison of the HAI GMTs at baseline (Day 0) and 21 days after vaccination with NVX-CoV2373 or placebo with either QIVc or aTIV influenza vaccine by influenza strain. For NVX-CoV2373 + QIVc (n=178), Placebo + QIVc (n=179), NVX-CoV2373 + aTIV (n=13), Placebo + aTIV (n=11). Error bars represent 95% confidence intervals. aTIV= adjuvanted trivalent influenza vaccine; GMT=geometric mean titre; HAI=haemagglutination inhibition; QIVc=influenza vaccine quadrivalent, cellular.



3B

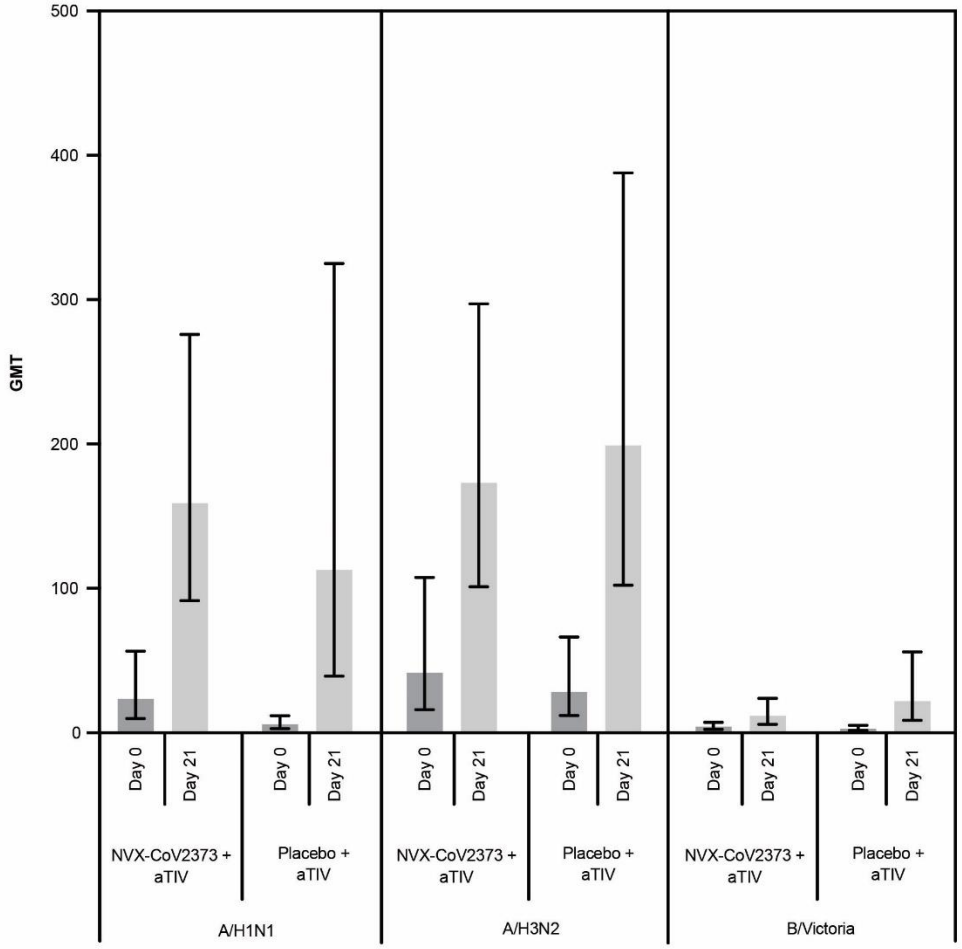
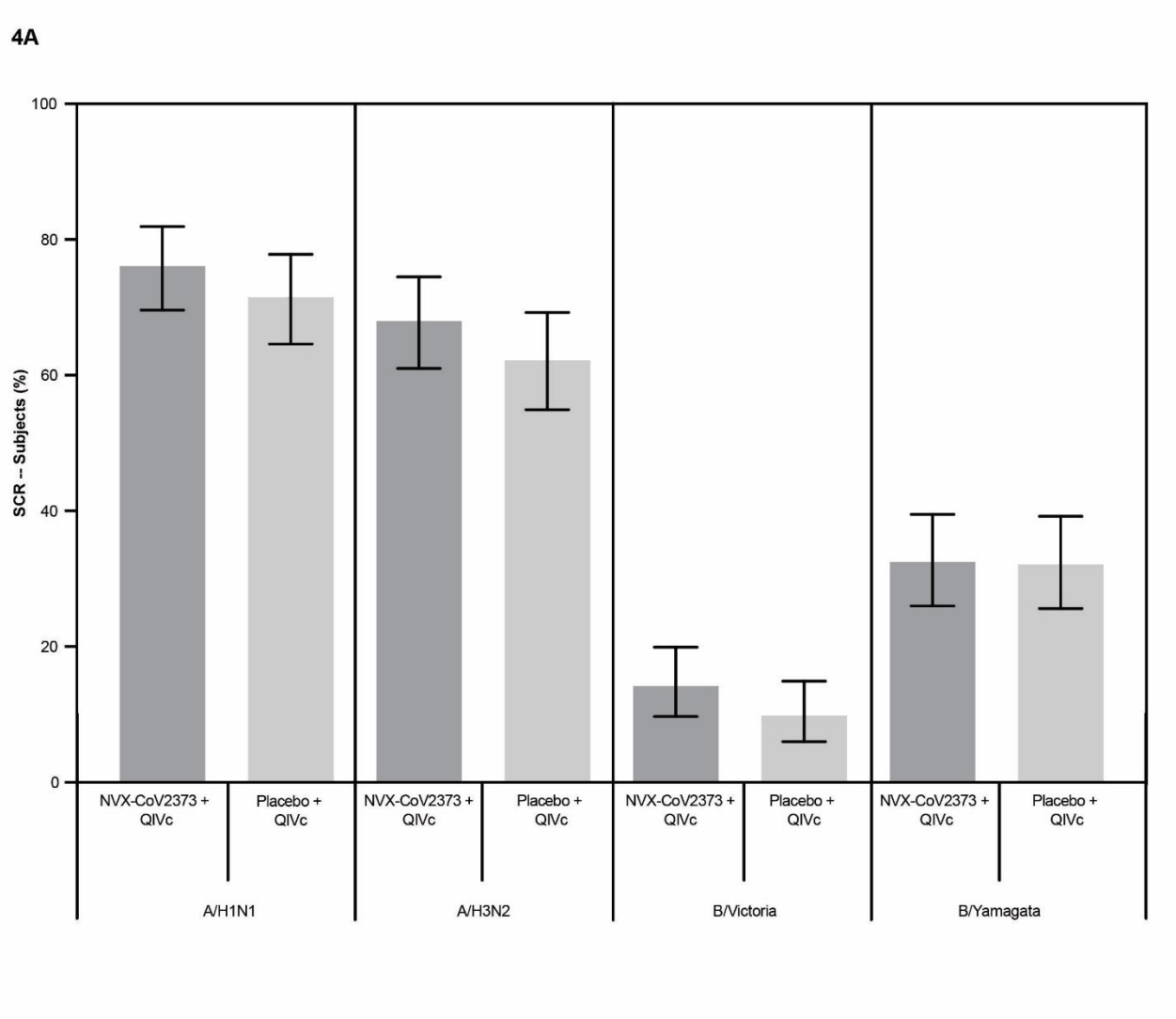
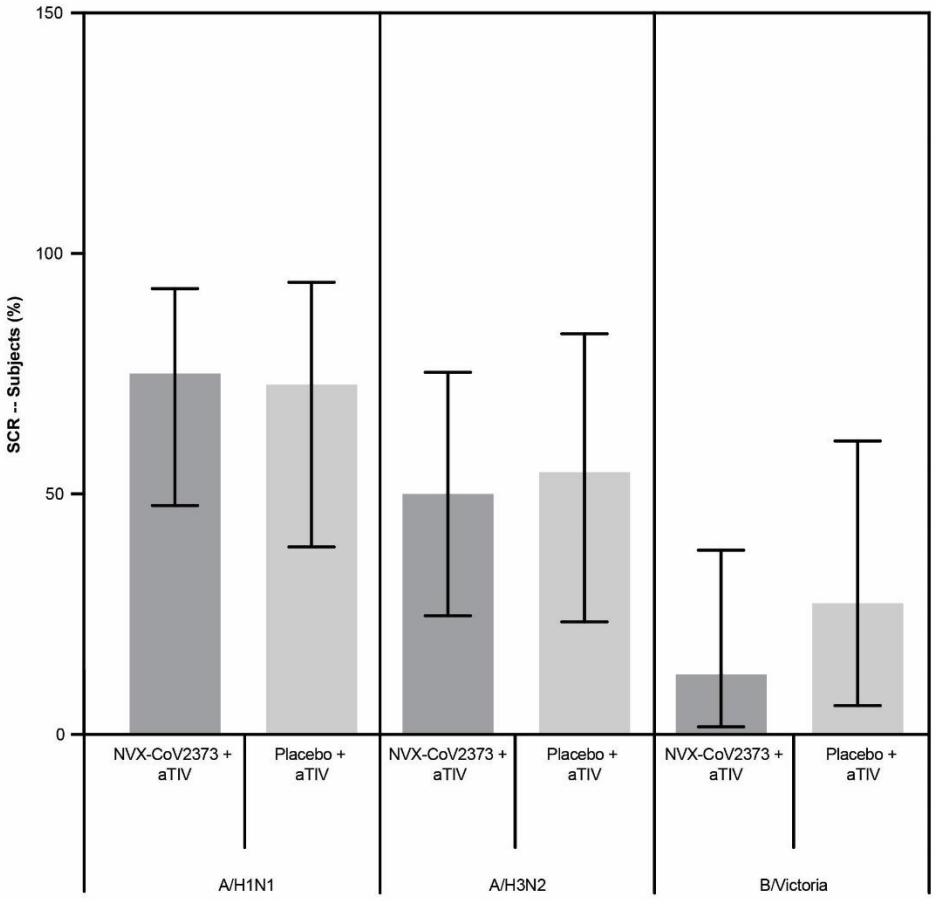

GMT
500
400
300
200
100
0
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H1N1
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H3N2
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
B/Victoria

Figure 4: A) HAI SCRs on Day 0 and Day 21 in the QIVc Group; B) HAI SCRs on Day 0 and Day 21 in the aTIV Group.

Comparison of the HAI SCRs 21 days after vaccination with NVX-CoV2373 or placebo with QIVc or aTIV influenza vaccine by influenza strain. aTIV= adjuvanted trivalent influenza vaccine; HAI=haemagglutination inhibition; QIVc=influenza vaccine quadrivalent, cellular; SCR=seroconversion rate.



4B


150
100
50
0
SCR -- Subjects (%)
NVX-CoV2373 + aTIV
Placebo + aTIV
NVX-CoV2373 + aTIV
Placebo + aTIV
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H1N1
A/H3N2
B/Victoria

[**Manuscript reference number***:* thelancetrm-D-21-00741]

Safety, Immunogenicity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered With Seasonal Influenza Vaccines Within a Randomised Controlled Trial

Seth Toback, M.D.[1], Eva Galiza, M.B., B.S.,[2], Catherine Cosgrove, Ph.D.[2], James Galloway, Ph.D.[3], Anna L. Goodman, D.Phil.,[4], Pauline A. Swift, Ph.D[5], Sankarasubramanian Rajaram[6], Alison Graves-Jones[7], Jonathan Edelman[8], Fiona Burns, Ph.D.,[9], Angela M. Minassian, D.Phil.,[10], Iksung Cho, M.S.,[1], Lakshmi Kumar[1], Joyce S. Plested[1], E. Joy Rivers, Ph.D.,[1], Andreana Robertson, M.S.[1], Filip Dubovsky, M.D.[1], Greg Glenn M.D.[1], Prof Paul T. Heath, FRCPCH[2] ; on behalf of the 2019nCoV-302 Study Group*

[1]Novavax, Inc., Gaithersburg, MD, USA; [2]Vaccine Institute, St. George's, University of London and St. Georges University Hospitals NHS Foundation Trust, London, UK; [3]Centre for Rheumatic Disease, King's College London, London, UK; [4]Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, and MRC Clinical Trials Unit at University College London, London, UK; [5]Department of Nephrology, Epsom and St. Helier University Hospitals NHS Trust, London, UK; [6]Seqirus UK Limited, Maidenhead, UK; [7]Seqirus Australia Pty. Ltd., Melbourne, Australia; [8]Seqirus USA Inc., Summit, NJ, USA; [9]Institute for Global Health, University College London, and Royal Free London NHS Foundation Trust; [10]Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford, and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

*Listed in the Supplemental Material.

Correspondence to:

Prof. Paul T. Heath, FRCPCH, Vaccine Institute, St. George's, University of London and St. Georges University Hospitals NHS Foundation Trust, London, UK; Email: pheath@sgul.ac.uk

Abstract word count (limit 250 words): 250; **Text word count:** 5650

Version 1: For Submission Portal [to meet 250-word limit]

Summary [word count 250/250-word limit]

Background Safety and immunogenicity of COVID-19 vaccines when co-administered with influenza vaccines haves not yet been reported.

Methods A sub-study on influenza vaccine co-administration was conducted as part of the phase 3 randomised trial of NVX-CoV2373's safety and efficacy; ~400 participants meeting main study entry criteria, with no contraindications to influenza vaccination, were enroled. After randomisation to receive NVX-CoV2373 or placebo, sub-study participants received an open-label influenza vaccine at the same time as the first dose of NVX-CoV2373. Reactogenicity was evaluated for 7 days post-vaccination plus monitoring for unsolicited adverse events (AEs), medically-attended AEs (MAAEs), and serious AEs (SAEs). Vaccine efficacy against COVID-19 was assessed.

Findings Sub-study participants were younger (median age 39; 6.7 % ≥65 years), more racially diverse, and had fewer comorbid conditions than main study participants. Reactogenicity events more common in co-administration group included tenderness (70.1% vs 57.6%) or pain (39.7% vs 29.3%) at injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and balanced between the two groups. Co-administration resulted in no change to influenza vaccine immune response, while a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. Vaccine efficacy against COVID-19 was 87.5% (95% CI: -0.2, 98.4) in those 18-<65 years in the sub-study while efficacy in the main study was 89.8% (95% CI: 79.7, 95.5).

Interpretation This is the first study to demonstrate safety, immunogenicity, and efficacy of a COVID-19 vaccine when co-administered with influenza vaccines.

Funding Funded by Novavax, Inc.

Registry Numbers: EudraCT No. 2020-004123-16; ClinicalTrials.gov Identifier: NCT04583995

Version 2: Preferred Summary for Publication

Summary [word count 298/250-word limit]

Background The safety and immunogenicity profile of COVID-19 vaccines when administered concomitantly with seasonal influenza vaccines haves not yet been reported.

Methods A sub-study on influenza vaccine co-administration was conducted as part of the phase 3 randomised trial of the safety and efficacy of NVX-CoV2373. The first ~400 participants meeting main study entry criteria and with no contraindications to influenza vaccination, were invited to join the sub-study. After randomiszation in a 1:1 ratio to receive NVX-CoV2373 (n=217) or placebo (n=214), sub-study participants received an age-appropriate, licensed, open-label influenza vaccine with dose 1 of NVX-CoV2373. Reactogenicity was evaluated via electronic diary for 7 days post-vaccination in addition to monitoring for unsolicited adverse events (AEs), medically-attended AEs (MAAEs), and serious AEs (SAEs). Influenza haemagglutination inhibition and SARS-CoV-2 anti-spike IgG assays were performed. Vaccine efficacy against PCR-confirmed, symptomatic COVID-19 was assessed. Comparisons were made between sub-study and main study participants.

Findings Sub-study participants were younger, more racially diverse, and had fewer comorbid conditions than main study participants. Reactogenicity events more common in the co-administration group included tenderness (70.1% vs 57.6%) or pain (39.7% vs 29.3%) at injection site, fatigue (27.7% vs 19.4%), and muscle pain (28.3% vs 21.4%). Rates of unsolicited AEs, MAAEs, and SAEs were low and balanced between the two groups. Co-administration resulted in no change to influenza vaccine immune response, while a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. Vaccine efficacy in the sub-study was 87.5% (95% CI: -0.2, 98.4) while efficacy in the main study was 89.8% (95% CI: 79.7, 95.5).

Interpretation This is the first study to demonstrate the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with seasonal influenza vaccines. The results suggest concomitant vaccination may be a viable immunisation strategy.

Funding This study was funded by Novavax, Inc.

Registry Numbers: EudraCT No. 2020-004123-16; ClinicalTrials.gov Identifier: NCT04583995

Research in Context

Evidence before this study

We searched PubMed for research articles published from December 2019 until 1 April 2021 with no language restrictions for the terms “SARS-CoV-2”, “COVID-19”, “vaccine”, “co-administration”, and “immunogenicity”. There were no peer-reviewed publications describing the simultaneous use of any SARS-CoV-2 vaccine and another vaccine. Several vaccine manufacturers had recent publications on phase 3 trials results (Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, and the Gamaleya Research Institute of Epidemiology and Microbiology). Neither these publications nor their clinical trials’ protocols (when publicly available) described co-administration and they often had trial criteria specifically excluding those with recent or planned vaccination with any licenced vaccine near or at the time of any study injection.

Added value of this study

Immune interference and safety are always a concern when two vaccines are administered at the same time. This is the first study to demonstrate the safety and immunogenicity profile and clinical vaccine efficacy of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine.

Implications of all the available evidence

This study provides much needed information to help guide national immunisation policy decision making on the critical issue of concomitant use of COVID-19 vaccines with influenza vaccines.

INTRODUCTION

It has beenis over a year since the start of the pandemic due to coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); a devastating disease with more than 209195 million cases and 4.31 million deaths reported as of 1929 AugustJuly 2021.[1] Seasonal influenza epidemics also occur globally and the World Health Organization (WHO) estimates that 290,000–650,000 individuals die from influenza each year, with the highest rates of death occurring in older adults and children younger than 2 years of age.[2] Public health recommendations in many countries include yearly influenza vaccination as a key preventative strategy.[3]

Global COVID-19 vaccination efforts are now well underway with over 4.53.8 billion vaccine doses administered as of 1829 AugustJuly 2021.[1] This continued mass COVID-19 vaccination programme will certainly coincide with influenza vaccination programmes. While the need for booster doses of COVID-19 vaccines has not yet been determined, the timing of such doses would likely overlap with the 2021–2022 influenza season in many settings. In addition, most countries will be still administering primary COVID-19 vaccine doses to the population when the need for influenza vaccines arises. Currently, there are no data regarding the co-administration of COVID-19 vaccines with other vaccines as most phase 3 trials of COVID-19 vaccines either excluded participants with recent or planned receipt of other licensed vaccines or required an interval of at least 1 week between them. In particular, knowledge of the effects of co-administration on immune responses and safety isare needed to formulate public health policy in light of simultaneous vaccination programmes. This is particularly important as immunosenescence may leave older adults more vulnerable to influenza infection, complications, and mortality, as well as reduce their immune responses to standard influenza vaccines.[4] Current guidance in the United Kingdom (UK) is to separate the administration of any deployed COVID-19 and influenza vaccines by at least 7 days to avoid incorrect attribution of potential adverse events (AEs).[3] The Centers for Disease Control in the United States recommends a 14-day interval between these vaccines.[5] However, the need for multiple clinic visits may lead to reduced compliance and hence reduced vaccination rates. To ensure

adequate vaccine uptake of both COVID-19 and influenza vaccines, co-administration would encourage the public to take up these vaccines in one visit rather than returning 7 or more days later.

Herein we report the results of a sub-study of a phase 3 UK trial that assessed the safety and efficacy of two doses of NVX-CoV2373 compared with placebo.[6] In the main trial, a total of 15,187 participants underwent randomisation, and 14,039 were included in the per-protocol (PP) efficacy population. Of the participants, 27.9% were 65 years of age or older, and 44.6% had coexisting illnesses. A vaccine efficacy of 89.7% (95% confidence interval [CI], 80.2 to 94.6) against symptomatic PCR-proven COVID-19 was demonstrated. The reactogenicity was generally mild and transient and the incidence of serious adverse events (SAEs) was low and similar in the two groups. [6]

This sub-study aimed to evaluate the safety, immunogenicity, and efficacy of NVX-CoV2373 when co-administered with a licensed seasonal influenza vaccine.

METHODS

Trial Design and Participants

This influenza and COVID-19 vaccine co-administration study was a planned sub-study of a phase 3, randomised, observer-blinded, placebo-controlled trial to evaluate the efficacy and safety of two 5-µg doses of NVX-CoV2373, administered intramuscularly 21 days apart, compared with placebo.[6] Briefly, this study enroled 15,139 participants at 33 sites in the UK beginning in September 2020. Eligible participants for the main trial were men and non-pregnant women 18 to 84 years of age (inclusive) who were healthy or had stable chronic medical conditions. Health status was assessed at screening and based on medical history, vital signs, and physical examination. Key exclusion criteria included a history of documented COVID-19, treatment with immunosuppressive therapy, or diagnosis with an unstable medical condition. Full details on the methods and design of the main trial are reported elsewhere.[6] The protocol is available with the full text of this article at xxxx.org.

The first approximately 400 participants who met additional sub-study criteria were invited to participate in the influenza co-administration sub-study (Figure 1). Additional specific inclusion criteria included having not already received a 2020/2021 seasonal, licensed influenza vaccine and having no prior history of allergy or severe reaction to influenza vaccines. All participants were excluded from receipt of any live vaccine within 4 weeks or any vaccine within 2 weeks of the first dose of study vaccine or placebo co-administered with the influenza vaccine. Sub-study enrolment was not randomised or stratified by age.

All participants provided written informed consent before enrolment in the trial. The trial was designed and funded by Novavax. The trial protocol was approved by the North West—Greater Manchester Central Research Ethics Committee (Ref 20/NW/03/99) and was performed in accordance with the International Council for Harmonisation Good Clinical Practice guidelines.

Safety oversight was performed by an independent safety monitoring committee.

Procedures

Seasonal influenza vaccine co-administration sub-study participants were selected prior to study vaccine randomisation. Approximately 400 consecutive, non-randomised, eligible participants from four study hospitals in the main study were enroled. Participants were then randomly assigned in a 1:1 ratio via block randomisation to receive two intramuscular injections (0.5 mL) of NVX-CoV2373 or placebo (normal saline), 21 days apart. Randomisation was stratified by site and by age ≥65 years. Participants in the seasonal influenza vaccine co-administration sub-study then received a concomitant dose of seasonal influenza vaccine with the first study injection only. This comprised a single intramuscular injection (0.5 mL) of a licensed influenza vaccine in the opposite deltoid to that of the study vaccine or placebo and was given at the same time. Although the main study was observer-blinded, the influenza vaccine was administered in an open-label manner.

The study vaccine NVX-CoV2373 consisted of 5-µg SARS-CoV-2 rS with 50-µg Matrix-M adjuvant. Two different influenza vaccines were utilised in the study to comply with national influenza vaccination recommendations[7]:

- Influenza vaccine quadrivalent, cellular (QIVc) (Flucelvax® Quadrivalent, Seqirus UK Limited, Maidenhead, UK) for those 18 to 64 years of age
- Adjuvanted trivalent influenza vaccine (aTIV) (Fluad®, Seqirus UK Limited, Maidenhead, UK) for those ≥65 years of age

Immunogenicity Assessments

Blood was collected from all trial participants at baseline and at Day 21 for those in the influenza sub-study and for all trial participants at baseline and Day 35 (14 days after the second dose of study vaccine). A haemagglutination inhibition (HAI) assay antibody was performed in all influenza sub-study participants at baseline and at Day 21. An enzyme-linked immunosorbent assay (ELISA) for SARS-CoV-2 anti-Spike (anti-S) protein immunoglobulin G (IgG) was performed at baseline and on Day 35 in approximately 900 non-randomised participants from two study sites in the main study (as part of an immunogenicity cohort) as well as in those in the influenza sub-study (see Supplemental Material for additional assay details).

Safety

After each study vaccination, participants remained under observation at the study site for at least 30 minutes to monitor for the presence of any acute reactions. Solicited local and systemic AEs were collected via an electronic diary for 7 days after each injection for approximately 2000 non-randomised participants from four study sites in the main study (as part of a reactogenicity cohort) as well as those in the influenza sub-study. Participants in the influenza sub-study were instructed to record local reactogenicity for the study vaccine (NVX-CoV2373 or placebo) injection site only. All participants were assessed for unsolicited AEs from the first injection or injections through 21 days; SAEs, AEs of special interest (AESIs) [including AESIs relevant to COVID and potentially-immune-mediated medical conditions (PIMMCs) – see

Supplemental Tables S1 and S2)] and medically-attended AEs (MAAEs) were assessed from the first injection(s) through the end of the study period while only treatment-related MAAEs were analysed from the first injection(s) through Day 35. Unsolicited AEs and other safety events were reported for all participants who provided informed consent and received at least one injection in the main study and a co-administered influenza vaccine in the sub-study. Data from this ongoing phase 3 trial for the purpose of this analysis were assessed at a median of approximately 4 months after the first study injection (i.e. the dose with which influenza vaccine was co-administered). The safety follow-up period was the same for both the main study and sub-study. Participants in the influenza vaccine co-administration sub-study, the main study immunogenicity cohort, and main study reactogenicity cohort were all enroled at separate, distinct locations.

Efficacy

The primary efficacy endpoint was the first occurrence of virologically-confirmed symptomatic mild, moderate, or severe Covid-19, with onset at least 7 days after the second vaccination in participants who were seronegative at baseline. Symptomatic Covid-19 was defined according to US Food and Drug Administration (FDA) criteria.[6] Symptoms of possible Covid-19 were assessed throughout the trial and collected using an electronic symptom diary for at least 10 days from symptom onset. At the onset of suspected Covid-19 symptoms, participants called their study site and when instructed, mucosal specimens from the nose and throat were collected daily over a 3-day period to assess for SARS-CoV-2 infection. Virological confirmation was performed using polymerase chain reaction testing. Daily temperature self-measurements were recorded at home for at least 10 days and participants were evaluated for an initial clinical assessment (in 1–3 days). A follow-up assessment was conducted (in 7–10 days) where physical examinations were performed and vital signs were collected.

Statistical Analysis

Safety Analysis

Unsolicited AEs, SAEs, MAAEs, and AESIs were analysed in all participants who received at least one dose of NVX-CoV2373 or placebo for the main study and one dose of NVX-CoV2373 or placebo plus one dose of influenza vaccine for the sub-study. Safety events were summarised descriptively. Solicited local and systemic AEs after the first injection(s) were also summarised by FDA toxicity grading criteria and duration after each injection (see **Supplementary Table S3**). Unsolicited AEs were coded by preferred term and system organ class using Version 23.1 of the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarised by severity and relationship to study vaccine. Participants in the sub-study were then compared with participants in the main study, by study vaccine and influenza vaccine received (NVX-CoV2373 plus influenza vaccine; NVX-CoV2373 alone; placebo plus influenza vaccine; placebo alone).

Immunogenicity Analysis

For participants who received the influenza vaccine, strain-specific immune responses to influenza vaccine were assessed, as measured by HAI and reported as geometric mean titres (GMTs), geometric man fold-rise (GMFR) comparing at Day 0 (baseline) and at Day 21, and seroconversion rates (SCRs) (defined as the proportion of subjects with either a baseline reciprocal titre of <10 and a post-vaccination reciprocal titre ≥40, or a baseline titre of ≥10 and a post-vaccination titre ≥4-fold higher). For influenza strain-specific GMTs according to group (influenza vaccine concomitantly administered with NVX-CoV2373 or with placebo), titres reported below the lower limit of quantitation (LLOQ; i.e. below the starting dilution of assay reported as "<10") were set to half that limit (i.e. 10 / 2 = 5).

For the SARS-CoV-2 anti-S protein IgG antibody levels measured by the ELISA assay, geometric mean ELISA units (GMEUs) at each study visit (Day 0 and Day 35), the geometric mean fold rises (GMFRs) comparing at Day 0 and at Day 35, along with 95% CI, were summarised by vaccine group (NVX-CoV2373 plus influenza vaccine; NVX-CoV2373 alone; placebo plus influenza vaccine; placebo alone). Data were also assessed by age group (18 to <65, ≥65 to 84) and corresponding influenza vaccine types (QIVc and aTIV, respectively). The SCR for the IgG antibody was defined as a proportion of participants with ≥4-fold rises. ELISA units (EUs)

reported below the lower limit of quantitation (LLOQ; i.e. below the starting dilution of assay reported as "<200") were set to half that limit (i.e. 200 / 2 = 100).

For both HAI and IgG antibody measured by treatment group, the 95% CIs were calculated based on the t distribution of the log-transformed values, then back transformed to the original scale for presentation as GMTs/GMEUs and GMFRs. The SCRs, along with 95% CIs based on the Clopper-Pearson method, were summarised by vaccine group. The PP immunogenicity analysis set was defined as those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2 infection prior to any visit where serology was measured.

Non-randomi~~s~~zed comparisons of the Day 35 anti-S EUs were performed using a geometric mean ratio (GMR) defined as the ratio of two GMEUs. An analysis of covariance on log transformed values with group, age, and baseline EUs was performed. The ratios of geometric least square means and 95% CIs for the ratios were calculated by back transforming the mean differences and 95% confidence limits for the differences of log (base 10) transformed EUs between the two groups. The two-sided 95% CIs for the absolute rate difference between two groups were constructed using the Newcombe method.

Efficacy Analysis

The main trial was designed and driven by the total number of events expected to achieve statistical significance for the primary endpoint – a target of 100 mild, moderate, or severe Covid-19 cases for the main study. The target number of 100 cases for the final analysis provides >95% power for 70% or higher vaccine efficacy. The main (hypothesis testing) event-driven analysis for the final analyses of the primary objective was carried out at an overall one-sided type I error rate of 0.025 for the primary endpoint. The primary endpoint (PP population) was analysed in participants who were seronegative at baseline, received both doses of study vaccine or placebo, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic Covid-19 from the first dose until 6 days after the second

dose (PP efficacy population). Vaccine efficacy was defined as VE (%) = (1 – RR) × 100, where RR = relative risk of incidence rates between the two study groups (NVX-CoV2373 or placebo). The estimated RR and its CI for the main study were derived using Poisson regression with robust error variance.[8] Hypothesis testing of the primary endpoint was carried out against the null hypothesis: H0: vaccine efficacy ≤30%. The study met success criterion by rejecting of the null hypothesis to demonstrate a statistically significant vaccine efficacy. As the influenza co-administration sub-study was an exploratory objective, no formal power calculation was performed to assess any specific endpoint.

Role of the Funding Source

The study was funded by Novavax, and the sponsor had primary responsibility for the study design, study vaccines, protocol development, study monitoring, data management, and statistical analyses. All data were gathered by the non-Novavax authors (representing trial sites) and their teams. Data interpretation, writing of the manuscript, and the decision to submit were undertaken by the first (ST, representing the Sponsor) and last (PTH, representing the trial sites) authors. All authors reviewed and approved the manuscript before submission.

RESULTS

Participants

Between 28 September and 28 November 2020, a total of 15,187 participants were randomised into the main phase 3 trial of which 431 were co-vaccinated with a seasonal influenza vaccine (QIVc or aTIV, depending on participant age); 217 sub-study participants received NVX-CoV2373 + QIVc / aTIV and 214 received placebo + QIVc / aTIV. In the influenza sub-study group, 43.3 % were female, 75.1% were White, 22.7% were from ethnic minorities or reported multiple races, 27.1% had at least one comorbid condition (based on Centers for Disease Control and Prevention definitions[5]). The median age of sub-study participants was 39 years, 32.9% were 50 years of age or older, and 6.7 % were 65 years of age or older (see **Supplementary Table S4**). Within the sub-study, there were 29 aTIV recipients with a median age of 66 years (n=16 in the NVX-CoV2373 arm) and 69 years (n=13 in the placebo arm) and

402 QIVc recipients with a median age of 38 years (n=201 in the NVX-CoV2372 arm) and 37 years (n=201 in the placebo arm) (**Table 1**). A total of 431 participants were assessed for unsolicited AEs, SAEs, MAAEs, and AESIs, while 404 participated in the assessment of reactogenicity. All 431 participants were part of the evaluable immunogenicity population for both HAI and anti-S IgG assays. The sub-study group overall was younger, more racially diverse, and had fewer comorbid conditions than participants in the main study and the main study reactogenicity and immunogenicity cohorts (**Table 1, Supplementary Tables S4 and S5**). The main study immunogenicity cohort for the anti-S IgG assay included 999 participants in the intention-to-treat population who had received either the NVX-CoV2373 vaccine or placebo alone. The main study reactogenicity cohort included 2310 from the safety population who had received at least one dose of the NVX-CoV2373 vaccine or placebo alone.

Safety and Reactogenicity

Overall local reactogenicity (assessed only at the non-influenza vaccine injection site) was largely absent or mild in the co-administration group, NVX-CoV2373 alone group, and placebo plus influenza vaccine group (**Figure 2**). Any local reaction was reported in 70.1% of those co-vaccinated (1.7% severe), 57.6% in the NVX-CoV2373 alone group (1.0% severe), 39.4% (0% severe) in the placebo plus influenza vaccine group, and 17.9% (0.2% severe) in the placebo alone group. The most commonly reported local reactions were injection site tenderness and injection site pain, occurring in 64.9% and 39.7% of those co-vaccinated and 53.3% and 29.3% of those given NVX-CoV2373 alone, respectively.

Any systemic reaction was reported in 60.1% of those co-vaccinated (2.9% severe), 45.7% in the NVX-CoV2373 alone group (1.3% severe), 47.2% in the placebo plus influenza vaccine group (2.8% severe), and 36.3% (1.1% severe) in the placebo alone group. In general, the incidence of specific systemic reactogenicity events was similar within all of these groups (**Figure 2**). The most commonly reported systemic events were muscle pain and fatigue, occurring in 28.3% and 27.7% of those co-vaccinated and 21.4% and 19.4% of those given NVX-CoV2373 alone, respectively, with muscle pain (28.3%) also occurring more frequently in the co-administration

group than the placebo plus influenza vaccine group (20.0%). Notably, fever (temperature ≥38°C) was reported in 4.3%, 2.0%, 1.7%, and 1.5% in the co-vaccinated, NVX-CoV2373 alone, placebo plus influenza vaccine, and placebo alone groups, respectively (see **Supplementary Tables S6–S9**).

When assessed by specific influenza vaccine type, QIVc in those <65 years of age and aTIV in those ≥65 years of age, among those administered concomitantly with NVX-CoV2373, there was a trend towards lower rates of local and systemic reactogenicity in the older group who received the aTIV. Of note, the median duration of reactogenicity events was generally 1–2 days for local events and approximately 1 day for systemic events in both the co-vaccinated group and the NVX-CoV2373 alone group. When assessed by specific influenza vaccine type, there was a general trend for a shorter duration of reactogenicity among those ≥65 years of age (aTIV recipients) (data not shown).

Unsolicited AEs reported up to 21 days after first vaccination were predominantly mild in severity and were similarly distributed across the co-vaccinated and NVX-CoV2373 alone groups (**Table 2**). The frequency of all and severe AEs in the co-vaccinated group (18.4% and 0.5%, respectively) was similar to those in the NVX-CoV2373 alone group (17.6% and 0.4%, respectively). These rates were also similar to the rates of all and severe AEs in the placebo plus influenza vaccine group (14.5% and 0.0%, respectively) and placebo alone group (14.0% and 0.4%, respectively). The unsolicited AEs occurring in >1% of the co-vaccinated group included headache (2.3%), fatigue (1.8%), and oropharyngeal pain (1.4%). Rates of all MAAEs were 7.8% and 3.8% in those co-vaccinated and those who received NVX-CoV2373 alone, respectively, while rates of MAAEs in the placebo plus influenza vaccine group and placebo group alone were 8.4% and 3.9%, respectively. Rates of treatment-related MAAEs were lower and balanced in all groups (**Table 2**). The rate of SAEs was also low and balanced among the sub-study participants and those not involved in the sub-study. No treatment-related SAEs were reported in sub-study participants. No PIMMCs and/or AESIs relevant to COVID-19 were seen in the influenza co-

administration sub-study, with resulting event rates similar to those not involved in the sub-study. There were no episodes of anaphylaxis or deaths within the sub-study.

Immunogenicity

Response to influenza vaccine

There were no statistically significant differences in baseline HAI GMT titres between those in the sub-study co-vaccinated with NVX-CoV2373 plus influenza vaccine group and those in the placebo plus influenza vaccine group (**Figure 3A&B**). In the QIVc groups, HAI GMTs were significantly higher after vaccination on Day 21 while in the much smaller aTIV groups, there was overlap in GMT CIs before and after vaccination. No difference in Day 21 HAI GMTs was seen between the NVX-CoV2373 plus influenza vaccine group and the placebo plus influenza vaccine group for any individual influenza strain (A/H1N1, A/H3N2, B/Victoria, or B/Yamagata) for either influenza vaccine. GMFR values followed the same pattern (see specific strain information in **Supplementary Table S10** and **Table S11**). For both QIVc and aTIV, HAI SCRs were generally high for the influenza A strains but lower for the influenza B strains (**Figure 4A&B**).

Response to NVX-CoV2373

Baseline anti-S EUs were similar in participants in the sub-study co-vaccinated with NVX-CoV2373 and influenza vaccine and those who received placebo plus influenza vaccine as well as in those vaccinated in the main study immunogenicity cohort with NVX-CoV2373 alone (data for the immunogenicity PP population are in **Table 3**). In both groups vaccinated with NVX-CoV2373 plus influenza vaccine or with NVX-CoV2373 alone, the Day 35 GMEUs were significantly higher than those at baseline. A difference in GMEUs was observed between the two PP groups (NVX-CoV2373 plus influenza vaccine [n=178]: 31,236.1 [95% CI: 26,295.51, 37,104.9] vs. NVX-CoV2373 alone [n=414]: 46,678.3 [95% CI: 40,352.2, 49,468.2]). A post hoc assessment of the ratio between the two geometric means when adjusted for baseline EUs, age, and treatment group was 0.57 (95% CI: 0.47, 0.70). This difference was also reflected in the GMFRs, but not in the SCRs, which were 97.8% and 99.0% in the two groups, respectively. The Day 35 GMEUs were numerically lower in the ≥65-year-old (aTIV) concomitant vaccination

group compared with the 18- to <65-year-old (QIVc) concomitant vaccination group, although the number of participants in the concomitant aTIV group was small. However, the GMFRs were large, >200, and the SCRs were both >97%. This diminution in immunogenicity with increasing age was also seen in the main study immunogenicity cohort. The subgroup of participants receiving concomitant NVX-CoV2373 and any influenza vaccine who were seropositive (n=19) at baseline achieved Day 35 GMEUs that were significantly greater than those in similar participants who were seronegative (n=198) at baseline (71,115.6 [95% CI: 46,813.8, 108,032.8] vs. 30,439.1 [95% CI: 25,713.4, 36,033.5], respectively) (see **Supplementary Table S12A**).

Efficacy

Among 386 participants in the influenza sub-study who were also in the efficacy PP population, there were two cases of virologically-confirmed, symptomatic Covid-19 with onset at least 7 days after the second dose among vaccine recipients and eight cases among placebo recipients. A post hoc analysis of the primary endpoint demonstrated a vaccine efficacy of 74.8% (95% CI, -19.7 to 94.7) Among those 18 to <65 years of age (n=360), there was one case of virologically-confirmed, symptomatic Covid-19 with onset at least 7 days after the second dose among vaccine recipients and eight cases among placebo recipients; vaccine efficacy of 87.5% (95% CI, -0.2 to 98.4) (**Supplementary Table S13**. There were too few cases among those in the PP population who were ≥65 years to calculate a vaccine efficacy. All influenza sub-study cases in the PP group were due to the Alpha (B.1.1.7) variant. Among 431 participants in the influenza sub-study ITT population, vaccine efficacy was 80.6% (95% CI, 13.3 to 95.7) (**Supplementary Table S13**). Vaccine efficacy in the entire main study PP population 18 to <65 years of age was ~~of~~ 89.8% (95% CI, 79.7 to 95.5) while vaccine efficacy against the Alpha variant alone in the main study PP population was ~~of~~ 86.3% (95% CI, 71.3 to 93.5).

DISCUSSION

This study is the first to demonstrate the safety, immunogenicity, and efficacy of any COVID-19 vaccine when co-administered with a seasonal influenza vaccine or any other vaccination. Most COVID-19 vaccine trials have excluded participants receiving other vaccinations at the time or

near the time of injection with study vaccine and therefore have no interaction studies addressed in their labels.[9–11] Although no specific comparative immunogenicity endpoints were pre-specified in this exploratory sub-study, we found no evidence for interference of the COVID-19 vaccine with the QIVc influenza vaccine. Definitive conclusions about aTIV were not possible because of the small number of participants older than 65 years of age. We did, however, observe an impact of concomitant administration of an influenza vaccine on the absolute magnitude of the anti-S antibody response. This impact did not seem to be clinically meaningful as vaccine efficacy appeared to be preserved. Co-administration also appeared to have no clinically meaningful effect on systemic or local reactogenicity and no additional safety concerns were found to be associated with co-vaccination. Solicited local and systemic reactogenicity events after co-administration were generally similar to the incidence and severity of those for each vaccine when administered separately. The incidence of more subjective local reactogenicity (pain and tenderness) was elevated in the co-vaccinated group above the level of either the NVX-CoV2373 alone or placebo plus influenza vaccine groups, but the rates for more objective local events (erythema and swelling) were low and indistinguishable between all groups. These increased rates were largely driven by an increase in mild symptoms. It is unclear if subjects were biased in their assessment of pain and tenderness at the study injection site having received two co-administered vaccinations; the fact that placebo injections were assessed as causing more local pain/tenderness when given concomitantly with an influenza vaccine (in the opposite arm) compared with placebo injections, when given alone, would suggest this is likely to be the case. Another explanation is that participants recorded local symptoms from the influenza injection site despite being instructed to consider symptoms at the injection site of the study vaccine only. The rate for any systemic reactogenicity event in those co-vaccinated was modestly elevated over the rate for either NVX-CoV2373 or influenza vaccine alone, consistent with an overall higher vaccine immunogen load and the relatively younger participant population in the sub-study. This was seen mainly for the events of muscle pain and fever, yet despite the relative increase in the rate of fever, the absolute fever rate in those who received two co-administered vaccinations was modest (4.3%). Rates of severe events were low in all groups and showed no clinically

meaningful pattern of increased reactogenicity. The elevation in some reactogenicity events may, in part, have been due to the overall younger age of the influenza vaccine sub-study participants compared with the main study reactogenicity cohort (median age 39.0 years [93.3% 18 to <65 years] vs. a median age of 52.0 years [80.1% 18 to <65 years]). Those ≥65 years of age who received two adjuvanted vaccines compared with those <65 years of age who received the adjuvanted NVX-CoV2373 and unadjuvanted QIVc had lower rates of reactogenicity; this effect of age was also seen in the NVX-CoV2373 alone group and in prior NVX-CoV2373 studies[6,12,13] and is consistent with immunosenescence.

The rates of AEs, SAEs, and AESIs were low and balanced between those given NVX-CoV2373, influenza vaccine, or both. The rate of any MAAE was higher in sub-study participants compared with non-sub-study participants. This difference was less apparent when assessing treatment-related MAAEs only. The increased rate of all MAAEs in the sub-study may represent a health-care seeking bias in those desiring an influenza vaccine rather than a true increase in medical visits due to AEs related to co-vaccination or receipt of the influenza vaccine plus placebo; an assessment of these excess medical visits revealed that most were general practice visits associated with health maintenance concerns (data not shown).

The magnitude of the humoral response to either influenza vaccine was not affected by co-administration with NVX-CoV2372 when assessed at 21 days after dosing, although care should be used in generalising this observation to aTIV because of the small sample size. The post-vaccination rise in GMTs and SCRs for each strain were high when either influenza vaccine was administered with placebo or NVX-CoV2373, although there was a generally lower response to the influenza B strains found in all influenza vaccine recipients. The humoral immune response to influenza B strains is dependent upon numerous factors, including age and prior influenza vaccine exposure.[14] Low influenza B SCRs[15] and lower SCRs relative to influenza A strains[16,17] have been seen with prior immunogenicity studies of quadrivalent inactivated influenza vaccines.

In contrast, there was a modest reduction in the anti-S EUs observed with the co-administration of NVX-CoV2373 and an influenza vaccine. It is unclear if this reduction was due to vaccine

interference or due to the non-randomised nature of the studied groups. In the absence of a correlate of protection, it is difficult to interpret the significance of this finding. The post hoc assessment of vaccine efficacy in this sub-study in those 18 to <65 years of age was 87.5% compared with the vaccine efficacy of 89.8% in the same age group from the PP efficacy populations in the main study, although given the small number of endpoint cases in the sub-study the lower bound of the CI was just below zero. The similar vaccine efficacy within the influenza vaccine co-administration group would suggest that the reduction in the anti-S EUs as a result of co-administration may not be clinically meaningful. In fact, the levels of anti-S EUs in those receiving both vaccines (in either those 18 to <65 or ≥65 years of age) was still over 3-fold greater than the anti-S EUs found in convalescent serum, suggesting that EUs in this range found in sub-study participants may be protective.[18,19] It should be also noted that no difference in the rates of SCRs were seen between those co-vaccinated and those who received NVX-CoV2373 alone.

It is also apparent that the extent of the reduction in anti-S EUs may be less relevant in participants who are seropositive at baseline, as they achieved high values post-vaccination with co-administration of influenza vaccine with a mean of 71,115 EUs in co-vaccinated seropositive participants of all ages compared with a mean of 44,678 EUs in PP NVX-CoV2373 alone recipients of all ages (yet this was not as large as the mean of 125,490 EUs in seropositive NVX-CoV2372 alone recipients) (**Table 3** and **Supplementary Table S12A**). One possible explanation for this finding is that seropositive individuals have pre-existing T-cell and B-cell populations with immune memory against the SARS-CoV2 spike protein minimizing any possible effect of immune interference. Therefore, it is possible that influenza vaccine co-administration may impact priming but have no impact on the immune response in previously primed individuals. An implication of this is that influenza vaccine co-administration with the second dose of any two-dose COVID-19 vaccine schedule, or with a subsequent booster dose of COVID-19 vaccine, may overcome any potential immune interference. This should be assessed further as it has important implications for public health vaccination strategies.

Although this is the first study to show the co-administration of a COVID-19 with a seasonal influenza vaccine, influenza vaccine co-administration has been well studied. Our study utilised two different influenza vaccines for different age groups in compliance with UK influenza vaccination guidelines.[20] For those <65 years of age, a cell culture–derived, inactivated quadrivalent influenza vaccine was used. QIVc was approved in the UK in December 2018 for individuals 9 years and older and extended to 2 years and older in 2020. For the older cohort, a MF59 squalene-based, oil-in-water aTIV was administered. This aTIV was approved in the UK in August 2017. In two studies of the MF59 aTIV given concomitantly with a pneumococcal vaccine, antibody responses to either vaccine were not affected and the safety data were consistent with expected rates of AEs for both vaccines.[21,22] No interference or safety concerns have been reported with a QIV co-administered with pneumococcal and herpes zoster vaccines.[23,24]

The strengths of this sub-study include the placebo-controlled design and its alignment with national influenza vaccine policy in the use of both adjuvanted and unadjuvanted influenza vaccines in different age groups. Study limitations include the small overall sub-study size (with few participants ≥65 years of age owing to the high rate of routine influenza vaccination among participants in this age group at study start), small number of sub-study efficacy endpoints, lack of formal pre-specified non-inferiority statistical assessment of immunogenicity, and the lack of randomisztion in recruiting the influenza sub-study, immunogenicity, and reactogenicity cohorts. A stronger design could have been four randomiszed arms consisting of NVX-CoV2373 plus influenza vaccine, NVX-CoV2373 plus placebo, influenza vaccine plus placebo, and placebo plus placebo. Another limitation was the open-label design in administering the influenza vaccine, but this was required to order to allow participants to consider only the study vaccine injection site for assessment of local symptoms. Finally, the assessment of neutralising antibody titres may have benefitted the immunogenicity investigation, yet prior studies with NVX-CoV2373 have shown a strong correlation between the anti-S and wild-type microneutralizations results.[18]

This is the first study to demonstrate the safety, immunogenicity, and efficacy profile of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine. These data

demonstrate no early safety concerns with the concomitant administration of NVX-CoV2373 with an influenza vaccine. Immunogenicity of the influenza vaccine was preserved with concomitant administration while a modest decrease in the immunogenicity of the NVX-CoV2373 vaccine was found. Vaccine efficacy in those 18 to <65 years appeared to be preserved in those receiving both vaccines compared with those vaccinated with NVX-CoV2373 alone. Future clinical trials and post-licensure studies of COVID-19 vaccines should include safety and immunogenicity data on co-administration with common adult and paediatric vaccines. More research on the concomitant vaccination of COVID-19 and influenza vaccines is needed, especially in those >65 years of age, to help guide national immunisation policy on this critical issue.

Contributors

ST, JSP, LK, FD, GG, IC, AR, and EJR are Novavax employees. PTH is the chief investigator. ST, PTH, JP, LK, FD, GG, IC, and AR contributed to the protocol and design of the study. EG, CG, ALG, JG, FB, AMM and PAS are study site principal investigators. SR, JE, and AG are Seqirus employees. EG, CG, ALG, JG, FB, AMM and PS contributed to the study or data collection. IC and AR verified the data and reviewed the statistical analysis. All authors reviewed, commented on, and approved this manuscript prior to submission for publication.

Declaration of interest

ST, JSP, LK, FD, GG, IC, AR, and EJR are Novavax employees and SR, JE, and AG are Seqirus employees as they receive a salary for their work. All other authors (PTH, FB, EG, CC, JG, ALG, AMM, PAS) declare no competing interest.

Data sharing

The protocol for this phase 3 study is publicly available from Novavax.

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[TABLES]

Table 1: Demographics and baseline characteristics of participants in the influenza vaccine co-administration sub-study and entire study populations (ITT population)

	NVX-CoV2373 + aTIV (n=16)	NVX-CoV2373 + QIVc (n=201)	Placebo + aTIV (n=13)	Placebo + QIVc (n=201)	Total Study, ITT Population (n=15139)
Age, yr (SD)	66.9 (1.86)	40.3 (12.72)	69.3 (3.73)	40.2 (11.57)	53.1 (14.91)
Median	66.0	38.0	69.0	37.0	55.0
Range	65, 71	20, 64	65, 77	23, 64	18, 84
Age group, n (%)					
18-64 yr	0 (0)	201 (100)	0 (0)	201 (100)	11014 (72.8)
≥65 yr	16 (100)	0 (0)	13 (100)	0 (0)	4125 (27.2)
Sex, n (%)					
Male	6 (37.5)	117 (58.2)	4 (30.8)	114 (56.7)	7808 (51.6)
Female	10 (62.5)	84 (41.8)	9 (69.2)	87(43.3)	7331 (48.4)
Race or ethnic group, n (%)					
White	12 (75.0)	151 (75.1)	11 (84.6)	153 (76.1)	14280 (94.3)
Black or African American	0 (0)	4 (2.0)	0	2 (1.0)	60 (0.4)
Asian	0 (0)	14 (7.0)	1 (7.7)	22 (10.9)	462 (3.1)
Multiple	4 (25.0)	25 (12.4)	0 (0)	23 (11.4)	136 (0.9)
Not reported	0 (0)	3 (1.5)	1 (7.7)	1 (0.5)	176 (1.2)
Other	0 (0)	3 (1.5)	0 (0)	0 (0)	17 (<0.1)
Missing	0 (0)	1 (0.5)	0 (0)	0 (0)	8
Hispanic or Latinx quadrivalent	1 (6.3)	9 (4.5)	1 (7.7)	4 (2.0)	125 (0.8)
SARS-CoV-2 serostatus, n (%)	15 (93.8)	183 (91.0)	12 (92.3)	184 (91.5)	14362 (94.9)
Negative	1 (6.3)	18 (9.0)	0 (0.0)	13 (6.5)	643 (4.2)
Positive	0 (0)	0 (0)	1 (0.7)	4 (2.0)	134 (0.9)
Missing					
Comorbidity status*					
Yes	5 (31.3)	50 (24.9)	7 (53.8)	55 (27.4)	6767 (44.7)
No	11 (68.8)	151 (75.1)	6 (46.2)	146 (72.6)	8372 (55.3)

*Comorbid subjects are those identified who have at least one of the comorbid conditions reported as a medical history or have a screening body mass index value greater than 30 kg/m^2.

Percentages are based on the intention-to-treat data set within the seasonal influenza vaccine sub-study (by vaccine type; aTIV for those ≥65 years of age and QIVc for those <65 years of age) and overall.

Abbreviations: aTIV=adjuvanted trivalent influenza vaccine; ITT=intention-to-treat; QIVc=influenza vaccine quadrivalent, cellular; SD=standard deviation.

Table 2: Safety data from participants in the influenza vaccine co-administration sub-study and participants in the entire study population (without sub-study participants)

	NVX-CoV2373 + Influenza Vaccine	Placebo + Influenza Vaccine	NVX-CoV2372 Alone	Placebo Alone
	n=217	n=214	n=7352	n=7356
Any AE	40 (18.4%)	31 (14.5%)	1297 (17.6%)	1030 (14.0%)
Any severe AE	1 (0.5%)	0 (0%)	33 (0.4%)	33 (0.4%)
SAE	1 (0.5%)	0 (0%)	43 (0.6%)	44 (0.6%)
MAAE	17 (7.8%)	18 (8.4%)	279 (3.8%)	288 (3.9%)
Treatment-related MAAE	3 (1.4%)	0 (0%)	34 (0.5%)	17 (0.2%)
PIMMC	0 (0%)	0 (0%)	5 (<0.1%)	8 (0.1%)
AESI related to COVID	0 (0%)	0 (0%)	8 (0.1%)	22 (0.3%)

Influenza vaccine co-administration sub-study participants compared with the entire ITT study population, excluding the co-vaccination sub-study group. Adverse events and severe adverse events are those within 21 days of study dose 1 (with or without co-administration of influenza vaccine). SAEs, MAAEs, AESIs, and PIMMCs are assessed for the entire study period.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ITT, intention-to-treat; MAAE=medically-attend adverse event; PIMMC= potentially-immune-mediated medical condition; SAE=serious adverse event.

Table 3: Anti-S IgG on Day 0 and Day 35 in the influenza vaccination sub-study and immunogenicity cohort, in the PP population, by age group

		NVX-CoV2373 + Influenza Vaccine					Placebo + Influenza Vaccine			
		Day 0		Day 35			Day 0		Day 35	
	n	Point estimate	(95% CI)	Point estimate	(95% CI)	n	Point estimate	(95% CI)	Point estimate	(95% CI)
GMEU										
IIV + NVX-CoV2372 or placebo, all ages	n=178	116.3	(107.7, 125.6)	31236.1	(26295.5, 37104.9)	n=181	111.4	(105.1, 118.1)	115.7	(106.1, 126.1)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168	115.8	(107.2, 125.0)	31516.9	(26316.2, 37745.3)	n=170	112.2	(105.4, 119.3)	116.8	(106.5, 128.0)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10	125.6	(75.0, 210.3)	26876.1	(15374.6, 46981.5)	n=11	100.0	(100.0, 100.0)	100.0	(100.0, 100.0)
GMFR										
IIV + NVX-CoV2372 or placebo, all ages	n=178			268.6	(221.0, 326.4)	n=181			1.0	(1.0, 1.1)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168			272.3	(222.3, 333.5)	n=170			1.0	(1.0, 1.1)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10			214.0	(96.5, 474.6)	n=11			1.0	(1.0, 1.0)
SCR										
IIV + NVX-CoV2372 or placebo, all ages	n=178			97.8	(94.3, 99.4)	n=181			0.6	(0.0, 3.0)
QIVc + NVX-CoV2373 or placebo, 18 to <65	n=168			97.6	(94.0, 99.3)	n=170			0.6	(0.0,3.2)
aTIV + NVX-CoV2373 or placebo, ≥65	n=10			100.0	(69.2, 100.0)	n=11			0.0	(0.0, 28.5)

Table 3: Anti-S IgG on Day 0 and Day 35 in the influenza vaccination sub-study and immunogenicity cohort, in the PP population, by age group (cont'd)

		NVX-CoV2373 Alone					Placebo Alone			
		Day 0		Day 35			Day 0		Day 35	
	n	Point estimate	(95% CI)	Point estimate	(95% CI)	n	Point estimate	(95% CI)	Point estimate	(95% CI)
GMEU										
NVX-CoV2373 or placebo alone, all ages	n=414	112.2	(107.5, 117.0)	44678.3	(40352.2, 49468.2)	n=417	110.3	(106.3, 114.5)	113.2	(106.8, 120.0)
NVX-CoV2373 or placebo alone, 18 to <65	n=300	111.9	(106.2, 117.9)	47564.3	(42327.3, 53449.4)	n=310	109.7	(105.2, 114.4)	113.5	(105.6, 122.0)
NVX-CoV2373 or placebo alone, ≥65	n=114	112.8	(105.0, 121.2)	37892.8	(30833.3, 46568.5)	n=107	112.1	(103.4, 121.4)	112.3	(103.1, 122.3)
GMFR										
NVX-CoV2373 or placebo alone, all ages	n=414			398.4	(358.6, 442.6)	n=417			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, 18 to <65	n=300			425.0	(375.7, 480.8)	n=310			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, ≥65	n=114			335.9	(274.4, 411.1)	n=107			1.0	(1.0, 1.0)
SCR										
NVX-CoV2373 or placebo alone, all ages	n=414			99.0	(97.5, 99.7)	n=417			0.7	(0.1, 2.1)
NVX-CoV2373 or placebo alone, 18 to <65	n=300			99.0	(97.1, 99.8)	n=310			1.0	(0.2, 2.8)
NVX-CoV2373 or placebo alone, ≥65	n=114			99.1	(95.2, 100.0)	n=107			0.0	(0.0, 3.4)

Influenza vaccine co-administration sub-study participants compared with the PP immunogenicity population (data are shown for participants who consented to have IgG levels assessed; data by all ages, those <65 and those ≥65). Comparison of the anti-S IgG GMEUs at baseline (Day 0) and 35 days and Day 35 GMRF and SCR after vaccination with NVX-CoV2373 or placebo with either aTIV, QIVc, or alone.

Abbreviations: aTIV=adjuvanted trivalent influenza vaccine; GMFR=geometric mean fold rise; GMEU=geometric mean ELISA unit; IgG=immunoglobulin G; IIV= inactivated influenza vaccine (both aTIV and QIVc); PP=per-protocol; QIVc=influenza vaccine quadrivalent, cellular; S=spike; SCR=seroconversion rate.

[FIGURE LEGENDS AND FIGURES]

Figure 1: Main study, influenza vaccine sub-study, and study cohorts. The main study intention-to-treat (ITT) population (n=15,139) were all participants who received at least one dose of NVX-CoV2373 or placebo. Those who were enroled in the influenza sub-study were then removed to create the main study safety population (n=14,708) used to make safety comparisons with the sub-study. The main study per-protocol (PP) efficacy population included all participants who were seronegative at baseline, received both doses of study vaccine, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic Covid-19 from the first dose until 6 days after the second dose. The influenza sub-study total ITT population included all those received at least one dose of NVX-CoV2373 or placebo and any influenza vaccine (n=431). This entire group was assessed for immunogenicity (haemagglutination inhibition assay and ELISA testing for anti-S IgG). Of these, 404 recorded data into the 7-day reactogenicity diary (influenza sub-study reactogenicity population). Those who did not record data included those who were unable to download the e-dairy or were non-compliant with its use. Of the 431 sub-study participants, 386 also met the PP efficacy definition as defined above. The immunogenicity cohort ITT population included all subjects from the main study who received at least one dose of NVX-CoV2373 or placebo and underwent ELISA testing for anti-S IgG. The per-PP immunogenicity subset were those who received two doses of vaccine, had all immunology samples available, had no major protocol deviations, and did not have a laboratory confirmed SARS-CoV-2 infection prior to any visit where serology was measured. The reactogenicity cohort ITT population included all subjects from the main study who received at least one dose of NVX-CoV2373 or placebo and recorded data into the e-diary. The influenza sub-study, immunogenicity cohort, and reactogenicity cohort were enroled at four, four, and two unique study hospitals, respectively, who had the resources to manage the additional study requirements.

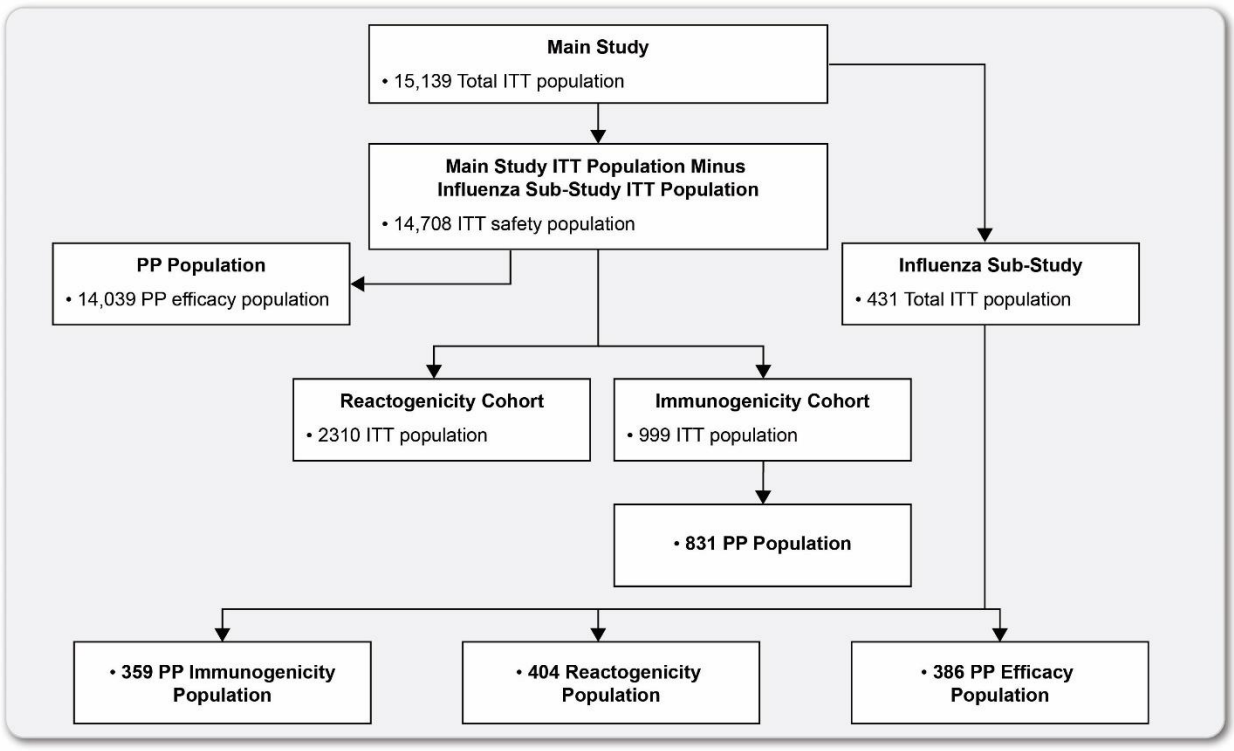

Main Study
• 15,139 Total ITT population
Main Study ITT Population Minus Influenza Sub-Study ITT Population
• 14,708 ITT safety population
PP Population
• 14,039 PP efficacy population
Influenza Sub-Study
• 431 Total ITT population
Reactogenicity Cohort
• 2310 ITT population
Immunogenicity Cohort
• 999 ITT population
• 831 PP Population
• 359 PP Immunogenicity Population
• 404 Reactogenicity Population
• 386 PP Efficacy Population

Figure 2: Reactogenicity data from participants in the influenza vaccine co-administration sub-study and participants in the reactogenicity cohort population after dose 1: local and systemic. The percentage of participants in each treatment group with solicited local and systemic adverse events during the 7 days after each vaccination is plotted according to the maximum toxicity grade (mild, moderate, severe, or potentially life-threatening) in participants included in the seasonal influenza vaccine sub-study and those included in the reactogenicity cohort.

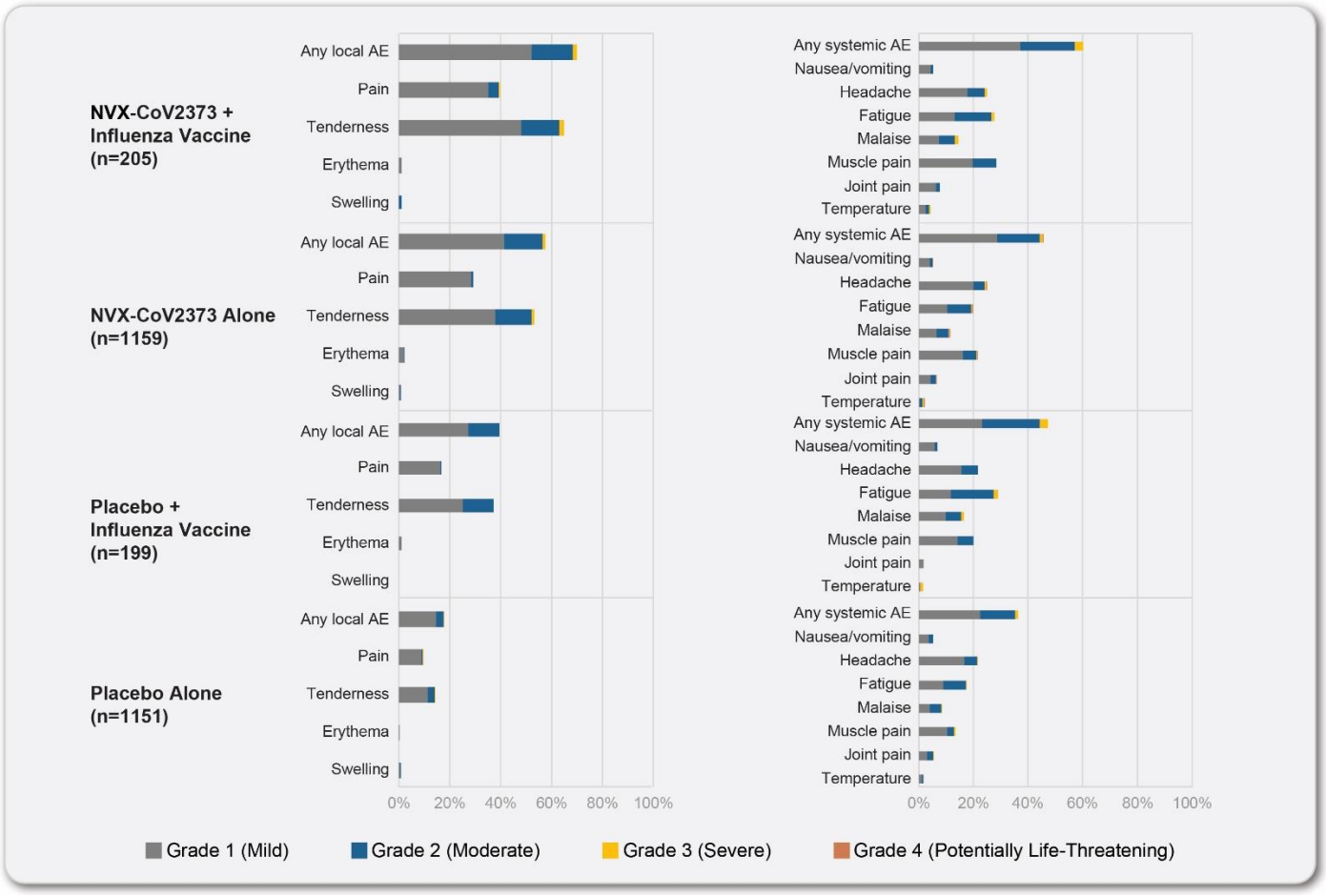
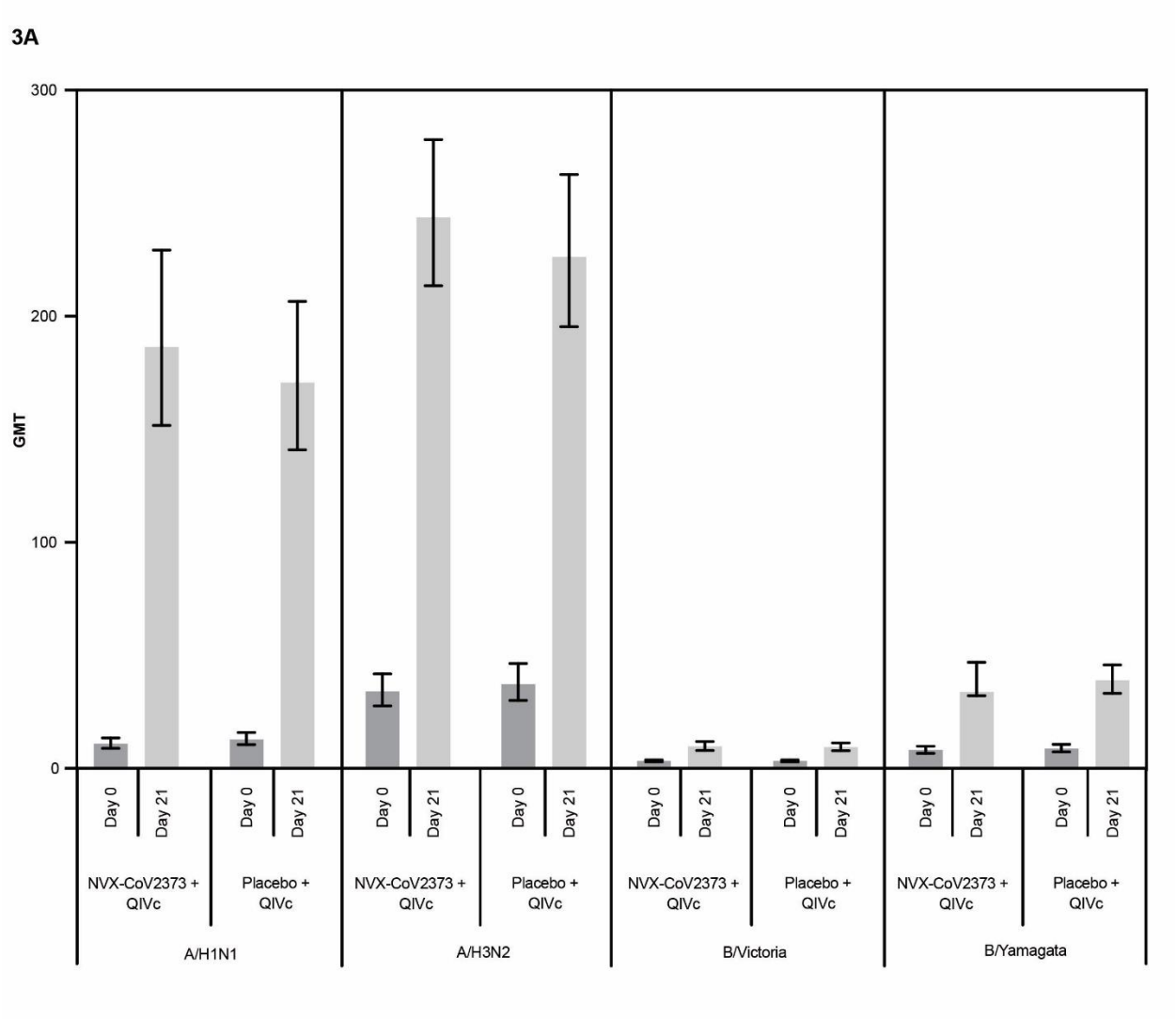


Figure 3: A) HAI GMTs on Day 0 and Day 21 in the QIVc Group; B) HAI GMTs on Day 0 and Day 21 in the aTIV Group.

Comparison of the HAI GMTs at baseline (Day 0) and 21 days after vaccination with NVX-CoV2373 or placebo with either QIVc or aTIV influenza vaccine by influenza strain. For NVX-CoV2373 + QIVc (n=178), Placebo + QIVc (n=179), NVX-CoV2373 + aTIV (n=13), Placebo + aTIV (n=11). Error bars represent 95% confidence intervals. aTIV= adjuvanted trivalent influenza vaccine; GMT=geometric mean titre; HAI=haemagglutination inhibition; QIVc=influenza vaccine quadrivalent, cellular.



3B

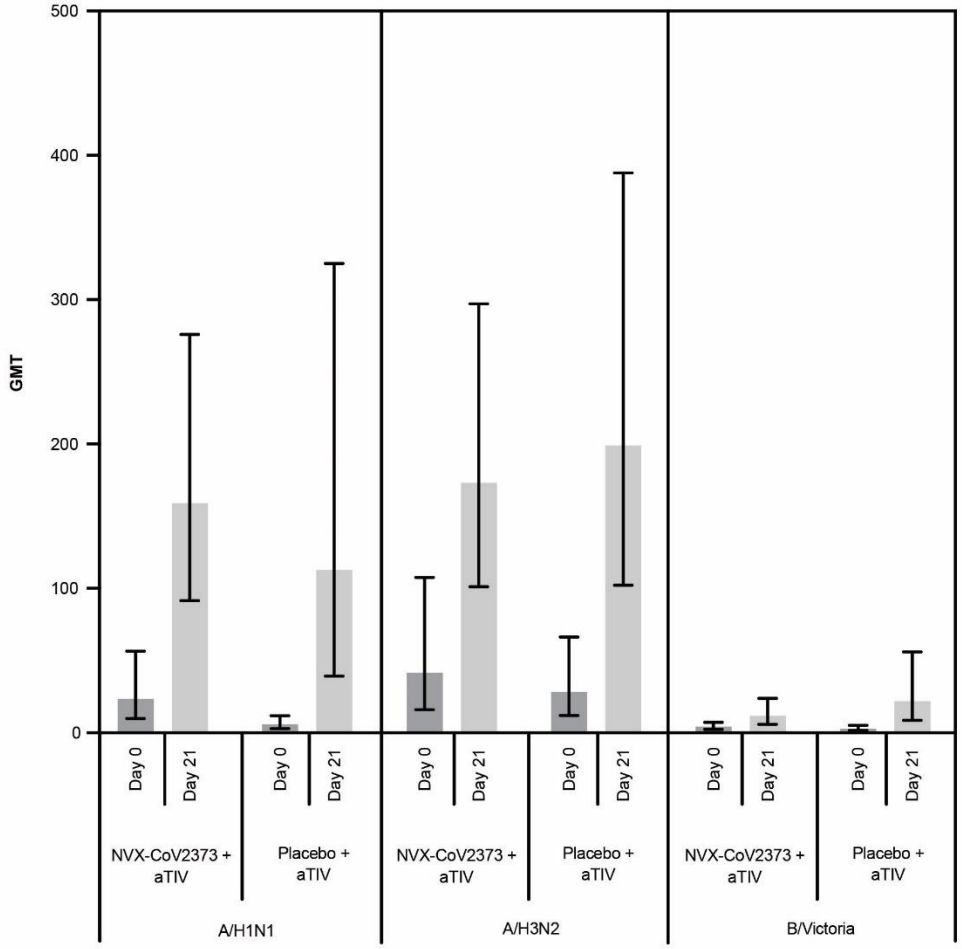
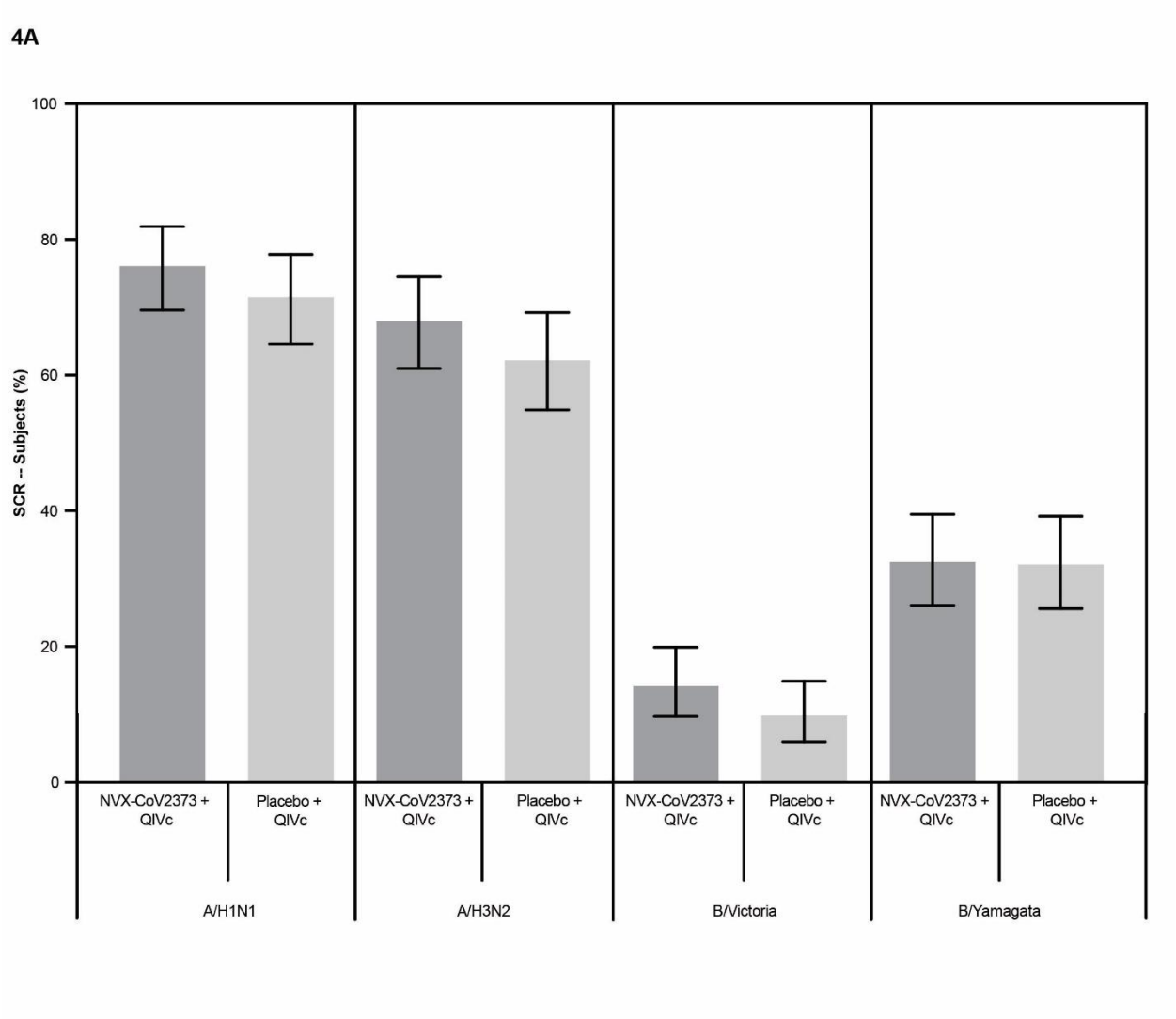
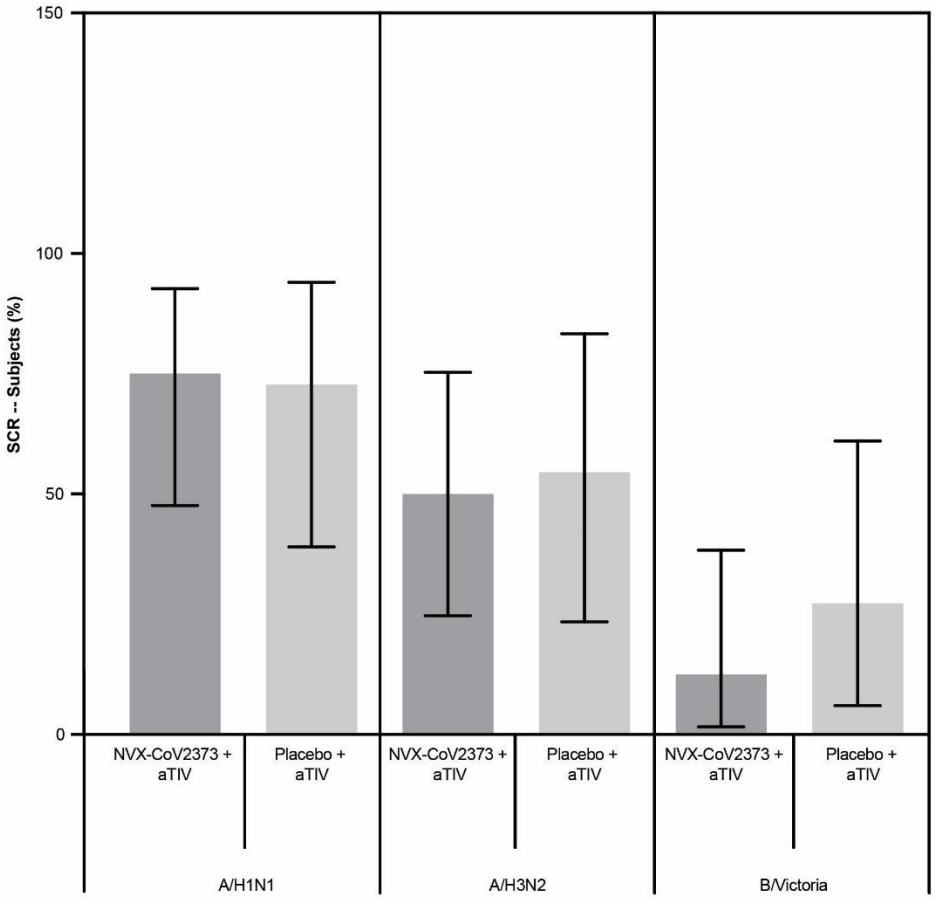

GMT
500
400
300
200
100
0
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H1N1
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H3N2
Day 0
Day 21
Day 0
Day 21
NVX-CoV2373 + aTIV
Placebo + aTIV
B/Victoria

Figure 4: A) HAI SCRs on Day 0 and Day 21 in the QIVc Group; B) HAI SCRs on Day 0 and Day 21 in the aTIV Group.

Comparison of the HAI SCRs 21 days after vaccination with NVX-CoV2373 or placebo with QIVc or aTIV influenza vaccine by influenza strain. aTIV= adjuvanted trivalent influenza vaccine; HAI=haemagglutination inhibition; QIVc=influenza vaccine quadrivalent, cellular; SCR=seroconversion rate.



4B


150
100
50
0
SCR -- Subjects (%)
NVX-CoV2373 + aTIV
Placebo + aTIV
NVX-CoV2373 + aTIV
Placebo + aTIV
NVX-CoV2373 + aTIV
Placebo + aTIV
A/H1N1
A/H3N2
B/Victoria

AUTHOR RESPONSES TO JOURNAL COMMENTS -- Manuscript ref. no. thelancetrm-D-21-00741 [20 August 2021]

Reviewers' Comments

Reviewer #1: Manuscript is improved and important.

Reviewer #2: It is a sub-study on influenza vaccine co-administration as part of the phase 3 randomized trial of NVX-CoV2373's safety and efficacy. This is the first study to demonstrate the safety and immunogenicity profile and clinical vaccine efficacy of a COVID-19 vaccine when co-administered with a seasonal influenza vaccine. The article became more rigorous after revision, but are still some shortcomings:

1. Table 3 Line 2: "Day 35" should be adjusted and needed to further optimize to make the table compact.

Response: **The authors thank you for the response. We had previously offered 2 options for the formatting of this table; we have now provided the version that is more compact (we deleted blank cells and categories).**

2. Figure 1 should give a detailed description of influenza sub-study(431 total).

Response: **Figure 1 currently has a legend with an extensive explanation of the sub-study. Was this available to the reviewer? The authors feel this level of detail is appropriate and sufficient for the figure.**

3. The public health vaccination strategy may suggest that influenza vaccine co-administration occur with the second dose of any two-dose COVID-19 vaccine. While this article only tested co-administration with first dose.

Response: **The authors agree that this is a possible conclusion from this study and have already indicated this in the Discussion.**

4. The elders (older than 60) were few in the sub-study and no research on children, but they are the main target for vaccination policy for concomitant vaccination Covid-19/Influenza. Conclusion is difficult to extrapolate.

Response: **The authors agree that the elderly population is a focus for concomitant vaccination and we have very limited data in this study. This is already acknowledged in the discussion. However, in the UK, all individuals over the age of 50 years (33% of the study population) are now included in the routine influenza programme. There are currently no data on the Novavax vaccine in young children and no national COVID-19 vaccine programmes which routinely include children < 12 years.**

5. There are some grammatical errors in the article, such as "It is over a year since the start of the pandemic"(Line 106), "Safety and immunogenicity of COVID-19 vaccines when co-administered with influenza vaccines has not yet been reported." (Line 32) (yeah-we should fix)

Response: **The authors thank you. We have now reviewed the manuscript for grammatical errors.**

6. The results of this study were relatively few, only the VE against PCR-confirmed cases were showed, additional analyses such as the VE against mild cases, or sever cases were not included in this study.

Response: **The authors acknowledge the limited vaccine efficacy data in this manuscript but it reflects the low numbers of symptomatic COVID-19 in the sub-study population. Please refer to the main manuscript for these additional analyses in the overall study.**

7. According to trial procedures, sub-study participants were not enrolled randomly, which is inconsistent with the title. (The authors were asked to put the term randomized into the title.

Response: **The authors agree that the sub-study participants were not randomised to receive influenza vaccine, although participants in the main study were randomised to receive vaccine or placebo. We have tried to reflect this in the title by indicating the substudy was performed "*Within* a Randomised Controlled Trial". We are happy to remove this from the title if the editor prefers.**

Reviewer #3: Authors have responded to my comments.

Reviewer #4: The authors have responded to all my comments and most of the comments from the other reviewers and the clarity of the manuscript has improved.

Reviewer #5: The authors have addressed my comments appropriately, thank you.

Editorial Comments

Response: **We had provided answers to most of these questions in the previous round. We have provided these answers again to make sure you have them.**

Authorship and reporting guidelines:

1. Please check that all author name spellings and affiliations are correct. We will not be able to correct author names or add in missing authors once published, so please do check these very carefully throughout.
2. Please indicate any authors who are full professors.

Response: **All author names and affiliations are correct. Paul Heath is a full professor.**

Title/summary:

3. Please inform us if you would like to have a translated summary published alongside your paper. If yes, please let us know now. At the final proof stage, please send the translated summary (it must be a true translation) and this will be included as an additional appendix.

Response: **We do not need a translated summary.**

Methods:

4. Please explain any deviations from the protocol.
5. Please ensure that all outcomes specified in the protocol (including all secondary outcomes) are reported in the manuscript. If there are any secondary endpoints that cannot be included please mention these explicitly and explain why and where they will be made available.
6. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.

Response: **As this paper is presenting the results of a sub-study within a larger study, not all trial outcomes are presented but all sub-study outcomes are presented. The protocol reflects the main study.**

Results:

7. For the main outcome measures, please include a result for each group, plus a point estimate (eg, RR, HR) with a measure of precision (e.g, 95% CI) for the absolute difference between groups, in both the Summary and the main Results section of the paper.
8. p values should be given to two significant figures, but no longer than 4 decimal places (eg p<0.0001).
9. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large (>1000 individuals).
10. For means, please provide standard deviation (or error, as appropriate).
11. Please provide interquartile ranges for medians.

Response: **All of the Results have the necessary measures as requested, if available, as completed by the authors.**

Additional requirements:

12. Please can you source the original, editable file formats for the figures - our illustrators redraw all figures but need them in a specific format to ensure accuracy. An EPS file would be ideal, or if you created the figure in a program such as Word, Excel, or PowerPoint, please send the .doc/.xls/.ppt file the figure was created on. When an image is editable, any text on it should be selectable and it should 'redraw' and retain its sharpness when zoomed into rather than pixelating. It is generally impossible to convert an uneditable file into an editable one (converting the uneditable file you have already sent us into another format will not make it editable). Often the best thing to do is to contact the individual who created the image and ask

for them to send the image in the program they used to create it." More information can be found here:https://www.thelancet.com/for-authors/forms?section=artwork.

***Response*: The figures are in EPS format, an acceptable format per journal artwork guidelines.**

13. Our production system is not compatible with Endnotes. Please convert references to normal text.

***Response:* We did not use EndNotes. The references are in normal text.**

14. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the main paper; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.

***Response:* At the request of the journal reviewers, we added a figure (Figure 1). We now have 7 figures/tables.**

15. Collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.

***Response:* We have provided a document with the names of the Study Group in two columns for PubMed listing, as suggested by the journal.**

16. In the data sharing statement, should there be a link for people to access the phase 2 protocol? In terms of contacting Novavax to access data, is there a contact people should get in touch with that can be included in this statement?

***Response:* The corresponding author may be contacted for any questions concerning the data.**
The protocol is available on two websites (as stated on the CONSORT form):
https://www.medrxiv.org/content/10.1101/2021.05.13.21256639v1.supplementary-material

https://www.novavax.com/resources#protocols

17. Authors' contribution form
18. Signed Conflict of interest form for ALL authors

***Response:* These forms have been provided.**

CLINICAL STUDY PROTOCOL

A PHASE 3, RANDOMISED, OBSERVER-BLINDED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF A SARS-COV-2 RECOMBINANT SPIKE PROTEIN NANOPARTICLE VACCINE (SARS-COV-2 RS) WITH MATRIX-M1™ ADJUVANT IN ADULT PARTICIPANTS 18-84 YEARS OF AGE IN THE UNITED KINGDOM

Investigational Materials:	SARS-CoV-2 rS with Matrix-M1™ adjuvant
Protocol Number:	2019nCoV-302
EudraCT Number:	2020-004123-16
Sponsor:	Novavax, Inc. 21 Firstfield Road Gaithersburg, MD 20878 United States
Responsible Clinical Operations Manager:	[redacted] Clinical Operations Telephone: [redacted]
Responsible Clinical Development Lead:	[redacted] Clinical Development Telephone: [redacted]
Chief Investigator:	[redacted] Telephone: [redacted]
Version – Date:	Version 4.0 – 25 February 2021

Prior Versions:	Version 1.0 – 24 August 2020 Version 1.1 – 17 September 2020 Version 1.2 – 21 September 2020 Version 2.0 – 23 October 2020 Version 3.0 – 23 December 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Phase 3, Randomised, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom

PROTOCOL NUMBER: 2019-nCoV-302

EUDRACT NUMBER: 2020-004123-16

[redacted]
Novavax, Inc.

Date

[redacted] Clinical Operations
Novavax, Inc.

Date

[redacted]

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Phase 3, Randomised, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom" in accordance with all guidelines, including International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and all applicable government regulations. I have read and understand all sections of the protocol.

_____ _____

Signature of Investigator | Date

_____

Printed Name of Investigator

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

PROTOCOL NO.: 2019nCoV-302

TITLE: A Phase 3, Randomised, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom

STUDY PHASE: Phase 3

STUDY SITES: 33 sites across the United Kingdom (UK).

OBJECTIVES:

- **The primary objective is:**
  - To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed **(**by polymerase chain reaction [PCR] to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), symptomatic coronavirus disease 2019 (COVID-19), when given as a 2-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adults.
- **The secondary objectives are:**
  - To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in adults regardless of their serostatus at baseline.
  - To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants requiring specific medical interventions as compared to placebo.
  - To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant on mild COVID-19 symptoms as compared to placebo.
  - To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant on occurrence of asymptomatic or undetected infections with SARS-CoV-2 as compared to placebo.
  - In a subset of adult participants, to evaluate the immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant as compared to placebo.
  - To evaluate safety in terms of serious adverse events (SAEs) and medically attended adverse events (MAAEs) related to study vaccination in all adult participants during the entire study period.
  - To evaluate safety in terms of adverse events of special interest (AESIs), which encompasses potential immune-mediated medical conditions (PIMMCs) and AESIs relevant to COVID-19 including possible vaccine-enhanced disease, in all adult participants at any time after the first dose. In a subset of adult participants,

to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) after the initial set of study vaccinations.

- To evaluate safety in terms of all MAAEs for 14 days after second vaccination and unsolicited AEs for 21 days after first study vaccination and 28 days after second study vaccination in the initial set of vaccinations.
- To assess the duration of vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.

- **The exploratory objectives are:**
  - In a subset of adult participants, to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in the initial set of vaccinations when co-administered with a licensed seasonal influenza vaccine.
  - In a subset of adult participants unblinded before the crossover, to explore the efficacy and safety of SARS-CoV-2 rS with Matrix-M1 adjuvant in the initial set of vaccinations and/or an approved or deployed SARS-CoV-2 vaccine.

ENDPOINTS

- **The primary endpoint is**:
  - First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- **The key secondary endpoint is:**
  - First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic moderate or severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- **The other secondary endpoints are**:
  - First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
  - First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.

- First occurrence of COVID-19 requiring hospitalisation, intensive care unit (ICU) admission or mechanical ventilation linked to any virologically confirmed (by PCR to SARS-CoV-2) COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild COVID-19 (with no progression to moderate or severe COVID-19 during the course of the COVID-19 episode) with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants, regardless of their serostatus at baseline.
- First occurrence of laboratory-confirmed (by PCR or nucleocapsid [N]-protein serology to SARS-CoV-2) symptomatic or asymptomatic COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants with negative serostatus at baseline.
- Analysis of antibodies binding to the SARS-CoV-2 spike (S) protein by enzyme-linked immunosorbent assay (ELISA) at Day 0 (baseline) and Day 35 (14 days after second study vaccination).
- Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA at Crossover Day 0 visit (baseline) and Crossover Day 35 visit (14 days after second study vaccination).
- The occurrence and relationship to study vaccination of SAEs and MAAEs related to study vaccination (in all adult participants) during the entire study period.
- The occurrence and relationship to study vaccination of AESIs and PIMMCs (in all adult participants) during the entire study period.
- The occurrence and severity of reactogenicity in terms of solicited local and systemic AEs (in sub-study participants) after the initial set of vaccinations.
- The occurrence, severity, and relationship to study vaccination of all MAAEs for 14 days after second vaccination and unsolicited AEs (in all adult participants) for 21 days after first study vaccination and 28 days after second study vaccination following the initial set of vaccinations.
- Relative vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.

- **Exploratory endpoints are:**
  - First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 with onset at least 14 days after first study vaccination (e.g., Day 14) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.

- Any occurrence of serologic conversion (by serology to SARS-CoV-2 N protein) between baseline and 1 year after last study vaccination in the initial set of vaccinations in adult participants seronegative at baseline.
- Any occurrence of serologic conversion (by serology to SARS-CoV-2 N protein) between Crossover Day 0 visit and the end of study (EOS) visit in the second set of vaccinations in adult participants seronegative at baseline.
- Analysis of the proportion of adult participants with evidence of seroconversion as demonstrated by binding antibodies to the SARS-CoV-2 S protein by ELISA at Day 35 (14 days after second study vaccination) and Crossover Day 35 visit (14 days after the Crossover Day 21visit).
- Analysis of the cell-mediated immune responses (for example, as measured by enzyme-linked immune absorbent spot (ELISpot) ± intracellular cytokine staining) on Days 0 (baseline) and 35 (14 days after second study vaccination) in the initial set of vaccinations.
- SARS-CoV-2 neutralisation as measured by virus neutralisation assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein) at Day 0 (baseline) and Day 35 (14 days after second study vaccination) in the initial set of vaccinations.
- Analysis of the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant when co-administered with seasonal influenza vaccine in a subset population.
- Analysis of the efficacy and safety of SARS-CoV-2 rS with Matrix-M1 adjuvant and/or an approved or deployed SARS-CoV-2 vaccine in a subset population.
- Analysis of the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in participants with asymptomatic COVID-19 who test positive for the disease by SARS-CoV-2 N protein serology but have no accompanying symptoms.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in seronegative adult participants by age (<65 and ≥ 65), in racial and ethnic minorities, and in those with co-morbid conditions.
- The occurrence, severity, and relationship to study vaccination of unsolicited AEs (in all adult participants) for 21 days after first study vaccination and 28 days after second study vaccination following the initial set of vaccinations with the adjustment to remove reactogenicity events that were recorded as unsolicited AEs within 7 days of each dose in the initial set of vaccinations.

STUDY DESIGN:

This is a Phase 3, multi-centre, randomised, observer-blind, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants 18 to 84 years of age (inclusive) in the UK. Following permission by regulatory bodies and based on achieving the primary efficacy endpoint and an acceptable safety profile, participants will be revaccinated with 2 injections 21 days apart of the alternate study vaccine ("blinded crossover"). That is, initial recipients of placebo will receive active SARS-CoV-2 rS with Matrix-M1 and initial recipients of active vaccine will receive placebo. Every effort will be made to identify sites of high SARS-CoV-2 activity, and populations within these sites who are at high risk of exposure to the virus will be enrolled such that the incidence of COVID-19 in the study will be higher than 1% and the sample size and enrolment period may be reduced.

After signing informed consent, participants may be screened within a window of up to approximately 30 days. During the screening period, nose/throat samples may be taken to detect SARS-CoV-2 by PCR, if the participant has any COVID-19 symptoms or significant exposure history.

Approximately 15,000 male and female adult participants 18 to 84 years of age (inclusive) with and without relevant comorbidities are planned for the study. An effort will be made to enrol a target of at least 25% of participants who are ≥ 65 years of age as well as prioritising other groups that are most affected by COVID-19, including racial and ethnic minorities. This will be under the assumption that the annual incidence of symptomatic COVID-19 will be approximately 1% to 5%.

The sample size may be adjusted by the Sponsor during the study, based on blinded data, to ensure sufficient power at the time of the primary analysis. Details on the possible sample-size reassessment will be described in the statistical analysis plan (SAP).

On Day 0 and Crossover Day 0, nose/throat samples will be taken to detect PCR for SARS-CoV-2 and blood samples will be taken to detect any existing SARS-CoV-2 antibodies at baseline. Participants will be randomised in a 1:1 ratio via block randomisation to receive 2 intramuscular (IM) injections of the SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo, as described in Table S1-1.

Table S1-1 Study Vaccine Groups

Study Vaccine Groups	Number of Randomised Participants	2 Vaccinations	
		Day 0	Day 21 (+ 7 days)
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N = 7,500	X	X
Placebo	N = 7,500	X	X

Randomisation will be stratified by site and by age ≥ 65 years. In addition, there will not be specific age sub-stratification recruitment targets within the ≥ 65-year age group, but through site recruitment; the aim is to allow a generally representative age distribution overall.

The study will consist of the screening period (Days -30 to 0); initial vaccination days (Days 0 and 21 [+7-day window]); and outpatient study visits on Day 0, Day 21 (+ 7 days), and Day 35 (14 days minimum after second study vaccination [+ 7 days]) after last study vaccination. Visits for the purpose of obtaining lab tests prior to unblinding may occur if

feasible. Additional study visits for blood draws and blinded crossover injections will occur after achieving the primary efficacy endpoint and an acceptable safety profile.

The duration of individual participation, including screening, will be a maximum of 1 year (Day 386 ± 15 days) from the initial set of vaccinations. This will be an event-driven study for the assessment of vaccine efficacy (VE) and will end when a sufficient number of events have been observed, yet all participants will be followed for the entire study duration for an assessment of duration of vaccine efficacy (placebo-controlled and actively controlled) and for safety endpoints.

A licensed seasonal influenza co-administration sub-study will be conducted in the first approximately 400 participants who meet the additional inclusion criteria for this study. Participants may be enrolled at selected study sites due to the availability of seasonal influenza vaccine. After being randomised to receive intramuscular (IM) injections of SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo, sub-study participants will receive a licensed seasonal influenza vaccine on Day 0 in the opposite deltoid. These participants will be part of the solicited AE safety subset analysis.

Given that this study and others will enrol during the influenza virus season and that the highest at-risk population, namely the elderly and adults with comorbid conditions for influenza mirrors that of SARS-CoV-2, a co-vaccination sub-study is included. This sub-group will undergo the same safety and efficacy evaluations as the entire study population. In addition, the entire sub-study will have reactogenicity assessed. This group must not have had a current season licensed influenza vaccine and have no prior history of allergy or severe reaction to seasonal influenza vaccine. To assess the possible impact of the study vaccine on the immunogenicity of the influenza vaccine, this group will also have a hemagglutination inhibition assay (HAI) performed.

A global Safety Monitoring Committee (SMC) was convened to oversee the safety of the ongoing Phase 1/2 study (Protocol 2019nCoV-101) and will oversee one or more additional studies across the SARS-CoV-2 rS vaccine program. A separate SMC will be convened for this study. The designated SMC will monitor the safety of participants in the study and will follow an SMC charter. The SMC will review blinded and unblinded safety and reactogenicity data. The SMC will also review sufficient clinical event data to ensure detection of any evidence of enhanced disease. The SMC will convene to perform safety reviews on a scheduled basis, for immediate concerns regarding safety observations during this study, and as needed.

Following achievement of the primary efficacy endpoint, blinded participants will be revaccinated with 2 injections 21 days apart of the alternate study vaccine (“blinded crossover”). That is, initial recipients of placebo will receive active SARS-CoV-2 rS with Matrix-M1 and initial recipients of active vaccine will receive placebo. Because the blinded crossover will provide all study participants with active SARS-CoV-2 rS vaccine, either initially or at the time of blinded crossover, unblinding of participants to allow receipt of another active vaccine is discouraged after the crossover. Yet all participants will be reminded that they always have the option to become unblinded for a deployed vaccine or withdraw from the study at any time for any reason. Previously unblinded participants still in the study will not be eligible for crossover vaccinations. Participants who are unblinded and receive another active vaccine outside of this protocol in this manner will be censored in the

final analysis at the time of unblinding but will be strongly encouraged to remain in safety follow-up as defined in this protocol.

Study Vaccination Pause Rules:

Study vaccination pause rules based on reactogenicity, AEs, and SAEs related to study participation will be in place to monitor participant safety for the initial set of vaccinations only.

AEs meeting any one of the following criteria will result in a hold being placed on subsequent study vaccinations pending further review by the SMC at the direction of the SMC chair:

- Any toxicity grade 3 or higher (severe or potentially life-threatening) solicited (local or systemic) single AE term occurring in ≥ 10% of participants (after a minimum of 100 subjects are enroled) in the SARS-CoV-2 rS with Matrix-M1 adjuvant group within the first 7 days after study vaccination.
- Any severe unsolicited single AE preferred term for which the investigator assesses as related that occurs in ≥ 5% of participants (after a minimum of 100 subjects are enroled) in the SARS-CoV-2 rS with Matrix-M1 adjuvant group, within the first 7 days after study vaccination.

In addition, any SAE assessed as related to vaccine (final assessment by the Sponsor) will be reported by the Sponsor to the SMC Chair as soon as possible, and within 24 hours of the sponsor's awareness of the event. Based on this initial report of the event to the SMC Chair, the Chair may advise the Sponsor to immediately pause enrolment and further dosing in either some or all participants in the study and to convene an ad hoc meeting, or make alternative recommendations. The SMC Charter defines processes for how this review will occur and how the Chair's recommendations will be documented.

The sponsor, along with medical monitor, may request an SMC review for any safety concerns that may arise in the study, even if they are not associated with any specific pause rule; for example, any SAE for which causality is at least possibly related.

The 400 subject influenza vaccine co-administration study will utilize the same pause rules with one difference due to the expectation of greater reactogenicity and the small size:

- Any grade 3 or higher (severe or potentially life-threatening) solicited (local or systemic) single AE term occurring in ≥ 20% of participants in the SARS-CoV-2 rS with Matrix-M1 adjuvant plus seasonal influenza vaccine group, within the first 7 days after study vaccination**.**

STUDY POPULATION:

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adult males or females aged 18 to 84 years (inclusive) at screening.
2. Able and willing (in the investigator's opinion) to comply with all study requirements.
3. Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
4. Willing and able to give informed consent prior to study enrolment.
5. Female participants of childbearing potential (defined as any female who has experienced menarche and who is NOT surgically sterile [i.e., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months or > 1 documented plasma follicle-stimulating hormone level ≥ 40 mIU/mL]) must agree to be heterosexually inactive from at least 28 days prior to enrolment and through 3 months after the last study vaccination OR agree to consistently use any of the following methods of contraception from at least 28 days prior to enrolment and through 3 months after the last study vaccination:
   a. Condoms (male or female)
   b. Diaphragm with spermicide
   c. Cervical cap with spermicide
   d. Intrauterine device
   e. Oral or patch contraceptives
   f. Norplant®, Depo-Provera®, or other in country regulatory-approved contraceptive method that is designed to protect against pregnancy
   g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle (other approaches to abstinence are not acceptable)

      NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
6. Room air oxygen saturation > 95% at Screening/Day 0.

Seasonal Influenza Vaccine Co-Administration Sub-Study Only

7. Participant should not have received a current season influenza vaccine, have no contraindication to the specific vaccine to be administered in the study, and no prior history of allergy or severe reaction to seasonal influenza vaccines.

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study:

1. Participation in COVID-19 prophylactic drug trials for the duration of the study.
2. Future participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.
3. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
4. History of laboratory-confirmed (by PCR or serology to SARS-CoV-2) COVID-19 infection at any time prior to randomisation.
5. Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of the study vaccine candidate.
6. Any confirmed or suspected immunosuppressive or immunodeficient state; chronic administration (defined as more than 14 continuous days) of immunosuppressant medication within the past 3 months, except topical steroids or short-term oral steroids (course lasting ≤ 14 days).

   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted if other chronic disease conditions are not exclusionary. Human immunodeficiency syndrome (HIV)-positive participants receiving highly active antiretroviral therapy and a history within 6 months of screening of viral load < 1000 copies/mL or CD4 count > 300 cells/mm^3 would be eligible.
7. History of allergic disease or reactions likely to be exacerbated by any component of the study vaccines.
8. Any history of anaphylaxis to any prior vaccine.
9. Pregnancy, lactation, or willingness/intention to become pregnant within 3 months following the last study vaccination.
10. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ, at the discretion of the investigator).
11. Bleeding disorder (e.g., factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
12. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants/anti-platelet agents.

    NOTE: The use of ≤ 325 mg of aspirin per day as prophylaxis is permitted.
13. Suspected or known current alcohol or drug dependency.
14. Study team member or first-degree relative of any study team member (inclusive of Sponsor, contract research organisation (CRO), and site personnel involved in the study).
15. Participants who are having any current workup of undiagnosed illness within the last 8 weeks that is either participant-reported or has been clinician-assessed, which could lead to a new condition or diagnosis.

16. Received any live vaccine within 4 weeks or **any vaccine** (excluding influenza) within 2 weeks prior to first study vaccination or any licensed influenza vaccine within 1 week prior to first study vaccination or plans to receive any vaccine from these time periods until 28 days after second study vaccination.

    NOTE: An influenza co-administration sub-study will occur in which 400 participants will receive a single dose of seasonal influenza vaccine at the same time as first study vaccination. In addition, a licensed seasonal influenza vaccine may be given 7 days after each vaccination but should not be given within 7 days prior to second vaccination.

17. Have clinically significant chronic cardiovascular, endocrine, gastrointestinal, hepatic (including hepatitis B and C), renal, neurological, respiratory, psychiatric or other medical disorders not excluded by other exclusion criteria, that are assessed by the investigator as being clinically unstable within the prior 4 weeks as evidenced by:
    a. Hospitalisation for the condition, including day surgical interventions.
    b. New significant organ function deterioration.
    c. Needing addition of new treatments or major dose adjustments of current treatments (mild or moderate well-controlled comorbidities are allowed).
18. History of chronic neurological disorders that have required prior specialist physician review for diagnosis and management (such as multiple sclerosis, dementia, transient ischemic attacks, Parkinson's disease, degenerative neurological conditions, and neuropathy) or a history of stroke or previous neurological disorder within 12 months with residual symptoms. Participants with a history of migraine or chronic headaches or nerve root compression that have been stable on treatment for the last 4 weeks are not excluded.
19. Any autoimmune disease/condition (iatrogenic or congenital) listed in Table 9-3 or being treated with a biologic therapy.

    NOTE: The Skin and Metabolic Disorders listed in Table 9-3 are eligible at the discretion of the investigator.

20. Any other significant disease, disorder or finding that, in the opinion of the investigator, may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data.
21. Participant requires the use of continuous oxygen therapy or any oxygen therapy while awake or is anticipated to require daytime oxygen therapy during the course of the study.

    NOTE: Nocturnal oxygen use only is acceptable for study inclusion.

    NOTE: Inclusion and exclusion criteria are applied at study entry and should not be used to determine whether to provide a second dose. Decision making regarding refraining from a second dose should be based on specific conditions such as pregnancy or anaphylaxis to the prior study dose or medical contraindications per the judgment of the investigator or medical monitor.

Other Considerations:

Participants meeting any of the following criteria may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment.

- Respiratory symptoms in the past 3 days (i.e., cough, sore throat, difficulty breathing). Participant may be vaccinated once all symptoms have been resolved for > 3 days. Out-of-window study vaccination is allowed for this reason (**see NOTE**).
- Temperature of > 38°C within 24 hours of planned study vaccination (site measured or participant measured). Participant may be vaccinated once the fever has resolved and there has not been any temperature measured as being > 38°C for > 3 days. Out-of-window study vaccination is allowed for this reason (**see NOTE**).

  NOTE: PCR testing for SARS-CoV-2 is likely to be indicated for either of the above reasons or if COVID-19 is suspected based on other symptoms, potential exposure to SARS-CoV-2 infection through either close contacts or based on local epidemiology. If a participant has a positive PCR for SARS-CoV-2 prior to enrolment that participant will not be eligible and will be considered a screen failure.
- Participants having any symptoms or signs of possible COVID-19 infection (Table 2-2) that may also be due to post-vaccination reactogenicity within 7 days of either study vaccine dose will NOT be required to be tested for SARS-CoV-2 PCR.
- Any participant with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Screening and prior to second study vaccination will not be removed from the study but must meet health requirements before receiving second study vaccination.
- Any participant who has a positive PCR for SARS-CoV-2 between the first and second study vaccination should also have PCR testing for SARS-CoV-2 on the day of the subsequent study vaccination, but the results of the PCR test are not needed before study vaccination can be given.
- Any participant with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Screening and prior to the end of immunogenicity assessments will be removed from applicable immunogenicity analyses as defined in the SAP.
- Any acute illness (cardiovascular, endocrine, gastrointestinal, hepatic, renal, neurological, respiratory, or other medical disorders) that is actively causing symptoms that could, in the opinion of the investigator, impact the assessment of reactogenicity or other study assessments may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment. Participant may be vaccinated once symptoms have resolved or are stabilised for > 3 days. Out-of-window study vaccination is allowed for this reason.
- Any participant who is otherwise eligible with a blood pressure of ≥ 160/100 mmHg may be retested onsite several times over a 3-hour interval to achieve a lower blood pressure. If the blood pressure remains ≥ 160/100 mmHg, study vaccination should be deferred for a later date if the baseline blood pressure is found to be < 160/100 mmHg.

STUDY VACCINES:

Study vaccinations (5-µg SARS-CoV-2 rS with 50-µg Matrix-M1 adjuvant or placebo [saline]) will comprise 2 IM injections on Days 0 and 21, ideally in alternating deltoids. For blinding purposes, all participants will be vaccinated using the same injection volume (i.e., 0.5 mL).

At the time of the blinded crossover, participants will receive the alternate study material in 2 IM injections 21 + 7 days apart.

The seasonal influenza vaccine co-administration sub-study will comprise a single IM injection (0.5 mL) of a licensed influenza vaccine on Day 0, ideally in the opposite deltoid of the study vaccine. Flucelvax Quadrivalent will be given to those 18 to 64 years of age, and an adjuvanted trivalent influenza vaccine will be given to those ≥ 65 years of age.

Whenever possible the RIGHT deltoid will be used for the influenza vaccine and the LEFT deltoid for the study vaccine.

All study vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. The influenza vaccine will not require blinding. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of participants.

STUDY PROCEDURES:

Study procedures, including efficacy, immunogenicity, and safety assessments are listed in the schedule of events (SOE) in Table 3-1.

Efficacy Assessments:

Nose/Throat Testing for SARS-CoV-2 Detection and Confirmation:

Nose/throat samples for virus detection will be taken at the study visits described in the SOE (Table 3-1).

Monitoring for COVID-19:

Identification and laboratory confirmation of SARS-CoV-2 infection and symptomatic COVID-19 will be performed throughout the study.

On study enrolment, participants will be given details of a 24/7 on-call number to contact the study team. Participants will be instructed to contact the study team within 24 hours via this number if they self-assess COVID-19 symptoms in Table 2-2 or are clinically concerned. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit. Please refer to Table 2-2 for the qualifying symptoms of suspected COVID-19 disease. Participants will receive weekly reminders (email or text messages) to immediately contact the study team if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit. If the participant is known to be COVID-19 positive at the time of scheduling for the Initial Surveillance Visit and cannot attend the visit due to extenuating circumstances (e.g., local government restrictions), then a phone call or phone calls can be substituted to assess the participant's status. However, the participant

should make every effort to attend the Follow-up Surveillance Visit (as per protocol timeline) when government restrictions or other circumstances allow. If a participant has made an Initial Surveillance phone contact or visit and is found to be COVID-19 negative on all swabs taken for this episode, then a phone call can be substituted for the Follow-up Surveillance Visit. A participant with suspected or confirmed COVID-19 will be asked to complete the COVID-19 symptom diary. Participants should start the diary on their first day of symptoms and complete this diary daily for a minimum of 10 days even if their symptoms have resolved and regardless of any SARS-CoV-2 PCR results. They should continue the diary beyond 10 days if they have any ongoing symptoms related to the episode and should continue to do so until all symptoms have resolved.

The occurrence of COVID-19-related hospitalisation and COVID-19-related complications (such as, but not limited to, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death) will be monitored throughout the study. Every episode of a new onset of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) with exceptions per protocol. A “new onset” episode will require at least a 7-day period of being symptom-free prior to the event to differentiate a specific episode from any prior illness.

Immunogenicity Assessments:

Blood will be collected from all participants for humoral immunogenicity according to the time points specified in the SOE (Table 3-1).

Immune measurements (ELISA) will be conducted on serum (immunoglobulin G [IgG]) for SARS-CoV-2 anti-S protein serology in approximately 900 participants in the Anti-S Protein Serology Subset (after both sets of vaccinations) and on anti-N protein serology in all participants. The immunologic test for SARS-CoV-2 serology based on a non-S protein (e.g., SARS-CoV-2 N protein) will be performed to identify cases of asymptomatic infection. Additional immunogenicity assessments specific to SARS-CoV-2 (or related variants) will include a neutralising antibody assay, which will be performed in approximately 900 participants in a Neutralisation Assay Subset. Cell-mediated immune responses, as assessed by ELISpot ± intracellular cytokine staining, will be performed in approximately 450 participants in the Cell-mediated Assay Subset. In addition, an HAI will be performed in the approximately 400 participants in the seasonal influenza vaccine co-administration sub-study.

Anti-S protein serology in the Anti-S Protein Serology Subset will be collected after the initial and second set of vaccinations.

Safety Assessments:

The timing and frequency of all safety assessments are listed in the SOE (Table 3-1).

After each study vaccination, including the licensed seasonal influenza vaccine for participants in the seasonal influenza vaccine co-administration sub-study, participants will remain under observation at the study site for at least 30 minutes for the presence of any acute reactions and solicited AEs. Solicited AEs, collected through an electronic diary (e-Diary), will be recorded from the time of study vaccination until 7 days after study vaccination in all participants in the seasonal influenza vaccine co-administration sub-study and a subgroup of all other participants after the initial set of vaccinations. As solicited AEs

are only being recorded in a subset of participants, it is expected that typical solicited AEs will be captured as unsolicited AEs in those participants who are not in the sub-study. An assessment of the impact of this decision will be part of an exploratory analysis. Participants in the licensed seasonal influenza vaccine co-administration sub-study will record local reactogenicity for the study vaccine injection site only.

All participants will be assessed for unsolicited AEs from the time of first study vaccination until Day 49 after the initial set of vaccinations; SAEs will be assessed from the time the informed consent is signed until completion of the participant's last study-related procedure; all MAAEs will be reported from the time of first study vaccination in the initial set of vaccinations until Day 35; MAAEs related to study vaccination and AESIs will be reported from the time of first study vaccination until completion of the participant's last study-related procedure. All AEs will be followed until resolution or until clinically stable.

Separate analyses of safety events received with respect to approved or deployed SARS-CoV-2 vaccines will be performed.

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs; MAAEs; AESI; SAEs; vital sign measurements on day of study vaccinations; and physical examination findings. Local and systemic reactogenicity events will not be recorded for the second set of vaccinations. COVID-19 severity will be categorised as mild, moderate, or severe according to protocol-specified criteria (Table 2-1). Recording of solicited and unsolicited AEs may be conducted by electronic data capture (EDC)/reporting. Potential immune-mediated medical conditions (PIMMC) and AESIs specific to potential disease enhancement for COVID-19 will also be monitored (see Section 9.5 [Appendix 4] for details).

STATISTICAL ANALYSIS PLANS:

Sample Size:

This study is designed to enrol approximately 15,000 participants, who will be initially randomised 1:1 into the 2 study vaccine groups. The sample size is driven by the total number of events expected to achieve statistical significance for the primary efficacy endpoint – a target of 100 mild, moderate, or severe COVID-19 cases. The target number of events of 100 was chosen to provide > 95% power for 70% or higher vaccine efficacy (VE). A single interim analysis of efficacy will be conducted based on the accumulation of approximately 50% (50 events) of the total anticipated primary endpoints using Pocock boundary conditions. Power calculations were performed using 10,000 simulated trials that were created under various assumptions of VEs and analysed using methods described in the "efficacy analysis" section without covariates. A 90% evaluability rate for the per-protocol (PP) efficacy (PP-EFF) population (assuming 10% unevaluable due to attrition and/or baseline-seropositive participants) was used for the power calculations. All simulations were performed in SAS V9.4.

Analysis Sets:

The all-randomised set will include all participants who were randomised regardless of the receipt of any study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The all-randomised set will be used for the subject disposition summaries.

The intent-to-treat (ITT) analysis set will include all participants who are randomised and receive at least 1 dose study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), regardless of protocol violations or missing data. The ITT analysis set will be used as a supportive analysis population for the immunogenicity and efficacy analyses and will be analysed according to the study vaccine group as randomised.

The safety analysis set will include all participants who receive at least 1 dose of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). Participants in the safety analysis set will be analysed according to the study vaccine actually received.

The PP-EFF will include baseline seronegative participants who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and have no major protocol deviations that occur before the first COVID-19 episode affecting the primary efficacy outcome (i.e., participants will be censored at the time of the protocol deviation) as assessed by the Sponsor prior to unblinding. All analyses of the PP-EFF population will also exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test occurring 6 days or less after the second study vaccination (e.g., Day 28).

The per-protocol immunogenicity (PP-IMM) analysis set for each post-randomisation visit will include participants who receive scheduled dose(s) of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), have at least a baseline and the serum sample result for the visit available after study vaccination, and have no major protocol violations that are considered clinically likely to impact the immunogenicity response at the corresponding study visit as assessed by the sponsor prior to unblinding. For each visit, the SARS-CoV-2 unexposed population will also exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test prior to each visit. Prior exposed participants will be determined using baseline SARS-CoV-2 immunity defined as positive SARS-CoV-2 by PCR or antibody test at baseline, or positive SARS-CoV-2 by qualitative PCR through Day 35, according to the specified analysis. Analysis will be performed to assess if immune responses differ between exposed and unexposed individuals (i.e., whether prior exposure alters dosing regimen considerations in a pandemic response).

The review and determination for exclusion from the PP populations will be carried out in a blinded fashion by a study clinician prior to unblinding for each interim analysis based on all available information from the locked database. Both PP populations will be analysed according to the study vaccine group as randomised.

Efficacy Analyses:

The primary endpoint will be analysed on the PP-EFF Analysis Set and supported by analysis of the ITT Analysis Set. Conclusions concerning declaration of attainment of the primary endpoint will only be based on the PP-EFF population.

Primary analysis of the primary and key secondary efficacy endpoints will be performed based on the data generated prior to the blinded crossover. The analysis of data generated after the blinded crossover or the combined analyses of both pre- and post-blinded crossover

will be performed using the approach described by Follmann et al (2020). Additional details on the analytical approach will be described in the Statistical Analysis Plan.

VE is defined as VE (%) = (1 – RR) × 100, where RR = relative risk of incidence rates between the 2 study vaccine groups (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The interim and final analyses for the primary objective in the PP-EFF population will be carried out at the overall one-sided Type I error rate of 0.025. The nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analysis and the numbers of endpoints to be used for the final analysis. The estimated RR and its CI will be derived using Poisson regression with robust error variance [Zou 2004]. The explanatory variables in the model will include study vaccine group. The dependent variable will be the incidence rate of the endpoint of interest. The robust error variances will be estimated using the repeated statement and the participant identifier. The Poisson distribution will be used with a logarithm link function. The site (depending on the distribution of endpoints) and the age strata will be included in the model as covariates. To assess incidence rates rather than absolute counts of cases, accounting for differences in follow-up times starting with 7 days after the second vaccination among participants, an offset will be utilized in the Poisson regression. In case the total number of events to be analysed may be too low for an asymptotic method proposed (i.e., ≤ 5 events in either treatment group), an alternative method based on the single sample exact binomial distribution may be used for the analysis. This method is based on the proportion of the events in the SARS-CoV-2 rS with Matrix-M1 adjuvant group among the total number of events observed in both treatment groups after adjusting for the differential number of subjects (or inclusive of differential lengths of follow-up) between the 2 treatment groups.

Hypothesis testing of the primary efficacy endpoint will be carried out against H0: VE ≤ 30%. Rejection of the null hypothesis, H0: VE ≤ 30% demonstrates a statistically significant vaccine effect (i.e., alpha-adjusted lower bound confidence interval [LBCI] > 30%) will be considered meeting the pre-specified study success criterion. The study will also continue for the intended duration to measure efficacy, immunogenicity, and safety endpoints, regardless of primary endpoint success at the interim or final analysis. The final analysis of the primary efficacy endpoint will be triggered when approximately 100 PP-EFF participants with symptomatic mild, moderate, or severe COVID-19 endpoints have accrued. Also, in order to be able to respond to the unexpected and rapidly evolving COVID-19 pandemic situation globally, other factors such as requests by government or public health agencies may also be factored into the decision-making to unblind the study for the final analysis, but this always occurs in consultation with lead regulatory agencies.

The secondary and exploratory efficacy endpoints will be analysed using the same method as the primary efficacy analysis described above. Analysis of secondary and exploratory efficacy endpoints will be performed without adjustment for multiple comparisons (i.e., two-sided alpha of 0.05). The final interpretation of the overall vaccine efficacy will be based on the totality of statistical evidence, including immunogenicity results and the clinical importance in discussions with the regulatory agencies and scientific communities.

The EOS analysis will be performed when the last participant completes the last visit (12 months after the last study vaccination) or discontinues earlier.

Immunogenicity Analyses:

The primary and secondary immunogenicity analyses will be performed using the PP-IMM and ITT analysis populations.

For the SARS-CoV-2 rS serum antibody levels measured by microneutralization and ELISA assays, the geometric mean at each study visit, geometric mean fold rises (GMFRs) comparing to Day 0 (baseline) at each follow-up study visit, along with 95% CI will be summarised by study vaccine group. The 95% CI will be calculated based on the t distribution of the log-transformed values for geometric means or GMFRs, then back transformed to the original scale for presentation. The seroconversion rate (SCR), proportion of participants with ≥ 4 fold rises if naïve at baseline, along with 95% CIs based on the Clopper-Pearson method will be summarised by study vaccine group at each follow-up study visit. Immunogenicity analyses performed after the second set of vaccinations will be conducted in a similar fashion.

For the subset of participants who receives the influenza vaccine concurrently with the study vaccines, comparisons of strain-specific immune responses to influenza vaccine as measured by HAI will be performed. The treatment comparison will be made by comparing the strain-specific geometric mean titres (GMTs) and the SCRs. The SCR is defined as the proportion of subjects with either a baseline reciprocal (Day 0) titre of < 10 and a post-vaccination reciprocal titre ≥ 40, or a baseline titre of ≥ 10 and a post-vaccination titre ≥ 4-fold higher.

For influenza strain-specific GMTs in each treatment group, titres reported below the lower limit of quantitation (LLOQ; i.e., below the starting dilution of assay reported as "< 10") will be set to half that limit (i.e., 10 / 2 = 5). Strain-specific GMTs will be summarized by treatment group and visit day along with the corresponding two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. The ratio of GMTs between treatment groups post-vaccination and the corresponding two-sided 95% CI will be calculated on log-transformed titres using the analysis of covariance (ANCOVA) with treatment group and baseline (Day 0) measurement as the covariate.

For influenza strain-specific SCRs, the rate in percent and the corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. The two-sided 95% CIs for the absolute rate difference between the 2 treatment groups will be constructed using the Newcombe method.

Similar summaries will be generated for the other immunogenicity endpoints and other assays if conducted.

Correlates of risk will be assessed where immune responses are measured in all available participants, and the results compared between participants who experience a SARS-CoV-2 event and participants who do not. The goal of this analysis is to assess correlates of risk of SARS-CoV-2 infection (and potential other secondary endpoints) in the study vaccine group by comparing study vaccine-induced immune responses associated with COVID-19.

Safety Analyses:

Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in the Safety Subset of approximately 2,000 participants and in the seasonal influenza vaccine co-administration sub-study of approximately 400 participants after the initial set of vaccinations only.

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after each study vaccination will be summarised by study vaccine group and the maximum toxicity grade over 7 days after each study vaccination. The duration of solicited local and systemic AEs after each study vaccination will also be summarised by treatment group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and summarised by study vaccine group as well as by severity and relationship to study vaccine. AEs through 49 days after first study vaccination for the initial set of vaccinations; all MAAEs through 35 days after first study vaccination for the initial set of vaccinations; and MAAEs related to study vaccine; SAEs; or AESIs through EOS will be listed separately and summarised by study vaccine group. As solicited AEs are only being recorded in a subset of participants, it is expected that typical solicited AEs will be captured as unsolicited AEs in those participants who are not in the sub-study if they occur through Day 49 after the initial set of vaccinations. An assessment of the impact of this decision will be part of an exploratory analysis and will be summarised.

Separate analyses of safety events received with respect to approved or deployed SARS-CoV-2 vaccines will be performed.

Vital sign measurements will be summarised by study vaccine group using descriptive statistics at baseline and following study vaccination.

Concomitant medications will be provided in a data listing with preferred drug name as coded using the World Health Organisation (WHO) drug dictionary.

Interim Analyses

Prior to the final analysis, a single interim analysis of efficacy will be conducted based on the accumulation of approximately 50% (50 events) of the total target number of the primary endpoint (100 events). For this analysis, the data needed to perform the analysis of the primary efficacy endpoint will be cleaned. The interim analysis will be performed by an unblinded Biostatistics and Programming team (PPD), and the unblinded statistician will communicate the results of the analysis to the Sponsor in terms of fulfillment or nonfulfillment of the pre-defined success criterion (yes/no). Novavax will be unblinded at the participant level at the time of the primary 100-event analysis. If the pre-defined success criterion of the interim analysis is unfulfilled (no), then the study will remain blinded to treatment assignment until the final analysis.

If the pre-defined success criterion of the interim analysis is fulfilled (yes), then the Sponsor may unblind selected accrued data at the treatment group level and continue the study while

maintaining the blind to achieve a more robust safety and efficacy data package. The unblinded Biostatistics and Programming team PPD will be isolated (by firewall) from study personnel. They will complete a review independent of the study team and Sponsor. The interim analysis will follow standard group-sequential design using the Lan-DeMets alpha-spending function for Pocock boundary conditions. Table 7-2 summarizes the timing, number of endpoints, and statistical success boundaries at the planned interim and final analyses.

Pre Blinded Crossover

Prior to the blinded crossover, an assessment of safety and efficacy will be made while there is a placebo-controlled comparator.

Post Blinded Crossover

Following blinded crossover, follow-up to assess safety and efficacy endpoints (assessment of MAAEs related to study vaccine, SAEs, and AESIs, blood testing for SARS-CoV-2 and vaccine efficacy) and will continue through study completion.

Planned Analyses Prior to Study Completion:

Analysis of the data will be provided on an ongoing basis for confirming success and to review safety as the study progresses. The statistical analysis plan (SAP) will outline the sequential nature of these reviews.

1. INTRODUCTION

1.1 Background

Coronaviruses are medium sized, enveloped, positive-stranded ribonucleic acid (RNA) viruses, with a characteristic crown-like appearance in electron micrographs due to circumferential studding of the viral envelope with projections comprising the spike (S) protein. There are 4 different strains (229E, OC43, NL63, and HKU1), which are ubiquitous in humans and generally result in mild upper respiratory illnesses and other common cold symptoms including malaise, headache, nasal discharge, sore throat, fever, and cough [Su 2016]. In addition, other coronavirus strains are widespread in animals, where they typically cause enteric disease. These zoonotic coronaviruses have been known to evolve into strains that can infect humans with serious consequences including severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, Middle Eastern Respiratory Syndrome (MERS)-CoV since 2012, and most recently, the novel SARS-CoV-2 since 2019 [Habibzadeh 2020].

In late December of 2019, an outbreak of respiratory disease caused by novel coronavirus (2019 nCoV) was detected in Wuhan, Hubei province, China. The virus' rapidly discerned genetic relationship with the 2002-2003 SARS-CoV has resulted in adoption of the name "SARS-CoV-2," with the disease being referred to as coronavirus disease 2019 (COVID-19). Despite containment efforts since the start of the outbreak, the SARS-CoV-2 has spread rapidly with over 214 countries/territories/areas outside of China reporting laboratory confirmed COVID-19 cases as of 15 May 2020 [WHO 2020]. On 30 January 2020, the International Health Regulations Emergency Committee of the World Health Organisation (WHO) designated the outbreak as a public health emergency of international concern (PHEIC) and subsequently declared a pandemic on 11 March 2020.

In December of 2020, the first SARS-CoV-2 vaccine was authorised for conditional use by the Medicines and Healthcare products Regulatory Authority (MHRA). Vaccination programs throughout the United Kingdom (UK) began on 08 December 2020, which resulted in questions concerning ongoing clinical trials for other SARS-CoV-2 vaccines. The following week the National Institute for Health Research (NIHR), with input from the MHRA and Health Research Authority [HRA]), released guidance to vaccine sponsors on conducting vaccine trials with a deployed vaccine in the UK. It is anticipated that additional SARS-CoV-2 vaccines will be authorised for conditional use or approved during the course of this study with increasing availability over time. This protocol has been amended to accommodate this change in the COVID-19 landscape.

Novavax, Inc. is developing a recombinant vaccine adjuvanted with the saponin-based Matrix-M1™ adjuvant for the prevention of disease caused by SARS-CoV-2. SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (GP) based upon the GenBank gene

sequence MN908947, nucleotides 21563-25384, from the 2019 SARS-CoV-2 genome. The S protein is a type 1 trimeric glycoprotein of 1,273 amino acids that is produced as an inactive S0 precursor. The S-gene was codon optimised for expression in *Spodoptera frugiperda* (Sf9) insect cells. The SARS-CoV-2 rS nanoparticle vaccine is intended for administration with Matrix-M1 adjuvant, which is a saponin-based adjuvant that has previously been shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies.

1.2 Nonclinical Experience

In support of the development of SARS-CoV-2 rS, Novavax has obtained nonclinical pharmacology data concerning several SARS-CoV-2 S protein variants, toxicity data concerning SARS-CoV-2 rS with Matrix-M1 adjuvant, and prior toxicity data concerning other viral glycoproteins manufactured in the baculovirus-Sf9 system and formulated with Matrix-M1 adjuvant.

1.2.1 Nonclinical Data from SARS-CoV-2 Spike Protein Constructs that Support SARS-CoV-2 rS Development

Mouse immunogenicity studies were conducted to evaluate several SARS-CoV-2 S protein variants and to select the vaccine candidate [Tian 2020]. The selected vaccine candidate, BV2373 (3Q-2P), was demonstrated to be immunogenic and elicited functional antibodies. For the tested constructs, shallow dose responses with Matrix-M1 adjuvant were observed, suggesting that the adjuvant may be significantly antigen-sparing in large animals and humans.

The candidate SARS-CoV-2 rS vaccine, based on the BV2373 construct, has been evaluated in dose-titration studies in [redacted] cynomolgus macaques, and baboons. [redacted] In cynomolgus macaques, 2 dose regimens of 5 or 25 µg SARS-CoV-2 rS/25 or 50 µg Matrix-Ml adjuvant were also highly immunogenic, resulting in high anti-S IgG levels, high hACE2 binding inhibition titres, and high neutralising antibody responses. The 5 and 25 µg antigen doses gave generally similar responses when administered twice with 50 µg of Matrix-Ml adjuvant. In baboons, which may be more predictive of responses in humans, 5 and 25 µg SARS-CoV-2 rS/50 µg Matrix-Ml adjuvant induced high levels of anti-S IgG, hACE2-binding inhibiting antibodies, and neutralising antibodies. Matrix-Ml adjuvant provided antigen-sparing, and supported induction of functional antibodies. Importantly, Matrix-Ml adjuvanted SARS-CoV-2 rS also appeared to induce strong T helper 1 (Thl) type $CD4^+$ T-cell responses to SARS-CoV-2 S protein that included polyfunctional effector phenotypes. Current data in this small

baboon study confirms that doses of 5 µg and 25 µg with 50 µg Matrix-M1 are the correct doses to test clinically, with Matrix-M1 adjuvant appearing critical for maximum responses.

Virus challenge studies were performed in mice and cynomolgus macaques. In 2 mouse challenge models, immunisation with 1 or 2 doses of SARS-CoV-2 rS/Matrix-M1 adjuvant suppressed viral replication, reduced lung inflammation, and reduced systemic morbidity (weight loss) after SARS-CoV-2 live virus challenge and were not associated with any obvious exacerbation of the inflammatory response to the virus or worsening of clinical outcomes. In cynomolgus macaques, administered with human doses of 5 or 25 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1, high and comparable levels of anti-S IgG titres and hACE2 receptor binding inhibition titres were detected 21 days after the first immunisation. All of the macaques immunised with any dose or regimen of SARS-CoV-2 rS/Matrix-M1 adjuvant were protected against live virus challenge as evidenced by the reduction of total viral RNA and subgenomic RNA to below the limit of quantitation in bronchoalveolar lavages and nasal swabs.

1.2.2 Nonclinical Data from Other Baculovirus-Sf9-Produced Nanoparticle Vaccines that Support SARS-CoV-2 rS Development

The immunogenicity and protective efficacy of 2002-2003 SARS-CoV S protein and chimeric influenza/SARS-CoV virus-like particle (VLP) vaccines produced in the baculovirus-Sf9 system and administered with and without aluminum hydroxide adjuvants was demonstrated in a mouse challenge study [Liu 2011]. Robust neutralising antibody titres were observed following vaccination, although both antigens required adsorption to aluminum hydroxide for optimal responses. The immunogenicity and protective efficacy of a MERS-CoV S nanoparticle vaccine with and without Matrix-M1 adjuvant was demonstrated in a mouse challenge study [Coleman 2017]. Following vaccination, the MERS-CoV S nanoparticle was immunogenic across all active treatment groups; however, the presence of Matrix-M1 adjuvant induced a 3- to > 10-fold enhancement of the binding and neutralising antibody responses. In addition, Matrix-M1 adjuvant essentially eliminated the antigen dose-

response, suggesting the potential for major antigen-sparing and consequent improved manufacturing efficiency and timeliness [Coleman 2017]. The Matrix-M1 adjuvant was also shown to enhance antibody, cellular, and protective immune responses in Balb/c mice administered Zaire ebolavirus (EBOV) GP vaccine with or without Matrix-M1 or aluminum phosphate adjuvants [Bengtsson 2016].

In addition, 3 GLP-compliant toxicology studies in NZW rabbits have been performed with 4 different antigens (influenza hemagglutinin [HA] ± respiratory syncytial virus [RSV] F, Zika virus envelope dimers [ZIKV EnvD], and EBOV GP), in which up to 100 µg Matrix-M1 adjuvant alone or with antigen was evaluated. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M1 adjuvant (up to 100 µg) were well tolerated in the animals tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation, enlargement of the lymph nodes draining the injection sites, and elevated serum markers of inflammation (including C-reactive protein), were transient and were considered consistent with immune system stimulation consequent to immunisation.

Further details are provided in the SARS-CoV-2 rS Investigator Brochure (IB).

1.3 Clinical Experience

The first clinical study with SARS-CoV-2 rS nanoparticle vaccine is 2019nCoV-101, which is a 2-part, randomised, observer-blinded, placebo-controlled, Phase 1/2 trial. Part 1 (Phase 1) is designed to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M1 adjuvant in 131 healthy participants ≥ 18 to ≤ 59 years of age. Results of an interim analysis at Day 35 showed that SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated and elicited robust immune responses [Keech 2020]. There were no serious adverse events (SAEs) or adverse events of special interest (AESIs). Reactogenicity was mainly mild in severity and of short duration (mean ≤ 2 days), with second vaccinations inducing greater local and systemic reactogenicity. The adjuvant significantly enhanced immune responses (anti-S IgG, hACE2 receptor binding inhibition antibody, and neutralising antibody) and was antigen dose-sparing, and the 2 dose 5µg SARS-CoV-2 rS/Matrix-M1 adjuvant induced mean anti-S IgG and neutralising antibody responses that exceeded the mean responses in convalescent sera from COVID-19 patients with clinically significant illnesses. The vaccine also induced antigen-specific T cells with a largely Th1 phenotype.

Part 2 (Phase 2) is designed to evaluate the immunogenicity, safety, and preliminary efficacy of SARS-CoV-2 rS and Matrix-M1 adjuvant in up to 1,500 healthy adults ≥ 18 to ≤ 84 years of age with more co-morbidities than the participant population in Part 1 of the study. An interim 5-day reactogenicity analysis was conducted on 846 participants following the first dose of study vaccine to support initiation of the Phase 3 study. This analysis comprised 607 participants aged 18 to 59 years (the same age range of Part 1 of the study) and

239 participants aged 60 to 84 years, with data presented in masked groups to maintain the integrity of the study. Overall, local and systemic reactogenicity data from this analysis were consistent with the reactogenicity data in Part 1 of the study, with no safety concerns between the younger and older age cohorts. Both local and systemic reactogenicity events occurred less frequently in older adults.

Novavax has, in its internally sponsored clinical trials, tested baculovirus-Sf9-produced nanoparticle vaccines in 14,848 participants comprising older adults, young adults, and a limited number of children 2 to 5 years of age; and also including 3,075 pregnant women, with acceptable safety. Matrix-M adjuvant has been given to 4,311 humans (of which, approximately 2,657 humans received nanoparticle vaccine) with acceptable short-term reactogenicity, and an unremarkable long-term safety profile. Additionally, interim results from the current study have indicated that the SARS-CoV-2 rS and Matrix-M1 adjuvant vaccine met the primary endpoint for the study and achieved an acceptable safety profile.

Further details on the clinical experience of the study vaccine can be found in the SARS-CoV-2 rS IB.

1.4 Rationale for Study

Both nonclinical and early clinical data to date have supported clinical development of SARS-CoV-2 rS and Matrix-M1 adjuvant as a potential vaccine against SARS-CoV-2. In rodent and nonhuman primate (NHP) challenge models, SARS-CoV-2 rS and Matrix-M1 adjuvant induced high titres of antibodies measured against anti-S protein and hACE2 receptor binding and achieved neutralisation of wild-type virus that exceeded the magnitude of responses measured in COVID-19 human convalescent sera and provided protection against SARS-CoV-2 challenge [Tian 2020; Mandolesi 2020; Guebre-Xabier 2020]. Notably in NHP studies, clinical doses of vaccine (5- and 25-µg SARS-CoV-2 rS/50-µg Matrix-M1) resulted in sterile immunity in the lungs and nasal passage following wild-type virus challenge, suggesting that the vaccine may both protect against upper and lower respiratory tract disease and interrupt transmission [Guebre-Xabier 2020].

Results from a Day 35 interim analysis of Part 1 (Phase 1) of Study 2019nCoV-101 indicate that in healthy adult participants 18 to 59 years of age two-dose regimens of 5- and 25-µg SARS-CoV-2 rS/50 µg Matrix-M1 (on Days 0 and 21) were well tolerated and induced the most robust immune responses with high levels of neutralising antibodies that closely correlated with anti-spike IgG [Keech 2020]. Furthermore, neutralising antibody responses following second vaccination were of the magnitude seen in convalescent serum from symptomatic COVID-19 patients and exceeded overall convalescent sera geometric mean titres (GMTs) by four-fold. The benefit of Matrix-M1 adjuvant was clear in the magnitude of the antibody and T-cell response, induction of functional antibodies, and dose sparing.

A Phase 2 clinical program is underway and will provide safety and immunogenicity results in older participants (> 60 years of age) and participants with comorbidities. Reactogenicity data following the first dose indicate that the reactogenicity profile between adults 18 to 59

years and older adults ≥ 60 years are comparable, with older adults generally reporting solicited events less frequently. Combining the current nonclinical and clinical data with positive Phase 1/2 data provide the impetus for early initiation of the Phase 3 clinical development program in the context of the current public health pandemic crisis.

The purpose of this study is to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adults 18-84 years of age (inclusive). The study will be conducted at anticipated high COVID-19 transmission areas in the United Kingdom (UK). The information provided in this study will inform progression of the study vaccine, to determine efficacy of the study vaccine to prevent COVID-19 in the general population, in participants regardless of serostatus, in participants who have required medical intervention, and in participants with mild or asymptomatic infections. The study will determine the safety of the study vaccine to use in the general population and to ensure that it elicits a robust immune response.

1.5 Rationale for Dose Selection

As previously described, clinical doses of vaccine and adjuvant (5- and 25-µg SARS-CoV-2 rS/50-µg Matrix-M1) resulted in sterile immunity in the lungs and nasal passage following wild-type virus challenge in NHP, suggesting that the vaccine may both protect against upper and lower respiratory tract disease and interrupt transmission [Guebre-Xabier 2020]. These doses are being evaluated in Part 1 of Study 2019nCoV-101 in 131 healthy adult participants ≥ 18 to ≤ 59 years of age and in Part 2 of Study 2019nCoV-101 in up to 1,500 participants ≥ 18 to ≤ 84 years of age, including participants with comorbidities. Results from the Part 1 Day 35 interim analysis support either dose of SARS-CoV-2 rS/Matrix-M1 in terms of safety and immunology, with the lower dose (5 µg) offering advantages in regards to dose sparing. All study vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of participants.

1.6 Benefit-Risk Assessment

The SARS-CoV-2 rS nanoparticle vaccine contains purified protein antigens. It cannot replicate, nor can it cause COVID-19. However, in common with all vaccines produced in cell culture or other systems, the SARS-CoV-2 rS nanoparticle vaccine contains residual non-vaccine proteins derived from the production system, and sensitisation to these, or the SARS-CoV-2 S protein itself, may theoretically occur. While the occurrence of immediate hypersensitivity is possible with the administration of any vaccine, whether licensed or in development, no such reactions have been observed in any of these clinical trials to date. As clinical data become available with increased exposure, it is possible that this profile may change.

The risk for enhanced COVID-19 in immunised participants is a theoretical risk. Enhanced disease in coronavirus vaccine-immunised animals after live virus challenge has been

demonstrated in nonclinical studies of several, but not all, coronavirus vaccine candidates. There is currently no evidence for immunoenhancement in nonclinical testing of SARS-CoV-2 rS or other Novavax baculovirus-Sf9-based vaccines taken into nonclinical evaluation or clinical trials.

No risks have been identified in nonclinical or early clinical testing of SARS-CoV-2 or other coronavirus vaccines (SARS-CoV and MERS-CoV) developed using the baculovirus-Sf9 system to date. In supportive toxicology studies with other viral GP nanoparticle vaccines developed using the baculovirus-Sf9 system with different antigens, findings were generally consistent with an immune response to the vaccine formulations. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M1 adjuvant (up to 100 µg) were well tolerated in the animal and antigen system tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation and serum chemical markers of inflammation (such as C-reactive protein), were transient and considered consistent with immune system stimulation consequent to immunisation.

Findings to date suggest that SARS-CoV-2 rS when administered with or without Matrix-M1 adjuvant can be reasonably expected to demonstrate an acceptable safety profile in healthy adult participants aged ≤ 59 years. Novavax baculovirus-Sf9-produced nanoparticle vaccines comprising viral glycoproteins, with and without Matrix-M1 or aluminum adjuvants, have been shown to induce robust and protective immune responses in relevant animal models to influenza HAs, RSV F protein, SARS-CoV and MERS-CoV S proteins, rabies GP, and EBOV GP. In addition, the Novavax SARS-CoV-2 candidate adsorbed to aluminum phosphate has induced antibodies in pregnant women which, when transferred transplacentally, were associated with reduced rates of SARS-CoV-2 lower respiratory tract infections in their infants during the first 90 to 180 days of life. The goal of this program is to investigate the efficacy, safety, and immunogenicity of the SARS-CoV-2 rS and Matrix-M1 adjuvant.

Further details are provided in the SARS-CoV-2 rS IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by polymerase chain reaction [PCR] to SARS-CoV-2), symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adults.

2.1.2 Secondary Objectives

- To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in adults regardless of their serostatus at baseline.
- To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants requiring specific medical interventions as compared to placebo.
- To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant on mild COVID-19 symptoms as compared to placebo.
- To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant on occurrence of asymptomatic or undetected infections with SARS-CoV-2 as compared to placebo.
- In a subset of adult participants, to evaluate the immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant as compared to placebo.
- To evaluate safety in terms of SAEs and medically attended adverse events (MAAEs) related to study vaccination in all adult participants during the entire study period.
- To evaluate safety in terms of AESIs, which encompasses potential immune-mediated medical conditions (PIMMCs) and AESIs relevant to COVID-19, including possible vaccine-enhanced disease, in all adult participants at any time after the first dose.
- In a subset of adult participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) after the initial set of study vaccinations.
- To evaluate safety in terms of all MAAEs for 14 days after second vaccination and unsolicited AEs for 21 days after first study vaccination and 28 days after second study vaccination in the initial set of vaccinations.
- To assess the duration of vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.

2.1.3 Exploratory Objectives

- In a subset of adult participants, to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in the initial set of vaccinations when co-administered with a licensed seasonal influenza vaccine.

- In a subset of adult participants unblinded before the crossover, to explore the efficacy and safety of SARS-CoV-2 rS with Matrix-M1 adjuvant in the initial set of vaccinations and/or an approved or deployed SARS-CoV-2 vaccine.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 (Table 2-1) with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.

Table 2-1: Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Mild	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table 2-2 **AND** • Does not meet criteria for moderate or severe disease
Moderate	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms in Table 2-2 for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant LRTI: – Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) – Tachypnea: 20 to 29 breaths per minute at rest* – SpO2: 94% to 95% on room air* – Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI – Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor) **AND** • Does not meet criteria for severe disease

Table 2-1: Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Severe	≥ 1 of: • Tachypnea: ≥ 30 breaths per minute at rest* • Resting heart rate ≥ 125 beats per minute* • SpO_2: ≤ 93% on room air or PAO_2/FiO_2 < 300* • High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: o ARDS o Acute renal failure o Acute hepatic failure o Acute right or left heart failure o Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg o Acute stroke (ischemic or hemorrhagic) o Acute thrombotic event: AMI, DVT, PE o Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPV = non-invasive positive pressure ventilation; PAO_2 = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO_2 = oxygen saturation.

*Participants with a single vital sign abnormality placing them in the moderate or severe categories must also meet the criteria for mild COVID-19.

Table 2-2: Qualifying Symptoms of Suspected COVID-19

- Fever
- New onset cough
- New onset or worsening of shortness of breath or difficulty breathing compared to baseline
- New onset fatigue
- New onset generalised muscle or body aches
- New onset headache
- New loss of taste or smell
- Acute onset of sore throat, congestion, and runny nose
- New onset nausea, vomiting, or diarrhea

Abbreviations: COVID-19 = coronavirus disease 2019.

2.2.2 Secondary Endpoints

2.2.2.1 Key Secondary Endpoint

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic moderate or severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.

2.2.2.2 Other Secondary Endpoints

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.
- First occurrence of COVID-19 requiring hospitalisation, intensive care unit (ICU) admission or mechanical ventilation linked to any virologically confirmed (by PCR to SARS-CoV-2) COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants regardless of their serostatus at baseline.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild COVID-19 (with no progression to moderate or severe COVID-19 during the course of the COVID-19 episode) with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants, regardless of their serostatus at baseline.
- First occurrence of laboratory-confirmed (by PCR or nucleocapsid [N] protein serology to SARS-CoV-2) symptomatic or asymptomatic COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in adult participants with negative serostatus at baseline.
- Analysis of antibodies binding to the SARS-CoV-2 spike (S) protein by enzyme-linked immunosorbent assay (ELISA) at Day 0 (baseline) and Day 35 (14 days after second study vaccination).
- Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA at Crossover Day 0 visit (baseline) and Crossover Day 35 visit (14 days after second study vaccination).

- The occurrence and relationship to study vaccination of SAEs and MAAEs related to study vaccination (in all adult participants) during the entire study period.
- The occurrence and relationship to study vaccination of AESIs and PIMMCs (in all adult participants) during the entire study period.
- The occurrence and severity of reactogenicity in terms of solicited local and systemic AEs (in all sub-study participants) after the initial set of vaccinations.
- The occurrence, severity, and relationship to study vaccination of all MAAEs for 14 days after second vaccination and unsolicited AEs (in all adult participants) for 21 days after first study vaccination and 28 days after second study vaccination following the initial set of vaccinations.
- Relative vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.

2.2.3 Exploratory Endpoints

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 with onset at least 14 days after first study vaccination (e.g., Day 14) in the initial set of vaccinations in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- Any occurrence of serologic conversion (by serology to SARS-CoV-2 N protein) between baseline and 1 year after last study vaccination in the initial set of vaccinations in adult participants seronegative at baseline.
- Any occurrence of serologic conversion (by serology to SARS-CoV-2 N protein) between Crossover Day 0 visit and the end of study (EOS) visit in the second set of vaccinations in adult participants seronegative at baseline.
- Analysis of the proportion of adult participants with evidence of seroconversion as demonstrated by binding antibodies to the SARS-CoV-2 S protein by ELISA at Day 35 (14 days after second study vaccination) and Crossover Day 35 visit (14 days after the Crossover Day 21 visit).
- Analysis of the cell-mediated immune responses (for example, as measured by enzyme-linked immune absorbent spot (ELISpot) ± intracellular cytokine staining) on Days 0 (baseline) and 35 (14 days after second study vaccination) in the initial set of vaccinations.
- SARS-CoV-2 neutralisation as measured by virus neutralisation assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein) at Day 0 (baseline) and Day 35 (14 days after second study vaccination) in the initial set of vaccinations.

- Analysis of the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant when co-administered with seasonal influenza vaccine in a subset population.
- Analysis of the efficacy and safety of SARS-CoV-2 rS with Matrix-M1 adjuvant and/or an approved or deployed SARS-CoV-2 vaccine in a subset population.
- Analysis of the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in participants with asymptomatic COVID-19 who test positive for the disease by SARS-CoV-2 N protein serology but have no accompanying symptoms.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in seronegative adult participants by age (<65 and ≥65), in racial and ethnic minorities, and in those with comorbid conditions.
- The occurrence, severity, and relationship to study vaccination of unsolicited AEs (in all adult participants) for 21 days after first study vaccination and 28 days after second study vaccination following the initial set of vaccinations with the adjustment to remove reactogenicity events that were recorded as unsolicited AEs within 7 days of each dose in the initial set of vaccinations.

3. STUDY DESIGN

This is a Phase 3, multi-centre, randomised, observer-blind, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants 18 to 84 years of age (inclusive) in the UK. Following permission by regulatory bodies based on achieving the primary efficacy endpoint and an acceptable safety profile, participants will be revaccinated with 2 injections 21 days apart of the alternate study vaccine ("blinded crossover"). That is, initial recipients of placebo will receive active SARS-CoV-2 rS with Matrix-M1 and initial recipients of active vaccine will receive placebo. Every effort will be made to identify sites of high SARS-CoV-2 activity, and populations within these sites who are at high risk of exposure to the virus will be enrolled such that the incidence of COVID-19 in the study will be higher than 1% and the sample size and enrolment period may be reduced.

After signing informed consent, participants may be screened within a window of up to approximately 30 days. Nose/throat samples may be taken during the screening period to detect SARS-CoV-2 by PCR, if the participant has any COVID-19 symptoms or significant exposure history.

Approximately 15,000 male and female adult participants 18 to 84 years of age (inclusive) with and without relevant comorbidities are planned for the study. An effort will be made to enrol a target of at least 25% of participants who are ≥ 65 years of age as well as prioritising other groups that are most affected by COVID-19, including racial and ethnic minorities. This will be under the assumption that the annual incidence of symptomatic COVID-19 will be approximately 1% to 5%.

The sample size may be adjusted by the Sponsor during the study, based on blinded data, to ensure sufficient power at the time of the primary analysis. Details on the possible sample-size reassessment will be described in the statistical analysis plan (SAP).

On Day 0 and Crossover Day 0, nose/throat samples will be taken to detect PCR for SARS-CoV-2 and blood samples will be taken to detect any existing SARS-CoV-2 antibodies at baseline. Participants will be randomised in a 1:1 ratio via block randomisation to receive 2 intramuscular (IM) injections of the SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo, as described in Figure 1a. Participants who are unblinded and ineligible for the blinded crossover will continue to follow the original study design depicted in Figure 1b.

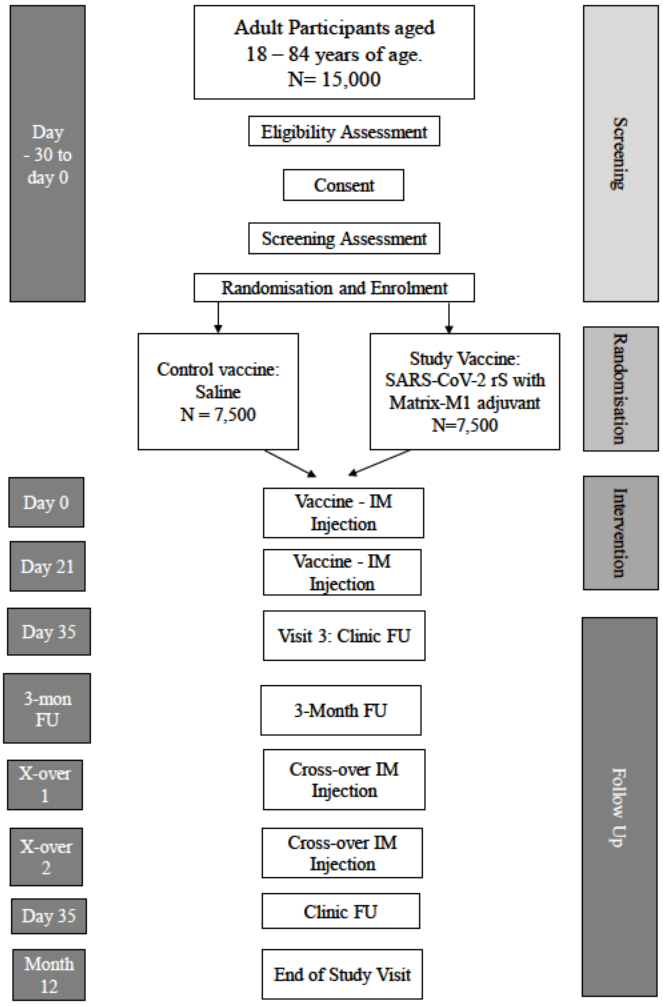


Figure 1a: Trial Schema with Blinded Crossover

FU = follow-up; IM = intramuscular; N = number of participants.

Note: The 3-month follow-up and Day 1 Crossover visits can be consolidated if they occur within 30 days of each other. The Day 35 Crossover visit is only for participants in the anti-S immunogenicity subgroup.

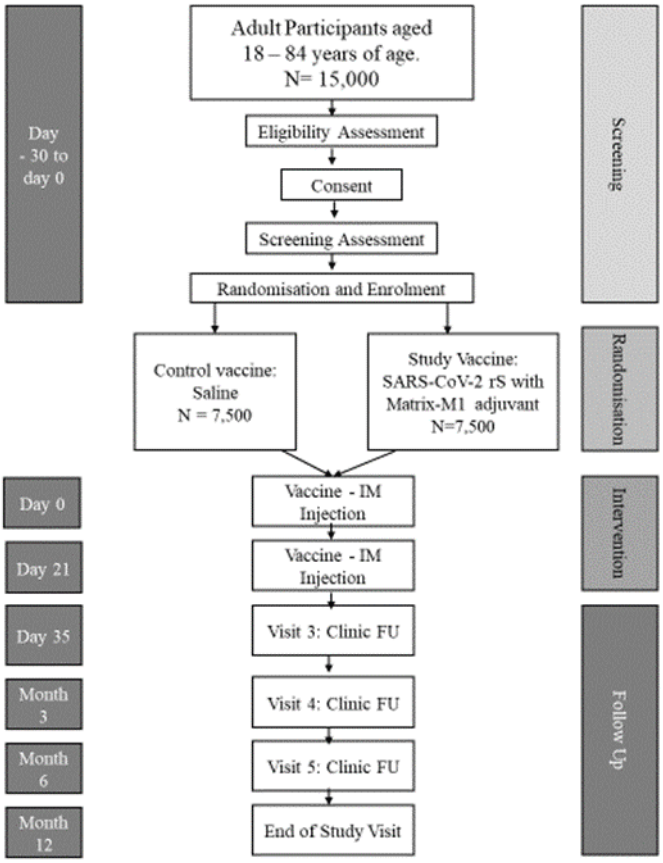


Figure 1b: Original Trial Schema

FU = follow-up; IM = intramuscular; N = number of participants.

Randomisation will be stratified by site and by age ≥ 65 years. In addition, there will not be specific age sub-stratification recruitment targets within the ≥ 65-year age group, but through site recruitment; the aim is to allow a generally representative age distribution overall.

The study will consist of the screening period (Days -30 to 0); initial vaccination Days 0 and 21 (+7-day window); and outpatient study visits on Day 0, Day 21 (+ 7 days), and Day 35 (14 days minimum after second study vaccination [+ 7 days]) after last study vaccination. Visits for the purpose of obtaining lab tests prior to unblinding may occur if feasible. Additional study visits for blood draws and blinded crossover injections will occur after achieving the primary efficacy endpoint and an acceptable safety profile.

The duration of individual participation, including screening, will be a maximum of 1 year (Day 386 ± 15 days) from the initial set of vaccinations. This will be an event-driven study for the assessment of vaccine efficacy (VE) and will end when a sufficient number of events have been observed, yet all participants will be followed for the entire study duration for an assessment of duration of vaccine efficacy (placebo-controlled and actively controlled) and for safety endpoints.

A licensed seasonal influenza co-administration sub-study will be conducted in the first approximately 400 participants who meet the additional inclusion criteria for this study. Participants may be enrolled at selected study sites due to the availability of seasonal influenza vaccine. After being randomised to receive IM injections of SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo, sub-study participants will receive a licensed seasonal influenza vaccine on Day 0 in the opposite deltoid. These participants will be part of the solicited AE safety subset analysis.

Given that this study and others will enrol during the influenza virus season and that the highest at-risk population, namely the elderly and adults with comorbid conditions for influenza mirrors that of SARS-CoV-2, a co-vaccination sub-study is included. This sub-group will undergo the same safety and efficacy evaluations as the entire study population. In addition, the entire sub-study will have reactogenicity assessed. This group must not have had a current season licensed influenza vaccine and have no prior history of allergy or severe reaction to seasonal influenza vaccine. To assess the possible impact of the study vaccine on the immunogenicity of the influenza vaccine, this group will also have a hemagglutination inhibition assay (HAI) performed.

A global Safety Monitoring Committee (SMC) was convened to oversee the safety of the ongoing Phase 1/2 study (Protocol 2019nCoV-101) and will oversee one or more additional studies across the SARS-CoV-2 rS vaccine program. A separate SMC will be convened for this study. The designated SMC will monitor the safety of participants in the study and will follow an SMC charter. The SMC will review blinded and unblinded safety and reactogenicity data. The SMC will also review sufficient clinical event data to ensure detection of any evidence of enhanced disease. The SMC will convene to perform safety reviews on a scheduled basis, for immediate concerns regarding safety observations during this study, and as needed.

Following achievement of the primary efficacy endpoint, blinded participants will be revaccinated with 2 injections 21 days apart of the alternate study vaccine (“blinded crossover”). That is, initial recipients of placebo will receive active SARS-CoV-2 rS with Matrix-M1 and initial recipients of active vaccine will receive placebo. Because the blinded crossover will provide all study participants with active SARS-CoV-2 rS vaccine, either initially or at the time of blinded crossover, unblinding of participants to allow receipt of another active vaccine is discouraged after the crossover. Yet all participants will be reminded that they always have the option to become unblinded for a deployed vaccine or withdraw from the study at any time for any reason. Previously unblinded participants still in the study will not be eligible for crossover vaccinations. Participants who are unblinded and receive another active vaccine outside of this protocol in this manner will be censored in the final analysis at the time of unblinding but will be strongly encouraged to remain in safety follow-up as defined in this protocol.

3.1 Study Vaccination Pause Rules

Study vaccination pause rules based on reactogenicity, AEs, and SAEs related to study participation will be in place to monitor participant safety after the initial set of vaccinations only.

AEs meeting any one of the following criteria will result in a hold being placed on subsequent study vaccinations pending further review by the SMC at the direction of the SMC chair:

- Any toxicity grade 3 or higher (severe or potentially life-threatening) solicited (local or systemic) single AE term occurring in ≥ 10% of participants (after a minimum of 100 subjects are enroled) in the SARS-CoV-2 rS with Matrix-M1 adjuvant group within the first 7 days after study vaccination.
- Any severe unsolicited single AE preferred term for which the investigator assesses as related that occurs in ≥ 5% of participants (after a minimum of 100 subjects are enroled) in the SARS-CoV-2 rS with Matrix-M1 adjuvant group, within the first 7 days after study vaccination.

In addition, any SAE assessed as related to vaccine (final assessment by the sponsor) will be reported by the sponsor to the SMC Chair as soon as possible, and within 24 hours of the sponsor's awareness of the event. Based on this initial report of the event to the SMC Chair, the Chair may advise the sponsor to immediately pause enrolment and further dosing in either some or all subjects in the study and to convene an ad hoc meeting or make alternative recommendations. The SMC Charter defines processes for how this review will occur and how the Chair's recommendations will be documented.

The sponsor, along with medical monitor, may request an SMC review for any safety concerns that may arise in the study, even if they are not associated with any specific pause rule; for example, any SAE for which causality is at least possibly related.

The 400 subject influenza vaccine co-administration study will utilize the same pause rules with one difference due to the expectation of greater reactogenicity and the small size:

- Any grade 3 or higher (severe or potentially life-threatening) solicited (local or systemic) single AE term occurring in ≥ 20% of participants in the SARS-CoV-2 rS with Matrix-M1 adjuvant plus seasonal influenza vaccine group, within the first 7 days after study vaccination.

3.2 Schedule of Events (SOE)

Table 3-1 lists the study procedures that will be performed during the study for participants who will participate in the blinded crossover. Detailed descriptions of each visit and details for those not participating in the blinded crossover are presented in Section 6.1.

Table 3-1 Schedule of Events

Study Period:	Screening Period [a]	Clinic Visits					Months After Last Study Vaccination	Crossover Vaccination Period[e]			Last Follow-up Visit
Study Day:	–30 to 0	0[a]	21	35	COVID-19 Surveillance Visits (Unscheduled)[c]	Unblinding Visit[d]	3	CO0	CO21	CO35	12
Window (days):[b]	–	0	+ 7	+ 7			± 15	± 30	+7	+7	±15
Minimum days following most recent study vaccination:[b]	–	0	21	14			–	–	21	35	--
Study Visit:	Screening	1	2	3			4	5	6	7	EOS[f]
Informed consent	X					X[e]		X			
Medical history [g]	X				X						
Inclusion/exclusion criteria [h]	X	X[i]	X[i]					X[h]	X[h]		
Demographics [j]	X										
Prior/concomitant medications [k]	X	X[i]	X[i]	X	X	X	X	X[i]	X[i]	X	X
Vital sign measurements[l]	X	X	X		X			X	X		
Urine pregnancy test (WOCBP) [m]	X	X[i]	X[i]					X[i]	X[i]		
Physical examination (targeted) [n]	X	X[i]	X[i]	X	X			X[o]	X[o]		
Nose/throat testing for SARS-CoV-2 (PCR) [p]	X	X[i]	X[i]		X			X[i]	X[q]		
Blood sampling for SARS-CoV-2 (ELISA for anti N-protein serology)[r]		X[i]		X		X[d]	X	X[i]			X
Blood sampling for SARS-CoV-2 (ELISA for anti S-protein serology – subset of participants) [s]		X[i]		X		X[d]		X[i]		X	
Blood sampling for SARS-CoV-2 neutralisation assay (subset) [t]		X[i]		X		X[d]					

Table 3-1 Schedule of Events

Study Period:	Screening Period [a]	Clinic Visits					Months After Last Study Vaccination	Crossover Vaccination Period[e]			Last Follow-up Visit
Study Day:	–30 to 0	0[a]	21	35	COVID-19 Surveillance Visits (Unscheduled)[c]	Unblinding Visit[d]	3	CO0	CO21	CO35	12
Window (days):[b]	–	0	+ 7	+ 7			± 15	± 30	+7	+7	±15
Minimum days following most recent study vaccination:[b]	–	0	21	14			–	–	21	35	--
Study Visit:	Screening	1	2	3			4	5	6	7	EOS[f]
Blood sampling for HAI (influenza co-administration subset) [u]		X [i]	X			X[d]					
Cell-mediated assessments (subset of participants)[v]		X [i]		X							
Randomisation		X									
Study vaccination [w]		X	X					X	X		
Reactogenicity (subset of participants) [x]		X	X								
Monitoring for COVID-19 [y]		COVID-19 case ascertainment will commence from Day 0 until EOS									
COVID-19 Symptom Diary [z]					X						
All unsolicited AEs [aa]		X	X	X							
MAAEs [bb]		X	X	X	X	X	X	X	X	X	X
SAEs [cc]	X	X	X	X	X	X	X	X	X	X	X
AESI [dd]		X	X	X	X	X	X	X	X	X	X
EOS form [ee]											X

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; COVID-19 = coronavirus disease 2019; CO0= Crossover Day 0 visit. CO21= Crossover Day 21 visit; CO35 = Crossover Day 35 visit; EDC = electronic data capture; ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immune sorbent spot; EOS = end of study; HAI = hemagglutinin assay inhibition; HEENT = head, eye, ear, nose, and throat (exam); ID = identification; MAAE = medically attended adverse event; N = nucleocapsid; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; S = spike protein; SAE = serious adverse event; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBA = women of childbearing age.

[a] The Screening visit and Day 0 visit may be combined if feasible at any given study site.

[b] Days relative to study vaccination are only estimates because the window allowance is not inclusive. Should a study pause occur, visits/windows will be adjusted to allow participants to continue without protocol deviation. Visit schedules after second study vaccination are calculated relative to the day the study vaccinations were received. The precise timing of the first crossover visit is dependent on the timing of the protocol amendment and available crossover vaccination doses; however, it is expected that the blinded crossover will be implemented approximately 3-4 months after the Day 21 visit for the majority of participants.

[c] COVID-19 Surveillance Visits will occur during the initial vaccination period as well as during the crossover period. If the participant is known to be COVID-19 positive at the time of scheduling for the Initial Surveillance Visit and cannot attend the visit due to extenuating circumstances (e.g., local government restrictions), then a phone call or

Table 3-1 Schedule of Events

Study Period:	Screening Period [a]	Clinic Visits					Months After Last Study Vaccination	Crossover Vaccination Period[e]			Last Follow-up Visit
Study Day:	–30 to 0	0[a]	21	35	COVID-19 Surveillance Visits (Unscheduled)[c]	Unblinding Visit[d]	3	CO0	CO21	CO35	12
Window (days):[b]	–	0	+ 7	+ 7			± 15	± 30	+7	+7	±15
Minimum days following most recent study vaccination:[b]	–	0	21	14			–	–	21	35	--
Study Visit:	Screening	1	2	3			4	5	6	7	EOS[f]

phone calls can be substituted to assess the participant's status. However, the participant should make every effort to attend the Follow-up Surveillance Visit (as per protocol timeline) when government restrictions or other circumstances allow. If the participant has made an Initial Surveillance phone contact or visit and is found to be COVID-19 negative on all swabs taken for this episode, then a phone call can be substituted for the Follow-up Surveillance Visit.

[d] An Unscheduled Unblinding Visit should be arranged (where possible and practical to do so) for those who are offered and are willing to accept an approved or deployed SARS-CoV-2 approved or deployed vaccine. Serology will be obtained as per Section 6.1.6. Visits on Days 21 and 35 may be skipped for those who have been unblinded as per Section 6.1.6. Participants who are unblinded are not eligible for participation in the blinded crossover.

[e] Crossover Day 0 visit and Crossover Day 21 visit will be in lieu of the 3- and 6-Month visit unless the participant has already had a 3-Month visit; in this case, Crossover Day 0 visit should occur as soon as feasible and Crossover Day 21 visit will replace the 6-Month visit. These visits will not be 3 months apart but will be 21 +7 days apart. The Crossover Day 35 visit will only be for those in the anti-S serology subset and will occur approximately 35 days after the second dose 1. For participants who have been unblinded and are ineligible for the blinded crossover, follow the schedule for the 3- and 6-Month Visits in Section 6.1.

[f] EOS visit. Should participants decide to terminate early, an EOS telephone call will occur to collect the maximum safety data possible.

[g] Including prior and concomitant medical conditions (as appropriate), recent vaccinations (≤ 90 days), and significant surgical procedures.

[h] Specific exclusions to study vaccination (e.g., anaphylaxis to dose 1, pregnancy) will be assessed before any vaccination. Waivers to enrolling participants with exclusions will not be given.

[i] Performed prior to study vaccination (each set).

[j] Screening only. Including date of birth (day, month, and year), sex, race, ethnicity, weight, and height.

[k] Recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include all medications (including vaccines) taken by the participant. Concomitant medications will be collected through Day 49 only unless related to an SAE, AESI, related MAAE, or is an approved or deployed COVID-19 vaccine.

[l] Including respiratory rate, blood pressure, pulse rate, pulse oximetry and oral temperature (or via forehead/ear reader). On all study vaccination days, vital sign measurements will be collected once before study vaccination to ensure participant has no evidence of fever prior to study vaccination. Vital sign measurements will also be collected once again, approximately 15 to 30 minutes after study vaccination, to check for any reactions to the vaccine.

[m] Women of childbearing potential only. A urine pregnancy test will be performed at Screening and prior to each study vaccination. A positive urine pregnancy test at any of the vaccination visits will result in the participant not receiving any further study vaccination. A positive urine pregnancy test at Screening will result in screen failure.

[n] Examination at screening to include height and weight; HEENT, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck; and musculoskeletal system/extremities to allow for study vaccination; symptom-directed (targeted) physical examination at all other scheduled time points but always to include lymphatic assessment of injected upper extremity on study vaccination days. Physical examination on study vaccination visits must be done prior to vaccination. Interim physical examinations will be performed at any unscheduled visit at the discretion of the investigator, if necessary.

[o] Crossover Day 0 and Day 21 visits—targeted PE is optional and may be conducted if participants have specific complaints or as per investigator judgment.

Table 3-1 Schedule of Events

Study Period:	Screening Period [a]	Clinic Visits					Months After Last Study Vaccination	Crossover Vaccination Period[e]			Last Follow-up Visit
Study Day:	–30 to 0	0[a]	21	35	COVID-19 Surveillance Visits (Unscheduled)[c]	Unblinding Visit[d]	3	CO0	CO21	CO35	12
Window (days):[b]	–	0	+ 7	+ 7			± 15	± 30	+7	+7	±15
Minimum days following most recent study vaccination:[b]	–	0	21	14			–	–	21	35	--
Study Visit:	Screening	1	2	3			4	5	6	7	EOS[f]

[p] Samples will be collected at Screening only if the participant has any COVID-19 symptoms or significant exposure history. If a participant has a positive PCR prior to enrolment, they will be considered a screen failure. Samples will be collected on Day 0 and the method of collection will be taught. Participants found to be SARS-CoV-2 positive on Day 0 will be excluded from some analyses of the study as per the SAP. Samples may be collected on Day 21 only if the participant has any COVID-19 symptoms or significant exposure history between Days 0 and 21. Results of that test are not required for study vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol. Participants found to be SARS-CoV-2 positive on Day 21 will be excluded from some analyses of the study as per the SAP. A sample will be taken at Crossover Day 0 visit. The sample bar code should be put in EDC as soon as is feasible.

[q] PCR to be done for symptomatic cases. If a sample is taken the sample bar code should be put in EDC as soon as feasible.

[r] The ELISA for anti-S protein serology will be performed in the approximately 900 participants in the Anti-S Protein Serology Subset after each set of vaccinations. These participants will have an extra visit the Crossover Day 35 visit, which will occur approximately 35 days after the second dose 1.

[s] The neutralising antibody assay will be performed in the approximately 900 participants in the Neutralisation Assay Subset.

[t] The HAI assay will be performed in the approximately 400 participants in the licensed seasonal influenza co-administration sub-study.

[u] Cell-mediated immune responses, as assessed by ELISpot ± intracellular cytokine staining, will be performed in approximately 450 participants in the Cell-mediated Assay Subset.

[v] Study vaccination on Day 0 will consist of study vaccine plus, in the seasonal influenza vaccine co-administration sub-study, a single dose of licensed influenza vaccine. Study vaccination on Day 21 will consist of study vaccine.

[w] Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in the Safety Subset of approximately 2,000 participants and in the first approximately 400 participants who qualify for the seasonal influenza vaccine co-administration sub-study after the initial set of vaccinations only. On study vaccination days, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.

[x] Participants will monitor for COVID-19 symptoms. This will include provision of a Study ID Card that provides details on study participation, study site contact information and assessment of symptoms of suspected COVID-19 (see Table 2-2). Instructions to participants to contact the study site within 24 hours for symptoms of suspected COVID-19 will be given. A participant with suspected or confirmed COVID-19 will be asked to complete a COVID-19 symptom diary for 10 days. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter participants with symptoms of suspected COVID-19.

[y] Samples will be self-collected by the participants in an effort to determine if the current symptoms are due to SARS-CoV-2 infection. Approximately 24 hours after the onset of symptoms the participants will swab themselves daily for up to 3 days but only until the point that 1 of the samples tests positive for SARS-CoV-2.

[z] A participant with suspected or confirmed COVID-19 will be asked to complete the COVID-19 symptom diary. Participants should start the diary on their first day of symptoms and complete this diary daily for a minimum of 10 days even if their symptoms have resolved and regardless of any SARS-CoV-2 PCR results. They should continue the diary beyond 10 days if they have any ongoing symptoms related to the episode and should continue to do so until all symptoms have resolved.

[aa] All unsolicited AEs are to be reported from the time of first study vaccination until 21 days after first study vaccination and 28 days after second study vaccination in all participants after the initial set of vaccinations only.

Table 3-1 Schedule of Events

Study Period:	Screening Period [a]	Clinic Visits					Months After Last Study Vaccination	Crossover Vaccination Period[e]			Last Follow-up Visit
Study Day:	–30 to 0	0[a]	21	35	COVID-19 Surveillance Visits (Unscheduled)[c]	Unblinding Visit[d]	3	CO0	CO21	CO35	12
Window (days):[b]	–	0	+ 7	+ 7			± 15	± 30	+7	+7	±15
Minimum days following most recent study vaccination:[b]	–	0	21	14			–	–	21	35	--
Study Visit:	Screening	1	2	3			4	5	6	7	EOS[f]

[bb] MAAEs are to be collected from the time of first study vaccination until Day 35 in the initial set of vaccinations, and MAAEs assessed as related to study vaccination from the time of first study vaccination until completion of the participant's last study-related procedure.

[cc] SAEs are to be collected from the time of informed consent until completion of the participant's last study-related procedure.

[dd] AESI: To include PIMMC and AEs related to COVID-19 are to be collected from the time of first study vaccination until completion of the participant's last study-related procedure.

[ee] EOS form will be completed for all participants, including participants who are terminated early.

4. STUDY POPULATION

Approximately 15,000 male and female adult participants 18 to 84 years of age (inclusive) with and without relevant comorbidities will be randomised in a 1:1 ratio via block randomisation to receive 2 intramuscular (IM) injections of SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo in a blinded fashion in up to 28 sites across the UK.

4.1 Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adult males or females aged 18 to 84 years (inclusive) at screening.
2. Able and willing (in the investigator's opinion) to comply with all study requirements.
3. Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
4. Willing and able to give informed consent prior to study enrolment.
5. Female participants of childbearing potential (defined as any female who has experienced menarche and who is NOT surgically sterile [i.e., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months or > 1 documented plasma follicle-stimulating hormone level ≥ 40 mIU/mL]) must agree to be heterosexually inactive from at least 28 days prior to enrolment and through 3 months after the last study vaccination OR agree to consistently use any of the following methods of contraception from at least 28 days prior to enrolment and through 3 months after the last study vaccination:
    a. Condoms (male or female)
    b. Diaphragm with spermicide
    c. Cervical cap with spermicide
    d. Intrauterine device
    e. Oral or patch contraceptives
    f. Norplant®, Depo-Provera®, or other in country regulatory-approved contraceptive method that is designed to protect against pregnancy
    g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle (other approaches to abstinence are not acceptable)

       NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
6. Room air oxygen saturation > 95% at Screening/Day 0.

Seasonal Influenza Vaccine Co-Administration Sub-Study Only

7. Participant should not have received a current season influenza vaccine, have no contraindication to the specific vaccine to be administered in the study, and no prior history of allergy or severe reaction to seasonal influenza vaccines.

4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Participation in COVID-19 prophylactic drug trials for the duration of the study.
2. Future participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.
3. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
4. History of laboratory-confirmed (by PCR or serology to SARS-CoV-2) COVID-19 infection at any time prior to randomisation.
5. Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of the study vaccine candidate.
6. Any confirmed or suspected immunosuppressive or immunodeficient state; chronic administration (defined as more than 14 continuous days) of immunosuppressant medication within the past 3 months, except topical steroids or short-term oral steroids (course lasting ≤ 14 days).

   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted if other chronic disease conditions are not exclusionary. Human immunodeficiency syndrome (HIV)-positive participants receiving highly active antiretroviral therapy and a history within 6 months of screening of viral load < 1000 copies/mL or CD4 count > 300 cells/mm^3 would be eligible.
7. History of allergic disease or reactions likely to be exacerbated by any component of the study vaccines.
8. Any history of anaphylaxis to any prior vaccine.
9. Pregnancy, lactation, or willingness/intention to become pregnant within 3 months following the last study vaccination.
10. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ, at the discretion of the investigator).
11. Bleeding disorder (e.g., factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.

12. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants/anti-platelet agents.

    NOTE: The use of ≤ 325 mg of aspirin per day as prophylaxis is permitted.

13. Suspected or known current alcohol or drug dependency.

14. Study team member or first-degree relative of any study team member (inclusive of sponsor, contract research organisation (CRO), and site personnel involved in the study).

15. Participants who are having any current workup of undiagnosed illness within the last 8 weeks that is either participant-reported or has been clinician-assessed, which could lead to a new condition or diagnosis.

16. Received any live vaccine within 4 weeks or **any vaccine** (excluding influenza) within 2 weeks prior to first study vaccination or any licensed influenza vaccine within 1 week prior to first study vaccination or plans to receive any vaccine from these time periods until 28 days after second study vaccination.

    NOTE: An influenza co-administration sub-study will occur in which 400 participants will receive a single dose of seasonal influenza vaccine at the same time as first study vaccination. In addition, a licensed seasonal influenza vaccine may be given 7 days after each vaccination but should not be given within 7 days prior to second vaccination.

17. Have clinically significant chronic cardiovascular, endocrine, gastrointestinal, hepatic (including hepatitis B and C), renal, neurological, respiratory, psychiatric or other medical disorders not excluded by other exclusion criteria, that are assessed by the investigator as being clinically unstable within the prior 4 weeks as evidenced by:

    a. Hospitalisation for the condition, including day surgical interventions.

    b. New significant organ function deterioration.

    c. Needing addition of new treatments or major dose adjustments of current treatments (mild or moderate well-controlled comorbidities are allowed).

18. History of chronic neurological disorders that have required prior specialist physician review for diagnosis and management (such as multiple sclerosis, dementia, transient ischemic attacks, Parkinson's disease, degenerative neurological conditions, and neuropathy) or a history of stroke or previous neurological disorder within 12 months with residual symptoms. Participants with a history of migraine or chronic headaches or nerve root compression that have been stable on treatment for the last 4 weeks are not excluded.

19. Any autoimmune disease/condition (iatrogenic or congenital) listed in Table 9-3 or being treated with a biologic therapy.

    NOTE: The Skin and Metabolic Disorders listed in Table 9-3 are eligible at the discretion of the investigator.

20. Any other significant disease, disorder or finding that, in the opinion of the investigator, may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data.
21. Participant requires the use of continuous oxygen therapy or any oxygen therapy while awake or is anticipated to require daytime oxygen therapy during the course of the study.

    NOTE: Nocturnal oxygen use only is acceptable for study inclusion.

NOTE: Inclusion and exclusion criteria are applied at study entry and should not be used to determine whether to provide a second dose. Decision making regarding refraining from a second dose should be based on specific conditions such as pregnancy or anaphylaxis to the prior study dose or medical contraindications per the judgment of the investigator or medical monitor.

4.3 Other Considerations

Participants meeting any of the following criteria may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment.

- Respiratory symptoms in the past 3 days (i.e., cough, sore throat, difficulty breathing). Participant may be vaccinated once all symptoms have been resolved for > 3 days. Out-of-window study vaccination is allowed for this reason (**see NOTE**).
- Temperature of > 38°C within 24 hours of planned study vaccination (site measured or participant measured). Participant may be vaccinated once the fever has resolved and there has not been any temperature measured as being > 38°C for > 3 days. Out-of-window study vaccination is allowed for this reason (**see NOTE**).

  NOTE: PCR testing for SARS-CoV-2 is likely to be indicated for either of the above reasons or if COVID-19 is suspected based on other symptoms, potential exposure to SARS-CoV-2 infection through either close contacts or based on local epidemiology. If a participant has a positive PCR for SARS-CoV-2 prior to enrolment that participant will not be eligible and will be considered a screen failure.
- Participants having any symptoms or signs of possible COVID-19 infection (Table 2-2) that may also be due to post-vaccination reactogenicity within 7 days of either study vaccine dose will NOT be required to be tested for SARS-CoV-2 PCR.
- Any participant with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Screening and prior to second study vaccination will not be removed from the study but must meet health requirements before receiving the second study vaccination.
- Any participant who has a positive PCR for SARS-CoV-2 between the first and second study vaccination should also have PCR testing for SARS-CoV-2 on the day

of the subsequent study vaccination, but the results of the PCR test are not needed before study vaccination can be given.

- Any participant with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Screening and prior to the end of immunogenicity assessments will be removed from applicable immunogenicity analyses as defined in the SAP.
- Any acute illness (cardiovascular, endocrine, gastrointestinal, hepatic, renal, neurological, respiratory, or other medical disorders) that is actively causing symptoms that could, in the opinion of the investigator, impact the assessment of reactogenicity or other study assessments may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment. Participant may be vaccinated once symptoms have resolved or are stabilised for > 3 days. Out-of-window study vaccination is allowed for this reason.
- Any participant who is otherwise eligible with a blood pressure of ≥ 160/100 mmHg may be retested onsite several times over a 3-hour interval to achieve a lower blood pressure. If the blood pressure remains ≥ 160/100 mmHg, study vaccination should be deferred for a later date if the baseline blood pressure is found to be < 160/100 mmHg.

4.4 Withdrawal of Participants from the Study

4.4.1 Reasons for Withdrawal

Participants can withdraw consent and discontinue from the study at any time, for any reason. Participants may refuse further procedures (including study vaccination) but are encouraged to remain in the study for safety follow-up. In such cases where only safety is being conducted, participant contact could be managed via telemedicine contact (e.g., telephone, web chat, video, FaceTime).

The investigator will **withhold** further study vaccination from a participant in the study if the participant:

1. Is noncompliant with the protocol.
2. Experiences an SAE or intolerable AE(s) for which study vaccination is not advised by the investigator.
3. Becomes pregnant (discontinuation of further study vaccination required).

The investigator can also withdraw a participant upon the request of the sponsor or if the sponsor terminates the study.

Vaccination with an approved or deployed SARS-CoV-2 vaccine alone will not be considered a withdrawal from the study.

4.4.2 Handling of Withdrawals

Participants are free to withdraw from the study at any time upon request. Participant participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a participant withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any participant who withdraws from the study prematurely will undergo all end of study (EOS) assessments. Any participant who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of participants who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

Participants who withdraw, are withdrawn or terminated from this study, or are lost to follow-up after signing the informed consent form (ICF) but prior to first study vaccination may be replaced. Participants who receive study vaccine and subsequently withdraw, are discontinued from further study vaccination, are terminated from the study, or are lost to follow-up will not be replaced.

5. TEST ARTICLES

5.1 Study Vaccines Administered

Study vaccinations (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo [saline]) will comprise 2 IM injections (Day 0 and Day 21), ideally in alternating deltoids. For blinding purposes, all participants will be vaccinated using the same injection volume (i.e., 0.5 mL). The dose level will be 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant (co-formulated in a single vial); placebo will be saline for injection. Study vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of participants.

At the time of the blinded crossover, participants will receive the alternate study material in 2 IM injections 21 + 7 days apart.

The seasonal influenza vaccine co-administration sub-study will comprise a single IM injection (0.5 mL) of a licensed influenza vaccine on Day 0, ideally in the opposite deltoid of the study vaccine. Seasonal influenza vaccine will be administered in an open-label manner. Flucelvax Quadrivalent will be given to those 18 to 64 years of age, and an adjuvanted trivalent influenza vaccine will be given to those ≥ 65 years of age.

Whenever possible the RIGHT deltoid will be used for the influenza vaccine and the LEFT deltoid for the study vaccine.

5.2 Investigational Products

The following supplies will be used for vaccination in the study:

Investigational Product	Supplied Formulation
SARS-CoV-2 rS with Matrix-M1 adjuvant	Solution for preparation for injection, at a concentration of 5 µg antigen and 50 µg adjuvant.
Placebo	Sodium chloride injection (BP, sterile), 0.9%
Seasonal Influenza Vaccine Co-Administration Sub-Study	
Flucelvax Quadrivalent seasonal influenza vaccine	Single-dose pre-filled syringe (0.5 mL) or multi-dose vial
Adjuvanted trivalent seasonal influenza vaccine	Single-dose pre-filled syringe (0.5 mL)
Abbreviations: BP = British Pharmacopoeia; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.	

It is anticipated that the product will be available in a co-formulated single vial.

Further details on the study vaccine can be found in the SARS-CoV-2 rS IB.

5.2.1 Investigational Product Packaging and Storage

Novavax, Inc., will provide adequate quantities and appropriate labelling of SARS-CoV-2 rS with Matrix-M1 adjuvant and PPD will ensure distribution to the clinical sites from a designated depot. Sodium chloride injection (British Pharmacopoeia, sterile) and licensed seasonal influenza vaccine are commercially available and will be supplied by PPD. The clinical unit pharmacy will prepare the study vaccines for each participant. Detailed instructions for the preparation of study vaccine will be provided in a separate pharmacy manual.

All investigational products must be stored according to the labelled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Investigational Product Accountability

The investigator (or delegate) will maintain accurate records of receipt of all investigational product, including dates of receipt. Accurate records will be kept regarding when and how much investigational product is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding investigational product accountability, all investigational product will be reconciled and retained or destroyed according to applicable regulations. No investigational product will be destroyed until authorised in writing by the sponsor.

5.3 Method of Assigning Participants to Study Vaccine Groups

Participants will be randomly assigned in a blinded manner using the centralised Interactive Response Technology (IRT) according to pre-generated randomisation schedules. Participants will be randomised in a 1:1 ratio via block randomisation to receive 2 IM injections of the SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo. Randomisation will be stratified by site and by age ≥ 65 years. The first approximately 400 participants who qualify for the seasonal influenza vaccine co-administration sub-study (which may be at select study locations only) will be assigned prior to randomisation. These participants will be part of the solicited AE safety subset analysis. Details regarding the IRT process will be provided separately to the sites. The IRT system will be utilized to assign the crossover doses in a blinded fashion.

5.3.1 Blinding Procedures

This is an observer-blinded study. To maintain the blind, placebo vaccination via IM route will be included and unblinded site personnel will manage study vaccine logistics, preparation, and administration so as to maintain the blind from the remainder of the site personnel and participants. The unblinded site personnel will not be involved in study-related

assessments or have participant contact for data collection following study vaccine administration.

Unblinding of treatment assignment may occur in order to allow a participant to make an informed decision regarding receipt of an approved or deployed SARS-CoV-2 vaccine. Participants who choose to receive an approved or deployed SARS-CoV-2 vaccine as per UK government guidance will be encouraged to remain in the study for scheduled safety assessments. At the time of implementation of the blinded crossover process, a similar procedure will be employed to ensure that all study participants and personnel remain blinded as to initial and subsequent treatment assignment.

Seasonal influenza vaccine will be administered in an open-label manner.

5.3.2 Breaking the Blind

A participant's study vaccine assignment will not be broken until the end of the study for the clinical site study team unless medical treatment of the participant depends on knowing the study vaccine the participant received. In the event that the blind needs to be broken because of a medical emergency or because the participant chooses to receive an approved or deployed SARS-CoV-2 vaccine, the investigator may unblind an individual participant's study vaccine allocation.

Whenever possible, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual study vaccine received by that participant. In the event that the investigator cannot contact the medical monitor in a timely manner the blind may be broken by the investigator. The medical monitor should be contacted as soon as feasible after the unblinding. The study vaccine assignment will be unblinded through IRT. Reasons for study vaccine unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

As of December 2020, an approved SARS-CoV-2 vaccine has been deployed in the UK and regulatory agencies have issued advice concerning unblinding of treatment assignment. Those who are eligible (as per the UK government prioritisation strategy) and have been invited to receive an approved or deployed SARS-CoV-2 vaccine may request to be unblinded. Participants should only request to be unblinded if they are willing to receive an approved or deployed SARS-CoV-2 vaccine and may wish to discuss this decision with the investigator and others so as to make an informed choice. Participants who decline the approved or deployed vaccine should remain blinded to treatment assignment for the entire duration of the study or until other study continuation decisions are made in accordance with the appropriate regulatory agencies. All participants will be encouraged to remain in the study regardless of the UK government approved combination of SARS-CoV-2 vaccines received. For non-emergency unblinding, there is no requirement to seek approval or to contact the medical monitor.

An Unscheduled Visit should be arranged (where possible and practical to do so) for those who are offered and are willing to accept an approved or deployed SARS-CoV-2 vaccine where a blood sample for immunogenicity assessment may be drawn, regardless of which arm of the study they have been allocated to as outlined in Section 6.1.6.

The blind may also be broken in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) to determine regulatory reporting.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for planned analyses prior to study completion, as outlined in Section 7.6.

5.4 Study Vaccine Compliance

All doses of the study vaccine should be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has received the entire dose.

The location (right or left arm), date, and timing of all doses of study vaccine will be recorded in the participants' eCRF. If a participant is not administered study vaccine, the reason for the missed dose will be recorded.

5.5 Concomitant Medications and Prohibitive Therapy

5.5.1 Concomitant Medications

Administration of medications, therapies, or vaccines will be recorded in the eCRF. Concomitant medications will include all medications (including vaccines) taken by the participant from the time of signing the ICF through 49 days after dose 1 in the initial and second set of vaccinations (or through the early termination visit if prior to that time). Prescription and over-the-counter (OTC) drugs, as well as herbals, vitamins, and supplements, will be included.

Concomitant medications will be collected through EOS for all related MAAEs, SAEs, or AESIs. Receipt of any approved or deployed COVID-19 vaccine should also be recorded through EOS.

Participants will be asked to record the date(s) and brand of the approved or deployed SARS-CoV-2 vaccine received.

5.5.2 Prohibitive Therapy

- No live vaccine will be allowed within 4 weeks of first study vaccination until 28 days after second study vaccination (Day 49).

- No vaccine (except for a licensed seasonal influenza vaccine or an approved or deployed SARS-CoV-2 vaccine and vaccines given to participants in the seasonal influenza co-administration sub-study) will be allowed within 2 weeks of first study vaccination until 28 days after second study vaccination (Day 49). Any approved or deployed SARS-CoV-2 vaccine should only be given at least 21 days after the most recent study vaccination.
- No influenza vaccine (except participants in the seasonal influenza co-administration sub-study) will be allowed 7 days before each vaccination.

  NOTE: Participants in the seasonal influenza co-administration sub-study will be allowed to have the co-administration of a licensed seasonal influenza vaccine at the same time as first study vaccination.
- No unlicensed vaccine should be given within 45 days prior to first study vaccination until after the last study visit.
- No investigational product (drug/biologic/device) within 45 days prior to first study vaccination until after the last study visit.
- No chronic administration (defined as more than 14 continuous days) of any immunosuppressant medication within 3 months of first study vaccination until the last study visit (except topical steroids or short-term oral steroids with course lasting ≤ 14 days). The use of topical, inhaled, and nasal glucocorticoids will be permitted if other chronic disease conditions are not exclusionary.
- No continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants/anti-platelet agents. Use of ≤ 325 mg of aspirin per day as prophylaxis is permitted.

6. STUDY PROCEDURES

Written informed consent will be obtained after explanation of the aims, benefits and all safety concerns of the trial as detailed in the information sheet BEFORE any trial specific procedures are performed. They should take as much time as they need to consider joining the study. Signed consent will be kept by the investigator and documented in medical notes and a copy given to the participant, as described in Section 9.3.2.3 (Appendix 2).

Due to the ongoing pandemic, recent national regulatory and local Ethics Committee and public health guidance will be applied at the site locations regarding alternations in the ability of study participants to attend an investigational site for protocol-specified visits, with the site's investigator being allowed to conduct safety assessments (e.g., telephone contact, alternative location for assessment, including local laboratories or imaging centres) when necessary and feasible, as long as such visits are sufficient to assure the safety of study participants. Serum samples may be drawn using local phlebotomy services, home health, or other modalities if site visits cannot occur. Study vaccination visits must have adequate oversight for issues associated with immediate severe reactions.

6.1 Study Visit Procedures

6.1.1 Days -30 to 0 – Screening

The following procedures will be performed within 30 days of first study vaccination. The Screening visit and Day 0 visit may be combined, if feasible, at any given study site.

- Written informed consent will be obtained in conformance with Section 9.3.2.3 of this protocol.
- Review of medical history, including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
- Inclusion and exclusion criteria review consistent with Section 4. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers to enrolling participants with exclusions will not be given.
- Demographics, including date of birth (day, month, and year), sex, race, ethnicity, weight, and height.
- Prior and concomitant medications, including recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include all medications (including vaccines) taken by the participant.
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature (or via forehead/ear reader).
- Urine pregnancy test for women of childbearing potential only. A positive urine pregnancy test at Screening will result in screen failure.

- Physical examination to include height and weight; head, eyes, ears, nose, and throat (HEENT), neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck; and musculoskeletal system/extremities to allow for study vaccination.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) only if the participant has any COVID-19 symptoms or significant exposure history. If a participant has a positive PCR for SARS-CoV-2 prior to enrolment that participant will not be eligible and will be considered a screen failure.
- Assessment of SAEs, starting from the time of informed consent.

6.1.2 Day 0 – First Study Vaccination

The Screening and Day 0 Visits may be combined whenever feasible.

All participants with confirmed eligibility will have the following procedures performed:

- Inclusion and exclusion criteria review consistent with Section 4. Specific exclusions to study vaccination will be assessed before any study vaccination.
- Prior and concomitant medications, including recent and current medications to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include all medications (including vaccines) taken by the participant.
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature (or via forehead/ear reader).
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- Symptom-directed (targeted) physical examination, including lymphatic assessment of injected upper extremity. Physical examination must be done prior to study vaccination.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) to determine current infection with SARS-CoV-2 and to demonstrate the methods required for nose/throat sample collection; participants will be taught how to self-sample at this time. Participants with possible COVID-19 symptoms will not be randomised but may return when symptoms have resolved per protocol. Participants found to be SARS-CoV-2 positive on Day 0 will be excluded from some analyses of the study as per the SAP.
- Blood sampling for SARS-CoV-2 prior to study vaccination (ELISA for anti-N-protein serology) in all participants.
- Blood sampling for SARS-CoV-2 prior to study vaccination (ELISA for anti-S-protein serology) in approximately 900 participants in the Anti-S Protein Serology Subset.

- Blood sampling for SARS-CoV-2 neutralisation assay prior to study vaccination in approximately 900 participants in the Neutralisation Assay Subset.
- Blood sampling for HAI prior to study vaccination for participants who received licensed seasonal influenza vaccine on Day 0 in the approximately 400 participants in the licensed seasonal influenza co-administration sub-study.
- Blood sampling for cell-mediated assessments prior to study vaccination, as measured by enzyme-linked immune absorbent spot (ELISpot) ± intracellular cytokine staining, in approximately 450 participants in the Cell-mediated Assay Subset.
- Randomisation.
- Pre-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
- Alcohol swab cleansing of the injection sites for both study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and licensed seasonal influenza vaccination (first approximately 400 eligible participants).
- Vaccination of study vaccine as an IM injection into the deltoid muscle. The first approximately 400 eligible participants will also receive an IM injection of a licensed seasonal influenza vaccine in the opposite deltoid following study vaccination.
- Monitoring for reactogenicity, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.
- Post-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) at approximately 15 to 30 minutes after study vaccination to check for any reactions to the study vaccine.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms. This will include provision of a Study Identification (ID) Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 (see Table 2-2). Instructions to participants to contact the study site within 24 hours for symptoms of suspected COVID-19 will be given. A participant with suspected or confirmed COVID-19 will be asked to complete a COVID-19 symptom diary for 10 days. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter participants with symptoms of suspected COVID-19. Symptoms of reactogenicity within 7 days post-vaccination may not trigger the actions associated with COVID-19 monitoring.
- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), SAEs, and AESIs.

6.1.3 Day 21 – Second Study Vaccination (+ 7 days)

All participants will have the following procedures performed:

- Inclusion and exclusion criteria review consistent with Section 4. Specific exclusions to study vaccination will be assessed before any study vaccination.
- Prior and concomitant medications. Concomitant medications include all medications (including vaccines) taken by the participant.
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- Symptom-directed (targeted) physical examination, including lymphatic assessment of injected upper extremity. Physical examination must be done prior to study vaccination.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) only if the participant has any COVID-19 symptoms or significant exposure history between Days 0 and 21. Results of that test are not required for study vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol. Participants found to be SARS-CoV-2 positive on Day 21 will be excluded from the immunogenicity analyses of the study as per the SAP.
- Blood sampling for HAI for participants who received licensed seasonal influenza vaccine on Day 0 in the approximately 400 participants in the licensed seasonal influenza co-administration sub-study.
- Pre-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
- Alcohol swab cleansing of the injection site for study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo).
- Vaccination of study vaccine as an IM injection into the opposite deltoid muscle of the Day 0 study vaccine.
- Monitoring for reactogenicity, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.
- Post-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) at approximately 15 to 30 minutes after study vaccination to check for any reactions to the study vaccine.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms. This will include provision of a Study ID Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 (see Table 2-2). Instructions to participants to contact the study site within 24 hours for symptoms of suspected COVID-19 will be given. A participant with suspected or

confirmed COVID-19 will be asked to complete a COVID-19 symptom diary for 10 days. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter participants with symptoms of suspected COVID-19. Symptoms of reactogenicity within 7 days post-vaccination may not trigger the actions associated with COVID-19 monitoring.

- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), SAEs, and AESIs.

6.1.4 Day 35 – Follow-up Visit (+ 7 days)

All participants will have the following procedures performed:

- Prior and concomitant medications. Concomitant medications include all medications (including vaccines) taken by the participant.
- Symptom-directed (targeted) physical examination may be performed if participant has any ongoing complaints.
- Blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants unless the participant has had an Unblinding Visit in the prior 14 days where anti-N serology was drawn.
- Blood sampling for SARS-CoV-2 (ELISA for anti-S-protein serology) in approximately 900 participants in the Anti-S Protein Serology Subset.
- Blood sampling for SARS-CoV-2 neutralisation assay in approximately 900 participants in the Neutralisation Assay Subset.
- Blood sampling for cell-mediated assessments, as measured by ELISpot ± intracellular cytokine staining, in approximately 450 participants in the Cell-mediated Assay Subset.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms. This will include provision of a Study ID Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 (see Table 2-2). Instructions to participants to contact the study site within 24 hours for symptoms of suspected COVID-19 will be given. A participant with suspected or confirmed COVID-19 will be asked to complete a COVID-19 symptom diary for 10 days. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter participants with symptoms of suspected COVID-19.
- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), SAEs, and AESIs.

6.1.5 COVID-19 Surveillance Visits (Unscheduled)

6.1.5.1 Initial COVID-19 Surveillance Visit

If the participant is known to be COVID-19 positive at the time of scheduling of the Initial Surveillance Visit and cannot attend the visit due to extenuating circumstances (e.g., local government restrictions), then a phone call or phone calls can be substituted to assess the participant's status.

All participants (including those who have been unblinded to treatment assignment due to receipt of an approved or deployed SARS-CoV-2 vaccine) will have the following procedures performed:

- Review of medical history, including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
- Prior and concomitant medications (as appropriate). Concomitant medications include all medications (including vaccines) taken by the participant.
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature (or via forehead/ear reader).
- Symptom-directed (targeted) physical examination, including a respiratory assessment.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) only if the participant has any COVID-19 symptoms or significant exposure history between Days 0 and 21. Results of that test are not required for study vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol. Participants found to be SARS-CoV-2 positive on Day 21 will be excluded from the immunogenicity analyses of the study as per the SAP.
- COVID-19 Symptom Diary. A participant with suspected or confirmed COVID-19 will be asked to complete the COVID-19 symptom diary. Participants should start the diary on their first day of symptoms and complete this diary daily for a minimum of 10 days even if their symptoms have resolved and regardless of any SARS-CoV-2 PCR results. They should continue the diary beyond 10 days if they have any ongoing symptoms related to the episode and should continue to do so until all symptoms have resolved.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.5.2 Follow-up COVID-19 Surveillance Visit

A Follow-Up COVID-19 Surveillance Visit will occur approximately 7 (+ 3) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/progression of COVID-19 symptoms.

If the participant is known to be COVID-19 positive at the time of scheduling of the Initial Surveillance Visit and cannot attend the visit due to extenuating circumstances (e.g., local government restrictions), then a phone call or phone calls can be substituted to assess the participant's status. However, the participant should make every effort to attend the Follow-up Surveillance Visit (as per protocol timeline) when government restrictions or other circumstances allow. If a participant has made an Initial Surveillance phone contact or visit and is found to be COVID-19 negative on all swabs taken for this episode, then a phone call can be substituted for the Follow-up Surveillance Visit.

All participants (including those who have been unblinded to treatment assignment due to receipt of an approved or deployed SARS-CoV-2 vaccine) will have the following procedures performed:

- Review of medical history, including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
- Prior and concomitant medications (as appropriate). Concomitant medications include all medications (including vaccines) taken by the participant.
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature (or via forehead/ear reader).
- Symptom-directed (targeted) physical examination, including a respiratory assessment.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) only if the participant has any COVID-19 symptoms or significant exposure history between Days 0 and 21. Results of that test are not required for study vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol. Participants found to be SARS-CoV-2 positive on Day 21 will be excluded from the immunogenicity analyses of the study as per the SAP.
- COVID-19 Symptom Diary. A participant with suspected or confirmed COVID-19 will be asked to complete the COVID-19 symptom diary. Participants should start the diary on their first day of symptoms and complete this diary daily for a minimum of 10 days even if their symptoms have resolved and regardless of any SARS-CoV-2 PCR results. They should continue the diary beyond 10 days if they have any ongoing symptoms related to the episode and should continue to do so until all symptoms have resolved.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.6 Unblinding Visit

An Unblinding Visit should be arranged (where possible and practical to do so) for those who are offered and are willing to accept an approved or deployed SARS-CoV-2 vaccine.

If an unblinding visit occurs within 30 days of the scheduled 3- or 6-Month visit, the 3- or 6-Month visit may be skipped.

Unblinding after the blinded crossover is discouraged. If a participant has undergone both blinded crossover vaccinations and still desires to be unblinded and vaccinated with a deployed or approved vaccine, against national guidance, that participant should be withdrawn from the trial.

All participants will have the following procedures performed prior to unblinding of treatment assignment:

- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), SAEs, and AESIs.
- Prior and concomitant medications (as appropriate). Concomitant medications include all medications (including vaccines) taken by the participant.
- Blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants. If a visit for anti-N-protein sampling has occurred 30 days before an unblinding visit this blood sampling may be skipped.

All participants should follow the following guidance after unblinding:

For those who have received 1 or 2 doses of placebo:

- The participant should be advised to receive the approved or deployed SARS-CoV-2 vaccine through the National Health Service (NHS). Participants will be asked to record the date and type of SARS-CoV-2 vaccine received.
- The participant should be advised that if they have not had a Day 21/35 Visit they may skip the Day 21 and Day 35 Visits and resume the protocol visits with the 3-Month Visit.

For those who have received a single dose of the Sponsor's study vaccine:

Those who are eligible to receive an approved or deployed SARS-CoV-2 vaccine and who, after unblinding to treatment assignment, are found to have received a single dose of study vaccine will be given an option to receive the second dose of study vaccine as per their current study vaccination schedule (in accordance with national policy). Alternatively, the participant may choose to receive a single dose of approved or deployed SARS-CoV-2 vaccine through the NHS. The safety and benefit of mixed SARS-CoV-2 vaccine schedules is unknown.

Any participant receiving the approved or deployed SARS-CoV-2 vaccine will be advised to allow a period of at least 3 weeks between vaccination with the Sponsor's study vaccine and the approved or deployed SARS-CoV-2 vaccine. Participants will be asked to record the date and type of vaccine received.

Participants who desire the option to receive the second dose of the Sponsor's study vaccine should attend the Day 21 Visit as scheduled and follow all protocol visits from that time forward.

Participants who would like a second dose of the approved or deployed SARS-CoV-2 vaccine should be vaccinated through the NHS; if they have not had a Day 21/35 Visit they may skip the Day 21 and Day 35 Visits and resume the protocol visits with the 3-Month Visit.

For those who have received 2 doses of the Sponsor's study vaccine:

In accordance with UK national policy, those participants who have received 2 doses of study vaccine will be advised to not receive the approved or deployed SARS-CoV-2 vaccine. The safety and benefit of mixed SARS-CoV-2 vaccine schedules is unknown. Any participant who still desires the approved or deployed SARS-CoV-2 vaccine after receiving 2 doses of study vaccine, against national policy, should be withdrawn from the study.

Any participant receiving the approved or deployed SARS-CoV-2 vaccine will be advised to allow a period of at least 3 weeks between vaccination with the Sponsor's study vaccine and the approved or deployed SARS-CoV-2 vaccine.

6.1.7 3 Months (± 15 days) After Second Study Vaccination

This visit will apply to only those participants who have had this visit prior to enacting the blinded crossover or for those unblinded participants who are ineligible for the blinded crossover visits. If an unblinding visit has occurred within 30 days of the 3-Month visit, the 3-Month visit may be skipped.

This visit will be substituted for the Crossover Day 0 visit. In the event that the 3-Month visit falls within 30 days of the time the site is able to begin Crossover Day 0 visits, this visit may be skipped and the Crossover Day 0 visit will be scheduled as soon as is feasible.

All participants will have the following procedures performed:

- Prior and concomitant medications (as appropriate). Concomitant medications include all medications (including vaccines) taken by the participant.
- Blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants unless the participant has had an Unblinding Visit in the prior 14 days where anti-N serology was drawn.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms. This will include provision of a Study ID Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 (see Table 2-2). Instructions to participants to contact the study site within 24 hours for symptoms of suspected COVID-19 will be given. A participant with suspected or confirmed COVID-19 will be asked to complete a COVID-19 symptom diary for 10 days. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter participants with symptoms of suspected COVID-19.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.8 Crossover Day 0 Visit

This visit may take the place of the 3-Month visit and should occur approximately 3 months after the second dose of the initial set of vaccinations.

All blinded participants with no vaccination exclusions will have the following procedures performed:

- Written informed consent will be obtained in conformance with Section 9.3.2.3 of this protocol.
- Specific exclusions to study vaccination (e.g., anaphylaxis to previous doses, pregnancy) will be assessed before any study vaccination.
- Concomitant medications (as appropriate).
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- A symptom-directed (targeted) physical examination may be performed if the participant has any specific complaints or at investigator discretion.
- Blood sampling for SARS-CoV-2 prior to study vaccination (ELISA for anti-N-protein serology) in all participants.
- Blood sampling for SARS-CoV-2 prior to study vaccination (ELISA for anti-S-protein serology) in approximately 900 participants in the Anti-S Protein Serology Subset.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) to determine current infection with SARS-CoV-2. Participants with possible COVID-19 symptoms will not be dosed but may return when symptoms have resolved per protocol. Participants found to be SARS-CoV-2 positive will be excluded from some analyses of the study as per the SAP.
- IRT assignment of vaccination.
- Pre-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
- Alcohol swab cleansing of the injection sites for study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo).
- Vaccination of study vaccine as an IM injection into the deltoid muscle.
- Monitoring for reactogenicity, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.

- Post-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) at approximately 15 to 30 minutes after study vaccination to check for any reactions to the study vaccine.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.9 Crossover Day 21 Visit (+7 days)

All blinded participants will have the following procedures performed:

- Concomitant medications (as appropriate).
- Urine pregnancy test for women of childbearing potential only. A urine pregnancy test will be performed prior to each study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- A symptom-directed (targeted) physical examination may be performed if the participant has any specific complaints or at investigator discretion.
- Nose/throat samples will be collected to test for SARS-CoV-2 (PCR) only if the participant has any COVID-19 symptoms or significant exposure history between Crossover Day 0 and Crossover Day 21. Results of that test are not required for study vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol.
- Pre-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
- Alcohol swab cleansing of the injection site for study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo).
- Vaccination of study vaccine as an IM injection into the opposite deltoid muscle of the Crossover Day 0 study vaccine.
- Monitoring for reactogenicity, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of study vaccination.
- Post-injection vital sign collection (respiratory rate, blood pressure, pulse rate, pulse oximetry, and oral temperature [or via forehead/ear reader]) at approximately 15 to 30 minutes after study vaccination to check for any reactions to the study vaccine.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

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6.1.10 Crossover Day 35 Visit (+7 days)

Only for participants in Anti-S Protein Serology Subset. These participants will have the following procedures performed:

- Concomitant medications (as appropriate).
- Blood sampling for SARS-CoV-2 prior to study vaccination (ELISA for anti-S-protein serology)
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.11 6 Months (± 15 days) After Second Study Vaccination

This visit will apply to only those participants who have had this visit prior to enacting the blinded crossover or for those unblinded participants who are ineligible for the blinded crossover visits. If an unblinding visit has occurred within 30 days of the 6-Month visit, the 6-Month visit may be skipped.

- Concomitant medications (as appropriate)
- Blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants.
- Monitoring for COVID-19. Participants will monitor for COVID-19 symptoms.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.

6.1.12 12 Months (± 15 days) After Second Study Vaccination

All participants will have the following procedures performed:

- Prior and concomitant medications (as appropriate). Concomitant medications include all medications (including vaccines) taken by the participant.
- Blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants.
- Assessment of MAAEs (related to study vaccination), SAEs, and AESIs.
- End of study form

6.2 Efficacy assessments

6.2.1 Nose/Throat Samples for Virus Detection

Nose/throat samples for virus detection will be taken at the study visits described in the schedule of events (SOE) (Table 3-1).

- Nose/throat samples will not be taken at Screening unless participants have symptoms or significant exposure to SARS-CoV-2. If a participant has a positive PCR for SARS-CoV-2 prior to enrolment that participant will not be eligible and will be considered a screen failure.
- Nose/throat samples will be taken on Day 0/Crossover Day 0 to determine current infection with SARS-CoV-2 and to demonstrate the methods required for nose/throat sample collection. Participants will be taught how to self-sample at this time. Participants with possible COVID-19 symptoms will not be randomised but may return when symptoms have resolved per protocol. Participants found to be SARS-CoV-2 positive on Day 0 will be excluded from the immunogenicity analyses of the study as per the SAP.
- Nose/throat samples will not be routinely taken on Day 21/Crossover Day 21. Participants with possible COVID-19 symptoms that develop between Day 0 and Day 21 or Crossover Day 0 and 21 may have a SARS-CoV-2 PCR test performed prior to second study vaccination on Day 21/Crossover Day 21. Results of that test are not required for vaccination, but participants who are symptomatic may have the second study vaccination delayed per protocol. Participants found to be SARS-CoV-2 positive on Day 21/Crossover Day 21 will be excluded from the immunogenicity analyses of the study as per the SAP.

6.2.2 Monitoring for Suspected COVID-19

Identification and laboratory confirmation of SARS-CoV-2 infection and symptomatic COVID-19 will be performed throughout the study. This is the case for both blinded and unblinded participants.

On study enrolment, participants will be given details of a 24/7 on-call number to contact the study team. Participants will be instructed to contact the study team within 24 hours via this number if they self-assess COVID-19 symptoms in Table 2-2 or are clinically concerned. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit.

Please refer to Table 2-2 for the qualifying symptoms of suspected COVID-19 disease.

Participants will receive weekly reminders (email or text messages) to immediately contact the study team if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit.

A participant with suspected or confirmed COVID-19 will be asked to complete the COVID-19 symptom diary. Participants should start the diary on their first day of symptoms and complete this diary daily for a minimum of 10 days even if their symptoms have resolved and regardless of any SARS-CoV-2 PCR results. They should continue the diary beyond 10 days if they have any ongoing symptoms related to the episode and should continue to do so until all symptoms have resolved.

The occurrence of COVID-19-related hospitalisation and COVID-19-related complications (such as, but not limited to, pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death) will be monitored throughout the study.

Every episode of a new onset of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) with exceptions per protocol. A "new onset" episode will require at least a 7-day period of being symptom-free prior to the event to differentiate a specific episode from any prior illness.

6.2.2.1 Severity of COVID-19 Symptoms

COVID-19 symptoms will be categorised as mild, moderate, or severe as described in Table 2-1. Participants with a single vital sign abnormality placing them in the moderate or severe COVID-19 severity categories must also meet the criteria for mild COVID-19.

6.2.2.2 COVID-19 Surveillance Visit (Initial and Follow-up)

A COVID-19 Surveillance Visit (Initial and Follow-Up) will be triggered by symptoms of suspected COVID-19 captured by surveillance. See Section 6.1.5.1 for exceptions for participants affected by extenuating circumstances (e.g., local government restrictions).

When a participant is determined to have a new onset of symptoms, the participant will contact the study team immediately, begin their COVID-19 symptom diary and begin the 3 consecutive days of PCR self-testing (beginning approximately 24 hours after the start of symptoms) as above. Participants will be asked to attend an Initial COVID-19 Surveillance Visit at the study clinic or will be seen at an in-home visit by study staff depending on local conditions.

6.2.2.2.1 Initial COVID-19 Surveillance Visit

An Initial COVID-19 Surveillance Visit will be performed at the study site (or home) and will occur as soon as possible within approximately **1-3 days** of new symptom onset (however, data from specimens obtained up to 14 days will be accepted). The visit will consist of the following:

- Review and confirmation of the history of COVID-19 symptoms, including approximate date of onset of illness and solicitation of each symptom (see Table 2-2).

- Vital signs, including resting respiratory rate (on room air) and pulse oximetry, will be captured as numerical values. Lung auscultation (exam) will be performed.
- Ascertainment of any unscheduled healthcare visit by the participant (or home visit by a healthcare provider) in response to symptoms of suspected COVID-19.
- Ascertainment of new concomitant medications as appropriate (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from symptoms of suspected COVID-19.
- Proper documentation in the eCRF of the dates, bar codes, and results of all self-swabs taken in proximity of this visit.

6.2.2.2.2 Follow-Up COVID-19 Surveillance Visit

A Follow-Up COVID-19 Surveillance Visit will occur approximately 7 (+ 3) days after the Initial COVID-19 Surveillance Visit. This visit will consist of the following:

- Study staff will conduct the Follow-Up COVID-19 Surveillance Visit approximately 7 (+ 3) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/ progression of COVID-19 symptoms. This follow-up visit by study staff will include all of the same procedures outlined in this section, including review of symptom history, measurement of vital signs (including pulse oximetry), and lung auscultation.

After the Follow-Up COVID-19 Surveillance Visit, participants will continue to receive telephone contacts approximately every week for ascertainment of COVID-19 symptom status until resolution of symptoms. Subsequent calls will document resolution or return to baseline of COVID-19 symptoms in order to calculate illness duration (date of symptom onset to day of symptom resolution) and will collect any additional healthcare visits, hospitalisations, and/or concomitant medications due to the suspected COVID-19.

Should a participant visit an emergency room, be admitted to the hospital or a COVID-19 ward, and PCR sampling is missed, then the local public health COVID-19 diagnostic test (or COVID-19 diagnostic test performed in the healthcare setting) will be taken as a valid result. Importantly, clinical data on symptoms, vital signs, exam findings, COVID-19 and other diagnostic testing, diagnoses, and complications occurring during the suspected COVID-19 emergency room and/or hospitalisation episode will be collected from available medical records on a study specific hospitalisation/emergency room data collection form in order to assess severity.

Participants will be notified of positive SARS-CoV-2 results as soon as locally practicable due to requirements of self-isolation and potential transmission.

Note that PCR-positive COVID-19 symptoms and events captured as efficacy endpoints will NOT be doubly recorded in the AE eCRF, unless a particular illness fulfils the definition of an SAE.

6.3 Immunogenicity Assessments

Blood will be collected from all participants for humoral immunogenicity according to the time points specified in the SOE (Table 3-1).

Immune measurements (ELISA) will be conducted on serum (IgG) for SARS-CoV-2 anti-S protein serology in approximately 900 participants in the Anti-S Protein Serology Subset (after both sets of vaccinations) and on anti-N protein serology in all participants. The immunologic test for SARS-CoV-2 serology based on a non-S protein (e.g., SARS-CoV-2 N protein) will be performed to identify cases of asymptomatic infection. Additional immunogenicity assessments specific to SARS-CoV-2 (or related variants) will include a neutralising antibody assay, which will be performed in approximately 900 participants in a Neutralisation Assay Subset. Cell-mediated immune responses, as assessed by ELISpot ± intracellular cytokine staining, will be performed in approximately 450 participants in the Cell-mediated Assay Subset. In addition, an HAI will be performed in the approximately 400 participants in the seasonal influenza vaccine co-administration sub-study.

Anti-S protein serology in the Anti-S Protein Serology Subset will be collected after the initial and second set of vaccinations.

Details on the handling, processing, and shipping of immunogenicity samples will be provided separately in a laboratory manual.

Participants will be asked to provide consent for the use of samples for future testing or assay development specific to SARS-CoV-2 (or related variants). Aliquots of all collected samples from this study may be retained for additional testing with antigens specific to SARS-CoV-2 (or related variants) for a maximum of 25 years (starting from the date at which the last participant had the last study visit), unless local rules, regulations, or guidelines require different timeframes or different procedures, in accord with participant consent.

6.4 Safety Assessments

The timing and frequency of all safety assessments are listed in the SOE (Table 3-1).

After each study vaccination, including the licensed seasonal influenza vaccine for participants in the seasonal influenza vaccine co-administration sub-study, participants will remain under observation at the study site for at least 30 minutes for the presence of any acute reactions and solicited AEs. Solicited AEs, collected through an electronic diary (e-Diary), will be recorded from the time of study vaccination until 7 days after study vaccination in all participants in the seasonal influenza vaccine co-administration sub-study and a subgroup of all other participants after the initial set of vaccinations. As solicited AEs are only being recorded in a subset of participants, it is expected that typical solicited AEs will be captured as unsolicited AEs in those participants who are not in the sub-study. An assessment of the impact of this decision will be part of an exploratory analysis. Participants in the licensed seasonal influenza vaccine co-administration sub-study will record local reactogenicity for the study vaccine injection site only.

All participants will be assessed for unsolicited AEs from the time of first study vaccination until Day 49 after the initial set of vaccinations; SAEs will be assessed from the time the informed consent is signed until completion of the participant's last study-related procedure; all MAAEs will be reported from the time of first study vaccination until Day 35 in the initial set of vaccinations; MAAEs related to study vaccination and AESIs will be reported from the time of first study vaccination until completion of the participant's last study-related procedure. All AEs will be followed until resolution or until clinically stable.

Separate analyses of safety events received with respect to approved or deployed SARS-CoV-2 vaccines will be performed.

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs; MAAEs; AESI; SAEs; vital sign measurements on day of study vaccinations; and physical examination findings. Local and systemic reactogenicity events will not be recorded for the second set of vaccinations. COVID-19 severity will be categorised as mild, moderate, or severe according to protocol-specified criteria (Table 2-1). Recording of solicited and unsolicited AEs may be conducted by electronic data capture (EDC)/reporting. PIMMCs and AESIs specific to potential disease enhancement for COVID-19 will also be monitored (see Section 9.5 [Appendix 4] for details).

Participants who are unblinded to treatment assignment for the purpose of receiving an approved or deployed vaccine as per UK guidance will be encouraged to remain in the study for safety follow-up, and safety assessments will be performed via the timelines and mechanisms as described above and throughout Section 6.4. Unblinded participants should not be included in the blinded crossover.

In addition, investigators will be required to report any suspected adverse reactions to another manufacturer's approved or deployed SARS-CoV-2 vaccine to healthcare authorities via the Coronavirus Yellow Card reporting site: https://coronavirus-yellowcard.mhra.gov.uk/.

6.4.1 Adverse Events

AEs will be assessed during the study as described in the SOE (Table 3-1) and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. AEs will be captured after the first dose of study vaccine administered with the exception of an AE related to study procedure or one that causes a delay in study vaccine administration (e.g., acute illness).

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study vaccine or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.4.1.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study vaccination or their clinical significance.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to study vaccination. Participants will be instructed to contact the investigator at any time after randomisation if any symptoms develop.

6.4.1.1.1 Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardise the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

6.4.1.1.2 Local and General Systemic Reactogenicity Symptoms

Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in the Safety Subset of approximately 2,000 participants and in the seasonal influenza vaccine co-administration sub-study of approximately 400 participants after the initial set of vaccinations only. Participants will record all local reactogenicity symptoms for each injection of study vaccine at each location (ideally in opposite deltoids) while recording of general systemic reactogenicity symptoms may not be assigned to either injection site. Local reactogenicity symptoms should not be recorded for the influenza vaccine injection site. Solicited AEs, collected through an electronic diary (e-Diary), will be recorded from the time of study vaccination until 7 days after study vaccination.

Site-specific local (arm) and general systemic reactogenicity reactions including start and stop dates will be recorded and the investigator will apply a standard toxicology grading at the subsequent study visit (Section 9.4, Appendix 3). Should any reactogenicity event extend beyond 7 days after study vaccination and be clinically significant by toxicity grade 1 or greater, then it will be recorded as an unsolicited AE with a start date on the 8th day following study vaccination and followed to resolution.

Solicited AEs will not be captured for any approved or deployed SARS-CoV-2 vaccines.

6.4.1.1.3 Adverse Events of Special Interest

Participants will be assessed for diagnosis of an AESI at all study visits. AESIs include PIMMCs, AEs specific to COVID-19, or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Given the concern for cytokine storm, an AESI of cytokine release syndrome will be included as an AE specific to COVID-19. Listings of AESI are presented in Section 9.5, Appendix 4.

6.4.1.1.4 Medically Attended Adverse Events

MAAEs are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits (including COVID-19 Surveillance Visits) will not be considered medically attended visits. MAAEs are to be reported from the time of first study vaccination until Day 35 for the initial set of vaccinations only. MAAEs related to study vaccination are to be reported from the time of first study vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

6.4.1.1.5 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that

occurs during study participation must be reported using a clinical study pregnancy form. To ensure participant safety, each pregnancy must be reported to Novavax, Inc. within 2 weeks of learning of its occurrence. If pregnancy occurs, further study vaccination will be discontinued. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of both mother and child, even if the participant was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any pregnancy brought to the investigator's attention after the participant has completed the study but occurring while the participant was in the study must be promptly reported to:

Sponsor Safety Monitor: [redacted]

6.4.1.2 Eliciting and Documenting Adverse Events

At every study visit, participants will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, AEs will be documented from any data collected on the AE page of the eCRF or other documents that are relevant to participant safety.

6.4.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes study vaccine, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study vaccine and/or study procedure, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or that meets SAE criteria (Section 6.4.1.1.1) must be reported to the sponsor within 24 hours after the investigator has confirmed the occurrence of the SAE. The investigator will provide a causality assessment (whether there is a reasonable possibility that the study vaccine caused the event) to the study vaccine. The sponsor will be responsible for notifying the relevant regulatory authorities of

any SAE, in compliance with health authority requirements, as outlined in the relevant clinical study guidelines. SAE reports that may be attributed to a combination of the Novavax vaccine and an approved or deployed SARS-CoV-2 vaccine will be reported to the regulatory authorities as applicable.

SAE reporting forms allow for the notation of other factors that may have impacted the investigator's assessment of causality. Investigators will be instructed to utilize this section of the reporting form to note the impact of an approved or deployed SARS-CoV-2 vaccine on the event, if applicable. Investigators will be required to report any suspected adverse reactions to another manufacturer's approved or deployed SARS-CoV-2 vaccine to health care authorities via the Coronavirus Yellow Card reporting site: https://coronavirus-yellowcard.mhra.gov.uk/.

For this study, the following contact information will be used for SAE reporting:

Phone: [redacted]
Fax: [redacted]
Email: [redacted]

6.4.1.4 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild (grade 1): These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (grade 2): These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe (grade 3): These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

If the severity of an AE changes, the most intense severity should be reported. An AE characterised as intermittent does not require documentation of the onset and duration of each episode.

6.4.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study vaccine is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study vaccine caused the event) for all AEs and SAEs (solicited reactions are to be considered as being related to study vaccination). The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study vaccine or can be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
- Related: There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine (and/or recurs with re-challenge, if applicable).

6.4.1.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

6.4.2 Vital Sign Measurements

Vital sign measurements will include oral temperature (or via forehead/ear reader), pulse rate and diastolic and systolic blood pressure (after participant is seated for at least 5 minutes), and pulse oximetry. Temperature will be recorded and graded during general systemic reactogenicity evaluation (Section 6.4.1.1.2). The other vital sign measurements will be recorded as continuous variables prior to each study vaccination. Pulse oximetry and other vital signs will be taken on room air.

On study vaccination days, vital sign measurements will be collected once before study vaccination to ensure participant has controlled blood pressure and heart rate and no evidence of fever prior to study vaccination and once more, at approximately 15 to 30 minutes after study vaccination, to check for any reactions to the study vaccine. The investigator will only apply standard toxicology grading on the day of study vaccination, both before and after study vaccination (Section 9.4, Appendix 3). If individual vital sign measurements are considered clinically significant by the investigator, study vaccination may be withheld that day, and participants may return on a subsequent day for re-evaluation and study vaccination, ideally, within the time window specified in the SOE (Table 3-1).

6.4.3 Physical Examinations

A physical examination will be performed at screening/Day 0 (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck, and musculoskeletal system/extremities). Height and weight will be measured at screening only.

A targeted or symptom-directed physical examination will be performed at the time points specified in the SOE (Table 3-1). Special attention should be made to examine the lymph nodes of the upper extremities on vaccination days for the initial set of vaccinations and the respiratory system at all COVID-19 Surveillance Visits.

6.4.4 Safety Monitoring

Safety oversight will be conducted by an SMC during the course of the study. The SMC is an independent group of experts that monitors participant safety and advises the sponsor. The SMC members will be separate and independent of site personnel participating in this study and should not have a scientific, financial, or other conflict of interest related to this study or the sponsor. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this study.

A global SMC was convened to oversee the safety of the ongoing Phase 1/2 study (Protocol 2019nCoV-101) and will oversee 1 or more additional studies across the SARS-CoV-2 rS vaccine program. A separate SMC will be convened for this study. The designated SMC will monitor the safety of participants in the study and will follow an SMC charter. The SMC will review blinded and unblinded safety and reactogenicity data. The SMC will also review sufficient clinical event data to ensure detection of evidence of enhanced disease. The SMC will convene to perform safety reviews on a scheduled basis as per the SMC charter; for immediate concerns regarding safety observations during this study; and as needed.

The SMC will operate under the rules of a sponsor-approved charter that will be approved at the organisational meeting of the SMC. At this time, each data element that the SMC needs to assess will be clearly defined. Procedures for SMC reviews/meetings will be defined in the charter. The SMC will review applicable data for safety assessments (AEs by classifications) and any clinical data that may be of significance to this review (e.g., demographics, study vaccination timing, and medications). Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate for this review. The SMC may receive data in aggregate and presented by study vaccine group. The SMC may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the study vaccine assignment be unblinded for an individual participant if required for safety assessment.

7. STATISTICAL ANALYSIS PLANS

7.1 Sample Size Calculations

This study is designed to enrol approximately 15,000 participants, who will be initially randomised 1:1 into the 2 study vaccine groups. The sample size is driven by the total number of events expected to achieve statistical significance for the primary efficacy endpoint – a target of 100mild, moderate, or severe COVID-19 cases. The target number of events of 100 was chosen to provide > 95% power for 70% or higher vaccine efficacy (VE) (Table 7-1). A single interim analysis of efficacy will be conducted based on the accumulation of approximately 50% (50 events) of the total anticipated primary endpoints using Pocock boundary conditions. Power calculations were performed by 10,000 simulated trials that were created under various assumptions of VEs and analyzed using methods described in the "efficacy analysis" section without covariates. A 90% evaluability rate for the per-protocol (PP) efficacy (PP-EFF) population (assuming 10% unevaluable due to attrition and/or baseline-seropositive participants) was used for the power calculations. All simulations were performed in SAS V9.4.

Table 7-1 Power Under Various Vaccine Efficacy Assumptions

Assumed Vaccine Efficacy	Estimated Power		
Symptomatic COVID-19 Illness PCR-Confirmed SARS-CoV-2 Infection	At Planned Interim Analysis with 50 Events	At Final Analysis with 100 Events	Overall (At Interim Analysis or Final Analysis)
60%	29%	39%	68%
65%	45%	41%	87%
70%	64%	32%	96%
75%	81%	18%	>99%
80%	94%	6%	>99%
85%	99%	1%	>99%
90%	>99%	<10%	>99%

Abbreviations: COVID-19 = coronavirus disease 2019; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

7.2 Analysis Sets

The all-randomised set will include all participants who were randomised regardless of the receipt of any study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The all randomised set will be used for the subject disposition summaries.

The intent-to-treat (ITT) analysis set will include all participants who are randomised and receive at least 1 dose study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), regardless of protocol violations or missing data. The ITT analysis set will be used as a

supportive analysis population for the immunogenicity and efficacy analyses and will be analysed according to the study vaccine group as randomised.

The safety analysis set will include all participants who receive at least 1 dose of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). Participants in the safety analysis set will be analysed according to the study vaccine actually received.

The PP-EFF will include baseline seronegative participants who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and have no major protocol deviations that occur before the first COVID-19 episode affecting the primary efficacy outcome (i.e., participants will be censored at the time of the protocol deviation) as assessed by the sponsor prior to unblinding. All analyses of the PP-EFF population will also exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test occurring 6 days or less after the second study vaccination (e.g., Day 28).

The per-protocol immunogenicity (PP-IMM) analysis set for each post-randomisation visit will include participants who receive scheduled dose(s) of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), have at least a baseline and the serum sample result for the visit available after study vaccination, and have no major protocol violations that are considered clinically likely to impact the immunogenicity response at the corresponding study visit as assessed by the sponsor prior to unblinding. For each visit, the SARS-CoV-2 unexposed population will also exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test prior to each visit. Prior exposed participants will be determined using baseline SARS-CoV-2 immunity defined as positive SARS-CoV-2 by PCR or antibody test at baseline, or positive SARS-CoV-2 by qualitative PCR through Day 35, according to the specified analysis. Analysis will be performed to assess if immune responses differ between exposed and unexposed individuals (i.e., whether prior exposure alters dosing regimen considerations in a pandemic response).

The review and determination for exclusion from the PP populations will be carried out in a blinded fashion by a study clinician prior to unblinding for each interim analysis based on all available information from the locked database. Both PP populations will be analysed according to the study vaccine group as randomised.

7.3 Statistical Analysis

Details of all statistical analyses will be described in the SAP.

All data collected will be presented in data listings. Data from participants excluded from an analysis set will be presented in the data listings but not included in the calculation of summary statistics for that analysis set.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarised using descriptive statistics (number of participants, mean, median, minimum, and maximum).

Baseline demographic and background variables will be summarised by study vaccine group. The number of participants who enrol in the study and the number and percentage of participants who complete the study will be presented. Frequency and percentage of participants who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarised.

In order to manage unblinded participants, unblinding will result in censoring of all efficacy and immunogenicity endpoints. The main presentation of data based on the Safety Analysis set will include all participant data, with supporting presentations to exclude the data post unblinding. Sensitivity analysis of reactogenicity and unsolicited AEs will be conducted for the Safety analysis subset of participants not unblinded. Additional analysis of AEs collected after unblinding may be undertaken as exploratory safety analyses.

7.3.1 Efficacy Analyses

The primary endpoint will be analysed on the PP-EFF Analysis Set and supported by analysis of the ITT Analysis Set. Conclusions concerning declaration of attainment of the primary endpoint will only be based on the PP-EFF population.

Primary analysis of the primary and key secondary efficacy endpoints will be performed based on the data generated prior to the blinded crossover. The analysis of data generated after the blinded crossover or the combined analyses of both pre- and post-blinded crossover will be performed using the approach described by Follmann et al (2020). Additional details on the analytical approach will be described in the Statistical Analysis Plan.

VE is defined as VE (%) = (1 – RR) × 100, where RR = relative risk of incidence rates between the 2 study vaccine groups (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The interim and final analyses for the primary objective in the PP-EFF population will be carried out at the overall one-sided Type I error rate of 0.025. The nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analysis and the numbers of endpoints to be used for the final analysis. The estimated RR and its CI will be derived using Poisson regression with robust error variance [Zou 2004]. The explanatory variables in the

model will include study vaccine group. The dependent variable will be the incidence rate of the endpoint of interest. The robust error variances will be estimated using the repeated statement and the participant identifier. The Poisson distribution will be used with a logarithm link function. The site (depending on the distribution of endpoints) and the age strata will be included in the model as covariates. To assess incidence rates rather than absolute counts of cases, accounting for differences in follow-up times starting with 7 days after the second vaccination among participants, an offset will be utilized in the Poisson regression. In case the total number of events to be analysed may be too low for an asymptotic method proposed (i.e., ≤ 5 events in either treatment group), an alternative method based on the single sample exact binomial distribution may be used for the analysis. This method is based on the proportion of the events in the SARS-CoV-2 rS with Matrix-M1 adjuvant group among the total number of events observed in both treatment groups after adjusting for the differential number of subjects (or inclusive of differential lengths of follow-up) between the 2 treatment groups.

Hypothesis testing of the primary efficacy endpoint will be carried out against H0: VE ≤ 30%. Rejection of the null hypothesis, H0: VE ≤ 30% demonstrates a statistically significant vaccine effect (i.e., alpha-adjusted lower bound confidence interval [LBCI] > 30%) will be considered meeting the prespecified study success criterion. The study will also continue for the intended duration to measure efficacy, immunogenicity, and safety endpoints, regardless of primary endpoint success at the interim or final analysis. The final analysis of the primary efficacy endpoint will be triggered when approximately 100 PP-EFF participants with symptomatic mild, moderate, or severe COVID-19 endpoints have accrued. Also, in order to be able to respond to the unexpected and rapidly evolving COVID-19 pandemic situation globally, other factors such as requests by government or public health agencies may also be factored into the decision-making to unblind the study for the final analysis, but this always occurs in consultation with lead regulatory agencies.

The secondary and exploratory efficacy endpoints will be analysed using the same method as the primary efficacy analysis described above. Analysis of secondary and exploratory efficacy endpoints will be performed without adjustment for multiple comparisons (i.e., two-sided alpha of 0.05). The final interpretation of the overall vaccine efficacy will be based on the totality of statistical evidence, including immunogenicity results and the clinical importance in discussions with the regulatory agencies and scientific communities. The EOS analysis will be performed when the last participant completes the last visit (12 months after the last study vaccination) or discontinues earlier.

7.3.2 Immunogenicity Analysis and Correlates of Risk

The primary and secondary immunogenicity analyses will be performed using the PP-IMM and ITT analysis populations.

For the SARS-CoV-2 rS serum antibody levels measured by microneutralization and ELISA assays, geometric mean at each study visit, the geometric mean fold rises (GMFRs)

comparing to Day 0 (baseline) at each follow-up study visit, along with 95% CI will be summarised by study vaccine group. The 95% CI will be calculated based on the t distribution of the log-transformed values for geometric means or GMFRs, then back transformed to the original scale for presentation. The seroconversion rate (SCR), proportion of participants with ≥ 4 fold rises if naïve at baseline, along with 95% CIs based on the Clopper-Pearson method will be summarised by study vaccine group at each follow-up study visit. Immunogenicity analyses performed after the second set of vaccinations will be conducted in a similar fashion.

For the subset of participants who receives the influenza vaccine concurrently with the study vaccines, comparisons of strain-specific immune responses to influenza vaccine as measured by HAI will be performed. The treatment comparison will be made by comparing the strain-specific GMTs and the SCRs. The SCR is defined as the proportion of subjects with either a baseline reciprocal (Day 0) titre of < 10 and a post-vaccination reciprocal titre ≥ 40, or a baseline titre of ≥ 10 and a post-vaccination titre ≥ 4-fold higher.

For influenza strain-specific GMTs in each treatment group, titres reported below the lower limit of quantitation (LLOQ; i.e., below the starting dilution of assay reported as "< 10") will be set to half that limit (i.e., 10 / 2 = 5). Strain-specific GMTs will be summarized by treatment group and visit day along with the corresponding two-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs. The ratio of GMTs between treatment groups post-vaccination and the corresponding two-sided 95% CI will be calculated on log-transformed titres using the analysis of covariance (ANCOVA) with treatment group and baseline (Day 0) measurement as the covariate.

For influenza strain-specific SCRs, the rate in percent and the corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. The two-sided 95% CIs for the absolute rate difference between the 2 treatment groups will be constructed using the Newcombe method.

Similar summaries will be generated for the other immunogenicity endpoints and other assays if conducted.

Correlates of risk will be assessed where immune responses are measured in all available participants, and the results compared between participants who experience a SARS-CoV-2 event and participants who do not. The goal of this analysis is to assess correlates of risk of SARS-CoV-2 infection (and potential other secondary endpoints) in the study vaccine group by comparing study vaccine-induced immune responses associated with COVID-19.

7.3.3 Safety Analyses

Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in the Safety Subset of approximately 2,000 participants and in the seasonal influenza vaccine

co-administration sub-study of approximately 400 participants after the initial set of vaccinations only.

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after each study vaccination will be summarised by study vaccine group and the maximum toxicity grade over 7 days after each study vaccination. The duration of solicited local and systemic AEs after each study vaccination will also be summarised by treatment group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of the MedDRA and summarised by study vaccine group as well as by severity and relationship to study vaccine. AEs through 49 days after first study vaccination for the initial set of vaccinations; all MAAEs through 35 days after first study vaccination for the initial set of vaccinations; and MAAEs related to study vaccine; SAEs; or AESI through EOS will be listed separately and summarised by study vaccine group. As solicited AEs are only being recorded in a subset of participants, it is expected that typical solicited AEs will be captured as unsolicited AEs in those who are not in the sub-study if they occur through Day 49 after the initial set of vaccinations. An assessment of the impact of this decision will be part of an exploratory analysis and will be summarised.

Separate analyses of safety events received with respect to approved or deployed SARS-CoV-2 vaccines will be performed.

Vital sign measurements will be summarised by study vaccine group using descriptive statistics at baseline and following study vaccination.

Concomitant medications will be provided in a data listing with preferred drug name as coded using the World Health Organisation drug dictionary.

7.3.3.1 Safety: Study Vaccine-Associated Enhanced Disease

Continuous monitoring for study vaccine-associated enhanced disease will be performed through the CRO and sponsor medical monitors. These events will be monitored in real-time and after each confirmed respective case. The SMC will review this data at scheduled SMC meetings throughout the study or at an ad hoc meeting if the medical monitors would like a more immediate review of the data.

7.4 Handling of Missing Data

For calculating geometric means and GMFR, immunogenicity values reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper level of quantitation (ULOQ) will be replaced by the ULOQ. Missing results will not be imputed.

7.5 Interim Analyses

Prior to the final analysis, a single interim analysis of efficacy will be conducted based on the accumulation of approximately 50% (50 events) of the total anticipated target number of the primary endpoint (100 events). For this analysis, the data needed to perform the analysis of the primary efficacy endpoint will be cleaned. The interim analysis will be performed by an unblinded Biostatistics and Programming team (PPD), and the unblinded statistician will communicate the results of the analyses to the Sponsor in terms of fulfillment or nonfulfillment of the predefined success criterion (yes/no). Novavax will be unblinded at the participant level at the time of the primary 100-event analysis. If the pre-defined success criterion of the interim analysis is unfulfilled (no), then the study will remain blinded to treatment assignment until the final analysis.

If the pre-defined success criterion of the interim analysis is fulfilled (yes), then the Sponsor may unblind selected accrued data at the treatment group level and continue the study while maintaining the blind to achieve a more robust safety and efficacy data package. The unblinded Biostatistics and Programming team (PPD) will be isolated (by firewall) from study personnel. They will complete a review independent of the study team and Sponsor. The interim analysis will follow standard group-sequential design using the Lan-DeMets alpha-spending function for Pocock boundary conditions. Table 7-2 summarises the timing, number of endpoints, and statistical success boundaries at the planned interim and final analyses.

Table 7-2: Interim and Final Boundaries Using Pocock Spending Function

Planned Information Fraction (% of total endpoints)	Planned Blinded Total Number of Endpoints	Planned One-Sided Nominal Alpha	VE Boundary for LBCI > 30%
Interim analysis at 50%	50	0.01550	~68%
Final analysis at 100%	100	0.01387	~57%

Abbreviations: LBCI = lower bound confidence interval; VE = vaccine efficacy.

If an unplanned additional interim analysis is to be added or the timing of a planned analysis is modified, the Lan-DeMets alpha-spending function will be used to adjust the nominal alphas to maintain the pre-specified overall one-sided type I error at 0.025.

7.6 Pre Blinded Crossover

Prior to the blinded crossover, assessment of safety and efficacy will be made while there is a placebo-controlled comparator.

7.7 Post Blinded Crossover

Following blinded crossover, follow-up to assess safety and efficacy endpoints (assessment of MAAEs related to study vaccine, SAEs, and AESIs, blood testing for SARS-CoV-2 and vaccine efficacy) will continue through study completion.

7.8 Planned Analyses Prior to Study Completion

Analysis of the data will be provided on an ongoing basis for confirming success and to review safety as the study progresses. The SAP will outline the sequential nature of these reviews.

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9. APPENDICES

9.1 Appendix 1: Protocol Change History

Protocol Version 4.0, 25 February 2021 (revised from Version 3.0, 23 December 2020)

The following is a summary of the changes made from Version 3.0 (23 December 2020) to Version 4.0 (25 February 2021).

Location of change	Change/Modification
Changes Made from Version 3.0 (December 23, 2020) to Version 4.0 (25 February 2021) The primary purpose of this amendment is to add the blinded crossover design. All changes were made because of addition of crossover design except as noted below.	
Synopsis; Secondary Objectives (Section 2.1.2)	• Deleted "in SARS CoV-2 seropositive" from the second objective to correct error. • Added "in the initial set of vaccinations" to the 9th secondary objective per MHRA recommendation. • Changed safety and reactogenicity objectives from 7 days after each study vaccination to "the initial set of study vaccinations." • Added the following secondary objective: "To assess the duration of vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.
Synopsis; Exploratory Objectives (Section 2.1.3)	• Added "in the initial set of vaccinations" to the first and second exploratory objective. • Added "unblinded before the crossover" to second exploratory objective.
Synopsis; Primary Endpoint (Section 2.2.1) and Secondary Endpoints (Section 2.2.2)	• Added "in the initial set of vaccinations" to the primary endpoint and the first 6 secondary endpoints. • Changed "First occurrence of laboratory-confirmed COVID-19 to participants with negative serostatus at baseline.
Synopsis; Other Secondary Endpoints (Section 2.2.2.2)	• Added analysis of antibodies endpoint for Crossover Day 0 and Day 35. • Deleted "for 7 days" and added "the initial set of vaccinations" to reactogenicity endpoint. • Added "following the initial set of vaccinations" to MAAE and unsolicited AE endpoint. • Added the following secondary endpoint: "Relative vaccine efficacy (measured by all efficacy endpoints) in initial active vaccine recipients vs. crossover (delayed) active vaccine recipients.
Synopsis; Exploratory Endpoints (Section 2.2.3)	• Added "in the initial set of vaccinations" to the first 2 exploratory endpoints. • Added the following endpoint: "Any occurrence of serologic conversion (by serology to SARS-CoV-2 N protein) between Crossover Day 0 visit and the end of study visit in the second set of vaccinations in adult participants seronegative at baseline." • Added "and Crossover Day 35 visit (14 days after the Crossover Day 21 visit" to seroconversion and VNA endpoint. • Added the following endpoint: First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in seronegative adult participants by age (<65 and ≥65) in racial and ethnic minorities and in those with co-morbid conditions.

	• Added "The occurrence, severity, and relationship to study vaccination of unsolicited AEs (in all adult participants) for 21 days after first study vaccination and 28 days after second study vaccination following the initial set of vaccinations with the adjustment to remove reactogenicity events which were recorded as unsolicited AEs within 7 days of each dose in the initial set of vaccinations."
Synopsis; Study Design (Section 3)	• Added description of crossover design. • Added "and Crossover Day 0 visit" for nose/throat samples. • Updated paragraph about participants receiving an approved vaccine to include crossover portion; added a sentence about participants who are unblinded and receive another vaccine. • Added "Participants who are unblinded and ineligible for the blinded crossover will continue to follow the original study design featured in Figure 1b. • Clarified that the duration of individual participation is 1 year from the initial set of vaccinations to correct error. • Added information about blood draws and assessment of vaccine efficacy. • Added information about unblinded participants who receive another vaccine
Synopsis; Study Vaccination Pause Rules (Section 3.1)	• Added "for the first set of vaccinations only" to pause rules based on reactogenicity.
Synopsis; Exclusion Criteria (Section 4.2)	• Added statement about inclusion/exclusion criteria at crossover.
Synopsis ; Study Vaccine Administration (Section 5.1)	• Added "At the time of the blinded crossover, participants will receive the alternate study material in 2 IM injections 21 + 7 days apart" to description of study vaccines. • Deleted description of nose/throat samples and referred to SOE.
Day21 (Section 6.1.3)	• Added sentence about assessment of exclusion criteria prior to second dose.
COVID Surveillance Visits (Section 6.1.5.1 and 6.1.5.2)	• Added "as appropriate" to collection of concomitant medications and added collection of nose/throat samples.
Synopsis; Immunogenetic Assessments (Section 6.3)	• Added "Anti-S protein serology in the Anti-S Protein Serology Subset will be collected after the first and second set of vaccinations."
Synopsis; Safety Assessments (Section 6.4) and Local and General Systemic Reactogenicity Symptoms (Section 6.4.1.1.2)	• Added "after the first set of vaccinations" and "in the initial set of vaccinations to Safety Assessments. • Added "Local and systemic reactogenicity events will not be recorded for the second set of vaccinations." • Added statement about unsolicited AEs in participants who are not in the sub-study. • Deleted 'virologically confirmed" to correct error. • Added "who will be initially" to description of randomization. • Added "unblinded participants should not be included in the blinded crossover."
MAAEs (Section 6.4.1.1.4)	• Added "for the first set of vaccinations only."
Synopsis; Analysis Sets (Section 7.2)	• Changed 7 to 6 days or less for positive SARS-CoV-2 test to correct error. • Deleted serum IgG antibody and changed to antibody tests to correct error.
Synopsis; Efficacy Analyses (Section 7.3.1)	• Added a paragraph about primary analysis of primary and key secondary efficacy endpoints pre and post crossover.
Synopsis; Immunogenicity Analysis (Section 7.3.2)	•Added description of immunogenicity analysis after the second set of vaccinations. •Deleted sentence about EOS analysis.
Synopsis; Safety Analysis (Section 7.3.3)	•Added "after the initial set of vaccinations only" to capture of solicited AEs. •Added clarification about solicited AEs in participants who are not part of the sub-study.

Synopsis; Interim Analyses (Section 7.5)	•Added "Novavax will be unblinded at the participant level at the time of the primary 100-event analysis."
Synopsis; Pre- and Post-Blinded Crossover (Sections 7.6 and 7.7)	•Added sections on pre- and post-blinded crossover.
Clinical Experience (Section 1.3)	•Added sentence about 302 interim analysis.
Figure 1a: Trial Design	•Updated figure to portray crossover design (Figure 1a) and changed Figure 1 to Figure 1b. •Added footnote to Figure 1a to describe possible consolidation of crossover visits.
Table 3-1: Schedule of Events	•Updated to include crossover design
Method of Assigning Participants (Section 5.3)	•Added sentence about the use of the IRT system.
Blinding Procedures (Section 5.3.1)	•Added sentence about keeping study participants and personnel blinded. •Added information about reconsenting participants at crossover.
Concomitant Medications (Section 5.5.1)	•Added clarification about concomitant medications based on new study design.
Initial COVID-19 Surveillance Visit (Section 6.1.5) and Follow-Up Visit (Section 6.1.5.2)	•Added "as appropriate" to collection of prior and concomitant medications. •Added paragraph about nose/throat sampling.
Unblinding Visit (Section 6.1.6)	•Changed instructions for unblinding visit. •Added written informed consent •Added "as appropriate" to collection of prior and concomitant medication. •Deleted "If prior to participant's Day 21 and Day 35 visit."
3 Month Visit (Section 6.1.7)	•Added a paragraph changing the requirement for the 3-month visit. •Added "as appropriate" to collection of prior and concomitant medications.
Crossover Day 0 visit (Section 6.1.8)	•Added section
Crossover Day 21 visit	•Added section. •Deleted 6-month visit.
Crossover Day 35 visit	•Added section
12 months After Second Vaccination (Section 6.1.11)	•Updated instructions for EOS visit.
Day 35—Follow-up Visit (Section 6.1.4)	•Deleted "Visit may be skipped as per unblinding visit below."
Nose/Throat Samples (Section 6.2.1)	•Added Crossover Day 0 and 21 for Nose/Throat samples.
Virologic Confirmation of SARS-CoV-2 (Section 6.2.2	•Deleted section
Initial COVID-19 Surveillance Visit	•Added "as appropriate" to ascertainment of new concomitant medications.
Safety Assessment (Section 6.4)	•Added "unblinded participants should not be included in the blinded crossover."
MAAEs (Section 6.4.1.1.4	•Added "after the first set of vaccinations only" to MAAE collection.
Statistical analysis (Section 7.3)	•Changed information about management of unblinded participants.
Reference List (Section 8)	•Updated based on new text.
Changes Made from Version 2.0 (23 October 2020) to Version 3.0 (23 December 2020)	

Synopsis	• Updated number of study sites from 28 to 33.
Synopsis; Exploratory Objectives (Section 2.1.3)	• Added an objective to exploratory endpoint to explore the efficacy and safety of SARS-CoV-2rS with Matrix-M1 adjuvant with an approved or deployed vaccine to take into account the changing vaccine landscape.
Synopsis; Secondary Endpoints (Section 2.2.2)	• Added a secondary endpoint to measure severe COVID-19 separately.
Synopsis; Exploratory Endpoints (Section 2.2.3)	• Added 2 exploratory endpoints, one due to changes in vaccine landscape and one to address asymptomatic disease.
Synopsis; Study Design (Section 3)	• Added "approximately" to description of 400 participants in substudy to allow for greater flexibility.
Synopsis; Section 1 (Introduction); Section 3 (Study Design); Section 5.3.2 (Breaking the Blind)	• Added advice from regulatory agencies concerning unblinding of treatment assignment for participants receiving an approved or deployed SARS-CoV-2 vaccine during the study.
Synopsis, Schedule of Events, Section 6.1.5.1 (Initial COVID-19 Surveillance Visit); Follow-up COVID-19 Surveillance Visit (Section 6.1.5.2); and 6.2.3.2 (COVID-19 Surveillance Visit [Initial and Follow-up])	• Added information about replacing in-person COVID-19 Surveillance Visits with phone calls if government restrictions are in place. Also added "with exception per protocol" to accommodate this new recommendation.
Synopsis, Section 7.1 (Sample Size), Table 7-1	• Reduced number of target endpoints from 152 to 100 based on higher than predicted vaccine efficacy observed in the recent Phase 3 trials by Pfizer and Moderna. This reduced number was chosen to provide > 95% power for 70% or higher vaccine efficacy. • Reduced number of planned interim analyses from 2 to 1 and revised timing of the single interim and final analyses of the primary efficacy endpoint to 50 and 100 events, respectively.
Synopsis, Section 7.2 (Analysis Sets)	• Clarified the wording of the PP-EFF analysis set.
Synopsis, Section 7.3.1 (Efficacy Analysis)	• Clarified the wording of the primary efficacy analyses at the interim and final analyses of the primary efficacy endpoint.
Synopsis, Section 7.3.2 (Immunogenicity Analysis and Correlates of Risk)	• Changed HAI to ELISA for SARS-CoV-2 rS serum antibody levels to correct error and added influenza vaccine to later sentences for greater clarity.
Synopsis, Section 7.5 (Interim Analysis); Table 7-2	• Reduced the number of interim analyses for the primary efficacy endpoint from 2 to 1, with the timing of the single interim analysis based on the accumulation of approximately 50% (50 events). • Clarified that the unblinded Biostatistics and Programming team is from the CRO, PPD. • Clarified the wording of the single interim and final analyses of the primary efficacy endpoint.
Synopsis (2 times); Section 6.4 (Safety	• Added "Separate analyses of safety events received with respect to approved or deployed SARS-CoV-2 vaccines will be performed" to

Assessments); Section 7.3.3. (Safety Analyses)	synopsis. Added specific information about safety reporting for participants who receive an approved or deployed SARS-CoV-2 vaccine.
Introduction	• Added a paragraph about changes due to approved or deployed SARS-CoV-2 vaccines.
Section 2.2.1 (Primary Endpoints); Table 2-1; Section 6.2.3 (Severity of COVID-19 Symptoms)	• Added the following footnote: "Participants with vital sign abnormalities in the moderate or severe categories must meet the criteria for mild COVID-19" and added the same information in text.
Section 2.2.1 (Primary Endpoints); Table 2-2	• Removed duration of ≥ 48 hours for headache, nausea, vomiting, and diarrhea for consistency with other SARS-CoV-2 rS trials.
Section 4.4.1 (Reasons for Withdrawal)	• Added a statement that vaccination with an approved or deployed SARS-CoV-2 vaccine does not constitute a withdrawal, this is based on MHRA guidance.
Section 5.3.1 (Blinding Procedures); Section 5.3.2 (Breaking the Blind)	• Added specific information on unblinding if participants wish to receive an approved or deployed SARS-CoV-2 vaccine.
Section 5.5.1 (Concomitant Medications)	• Added that participants will be asked to record the date and brand of the approved or deployed vaccine that they receive.
Section 5.5.2 (Prohibitive Therapy)	• Added an exception to vaccine restrictions for participants who wish to receive an approved or deployed vaccine at least 21 days after study vaccine.
Section 6.1 (Study Visit Procedures)	• Added "Visit may be skipped as per the Unblinding Visit described below" in Sections 6.1.3 and 6.1.4. • Clarified that a targeted physical examination may be performed if participant has any ongoing complaints in Section 6.1.4. • Clarified that blood sampling for SARS-CoV-2 (ELISA for anti-N-protein serology) in all participants "unless the participant has had an Unblinding Visit in the prior 14 days where anti-N serology was drawn" in Sections 6.1.4, 6.1.7, and 6.1.8.
Section 6.1.5.1 (Initial COVID-19 Surveillance Visit)	• Added "including those who have been unblinded" to list of requirements at this visit.
Section 6.1.6 (Unscheduled Blinding Visit)	• Added section to describe unblinding process for people who wish to receive approved or deployed SARS-CoV-2 vaccine.
Section 6.2.2 (Virologic Confirmation of SARS-CoV-2)	• Clarified that nose/throat self-sampling may be skipped is a participant is known to be PCR positive to SARS-CoV-2 from the Screening or Day 0 PCR within 14 days of the positive test. • Clarified that if a participant obtains a PCR test for SARS-CoV-2 outside of the study for any other reason than having suspected COVID-19 symptoms, then this result should not be noted or reported. • Clarified that if a participant obtains a PCR test for SARS-CoV-2 outside of the study for suspected COVID-19 symptoms, then the participant should begin all protocol-required assessments for participants with suspected COVID-19 symptoms.
Section 6.2.3 (Monitoring for Suspected COVID-19)	• Added "This is the case for blinded and unblinded participants."

Section 6.2.3.2 (COVID-19 Surveillance Visit)	• Added "See Section 6.1.5.1 for exceptions for participants affected by extenuating circumstances (e.g., local government restrictions).
Section 6.2.3.2.1 (Initial COVID-19 Surveillance Visit)	• Added "Proper documentation in the eCRF of the dates, bar codes, and results of all self-swabs taken in proximity of this visit."
Section 6.4 (Safety Assessments)	• Added safety requirements for unblinded patients.
Section 6.4.1.1.2 (Local and General Systemic Reactogenicity Symptoms)	• Added "Solicited AEs will not be captured for any approved or deployed SARS-CoV-2 vaccine."
Section 6.4.1.3 (Reporting Adverse Events)	• Added information about SAE reporting for participants who receive an approved or deployed vaccine.
Section 7.3 (Statistical Analysis)	• Added "In order to manage unblinded participants, unblinding will result in censoring of all efficacy and immunogenicity endpoints. The main presentation of data based on the Safety Analysis set will include all participant data, with supporting presentations to exclude the data post unblinding. Sensitivity analysis of reactogenicity and unsolicited AEs will be conducted for the Safety analysis subset of participants not unblinded. Additional analysis of AEs collected after unblinding may be undertaken as exploratory safety analyses. ."

Abbreviations: COVID-19 = coronavirus disease 2019; CRO = contract research organisation; ELISA = enzyme-linked immunosorbent assay; HAI = hemagglutination inhibition assay; PCR = polymerase chain reaction; PP-EFF = per-protocol efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike nanoparticle vaccine.

Protocol Version 2.0, 23 October 2020 (revised from Version 1.0, 17 September 2020; Version 1.1, 17 September 2020; and Version 1.2, 21 September 2020

The following is a summary of the changes made from Version 1.0 (24 August 2020) to Version 1.1 (17 September 2020), Version 1.1 (17 September 2020) to Version 1.2 (21 September 2020), and Version 1.2 (21 September 2020) to Version 2.0 (23 October 2020).

Location of Change	Change/Modification
Changes Made from Version 1.0 (17 September 2020) to Version 1.1 (17 September 2020)	
Section 4.4.1 (Reasons for Withdrawal)	The following changes were made based on MHRA recommendations: • Changed "may withhold" to "will withhold" further vaccinations. • Deleted "The investigator will withhold further study vaccination from a participant in the study if the participant" prior to the bullet regarding pregnancy to indicate that all numbered items are required to withhold vaccination. • Deleted "Upon the occurrence of an SAE or intolerable AE, the investigator may confer with the sponsor before future study vaccination" for more restrictive requirements.
Changes Made from Version 1.1 (17 September 2020) to Version 1.2 (21 September 2020)	
Synopsis (Study Vaccination Pause Rules); Section 3.1	• Added: "for example, any SAE for which causality is at least possibly related" for greater clarity/MHRA recommendation.

Location of Change	Change/Modification
Section 6.1.4 [Day 35 – Follow-up Visit (+ 7 days)]	• Deleted "prior to study vaccination" from the blood sampling procedures on Day 35 since vaccination is only given on Days 0 and 21 (MHRA recommendation).
Section 6.1.6 [3 Months (± 15 days) After Second Study Vaccination]	• Deleted "prior to study vaccination" from the blood sampling procedure on Month 3 since vaccination is only given on Days 0 and 21 (MHRA recommendation).
Section 6.1.7 [6 Months (± 15 days) After Second Study Vaccination]	• Deleted "prior to study vaccination" from the blood sampling procedure on Month 6 since vaccination is only given on Days 0 and 21 (MHRA recommendation).
Section 6.1.8 [12 Months (± 15 days) After Second Study Vaccination]	• Deleted "prior to study vaccination" from the blood sampling procedure on Month 12 since vaccination is only given on Days 0 and 21 (MHRA recommendation).
Changes Made from Version 1.2 (21 September 2020) to Version 2.0 (23October 2020)	
Synopsis	• Changed "up to 18 regions" to "28 sites" across the United Kingdom (UK) based on updated information.
Synopsis (Secondary Objectives); Section 2.1.2	• Added "related to study vaccination" to 6th secondary objective for clarity. • Deleted "and in terms of unsolicited AEs for 21 days after first study vaccination and 28 days after second study vaccination" and added a separate bullet for MAAEs for greater clarity.
Synopsis (Primary Endpoints); Section 2.2.1	• Changed to only one primary endpoint and moved the second primary endpoint to key secondary endpoint • Added "mild, moderate, or severe" to COVID-19 description in primary endpoint for clarity
Synopsis (Secondary Endpoints); Section 2.2.2	• Added "mild, moderate, or severe" to COVID-19 description to 2nd secondary endpoint for clarity. • Added "symptomatic" to description of mild COVID19 to 4th primary endpoint for clarity. • Added N-protein to serology endpoint for greater clarity. • Eliminated ELISA testing from Day 21, as this was an oversight from a prior version. • Added "related to study vaccination" to endpoint for SAEs and MAAEs for greater clarity. • Added 3 safety endpoints (i.e., AESIs/PIMMCs, solicited AEs, and unsolicited AEs) to correlate with secondary objectives.
Synopsis (Exploratory Endpoints); Section 2.2.3	• Added "mild, moderate, or severe" to COVID-19 description to first exploratory endpoint
Synopsis (Study Design); Section 3	• Changed "regions" to "sites" in 2 places for clarity. • Changed mucosal to nose/throat and eliminated saliva samples for COVID-19 at Screening and Day 0 due to lack of saliva test availability in UK. • Changed study population from 9000 to 15,000 to increase accrual rate of COVID-19 endpoints. • Deleted information about enrolment of participants ≥age 65 and operational cutoff based on updated information.
Synopsis (Table S1-1)	• Changed both groups from 4,500 to 7,500 to accommodate increased enrolment.

Location of Change	Change/Modification
Synopsis (Study Vaccination Pause Rules); Section 3.1	• Allowed the SMC chair to review SAEs and decide on the need for a full SMC meeting before starting a study enrolment pause. • Expanded requirement for solicited and unsolicited AEs to also include Grade 4 (potentially life-threatening), in addition to Grade 3, for greater clarity. • Added "after a minimum of 100 participants were enrolled" to 5% and 10% cutoffs for solicited and unsolicited AEs to prevent a pause being triggered due to an early cluster of grade 3 events. • Changed grade 3 (severe) to severe and added "after a minimum of 100 subjects are enrolled" to third bullet for clarity. • Added "for example, any SAE for which causality is at least possibly related" to provide more clarity to pause rule. • Added specific text about analysis of grade 3 or higher solicited AEs in 400-subject influenza substudy for greater clarity.
Synopsis (Inclusion Criteria); Section 4.1	• Deleted "with spermicide" from condom criteria due to input from the UK ethics review. • Added "Other approaches to abstinence are not acceptable" to clarify how this method can be used as contraception due to input from the UK ethics review. . • Added "Room saturation of > 95% at Screening/Day 0 to inclusion criteria as this is aligned with the severity grading criteria which assigns a greater level of severity below 95%.
Synopsis (Exclusion Criteria); Section 4.2	• Changed participation in serologic surveys to future participation to allow participation to those who participated prior to enrollment. • Added text that allowed participants with controlled HIV to participate per investigator's suggestion. • Added "within 3 months following the last study vaccine" to pregnancy/lactation criteria participate per investigator's suggestion. • Added additional information to restrictions on administration of influenza vaccine for greater clarity. • Added "including hepatitis B and C" to hepatic exclusion for greater clarity per investigator's suggestion. • Deleted "and epilepsy" from neurological disorders per investigator's suggestion. • Deleted "or immunodeficiency" and added Table 9-3 (specific conditions) and the need for biologic therapy for greater clarity as it was repetitious of a prior exclusion. • Added "The Skin and Metabolic disorders listed in Table 9-3 are eligible at the discretion of the investigator" and eliminated caveat about endocrine disorders. • Added the use of continuous oxygen therapy as an Exclusion Criteria (allowing for nocturnal oxygen) as it would not be possible to grade severity levels based on oxygen saturation if someone is on continuous oxygen. Other Considerations: Added a bullet point addressing participants with hypertension.
Synopsis (Study Vaccine Administration); Section 5.1	• Added information about specific flu vaccines for participants 18-64 years of age and those ≥ 65 years of age.

Location of Change	Change/Modification
	• Added instructions for using the right deltoid for flu vaccine and the left deltoid for study vaccine on Day 0 whenever possible to allow for the majority of right handed people to more easily access the study vaccine injection site.
Synopsis (Efficacy Assessments); Section 6.1.1, 6.1.2, and 6.1.3	• Replaced mucosal with nose/throat and removed "or saliva" from testing method for efficacy assessments due to lack of saliva test availability in UK.
Synopsis (Safety Assessments); Section 6.4	• Added "Participants in the seasonal influenza vaccine co-administration substudy will record local reactogenicity for the study vaccine injection site only" as the symptom diary could not accommodate the measurement of 2 injection sites.
Synopsis (Statistical Analysis Plan); Section 7.1	• Changed sample size from 9000 to 15,000 to increase the rate of endpoint accumulation. • Updated the statistical analysis plan based on increased enrolment. • Deleted information designed about VE—information moved to Efficacy Section 7.3.1. • Deleted information about sample size based on updated information.
Synopsis (Analysis Sets); Section 7.2	• Defined the all randomized set and ITT set—deleted ITT-EFF and ITT-IMM analysis sets for further clarity. • Added "baseline" to describe seronegative participants in the PP-EFF set. • Added "that occur before the first COVID-19 episode" to the restriction for no major protocol deviations for the PP-EFF population for greater clarity. • Changed 14-day exclusion to 7 days for positive SARS-CoV-2 illness episodes occurring after the second vaccination (i.e., Day 35 to Day 28) for PP-EFF population analysis as this was a correction. • Changed Day 21 or Day 35 to Day 35 only for PP-IMM analysis as this was a correction. • Added "Both PP populations will be analysed according to the study vaccine group as randomized" for further clarity.
Synopsis (Efficacy Analysis); Section 7.3.1	• Changed 2 key decision points to 4 potential decision points and described them for greater clarity. • Changed ITT-EFF population to ITT analysis group. • Added extensive statistical information about planned analyses for greater clarity. • Moved EOS analysis to Immunogenicity section • Deleted reference to SAP because of expanded text. • VE definition was moved here.
Synopsis (Immunogenicity Analysis); Section 7.3.2	• Removed reference to ITT-IMM population—changed to ITT. Added further statistical details to the immunogenicity analysis for the influenza sub-study for greater clarity. • Moved EOS analysis in Neutralisation Assay subset to this section
Synopsis (Safety Analysis); 7.3.3	• Changed AE reporting window to 49 days from 35. • Added "through 35 days after first study vaccination" for greater clarity.
Synopsis (Interim Analysis); Section 7.5	• Added new section describing statistical information about planned interim analysis. These were added to potentially increase the speed of detecting vaccine efficacy during this global pandemic.

Location of Change	Change/Modification
Section 1.2.1 (Nonclinical Data)	• Updated study data.
Section 1.3 (Clinical Experience)	• Updated Part 1 data from Phase 1/2 study and added information about Part 2. • Specified number of healthy participants as 131.
Section 1.4 (Rationale for Study)	• Added information about results of 5-day reactogenicity data from the Phase 2 (Part 2) study. • Deleted information about enrolment of participants ≥ age 65.
Section 2.2.1 (Table 2-1)	• Deleted reference to virologically confirmed COVID-19.
Section 2.2.2 (Table 2-2)	• Updated information about qualifying symptoms of COVID-19 to clarify trigger should be based on new onset of symptoms.
Section 3 (Study Design); Figure 1	• Updated trial schema to include 15,000 participants to reflect increased enrolment.
Table 3-1 (Schedule of Events)	• Changed mucosal to nose/throat for greater clarity. • Footnote c: Changed EOS telephone call to visit to correct an error. • Footnote l: Added to provide further clarity on nose/throat testing. • Footnote z: Edited for clarity that swabbing refers to self collection by participants.
Section 4 (Study Population)	• Updated introduction from 9000 to 15,000 participants to increase the rate of endpoint accumulation.
Section 5.2 (Investigational Products)	• Added 2 choices of flu vaccine depending on age group to table and bullet points. This information was just made available.
Section 5.4 (Study Vaccine Compliance)	• Deleted information about home study vaccinations, as study sites were not able to perform home vaccinations.
Section 5.5.2 Prohibitive Therapy	• Added information to bullet point about administration of influenza vaccine for greater clarity.
Section 6 (Study Procedures)	• Deleted information about home vaccinations as study sites were not able to perform home vaccinations.
Section 6.1.5.1 (Initial COVID-19 Surveillance Visit)	• Deleted requirement for mucosal samples at this visit. • Changed target physical examination to respiratory from lymphatic and thus removed "of injected upper extremity." This was done at Surveillance visits to stress the importance of the respiratory exam for participants with possible COVID and not the need to assess the vaccination site unless symptomatic.
Section 6.1.5.2 (Follow-up Surveillance Visit)	• Deleted requirements for mucosal samples at this visit as these samples have a very high capture rate of RNA when shedding. • Changed target physical examination to respiratory from lymphatic and thus removed "of injected upper extremity." This was done at Surveillance visits to stress the importance of the respiratory exam for participants with possible COVID and not the need to assess the vaccination site unless symptomatic.
Section 6.2.1 (Nose/Throat Samples for Virus Detection)	• Changed mucosal to nose/throat and removed option for saliva testing for virus detection based on test availability in UK.
Section 6.2.2 (Virologic Confirmation)	• Changed mucosal to nose/throat and removed option for saliva testing for virus detection.

Location of Change	Change/Modification
	• Deleted HCP sampling option for mucosal sampling as these samples have a very high capture rate of RNA when shedding.
Section 6.2.3.2.1 (Initial COVID-19 Surveillance Visit)	• Deleted "or the participant's basal level of chronic supplemental oxygen use" from resting respiratory rate, eliminating the use of supplemental oxygen. This is aligned with the exclusion of those on basal oxygen treatment. • Deleted reference to nasal turbinate swab.
Section 6.2.3.2.2 (Follow-up COVID-19 Surveillance Visit)	• Changed mucosal to nose/throat and removed option for saliva testing for virus detection due to saliva test availability in UK. • Deleted "however, a repeat mucosal sampling will NOT be obtained since the participant has already tested positive." This was no longer needed, as sampling for this visit was removed. • Deleted paragraph reference nose/throat samples
Section 6.4.1.1.2 (Local and General Systemic Reactogenicity Symptoms)	• Added "of study vaccine" after injection for greater clarity. • Added "Local reactogenicity symptoms should not be recorded for the influenza vaccine injection site."
Section 6.4.14 (Medically Attended Adverse Events)	• Added "potentially life threatening (Grade 3)" to AE criteria
Section 6.4.2 (Vital Sign Measurements)	• Deleted text referring to supplemental oxygen due to new exclusion criteria.
Section 6.4.3 (Physical Examinations)	• Added Day 0 to physical exam. • Special attention should made to examine the lymph nodes of the upper extremities on vaccination days and the respiratory system at all Surveillance visits.
Section 7.1 (Sample Size Calculations and Table 7-1)	• Updated enrolment from 9000 to 15,000 participants. • Changed number of events based on increased enrollment. • Updated text to match new enrolment and revised statistical analysis.
Section 7.1 (Table 7-2)	• Revised table based on revised enrolment and statistical analysis. • Deleted information about increasing precision around VE
Section 7.5 (Interim Analysis; Tables 7-3 and 7-4)	• Revised numbers in tables and added text about an interim analysis.
Appendix 1	• Added Protocol Change History
Appendix 2	• Updated List of Abbreviations to accommodate text changes
Table 9-4	• Added a footnote: "To be recorded as AESIs relevant to COVID-19, these complications should be associated with a positive PCR test for SARS-CoV-2" for greater clarity.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; ELISA = enzyme-linked immunosorbent assay; EOS = end of study; HIV = human immunodeficiency virus; IM = intramuscular; ITT = intent-to-treat; ITT-EFF = intent-to-treat efficacy; ITT-IMM = intent-to-treat immunogenicity; MAAE = medically attended adverse event; MHRA = Medicines and Healthcare products Regulatory Agency; N-protein = nucleocapsid; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; PP = per-protocol; PP-EFF = per-protocol efficacy; PP-IMM = per-protocol immunogenicity; SAE = serious adverse event; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMC = safety monitoring committee; UK = United Kingdom; VE = vaccine efficacy.

9.2 Appendix 2: List of Abbreviations

Abbreviation	Term
ACE2	Angiotensin-converting enzyme 2
AE	Adverse event
AESI	Adverse event(s) of special interest
ANCOVA	Analysis of covariance
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
CT	Computed tomography
DHSC	Department of Health and Social Care
EBOV GP	Ebolavirus glycoprotein
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immune absorbent spot
EOS	End of study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titre
GP	Glycoprotein
hACE2	Human angiotensin-converting enzyme 2
HAI	Hemagglutination inhibition assay
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency syndrome
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification

Abbreviation	Term
IgG	Immunoglobulin G
IM	Intramuscular
IRT	Interactive Response Technology
ITT	Intent-to-treat
LBCI	Lower bound confidence interval
LLOQ	Lower limit of quantification
LRTI	Lower respiratory tract infection
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle Eastern Respiratory Syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
NHP	Nonhuman primate
NHS	National Health Service
N-protein	Nucleocapsid
NZW	New Zealand White
OTC	Over-the-counter
PCR	Polymerase chain reaction
PHEIC	Public health emergency of international concern
PIMMC	Potential immune-mediated medical conditions
PP	Per-protocol
PP-EFF	PP efficacy
PP-IMM	PP immunogenicity
RR	Relative risk
RSV F	Respiratory syncytial virus fusion (protein)
S-protein	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	SARS-CoV-2 recombinant spike (S) protein nanoparticle vaccine
SCR	Seroconversion rate
Sf9	*Spodoptera frugiperda* (insect cells)
SMC	Safety Monitoring Committee
SOE	Schedule of Events

Abbreviation	Term
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
ULOQ	Upper limit of quantitation
VE	Vaccine efficacy
VLP	Virus-like particle
VNA	Virus neutralisation assay
WHO	World Health Organisation
ZIKA EnvD	Zika virus envelope dimers

9.3 Appendix 3: Study Governance

9.3.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice (GCP) guidelines, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel. eCRFs and EDC will be utilised. The EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11 and local regulations. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.3.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the Research Ethics Committee (REC) but will not result in protocol amendments.

9.3.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, relevant regulatory authority(ies), or the REC.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.3.2.2 Institutional Review

Prior to initiation of a study site, regulatory authority regulations and the ICH E6(R2) guidelines require that approval be obtained from the REC before participation of human participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant must be approved by the REC. Documentation of all REC approvals and of the REC compliance with the ICH E6(R2) guidelines will be maintained by the study site and will be available for review by the sponsor or its designee.

All REC approvals should be signed by the REC chairman or designee and must identify the REC name and address, the clinical protocol by title or protocol number or both and the date approval or a favourable opinion was granted.

9.3.2.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 and local regulatory authority requirements shall be obtained from each participant before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the participant is performed. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor or its designee or both before REC submission. Once reviewed, the investigator will submit the ICF to the REC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrolment, each prospective participant will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF.

The investigator or designee will provide a copy of the ICF to the participant. The original form shall be maintained in the participant’s medical records at the study site.

9.3.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her REC as appropriate.

9.3.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD nor the study site is financially responsible for further treatment of the disease under study.

9.3.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2, US Title 21 of the CFR, and local regulations by providing essential documents, including but not limited to, the following:

- REC approval.
- An original investigator-signed investigator agreement page of the protocol.
- Curriculum vitae for the principal investigator and each sub-investigator. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An REC-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant.
- Laboratory certifications and reference ranges for any local laboratories used by the study site, in accordance with US Title 42 CFR Part 493 and local regulations.

9.3.2.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with

the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics committee. Any amendment to the protocol or consent materials must also be approved by the study sponsor and REC and must be submitted, notified, or approved to the regulatory authority, as required, before they are implemented.

9.3.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter participant data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

eCRFs and EDC will be utilised. The EDC system is validated and compliant with US Title 21 CFR Part 11 and local regulations. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.3.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.3.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her REC as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator’s participation in the study.

9.3.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the REC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports as required. Interim reports are expected to be provided to regulatory authorities to allow study vaccine development advancement given the pandemic situation. These reports are planned to be aggregate and at the study vaccine level unless the SMC deems additional data at the individual level (e.g., select listings of select participants) will be beneficial. In such a case, a firewall will be in place to maintain the blind for those individuals involved in the study conduct to ensure unbiased assessment continue.

9.3.2.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccine or per local regulation, whichever is longer. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. It is the sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

9.3.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorisation, but data and any publication thereof will not be unduly withheld.

9.3.3 Study Management

9.3.3.1 Monitoring

9.3.3.1.1 Monitoring of the Study

The clinical research organisation clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel. The monitor will be blinded to study vaccine assignment. A separate unblinded study monitor will be responsible for drug accountability.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.3.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, REC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or the regulatory authority access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.3.3.2 Management of Protocol Amendments and Deviations

9.3.3.2.1 Modification of the Protocol

This is a Phase 3 study to evaluate the efficacy, immunogenicity, and safety of SARS-CoV-2 rS with Matrix-M1 adjuvant. This protocol is written with some flexibility to accommodate the evolving pandemic and urgency for efficacious vaccine availability. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants:

- The timing of procedures for assessment of safety procedures may be modified based on newly available safety and tolerability data or evolving COVID-19 data.

- Up to an additional 25 mL of blood may be drawn for safety or immunogenicity analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his or her participation in the entire study.
- Additional database freezes may occur as the study evolves and should the ongoing epidemic progression warrant rapid decision-making on product manufacturing. The study will continue in a blinded fashion (at the participant level) until the EOS.
- Rapid diagnostic testing for SARS-CoV-2 by point-of-care tests may be available and substituted for centralised testing if accepted by regulatory authorities as a secondary endpoint in this study and hold validity for study vaccine advancement.

It is understood that the current study may employ some or none of the alterations described above. Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the participant, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be approved by the REC, and regulatory authority where applicable, before participants can be enrolled into an amended protocol.

9.3.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior REC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the REC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a participant being discontinued from the study or significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to regulatory authority including ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The REC should be notified of all protocol deviations, if appropriate, in a timely manner.

9.3.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last study visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.3.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

9.4 Appendix 4: FDA Toxicity Grading Scales

Table 9-1 FDA Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity)

Local Reaction to Injectable Product				
Clinical Abnormality	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness[a]	2.5 − 5 cm	5.1 − 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5 − 5 cm and does not interfere with activity	5.1 − 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Systemic (General)				
Clinical Abnormality	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) (°F)	38.0 − 38.4 100.4 − 101.1	38.5 − 38.9 101.2 − 102.0	39.0 − 40 102.1 − 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 − 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Abbreviations: DHHS = Department of Health and Human Services; ER = emergency room; FDA = United States Food and Drug Administration.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

[c] Oral temperature; no recent hot or cold beverages.

Source: DHHS 2007.

Table 9-2 FDA Toxicity Grading Scale for Clinical Abnormalities (Vital Signs)

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia (bpm)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (bpm)[a]	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviations: DHHS = Department of Health and Human Services; ER = emergency room; FDA = United States Food and Drug Administration.

Note: Participant should be at rest for all vital sign measurements, with toxicity scored on day of study vaccination (pre- and post-dose).

[a] When resting heart rate is between 60 – 100 bpm. Use clinical judgement when characterising bradycardia among some healthy participant populations (e.g., conditioned athletes).

Source: DHHS 2007.

9.5 Appendix 5: Listings of Adverse Events of Special Interest

Because it has been hypothesised that immunisations with or without adjuvant may be associated with autoimmunity, regulatory authorities have requested that Novavax instruct investigators to be especially vigilant regarding the PIMMC listed in Table 9-3.

Table 9-3 Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuro-inflammatory Disorders:	Acute disseminated encephalomyelitis (including site specific variants: e.g., noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (e.g., Bell's palsy), generalised convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome
Vasculidities:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotising vasculitis and anti-neutrophil cytoplasmic antibody [ANCA] positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis)
Gastrointestinal Disorders:	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis
Hepatic Disorders:	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis
Renal Disorders:	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis.
Cardiac Disorders:	Autoimmune myocarditis/cardiomyopathy
Skin Disorders:	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome
Haematologic Disorders:	Autoimmune hemolytic anaemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis[a], diabetes mellitus type 1, Addison's disease

Categories	Diagnoses (as MedDRA Preferred Terms)
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, sarcoidosis

Abbreviations: ANCA = anti-neutrophil cytoplasmic antibody; IgA = immunoglobulin A; MedDRA = Medical Dictionary for Regulatory Activities.
[a] For Hashimoto thyroiditis: new onset only.

AESIs relevant to COVID-19 are listed in Table 9-4. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI. It is anticipated that additional AESI may be associated with COVID-19. Investigators should stay updated regarding such public health notifications.

Table 9-4 Adverse Events of Special Interest Relevant to COVID-19[a]

Body System	Diagnoses[a]
Immunologic	Enhanced disease following immunisation,[b] cytokine release syndrome related to COVID-19[c], Multisystem inflammatory syndrome in children (MIS-C)
Respiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Haematologic	Coagulation disorder • Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Hemorrhagic disease • Thrombotic complications
Renal	Acute kidney injury
Gastrointestinal	Liver injury
Neurologic	Guillain-Barré Syndrome, anosmia, ageusia, meningoencephalitis
Dermatologic	Chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme

Abbreviations: AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS; PCR = polymerase chain reaction; SARS-CoV2 = severe acute respiratory syndrome coronavirus 2.
[a] To be recorded as AESIs relevant to COVID-19, these complications should be associated with a positive PCR test for SARS-CoV-2.
[b] COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential (SPEAC 2020).
[c] Cytokine release syndrome related to COVID-19 infection is a disorder characterised by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath (DAIDS 2017).