Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix to Manuscript Entitled

Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine

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The 2019nCoV-302 clinical trial was a collective group effort across multiple institutions and locations. Below is a list of sites and staff that significantly contributed to the implementation and conduct of the 2019nCoV-302 clinical trial.

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Supplemental Methods

Vaccination Pause Rules

Study vaccination pause rules based on reactogenicity, adverse events (AEs), and serious adverse events (SAEs) related to study participation were in place to monitor participant safety for the initial set of vaccinations only.

AEs meeting any one of the following criteria resulted in a hold being placed on subsequent study vaccinations pending further review by the safety monitoring committee (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 enrolled) 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 that the investigator assesses as related that occurs in ≥5% of participants (after a minimum of 100 subjects are enrolled) in the NVX2373 group within the first 7 days after study vaccination.

In addition, any SAE assessed as related to vaccine (final assessment by the Sponsor) was 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 could advise the Sponsor to immediately pause enrollment 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 occurred and how the Chair's recommendations were documented.

The Sponsor, along with the Medical Monitor, were able to request an SMC review for any safety concerns that arose in the study, even if they were not associated with any specific pause rule, for example, any SAE for which causality was at least possibly related.

RT-PCR Testing Assays

Virological confirmation was performed using polymerase chain reaction (PCR) testing at the United Kingdom (UK) Department of Health and Social Care (DHSC) laboratories, which utilized the TaqPath™ system (Thermo Fisher Scientific, Waltham, Massachusetts, USA). Testing using this system in the UK has shown a close correlation between VOC-202012/1 cases confirmed by genomic sequencing and TaqPath™ PCR results where the spike protein gene PCR target has not been detected but other PCR targets (N gene and ORF1ab gene) have been detected. Such a result is referred to as S gene negative, or S gene target failure (SGTF), is due to a 69–70del that causes a loss of two amino acids at positions 69 and 70, and has a strong association with the B.1.1.7 variant. S gene negative results are therefore used as a proxy for this variant. In the period of time over which endpoint accrual analysis took place (November 2020-January 2021), 95% of all 69–70del sequences reported from UK DHSC laboratories were due to the B.1.1.7 lineage permitting the use of the SGTF result as a proxy marker for this variant during this period.[1,2]

Swabbing

Education and assistance with the self-swab technique were provided at the initial study visit. An online National Health Service (NHS) video guide (https://www.youtube.com/watch?v=zCqo7MhQT6U) was also recommended to participants and played at some sites when available. Participants were each given three PCR swab kits after learning the self-swab technique on Day 0. Participants were then asked to self-assess for potential Covid-19 symptoms, with frequent text message reminders, listed in Table S2. A list of the Table S2 symptoms and the site contact number was provided to each participant. Upon assessing any symptom, the participant was asked to call the site to confirm that the symptoms were appropriate to begin self-swabbing. Swabbing was to be performed by participants and swabs mailed to the DHSC testing laboratories. Participants were asked to self-swab daily for 3 days beginning approximately 24 hours after the onset of symptoms. The nose/throat swab involved swabbing the back of the throat for 10 seconds and then swabbing the nose at a depth of approximately 2.5 cm for 10 to 15 seconds. All kits were registered online prior to posting. Participants were directly informed of their results by text or email from the NHS. Sites obtained bar-coded sample results from NHS digital.

Recruitment Strategy

The major method for recruiting potential participants for the NVX-CoV2373 Covid-19 vaccine trial was the NHS COVID-19 vaccine research registry (https://bepartofresearch.nihr.ac.uk/vaccine-studies/).

The purpose of this registry is to allow volunteers to be identified by researchers as potentially eligible for their studies. It is an online self-registration service that enables volunteers who are interested in taking part in coronavirus vaccine studies to give their permission for their data to be shared with researchers so that they can be contacted. The registry is open to those who live in the UK, are over 18, and have an email address. In the case of the NVX-CoV2373 Covid-19 vaccine study, registered volunteers who lived in the geographic areas covered by the respective trial sites were sent an email by the registry with a brief summary of the trial and a link to the trial website. If they were interested in learning more about the trial, they could go to the trial website where more information was available. If they then wished to volunteer for the trial, they would complete an online pre-screening questionnaire, and if they had no obvious exclusion criteria, their contact details would be sent to the local trial site that would make direct contact with the volunteers and invite them to a screening/vaccination visit.

Influenza Coadministration Sub-Study

Participants in the influenza coadministration sub-study were the first approximately 400 participants who met all study entry criteria and additional sub-study criteria, not already having received a 2020-2021 seasonal 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 coadministered with influenza vaccine. Sub-study enrollment was not randomized or stratified by age.

Participants 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. 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 influenza vaccines were utilized in the study to comply with Public Health England influenza vaccination recommendation (Flucelvax® Quadrivalent, for those 18 to 64 years of age and Fluad® for those ≥65 years of age).

Reactogenicity was evaluated via an electronic diary for 7 days post-vaccination (local events assessed for study injection only) in addition to monitoring for unsolicited AEs, medically attended AEs (MAAEs),

and SAEs. Influenza hemagglutination inhibition and SARS-CoV-2 anti-spike IgG assays were performed prior to and after co-vaccination.

Supplemental Tables and Figure

Primary Efficacy Endpoint

The primary efficacy endpoint was the first occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe Covid-19 (see definitions in Table S1), with onset at least 7 days after second study vaccination in serologically negative (to SARS-CoV-2) participants at baseline.

Table S1. Endpoint Definitions of Covid-19 Severity

Covid-19 Severity	Endpoint Definitions
	First episode of PCR-positive nasal swab and ≥1 of symptomatic mild, moderate, or severe Covid-19:

Mild	Virologically confirmed SARS-CoV-2 infection plus ≥1 of:
	• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
	• New onset cough
	• ≥2 additional Covid-19 symptoms:
	  ○ New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
	  ○ New onset fatigue.
	  ○ New onset generalized muscle or body aches.
	  ○ New onset headache.
	  ○ New loss of taste or smell.
	  ○ Acute onset of sore throat, congestion, or runny nose.
	  ○ New onset nausea, vomiting, or diarrhea.

Moderate	• High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days).
	• Any evidence of significant lower respiratory tract infection (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.
	  ○ SpO_2: 94% to 95% on room air.
	  ○ Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or LRTI.
	• Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor).

Severe	• 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 mmHg. • High flow oxygen (O_2) therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (eg, continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]). • Mechanical ventilation or extracorporeal membrane oxygenation (ECMO). • One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following: ○ Acute respiratory failure, including acute respiratory distress syndrome (ARDS).

Table S1. Endpoint Definitions of Covid-19 Severity

Covid-19 Severity	Endpoint Definitions
	○ Acute renal failure. ○ Acute hepatic failure. ○ Acute right or left heart failure. ○ Septic or cardiogenic shock (with shock defined as systolic blood pressure [SBP] <90 mm Hg OR diastolic blood pressure [DBP] <60 mm Hg). ○ Acute stroke (ischemic or hemorrhagic). ○ Acute thrombotic event: acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE). ○ Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an intensive care unit (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 S2 shows the qualifying symptoms of suspected Covid-19.

Table S2. Qualifying Symptoms of Suspected Covid-19

• Fever (body temperature >38°C, in the absence of other symptoms) or chills • New onset or worsening of cough compared with baseline • New onset or worsening of shortness of breath or difficulty breathing over baseline • Severe fatigue • New onset generalized muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea

Abbreviations: Covid-19 = coronavirus disease 2019.

Unsolicited Adverse Events

Unsolicited TEAEs classified as severe, medically attended, serious, leading to vaccination or study discontinuation, potential immune-mediated medical conditions, or adverse events of special interest were reported at similar frequencies between the NVX-CoV2373 and placebo groups (Table S3).

Table S3. Overall Summary of Unsolicited Adverse Events — Excluding Reactogenicity Adverse Events (Specific Preferred Terms) and Events Reported Post Unblinding or Post Receipt of an Approved or Deployed SARS-CoV-2 Vaccine (Safety Analysis Set)

Parameters	NVX-CoV2373 N=7569		Placebo N=7570	
	n (%)	[E]	n (%)	[E]
Any TEAEs	1912 (25.3)	[2916]	1551 (20.5)	[2514]
Any severe TEAEs	76 (1.0)	[92]	64 (0.8)	[88]
Any treatment-related TEAEs	824 (10.9)	[1071]	344 (4.5)	[464]
Any severe treatment-related TEAEs	13 (0.2)	[14]	3 (<0.1)	[3]
Any MAAEs	285 (3.8)	[335]	295 (3.9)	[355]
Any treatment-related MAAEs	33 (0.4)	[41]	13 (0.2)	[15]
Any serious TEAEs	41 (0.5)	[50]	41 (0.5)	[50]
Any treatment-related serious TEAEs	1 (<0.1)	[1]	0	0
Any TEAEs leading to vaccination discontinuation	23 (0.3)	[27]	22 (0.3)	[43]
Any treatment-related TEAEs leading to vaccination discontinuation	7 (<0.1)	[9]	8 (0.1)	[9]
Any TEAEs leading to study discontinuation	17 (0.2)	[17]	16 (0.2)	[16]
Any treatment-related TEAEs leading to study discontinuation	5 (<0.1)	[5]	2 (<0.1)	[2]
Any PIMMCs	5 (<0.1)	[5]	7 (<0.1)	[7]
Any AESIs: relevant to Covid-19	8 (0.1)	[12]	22 (0.3)	[32]

Abbreviations: AESIs = adverse event(s) of special interest; Covid-19 = coronavirus disease 2019; [E] = number of adverse events; MAAE = medically attended adverse event; PIMMC = potential immune-mediated medical conditions; SARS-CoV-2 = severe acute respiratory coronavirus 2; TEAE = treatment-emergent adverse event.
All counts exclude reactogenicity adverse events (selected preferred terms) where the event start date is on the day of either vaccination or within the 6 calendar days that follow either vaccination.
Any event that occurred after unblinding or after receipt of an approved or deployed SARS-CoV-2 vaccine was excluded from the analysis.

Unsolicited TEAEs reported for all participants who received at least one dose of NVX-CoV2373 or placebo during the entire study were predominantly mild or moderate in severity and occurred in 25.4% of participants receiving active vaccine and 20.8% of participants receiving placebo (Table S4). No unsolicited TEAE in the NVX-CoV2373 group occurred at a frequency that was one percentage point higher than in the placebo group. This analysis excludes reactogenicity TEAEs (selected preferred terms) with an event start date on the day of either vaccination or within 6 days after each vaccination.

Table S4. Summary of Unsolicited Treatment-Emergent Adverse Events (Excluding Reactogenicity Adverse Events) Reported in ≥1% of Participants in Any Group (Safety Analysis Set)

System Organ Class Preferred Term	NVX-CoV2373 N=7569 n (%)	Placebo N=7570 n (%)
Any TEAE	1925 (25.4)	1574 (20.8)
General disorders and administration site conditions	461 (6.1)	223 (2.9)
Pain	93 (1.2)	25 (0.3)
Nervous system disorders	325 (4.3)	313 (4.1)
Headache	109 (1.4)	131 (1.7)
Lethargy	77 (1.0)	32 (0.4)
Respiratory, thoracic, and mediastinal disorders	305 (4.0)	316 (4.2)
Oropharyngeal pain	114 (1.5)	116 (1.5)
Rhinorrhea	70 (0.9)	92 (1.2)
Cough	66 (0.9)	87 (1.1)
Infections and infestations	282 (3.7)	328 (4.3)
Musculoskeletal and connective tissue disorders	219 (2.9)	203 (2.7)
Gastrointestinal disorders	217 (2.9)	188 (2.5)
Diarrhea	82 (1.1)	66 (0.9)
Skin and subcutaneous tissue disorders	157 (2.1)	110 (1.5)
Injury, poisoning, and procedural complications	121 (1.6)	92 (1.2)
Vascular disorders	86 (1.1)	53 (0.7)
Blood and lymphatic system disorders	72 (1.0)	61 (0.8)

Abbreviations: MedDRA = *Medical Dictionary for Regulatory Activities;* TEAE = treatment-emergent adverse event.

Overall includes TEAE recorded during the entire study duration. If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), then it was recorded as an unsolicited TEAE with the start date as the 7th day following the relevant study vaccination and followed to resolution. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity after exposure. At each level of subject summarization, a participant is counted once if the participant reported one or more events.

n represents the number of participants at each level of summarization. Percentages were based on the number of participants in the safety analysis set within each treatment and total.

Adverse events were coded using MedDRA, version 23.1.

System organ class is displayed in descending order of frequency for the total column and then alphabetically.

Within class, preferred term is displayed in descending order of frequency for total and then alphabetically.

Efficacy Against UK Variant

A two-dose regimen of NVX-CoV2373 given 21 days apart was found to be safe and 89.7% effective against symptomatic Covid-19. The timing of accumulated cases in this study allowed for a post hoc assessment of vaccine efficacy against the non-B.1.1.7strains and the B.1.1.7 variant, which is now circulating widely outside of the UK and is soon expected to be the most prominent strain in the United States.[3] This variant is known to be more transmissible and to be associated with a higher case fatality rate than previous strains,[3] emphasizing the need for an effective vaccine. High vaccine efficacy was demonstrated against the on-B.1.1.7 strains (96.4%) and the B.1.1.7 variant (86.3%) (Table S5). This is

the first vaccine to demonstrate high vaccine efficacy (86.3%) against the B.1.1.7 variant in a phase 3 trial.

Table S5. Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe Covid-19 With an Onset at Least 7 Days After Second Study Vaccination in Serologically Negative Adult Participants by SARS-CoV-2 Strain (PP-EFF Analysis Set)

Parameter	Final Analysis	
	NVX-CoV2373 N=7020	Placebo N=7019
UK (Kent) Variant Strain (B.1.1.7)		
Participants in PP-EFF	7019*	7009*
Participants with first occurrence of event, n (%)	8 (0.1)	58 (0.8)
Severity of first occurrence, n (%)		
Mild	1 (<0.1)	15 (0.2)
Moderate	7 (<0.1)	39 (0.6)
Severe	0	4 (<0.1)
Median surveillance time (days)	56	55
Log-linear model using modified Poisson regression		
Mean disease incidence rate per year in 1000 people	4.94	36.11
95% CI	2.33, 10.48	23.15, 56.32
Relative risk	0.137	
95% CI	0.065, 0.287	
Vaccine efficacy (%)	86.3	
95% CI	71.3, 93.5	
Non-B.1.1.7 Strain		
Participants in PP-EFF	7019*	7009*
Participants with first occurrence of event, n (%)	1 (<0.1)	28 (0.4)
Severity of first occurrence, n (%)		
Mild	0	9 (0.1)
Moderate	1 (<0.1)	18 (0.3)
Severe	0	1 (<0.1)
Median surveillance time (days)	56	56
Log-linear model using modified Poisson regression		
Mean disease incidence rate per year in 1000 people	0.43	12.15
95% CI	0.05, 3.79	4.23, 34.92
Relative risk	0.036	
95% CI	0.005, 0.262	
Vaccine efficacy (%)	96.4	
95% CI	73.8, 99.5	

Abbreviations: CI = confidence interval; Covid-19 = coronavirus disease 2019; NVX CoV2373 = SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg); PCR = polymerase chain reaction; PP = per-protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant nanoparticle spike protein vaccine.

*Excludes 1 participant in the NVX-CoV2373 group and 10 participants in the placebo group who had no sequence data for either SARS-CoV-2 strain.

Demographics: Intention-to-Treat Population

Table S6. Demographics and Baseline Characteristics (Intention-to-Treat Analysis Set)

Parameter	NVX-CoV2373 N=7569	Placebo N=7570	Total N=15,139
Age, yr			
Median	55.0	55.0	55.0
Range	18, 84	18, 84	18, 84
Age group, n (%)			
18-64 yr	5503 (72.7)	5511 (72.8)	11014 (72.8)
≥65 yr	2066 (27.3)	2059 (27.2)	4125 (27.2)
Sex, n (%)			
Male	3890 (51.4)	3918 (51.8)	7808 (51.6)
Female	3679 (48.6)	3652 (48.2)	7331 (48.4)
Race or ethnic group, n (%)			
White	7127 (94.2)	7153 (94.5)	14280 (94.3)
Black or African American	31 (0.4)	29 (0.4)	60 (0.4)
Asian	230 (3.0)	232 (3.1)	462 (3.1)
American Indian or Alaska native	5 (<0.1)	0	5 (<0.1)
Native Hawaiian or other Pacific Islander	1 (<0.1)	0	1 (<0.1
Multiple	75 (1.0)	61 (0.8)	136 (0.9)
Not reported	91 (1.2)	85 (1.1)	176 (1.2)
Other	5 (<0.1)	6 (<0.1)	11 (<0.1)
Missing	4	4	8
Hispanic or Latinx	69 (0.9)	56 (0.7)	125 (0.8)
SARS-CoV-2 serostatus, n (%)			
Negative	7180 (94.9)	7182 (94.9)	14362 (94.9)
Positive	330 (4.4)	313 (4.1)	643 (4.2)
Missing	59	75	134
BMI, kg/m^2, n (%)			
≥30.0: obese	344 (4.5)	353 (4.7)	697 (4.6)
Comorbidity status*			
Yes	3368 (44.5)	3399 (44.9)	6767 (44.7)
No	4201 (55.5)	4171 (55.1)	8372 (55.3)

SD = standard deviation. Body mass index (BMI) is calculated as weight (kg) divided by squared height (m).
Percentages are based on per-protocol efficacy analysis set within each treatment and overall.
*Comorbid subjects are those identified who have at least one of the comorbid conditions reported as a medical history or have a screening BMI value greater than 30 kg/m^2.

Table S7. Summary of Unsolicited Serious Treatment-Emergent Adverse Events (Safety Analysis Set)

System Organ Class Preferred Term Severity	NVX-CoV2373 N=7569 n (%)	Placebo N=7570 n (%)	Total N=15139 n (%)
Any Serious TEAE	44 (0.6)	44 (0.6)	88 (0.6)
Infections and infestations	6 (<0.1)	11 (0.1)	17 (0.1)
Covid-19 pneumonia	1 (<0.1)	3 (<0.1)	4 (<0.1)
Appendicitis	1 (<0.1)	2 (<0.1)	3 (<0.1)
Covid-19	2 (<0.1)	0	2 (<0.1)
Pneumonia	0	2 (<0.1)	2 (<0.1)
Appendicitis perforated	1 (<0.1)	0	1 (<0.1)
Bacterial sepsis	0	1 (<0.1)	1 (<0.1)
Diverticulitis	0	1 (<0.1)	1 (<0.1)
Epiglottitis	0	1 (<0.1)	1 (<0.1)
Gastroenteritis	0	1 (<0.1)	1 (<0.1)
Intestinal gangrene	1 (<0.1)	0	1 (<0.1)
Otitis externa	0	1 (<0.1)	1 (<0.1)
Pharyngeal abscess	0	1 (<0.1)	1 (<0.1)
Postoperative wound infection	1 (<0.1)	0	1 (<0.1)
Wound infection	1 (<0.1)	0	1 (<0.1)
Injury, poisoning, and procedural complications	11 (0.1)	6 (<0.1)	17 (0.1)
Ankle fracture	3 (<0.1)	0	3 (<0.1)
Femoral neck fracture	0	3 (<0.1)	3 (<0.1)
Cervical vertebral fracture	1 (<0.1)	0	1 (<0.1)
Fall	0	1 (<0.1)	1 (<0.1)
Femur fracture	1 (<0.1)	0	1 (<0.1)
Intentional overdose	1 (<0.1)	0	1 (<0.1)
Joint dislocation	1 (<0.1)	0	1 (<0.1)
Limb injury	1 (<0.1)	0	1 (<0.1)
Overdose	0	1 (<0.1)	1 (<0.1)
Poisoning deliberate	1 (<0.1)	0	1 (<0.1)
Radius fracture	1 (<0.1)	0	1 (<0.1)
Skin laceration	1 (<0.1)	0	1 (<0.1)
Ulna fracture	1 (<0.1)	0	1 (<0.1)
Wrist fracture	0	1 (<0.1)	1 (<0.1)
Cardiac disorders	7 (<0.1)	5 (<0.1)	12 (<0.1)
Atrioventricular block complete	1 (<0.1)	1 (<0.1)	2 (<0.1)
Acute coronary syndrome	1 (<0.1)	0	1 (<0.1)
Acute myocardial infarction	1 (<0.1)	0	1 (<0.1)
Angina pectoris	0	1 (<0.1)	1 (<0.1)
Arrhythmia	0	1 (<0.1)	1 (<0.1)
Atrial fibrillation	0	1 (<0.1)	1 (<0.1)
Atrial flutter	0	1 (<0.1)	1 (<0.1)
Atrial tachycardia	1 (<0.1)	0	1 (<0.1)
Cardiac failure acute	1 (<0.1)	0	1 (<0.1)
Myocardial infarction	1 (<0.1)	0	1 (<0.1)
Myocarditis	1 (<0.1)	0	1 (<0.1)
Palpitations	1 (<0.1)	0	1 (<0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (<0.1)	5 (<0.1)	10 (<0.1)
Breast cancer	2 (<0.1)	0	2 (<0.1)
Adenocarcinoma of appendix	0	1 (<0.1)	1 (<0.1)

Bladder cancer	1 (<0.1)	0	1 (<0.1)
Glioblastoma	0	1 (<0.1)	1 (<0.1)
Intraductal proliferative breast lesion	0	1 (<0.1)	1 (<0.1)
Lung neoplasm malignant	1 (<0.1)	0	1 (<0.1)
Ovarian cancer	0	1 (<0.1)	1 (<0.1)
Squamous cell carcinoma of skin	1 (<0.1)	0	1 (<0.1)
Squamous cell carcinoma of the tongue	0	1 (<0.1)	1 (<0.1)
Nervous system disorders	5 (<0.1)	3 (<0.1)	8 (<0.1)
Migraine	3 (<0.1)	0	3 (<0.1)
Lumbar radiculopathy	0	1 (<0.1)	1 (<0.1)
Migraine with aura	0	1 (<0.1)	1 (<0.1)
Presyncope	1 (<0.1)	0	1 (<0.1)
Sciatica	1 (<0.1)	0	1 (<0.1)
Transient ischemic attack	0	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	2 (<0.1)	4 (<0.1)	6 (<0.1)
Abdominal pain lower	1 (<0.1)	0	1 (<0.1)
Ascites	0	1 (<0.1)	1 (<0.1)
Gastro-esophageal reflux disease	1 (<0.1)	0	1 (<0.1)
Intestinal perforation	0	1 (<0.1)	1 (<0.1)
Obstructive pancreatitis	0	1 (<0.1)	1 (<0.1)
Small intestinal obstruction	0	1 (<0.1)	1 (<0.1)
Upper gastrointestinal hemorrhage	1 (<0.1)	0	1 (<0.1)
Renal and urinary disorders	2 (<0.1)	3 (<0.1)	5 (<0.1)
Acute kidney injury	1 (<0.1)	1 (<0.1)	2 (<0.1)
Nephrolithiasis	0	1 (<0.1)	1 (<0.1)
Urethral dilatation	0	1 (<0.1)	1 (<0.1)
Urinary retention	1 (<0.1)	0	1 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)	3 (<0.1)	4 (<0.1)
Dehydration	1 (<0.1)	0	1 (<0.1)
Diabetic ketoacidosis	0	1 (<0.1)	1 (<0.1)
Diabetic ketosis	0	1 (<0.1)	1 (<0.1)
Hypoalbuminemia	0	1 (<0.1)	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	1 (<0.1)	3 (<0.1)	4 (<0.1)
Pulmonary embolism	1 (<0.1)	2 (<0.1)	3 (<0.1)
Epistaxis	0	1 (<0.1)	1 (<0.1)
Blood and lymphatic system disorders	0	3 (<0.1)	3 (<0.1)
Anemia	0	1 (<0.1)	1 (<0.1)
Hemolytic anemia	0	1 (<0.1)	1 (<0.1)
Iron deficiency anemia	0	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	2 (<0.1)	0	2 (<0.1)
Mass	1 (<0.1)	0	1 (<0.1)
Non-cardiac chest pain	1 (<0.1)	0	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)	2 (<0.1)
Cholecystitis	1 (<0.1)	0	1 (<0.1)
Liver injury	0	1 (<0.1)	1 (<0.1)
Reproductive system and breast disorders	2 (<0.1)	0	2 (<0.1)
Endometriosis	1 (<0.1)	0	1 (<0.1)

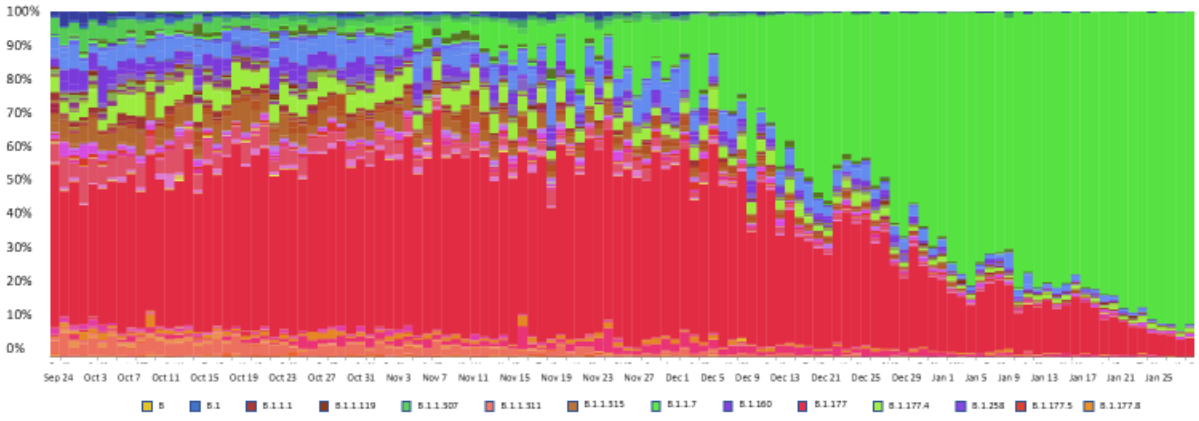
Vaginal prolapse	1 (<0.1)	0	1 (<0.1)
Vascular disorders	0	2 (<0.1)	2 (<0.1)
Hypertension	0	1 (<0.1)	1 (<0.1)
Peripheral ischemia	0	1 (<0.1)	1 (<0.1)
Investigations	0	1 (<0.1)	1 (<0.1)
Blood pressure systolic increased	0	1 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	1 (<0.1)	1 (<0.1)
Osteoarthritis	0	1 (<0.1)	1 (<0.1)
Pregnancy, puerperium, and perinatal conditions	1 (<0.1)	0	1 (<0.1)
Abortion spontaneous	1 (<0.1)	0	1 (<0.1)
Surgical and medical procedures	1 (<0.1)	0	1 (<0.1)
Cholecystectomy	1 (<0.1)	0	1 (<0.1)
UNCODED	1 (<0.1)	1 (<0.1)	2 (<0.1)

Vaccination Dose 1 includes serious TEAE with start date on or after first vaccination dose to end of study or second vaccination dose, whichever occurs earlier. Vaccination Dose 2 includes serious TEAE with start date on or after second vaccination dose to end of study. Overall includes TEAE recorded during the entire study duration. If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), then it is recorded as an unsolicited AE with the start date the 7th day following the relevant study vaccination and followed to resolution.
n represents the number of subjects at each level of summarization. Percentages are based on the number of subjects in the safety analysis set within each treatment and total.
SAEs were coded using MedDRA, version 23.1.
System organ class is displayed in descending order of frequency for the total column and then alphabetically.
Within class, preferred term is displayed in descending order of frequency for total and then alphabetically.

B1.1.1.7 Variant

The B.1.1.7 variant was first detected in the UK in September 2020 and has since been found in more than 100 countries. It has 23 mutations in its genetic code; some of these changes have increased its ability to spread. It is estimated that the B.1.1.7 variant is 40% to 70% more transmissible than previously dominant circulating coronavirus variants.[4] Figure S1 shows the growth of the B.1.1.7 variant over the course of the current study in the UK.

Figure S1. Evolution of Covid-19 Variants During the Endpoint Period.



Microreact has been developed by the Centre for Genomic Pathogen Surveillance at Imperial College London and the Wellcome Genome Campus. Argimón S et al, 2016.[5]

Statistical Method for Efficacy Endpoints

Summary statistics of a log-linear model using Zou 2004 modified Poisson regression approach[6] on efficacy were presented for relative risk (RR). The vaccine efficacy (VE) was defined as:

VE (%) = 100 x (1 – RR) where RR = relative risk of incidence rates between the two treatment groups (SARS-CoV-2 rS/placebo). Mean disease incidence rates were reported as incidence rate per year in 1000 people.

The VE and the corresponding two-sided 95% CI were calculated by modified Poisson regression with robust error variance[6] used to obtain the log RR (estimates) and RR (exponentiated). The one-sided alpha % was calculated using the alpha-spending for Pocock boundary conditions.

The main (hypothesis testing) analysis (i.e., event-driven) for the interim and final analyses for the primary objective was carried out at an overall one-sided Type I error rate of 0.025 for the primary endpoint.

The explanatory variables in the modified Poisson regression model included the treatment group and the stratification variables (region [pooled sites] and age group <65/≥65 years). The pooling of sites into regions was determined and documented prior to breaking the blind. If the model failed to converge,

then the conditional binomial approach using the Clopper Pearson method was used. The robust error variances were estimated using repeated statement and the subject identifier as well as the log of the surveillance time as an offset.

Hypothesis testing for the primary efficacy endpoint was carried out against

H_0: VE ≤ 30%

H_I: VE > 30%

Rejection of the null hypothesis (i.e., alpha-adjusted lower bound confidence interval [LBCI] >30%) was considered meeting the pre-specified study success criterion.

All other efficacy endpoints were analyzed using the same method as the primary efficacy endpoint without adjustment for multiple comparisons (i.e., two-sided alpha 0.05) against H_0: VE ≤ 0%. Since the successful demonstration of the primary efficacy endpoint was achieved at the interim analysis against the pre-specified success criterion using the adjusted alpha, the primary efficacy endpoint was summarized again using the unadjusted two-sided 95% CI for the estimation purpose using the final data cut.

Interim Analysis

Prior to the final analysis, a single interim analysis of efficacy was planned based on the accumulation of approximately 50% (50 events) of the total anticipated target number of the primary endpoint (100 events). The actual number of events included in the interim analysis was 62 events. The data needed to perform the analysis of the primary efficacy endpoint were cleaned. The interim analysis was performed by an unblinded Biostatistics and Programming team, and the unblinded statistician communicated that the predefined statistical success criterion was fulfilled. The study continued until the final analysis of 100 events while the unblinded Biostatistics and Programming team was isolated (by firewall) from study personnel. The interim analysis followed standard group-sequential design using the Pocock boundary conditions. Table S8 summarizes the timing, number of endpoints, and statistical success boundaries at the planned interim and final analyses. Power calculations were performed by 10,000 simulated trials that were created under various assumptions of VEs, as summarized in Table S9.

Table S8. 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.

Table S9. 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.

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