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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Material

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

Supplementary Material to Manuscript Entitled

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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The NVX-CoV2373-2019nCoV-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 NVX-CoV2373-2019nCoV-302 clinical trial.

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Supplemental Methods

Details on Vaccines

The influenza vaccine quadrivalent (QIVc) (Flucelvax® Quadrivalent, Seqirus UK Limited, Maidenhead, UK) is indicated for those 18 to 64 years of age. The QIVc dose contains 15 µg haemagglutinin (HA) per 0.5 mL dose from each of the following strains: A/Hawaii/70/2019 (H1N1)pdm09-like strain (A/Nebraska/14/2019, wild type), A/Hong Kong/45/2019 (H3N2)-like strain (A/Delaware/39/2019, wild type), B/Washington/02/2019-like strain (B/Darwin/7/2019, wild type), and B/Phuket/3073/2013-like strain (B/Singapore/INFTT-16-0610/2016, wild type).

The adjuvanted trivalent influenza vaccine (aTIV) (Fluad®, Seqirus UK Limited, Maidenhead, UK) is indicated for those ≥65 years of age. Within each 0.5 mL dose, the aTIV formulation contains the MF59 adjuvant (9.75 mg squalene, 1.175 mg polysorbate 80, 1.175 mg sorbitan trioleate, 0.66 mg sodium citrate, 0.04 mg citric acid, water for injections) plus 15 µg HA from each of the following strains: A/Guandong-Maonan/SWL1536/2019 (H1N1)pdm09-like strain (A/Victoria/2454/2019 IVR-207), A/Hong Kong/2671/2019 (H3N2)-like strain (A/Hong Kong/2671/2019 IVR-208), and B/Washington/02/2019-like strain (B/Victoria/705/2018 BVR-11).

Strains assessed in the haemagglutination inhibition assay (HAI):

Quadrivalent formulation of cell- or recombinant-based influenza vaccine

- A/Nebraska/14/2019 (an A/Hawaii/70/2019 (H1N1)pdm09-like virus)
- A/Delaware/39/2019 (an A/Hong Kong/45/2019 (H3N2)-like virus)
- B/Darwin/7/2019 (a B/Washington/02/2019-like virus)
- B/Singapore/INFTT-16-0610/2016 (a B/Phuket/3073/2013-like virus)

Trivalent formulation of egg-based influenza vaccine

- A/Victoria/2454/2019 IVR-207 (an A/Guangdong-Maonan/SWL1536/2019 (H1N1) pdm09-like virus
- A/Hong Kong/2671/2019 IVR-208 (an A/Hong Kong/2671/2019 (H3N2)-like virus)
- B/Victoria/705/2018 BVR-11 (a B/Washington/02/2019-like virus).

Details on the Assays

HAI

The haemagglutination inhibition assay was performed at the Public Health England Laboratory, Porton Down, UK. The HAI was developed at Public Health England laboratory and is based on the World Health Organization recommendations and is fit for purpose. Briefly, HAI was performed with human sera treated with receptor destroying enzyme incubated with standardized concentrations (4 haemagglutinin units) of influenza virus representing H1N1, H3N2 and influenza B (Victoria and Yamagata) 2020/21 viral strains. Chicken red blood cells were utilised as the source of RBCs for haemagglutination. HAI titres were determined as the reciprocal of the highest dilution of serum that completed inhibited haemagglutination.

SARS-CoV-2 spike protein serum IgG ELISA (performed at Novavax Clinical Immunology Laboratory, Gaithersburg, MD, USA)

Recombinant SARS-CoV-2 (rSARS-CoV-2) S protein was immobilised onto the surface of the 96-well microtitre plate wells (100 µL per well) by direct adsorption for 15 to 72 hours at 2°C to 8°C at a concentration of 1 µg/mL in PBS as per P_SOP_02483 (Validated method). Plates were washed 4 times with 300 µL/well PBST, blocked with 300 µL blocking buffer for 1-1.5 hours at 24°C ± 2°C. Diluted reference standard (2-fold dilution series of 12 dilutions starting 1:1000) and human serum samples (3-fold dilution series of 12 dilutions) in assay buffer (1% milk in PBS) starting at 1:100 dilution are then added in duplicate (100 µL per well) to the rSARS-CoV-2 S protein-coated wells and any specific antibodies are allowed to complex with the coated antigen for 2 hours ± 10 minutes at 24°C ± 2°C. Plates are washed 4 times with 300 µL/well PBST. Antibodies bound to the rSARS-CoV-2 S protein

are then detected using a horseradish peroxidase (HRP) conjugate goat anti-human IgG antibody diluted 1: 2000 (Southern Biotech cat no. 2040-05) incubated for 1 hour ± 10 minutes at 24°C ± 2°C, washed 6 times with 300 µL/well PBST, and a colorimetric signal generated by addition of 100 µL per well 3, 3′,5,5′-tetramethylbenzidine (TMB) chromogenic substrate for 10 minutes ± 2 minutes at 24°C ± 2°C. After incubation was complete, the TMB reaction was stopped with 100 µL per well of TMB Stop solution. The absorbance was measured at 450 nm using a Molecular Device 96-well plate reader. When binding reagents (coated antigen and secondary antibody) are in excess, the optical density (OD) of the chromogenic substrate at endpoint is proportional to the quantity of anti-rSARS-CoV-2 S IgG present in the serum sample. The total anti-rSARS-CoV-2 S protein IgG antibody level in a serum sample was quantitated in ELISA unit, EU/mL, by comparison to a reference standard curve. The results were analysed in singleton by SoftMax Pro software using 4-PL curve fit. Assay included control plates comprising of positive controls and negative control.

For the Day 35 IgG anti-S assay in all ages, 3/178 samples were below the LLOQ in the active arm and 164/181 samples were below the LLOQ in the placebo arm. For the Day 21 IgG HAI assay in all ages, 8/191, 0/191, 49/191, and 11/191 samples were below the LLOQ in the active arm and 5/190, 0/190, 44/190, and 6/190 samples were below the LLOQ in the placebo arm for H1N1, H3N2, B/Victoria, and B/Yamagata strains, respectively.

Supplemental Tables

Table S1. Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuro-inflammatory Disorders:	Acute disseminated encephalomyelitis (including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (eg, 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:	Anti-synthetase 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
Vasculitides:	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 haemolytic anaemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease
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.*

Table S2. Adverse Events of Special Interest Relevant to COVID-19*

Body System	Diagnoses
Immunologic	Enhanced disease following immunisation, cytokine release syndrome related to COVID-19, 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 ischaemia • Haemorrhagic 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.

*To be recorded as AESIs relevant to COVID-19, these complications should be associated with a positive PCR test for SARS-CoV-2.

Table S3. 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 non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalisation
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalisation
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. −102.0	39.0−40.0 102.1−104.0	>40.0 >104.0
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 hospitalisation for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalisation
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalisation
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalisation
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalisation

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

Table S4. Demographics for the Influenza Vaccination Sub-Study Population, Reactogenicity Cohort, and Intention-to-Treat Group (Without the Influenza Sub-Study Participants)

	NVX-CoV2373 + Influenza (n=217)	Placebo + Influenza (n=214)	Total Influenza Sub-Study (n=431)	Reactogenicity Cohort (Excluding Influenza Sub-Study) (n=2310)	ITT Population (Excluding Influenza Sub-Study) (n=14708)
Age, yr (SD)	42.3 (14.09)	41.9 (13.23)	42.1 (13.66)	50.2 (15.07)	53.5 (14.82)
Median	40.0	38.0	39.0	52.0	56.0
Range	20, 71	23, 77	20, 77	18, 84	18, 84
Age group, n (%)					
18-64 yr (SD)	201 (92.6)	201 (93.9)	402 (93.3)	1851 (80.1)	10612 (72.2)
≥65 yr (SD)	16 (7.3)	13 (6.1)	29 (6.7)	459 (19.9)	4096 (27.8)
Sex, n (%)					
Male	123 (56.7)	118 (55.1)	241 (55.9)	1105 (47.8)	7567 (51.4)
Female	94 (43.3)	96 (44.9)	190 (44.1)	1205 (52.2)	7141 (48.6)
Race or ethnic group, n (%)					
White	163 (75.1)	164 (76.6)	327 (75.9)	2218 (96.0)	13953 (94.9)
Black or African American	4 (1.8)	2 (0.9)	6 (1.4)	5 (0.2)	54 (0.4)
Asian	14 (6.5)	23 (10.7)	37 (8.6)	47 (2.0)	425 (2.9)
Multiple	29 (13.3)	23 (10.7)	52 (12.1)	8 (1.3)	84 (0.6)
Not reported	3 (1.4)	2 (0.9)	5 (1.2)	30 (1.3)	171 (1.2)
Other	3 (1.4)	0 (0)	3 (0.7)	0 (0)	14 (<0.1)
Missing	1 (0.4)	0 (0)	1 (0.2)	2 (<0.1)	7 (<0.1)
Hispanic or Latinx	10 (4.6)	5 (2.3)	15 (3.5)	12 (0.5)	110 (0.7)
Co-morbidity status					
Yes	55 (25.3)	62 (29.0)	117 (27.1)	1032 (44.7)	6650 (45.2)
No	162 (74.7)	152 (71.0)	314 (72.9)	1278 (55.3)	8054 (54.8)

Abbreviation: ITT=intention-to-treat; SD=standard deviation.

Table S5. Demographics for the Anti-S IgG Immunogenicity Cohort and Intention-to-Treat Population

	Immunogenicity Cohort, NVX-CoV2373 (n=502)	Immunogenicity Cohort, Placebo (n=497)	Total, ITT Population (n=15139)
Age, yr (SD)	51.6 (15.71)	51.4 (15.39)	53.1 (14.91)
Median	54.0	52	55.0
Range	18, 81	19, 93	18, 84
Age group, n (%)			
18-64 yr (SD)	370 (73.7)	368 (74.0)	11014 (72.8)
≥65 yr (SD)	132 (26.3)	129 (26.0)	4125 (27.2)
Sex, n (%)			
Male	258 (51.4)	290 (58.4)	7808 (51.6)
Female	244 (48.6)	207 (41.6)	7331 (48.4)
Race or ethnic group, n (%)			
White	437 (87.1)	436 (87.7)	14280 (94.3)
Black or African American	3 (0.6)	3 (0.6)	60 (0.4)
Asian	39 (7.8)	34 (6.8)	462 (3.1)
Multiple	4 (0.8)	2 (0.4)	136 (0.9)
Not reported	18 (3.6)	21 (4.2)	176 (1.2)
Other	1 (0.2)	1 (0.2)	17 (<0.1)
Missing	0	0	8
Hispanic or Latinx	10 (2.0)	6 (1.2)	125 (0.8)
SARS-CoV-2 serostatus, n (%)	475 (94.6)	475 (95.6)	14362 (94.9)
Negative	24 (3.8)	20 (4.0)	643 (4.2)
Positive	3	2	134
Missing			
Co-morbidity status			
Yes	171 (34.1)	170 (34.2)	6767 (44.7)
No	331 (65.9)	327 (65.8)	8372 (55.3)

Abbreviations: IgG=immunoglobulin G; ITT=intention-to-treat; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation.

Table S6. Reactogenicity for Participants in the Influenza Vaccination Sub-Study and Reactogenicity Cohort After Dose 1, All Ages

	NVX-CoV2373 + Influenza Vaccine (n=205)					NVX-CoV2373 Alone (n=1159)					Placebo + Influenza Vaccine (n=199)					Placebo Alone (n=1151)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
A) Local AEs																				
Any local AE	29.9	52.3	16.1	1.7	0.0	42.4	41.5	15.1	1.0	0.0	60.6	27.2	12.2	0.0	0.0	82.1	14.7	3.0	0.2	0.0
Pain	60.3	35.1	4.0	0.6	0.0	70.7	28.4	0.9	0.0	0.0	83.3	16.1	0.6	0.0	0.0	90.8	9.0	0.1	0.1	0.0
Tenderness	35.1	48.3	14.9	1.7	0.0	46.7	37.8	14.5	1.0	0.0	62.8	25.0	12.2	0.0	0.0	85.7	11.4	2.7	0.1	0.0
Erythema	98.9	1.1	0.0	0.0	0.0	97.9	1.8	0.3	0.0	0.0	98.9	1.1	0.0	0.0	0.0	99.7	0.3	0.0	0.0	0.0
Swelling	98.9	0.0	1.1	0.0	0.0	99.1	0.6	0.3	0.0	0.0	100.0	0.0	0.0	0.0	0.0	99.5	0.4	0.2	0.0	0.0
B) Systemic AEs																				
Any systemic AE	39.9	37.0	20.2	2.9	0.0	54.3	28.7	15.7	1.1	0.2	52.8	23.3	21.1	2.8	0.0	63.7	22.4	12.8	1.1	0.0
Nausea/vomiting	94.8	4.6	0.6	0.0	0.0	94.8	4.3	0.8	0.0	0.1	93.3	5.6	1.1	0.0	0.0	94.8	3.8	1.4	0.0	0.0
Headache	75.1	17.9	6.4	0.6	0.0	75.5	20.0	4.0	0.5	0.1	78.3	15.6	6.1	0.0	0.0	78.5	16.7	4.6	0.3	0.0
Fatigue	72.3	13.3	13.3	1.2	0.0	80.6	10.3	8.7	0.4	0.1	71.1	11.7	15.6	1.7	0.0	82.4	9.1	8.2	0.3	0.0
Malaise	85.5	7.5	5.8	1.2	0.0	88.8	6.4	4.5	0.2	0.1	83.3	10.0	5.6	1.1	0.0	91.6	4.0	4.2	0.2	0.0
Muscle pain	71.7	19.7	8.7	0.0	0.0	78.6	16.2	5.0	0.1	0.1	80.0	14.4	5.6	0.0	0.0	86.7	10.3	2.6	0.4	0.0
Joint pain	92.5	6.4	1.2	0.0	0.0	93.6	4.4	1.9	0.0	0.1	98.3	1.7	0.0	0.0	0.0	94.5	3.0	2.3	0.2	0.0
Temperature	95.7	2.5	1.2	0.6	0.0	98.0	0.4	1.1	0.4	0.1	98.3	0.6	0.0	1.2	0.0	98.5	1.0	0.5	0.0	0.0

Abbreviation: AE=adverse event.

Table S7. Reactogenicity for Participants in the Influenza Vaccination Sub-Study and Reactogenicity Cohort After Dose 1, Participants 18 to <65 Years Old

	NVX-CoV2373 + Influenza Vaccine (n=190)						NVX-CoV2373 Alone (n=931)						Placebo + Influenza Vaccine (n=186)						Placebo Alone (n=920)					
	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4
A) Local AEs																								
Any local AE	72.7	27.3	53.4	17.4	1.9	0.0	63.0	37.0	44.0	17.7	1.2	0.0	39.1	60.9	26.0	13.0	0.0	0.0	20.5	79.5	16.8	3.5	0.2	0.0
Pain	41.6	58.4	36.6	4.3	0.6	0.0	33.3	66.7	32.1	1.1	0.0	0.0	15.4	84.6	14.8	0.6	0.0	0.0	10.6	89.4	10.4	0.1	0.1	0.0
Tenderness	67.1	32.9	49.1	16.1	1.9	0.0	57.7	42.3	39.6	16.9	1.2	0.0	37.3	62.7	24.3	13.0	0.0	0.0	16.6	83.4	13.4	3.1	0.1	0.0
Erythema	1.2	98.8	1.2	0.0	0.0	0.0	2.2	97.8	1.9	0.3	0.0	0.0	1.2	98.8	1.2	0.0	0.0	0.0	0.3	99.7	0.3	0.0	0.0	0.0
Swelling	1.2	98.8	0.0	1.2	0.0	0.0	1.1	98.9	0.8	0.3	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.7	99.3	0.5	0.2	0.0	0.0
B) Systemic AEs																								
Any systemic AE	61.9	38.1	36.9	21.9	3.1	0.0	49.8	50.2	31.0	17.3	1.2	0.2	46.7	53.3	23.1	21.9	1.8	0.0	39.6	60.4	23.6	14.7	1.3	0.0
Nausea/ vomiting	5.6	94.4	5.0	0.6	0.0	0.0	5.2	94.8	4.2	0.9	0.0	0.1	6.5	93.5	5.3	1.2	0.0	0.0	6.3	93.7	4.8	1.5	0.0	0.0
Headache	25.0	75.0	17.5	6.9	0.6	0.0	26.6	73.4	21.3	4.7	0.4	0.0	21.9	78.1	16.0	5.9	0.0	0.0	24.1	75.9	18.1	5.6	0.3	0.0
Fatigue	29.4	70.6	13.8	14.4	1.3	0.0	21.9	78.1	11.6	9.7	0.4	0.1	29.0	71.0	11.8	16.0	1.2	0.0	20.0	80.0	10.0	9.8	0.2	0.0
Malaise	15.6	84.4	8.1	6.3	1.3	0.0	12.1	87.9	7.0	4.7	0.2	0.1	16.6	83.4	10.1	5.9	0.6	0.0	9.8	90.2	4.7	4.8	0.2	0.0
Muscle pain	30.0	70.0	20.6	9.4	0.0	0.0	23.7	76.3	17.7	5.7	0.1	0.1	20.7	79.3	15.4	5.3	0.0	0.0	15.0	85.0	11.5	3.0	0.5	0.0
Joint pain	8.1	91.9	6.9	1.3	0.0	0.0	6.6	93.4	4.7	1.8	0.0	0.1	1.8	98.2	1.8	0.0	0.0	0.0	5.8	94.2	3.1	2.5	0.1	0.0
Temperature	4.0	96.0	2.0	1.3	0.7	0.0	2.2	97.8	0.5	1.2	0.5	0.1	0.6	99.4	0.0	0.0	0.6	0.0	1.4	98.6	1.1	0.4	0.0	0.0

Abbreviations: AE=adverse event; Gr=grade.

Table S8. Reactogenicity for Participants in the Influenza Vaccination Sub-Study and Reactogenicity Cohort After Dose 1, Participants ≥65 Years Old

	NVX-CoV2373 + Influenza Vaccine (n=15)						NVX-CoV2373 Alone (n=228)						Placebo + Influenza Vaccine (n=13)						Placebo Alone (n=231)					
	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4
A) Local AEs																								
Any local AE	38.5	61.5	38.5	0.0	0.0	0.0	34.9	65.1	30.7	4.2	0.0	0.0	45.5	54.5	45.5	0.0	0.0	0.0	7.6	92.4	6.3	1.3	0.0	0.0
Pain	15.4	84.6	15.4	0.0	0.0	0.0	12.3	87.7	12.3	0.0	0.0	0.0	36.4	63.6	36.4	0.0	0.0	0.0	3.6	96.4	3.6	0.0	0.0	0.0
Tenderness	38.5	61.5	38.5	0.0	0.0	0.0	34.4	65.6	30.2	4.2	0.0	0.0	36.4	63.6	36.4	0.0	0.0	0.0	5.4	94.6	4.0	1.3	0.0	0.0
Erythema	0.0	100.0	0.0	0.0	0.0	0.0	1.4	98.6	1.4	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
Swelling	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
B) Systemic AEs																								
Any systemic AE	38.5	61.5	38.5	0.0	0.0	0.0	28.3	71.7	18.9	9.0	0.5	0.0	54.5	45.5	27.3	9.1	18.2	0.0	23.6	76.4	17.8	5.3	0.4	0.0
Nausea/ vomiting	0.0	100.0	0.0	0.0	0.0	0.0	5.2	94.8	4.7	0.5	0.0	0.0	9.1	90.9	9.1	0.0	0.0	0.0	0.9	99.1	0.0	0.9	0.0	0.0
Headache	23.1	76.9	23.1	0.0	0.0	0.0	15.6	84.4	14.2	0.9	0.5	0.0	18.2	81.8	9.1	9.1	0.0	0.0	11.6	88.4	11.1	0.4	0.0	0.0
Fatigue	7.7	92.3	7.7	0.0	0.0	0.0	9.0	91.0	4.7	4.2	0.0	0.0	27.3	72.7	9.1	9.1	9.1	0.0	8.0	92.0	5.3	2.2	0.4	0.0
Malaise	0.0	100.0	0.0	0.0	0.0	0.0	7.5	92.5	3.8	3.8	0.0	0.0	18.2	81.8	9.1	0.0	9.1	0.0	3.1	96.9	1.3	1.8	0.0	0.0
Muscle pain	7.7	92.3	7.7	0.0	0.0	0.0	11.8	88.2	9.9	1.9	0.0	0.0	9.1	90.9	0.0	9.1	0.0	0.0	6.7	93.3	5.8	0.9	0.0	0.0
Joint pain	0.0	100.0	0.0	0.0	0.0	0.0	5.7	94.3	3.3	2.4	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0	4.4	95.6	2.7	1.3	0.4	0.0
Temperature	8.3	91.7	8.3	0.0	0.0	0.0	1.0	99.0	0.0	1.0	0.0	0.0	20.0	80.0	10.0	0.0	10.0	0.0	1.8	98.2	0.9	0.9	0.0	0.0

Abbreviations: AE=adverse event; Gr=grade.

Table S9. Reactogenicity for Participants in the Influenza Vaccination Sub-Study After Dose 2 (No Concomitant Influenza Vaccine), All Ages

	NVX-CoV2373 Alone (n=203)						Placebo Alone (n=196)					
	Any Grade	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
A) Local												
Any local AE	85.5	15.0	36.1	42.9	6.0	0.0	21.6	78.4	20.0	1.6	0.0	0.0
Pain	57.1	42.9	44.4	12.0	0.8	0.0	11.2	88.8	10.4	0.8	0.0	
Tenderness	78.9	21.1	36.1	38.3	4.5	0.0	20.0	80.0	18.4	1.6	0.0	0.0
Erythema	11.3	88.7	3.8	4.5	3.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
Swelling	10.5	89.5	3.8	4.5	2.3	0.0	0.0	100.0	0.0	0.0	0.0	0.0
B) Systemic												
Any systemic AE	69.7	30.3	25.0	37.1	6.8	0.8	37.9	62.1	14.5	20.2	3.2	0.0
Nausea/vomiting	10.6	89.4	8.3	2.3	0.0	0.0	4.8	95.2	3.2	1.6	0.0	0.0
Headache	46.2	53.8	25.8	19.7	0.8	0.0	18.5	81.5	12.1	5.6	0.8	0.0
Fatigue	46.2	53.8	11.4	32.6	2.3	0.0	25.8	74.2	6.5	16.9	2.4	0.0
Malaise	42.4	57.6	15.2	25.8	1.5	0.0	16.1	83.9	4.0	8.9	3.2	0.0
Muscle pain	47.0	53.0	25.0	19.7	2.3	0.0	11.3	88.7	5.6	5.6	0.0	0.0
Joint pain	17.4	82.6	6.1	10.6	0.8	0.0	4.0	96.0	2.4	1.6	0.0	0.0
Temperature	8.3	91.7	6.6	0.0	0.8	0.8	0.0	100.0	0.0	0.0	0.0	0.0

Abbreviation: AE=adverse event.

Table S10. Influenza Haemagglutination Inhibition Assay: GMT, GMFR, and SCR Values by Influenza Strain for QIVc

	NVX-CoV2373 + QIVc (n=201)				Placebo + QIVc (n=201)			
	Day 0		Day 21		Day 0		Day 21	
		(95% CI)		(95% CI)		(95% CI)	GMT	(95% CI)
GMT								
A/H1N1	11.0	(8.9, 13.5)	186.5	(151.7, 229.3)	12.9	(10.5, 15.9)	170.6	(140.9, 206.6)
A/H3N2	34.0	(27.6, 41.8)	243.7	(213.5, 278.1)	37.3	(30.0, 46.4)	226.2	(195.4, 262.7)
B/Victoria	3.3	(2.9, 3.7)	9.7	(7.9, 11.9)	3.3	(2.9, 3.7)	9.4	(7.8, 11.3)
B/Yamagata	8.1	(6.7, 9.8)	38.8	(32.2, 46.9)	8.8	(7.3, 10.6)	39.0	(33.2, 45.8)
GMFR								
A/H1N1			17.0	(13.4, 21.5)			13.2	(10.5, 16.5)
A/H3N2			7.2	(5.8, 8.8)			6.1	(5.0, 7.4)
B/Victoria			2.9	(2.5, 3.5)			2.9	(2.4, 3.4)
B/Yamagata			4.8	(4.0, 5.7)			4.4	(3.8, 5.2)
SCR								
A/H1N1			76.1	(69.6, 81.9)			71.5	(64.6, 77.8)
A/H3N2			68.0	(61.0, 74.5)			62.2	(54.9. 69.0)
B/Victoria			14.2	(9.7, 19.9)			9.8	(6.0, 14.9)
B/Yamagata			32.5	(26.0, 39.5)			32.1	(25.6, 39.2)

Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT= geometric mean titre; QIVc=influenza vaccine quadrivalent, cellular; SCR=seroconversion rate.

Table S11. Influenza Haemagglutination Inhibition Assay: GMT, GMFR, and SCR Values by Influenza Strain for aTIV

	NVX-CoV2373 + aTIV (n=16)				Placebo + aTIV (n=13)			
	Day 0		Day 21		Day 0		Day 21	
		(95% CI)	GMT	(95% CI)	GMT	(95% CI)	GMT	(95% CI)
GMT								
A/H1N1	23.6	(9.9, 56.6)	159.0	(91.6, 275.9)	5.8	(2.9, 11.8)	112.8	(39.2, 325.1)
A/H3N2	41.5	(16.0, 107.6)	173.2	(101.1, 297.1)	28.2	(12.0, 66.3)	199.0	(102.1, 387.8)
B/Victoria	4.2	(2.4, 7.3)	11.8	(5.9, 23.8)	2.9	(1.7, 5.1)	21.9	(8.6, 56.1)
B/Yamagata*	8.4	(3.9, 18.0)	14.7	(7.2, 29.9)	7.5	(4.1, 13.8)	18.1	(8.4, 39.4)
GMFR								
A/H1N1			6.7	(3.5, 13.1)			19.3	(8.0, 46.9)
A/H3N2			4.2	(1.8, 9.9)			7.1	(2.7, 18.7)
B/Victoria			2.8	(1.5, 5.2)			7.5	(2.8, 20.2)
B/Yamagata*			1.8	(1.1, 2.8)			2.4	(1.4, 4.0)
SCR								
A/H1N1			75.0	(47.6, 92.7)			72.7	(39.0, 94.0)
A/H3N2			50.0	(24.7, 75.3)			54.5	(23.4, 83.3)
B/Victoria			12.5	(1.6, 38.3)			27.3	(6.0, 61.0)
B/Yamagata*			0.0	(0.0, 20.6)			9.1	(0.2, 41.3)

*Strain not contained in the vaccine.
Abbreviations: aTIV=adjuvanted trivalent influenza vaccine; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titre; SCR=seroconversion rate.

Table S12a. Anti-S IgG on Day 0 and Day 35 in the Influenza Vaccination Sub-Study (a) and Immunogenicity Cohort (b) by Serostatus, in the ITT Population, All Ages

		NVX-CoV2373 + Influenza Vaccine					Placebo + Influenza Vaccine			
		Day 0		Day 35			Day 0		Day 35	
			(95% CI)		(95% CI)			(95% CI)		(95% CI)
GMEU										
IIV + NVX-CoV2372 or placebo, all ages	n=214	146.5	(128.1, 167.7)	32724.4	(27862.1, 38435.2)	n=214	129.8	(116.8, 144.2)	142.7	(125.3, 162.6)
IIV+ NVX-CoV2373 or placebo, all ages, seronegative	n=198	117.9	(109.1,127.5)	30439.1	(25713.4, 36033.5)	n=196	110.9	(104.9, 117.3)	121.9	(110.0, 135.2)
IIV NVX-CoV2373 or placebo, all ages, seropositive	n=19	1504.4	(686.4, 3297.1)	71115.6	(46813.0, 108032.8)	n=13	1503.2	(775.8, 2912.4)	1624.4	(1083.3, 2435.7)
GMFR										
IIV + NVX-CoV2372 or placebo, all ages	n=214			223.2	(183.9, 271.2)	n=214			1.1	(1.0, 1.2)
IIV + NVX-CoV2373 or placebo, all ages, seronegative	n=198			258.1	(213.1, 312.5)	n=196			1.1	(1.0, 1.2)
IIV+ NVX-CoV2373 or placebo, all ages, seropositive	n=19			47.3	(23.2, 96.0)	n=13			1.1	(0.7, 1.8)
SCR										
IIV + NVX-CoV2372 or placebo, all ages	n=214			97.6	(94.6, 99.2)	n=214			3.0	(1.1, 6.3)
IIV + NVX-CoV2373 or placebo, all ages, seronegative	n=198			97.9	(94.8, 99.4)	n=196			2.6	(0.9, 6.1)
IIV+ NVX-CoV2373 or placebo, all ages, seropositive	n=19			94.4	(72.7, 99.9)	n=13			8.3	(0.2, 38.5)

Abbreviations: GMEU=geometric mean ELISA unit; GMFR=geometric mean fold rise; ELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; IIV=inactivated influenza vaccine (both aTIV and QIVc); ITT=intention-to-treat; S=spike; SCR=seroconversion rate.

Table S12b.

		NVX-CoV2373 Alone					Placebo Alone			
		Day 0		Day 35			Day 0		Day 35	
			(95% CI)		(95% CI)			(95% CI)		(95% CI)
GMEU										
NVX-CoV2373 or placebo alone, all ages	n=502	129.1	(119.9, 138.9)	46679.3	(42206.2, 51626.4)	n=497	124.7	(116.5, 133.5)	129.5	(119.5, 140.4)
NVX-CoV2373 or placebo alone, seronegative	n=475	112.2	(107.6, 117.0)	44229.9	(39920.0, 49005.3)	n=475	110.8	(106.6, 115.1)	115.4	(108.6, 122.6)
NVX-CoV2373 or placebo alone, seropositive	n=24	1698.8	(994.8, 2900.9)	125489.8	(91186.3, 172697.9)	n=20	1771.7	(915.0, 3430.2)	1756.9	(984.6, 3135.1)
GMFR										
NVX-CoV2373 or placebo alone, all ages	n=502			361.6	(324.6, 402.9)	n=497			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, seronegative	n=475			394.3	(354.8, 438.3)	n=475			1.0	(1.0, 1.1)
NVX-CoV2373 or placebo alone, seropositive	n=24			73.9	(46.8, 116.5)	n=20			1.0	(0.8, 1.2)
SCR										
NVX-CoV2373 or placebo alone, all ages	n=502			98.9	(97.4, 99.6)	n=497			1.1	(0.4, 2.6)
NVX-CoV2373 or placebo alone, seronegative	n=475			99.1	(97.6, 99.7)	n=475			1.2	(0.4, 2.7)
NVX-CoV2373 or placebo alone, seropositive	n=24			95.7	(78.1, 99.9)	n=20			0.0	(0.0, 17.6)

Abbreviations: GMEU=geometric mean ELISA unit; GMFR=geometric mean fold rise; ELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; ITT=intention-to-treat; ; S=spike; SCR=seroconversion rate.

Table S13. Vaccine Efficacy Against PCR-Confirmed Symptomatic COVID-19 in the Per-Protocol and Intention-to-Treat Sub-Study Groups and Per-Protocol Main Study Participants

Parameter	Analysis	
	NVX-CoV2373	Placebo
Participants, 18 to 84 years, per-protocol influenza sub-study, n	191	195
Participants with first occurrence of event, n	2	8
Vaccine efficacy (%)*	74.8	
95% CI	-19.7, 94.7	
Participants, 18 to <65 years, per-protocol influenza sub-study, n	178	182
Participants with first occurrence of event, n	1	8
Vaccine efficacy (%)*	87.5	
95% CI	-0.2, 98.4	
Participants, 18 to 84 years, intention-to-treat influenza sub-study, n	217	214
Participants with first occurrence of event, n	2	10
Vaccine efficacy (%)	80.6%	
95% CI	13.3, 95.7	
Participants, 18 to <65 years, main study per-protocol population, n	5067	5062
Participants with first occurrence of event, n	9	87
Vaccine efficacy (%)	89.8	
95% CI	79.7, 95.5	
Participants, 18 to 84 years, main study per-protocol population, n	7020	7019
Participants with first occurrence of event (due to Alpha variant), n	8	58
Vaccine efficacy for Alpha variant (%)	86.3	
95% CI	71.3, 93.5	

*All strains were characterized as Alpha (B.1.1.7) variants. Vaccine efficacy as assessed in those 18 to <65 years of age in the influenza co-administration sub-study within the per-protocol population. Vaccine efficacy was also calculated for the same population within the main study and in all per-protocol participants infected with the B.1.1.7 variant.
Abbreviations: CI=confidence interval; PCR=polymerase chain reaction.