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Supplementary appendix

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Supplementary Materials to:

Safety and immunogenicity of a SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in healthy adults: interim findings from a phase 2, randomised, dose-finding, multi-centre study

Sridhar S *et al.*

Contents

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Methods 1. Participant inclusion/exclusion criteria.

Adults, aged 18 years and older, were eligible. Exclusion criteria included women who were pregnant or lactating, or, for those of childbearing potential, not using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination; known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances; dementia or any other cognitive condition at a stage that could interfere with following the trial procedures based on Investigator or designee's judgment; self-reported thrombocytopenia, contraindicating intramuscular (IM) vaccination based on Investigator or designee's judgment; bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator or designee's judgment; unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation or that could interfere with the trial procedures; receipt of solid-organ or bone marrow transplants in the past 180 days; receipt of anti-cancer chemotherapy in the last 90 days; moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥38.0°C [≥100.4°F]). A prospective participant should not be included in the trial until the condition has resolved or the febrile event has subsided; receipt of any vaccine in the 30 days preceding or on the day of the first trial vaccination or planned receipt of any vaccine in the 30 days following the second trial vaccination except for influenza vaccination, which may be received at any time in relation to trial intervention; prior administration of a coronavirus vaccine (SARS-CoV-2, SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV]); participation at the time of trial enrollment (or in the 30 days preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.

To allow evaluation of vaccine performance in high-risk groups, individuals with pre-existing medical conditions (including controlled HIV infection, Hepatitis B and Hepatitis C), those who were immunocompromised (except those who had received solid-organ or bone marrow transplant in the past 180 days or chemotherapy in the past 90 days), and those with a potentially increased risk for severe COVID-19 were eligible for participation in the study.

Conditions considered to be associated with an increased risk of severe COVID-19 (available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidencetable.html) include:

• cancer
• chronic kidney disease
• chronic obstructive pulmonary disease (COPD)
• immunocompromised state from solid organ transplant
• immunocompromised state from other causes (blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors)
• obesity (body mass index of 30 or higher)
• heart conditions such as heart failure
• coronary artery disease or cardiomyopathies
• sickle cell disease
• thalassemia
• type 1 or type 2 diabetes mellitus
• moderate-to-severe asthma
• cerebrovascular disease
• cystic fibrosis
• hypertension/high blood pressure
• neurologic conditions
• hepatic disease
• pulmonary fibrosis
• smoking

Methods 2. Determination of SARS-CoV-2 naïve or non-naïve status for immunogenicity assessment

Status	S-ELECSYS	N-ELECSYS	NAAT	Test result
Naïve D1+D22	Neg at D1	Neg at D1 AND D22	Neg at D1 AND D22	All negative at D1 and D22
Naïve D1	Neg at D1	Neg at D1	Neg at D1	All negative at D1
Non-Naïve D1/D22	Pos at D1	Pos at D1 OR D22	Pos at D1 OR D22	Any positive result at D1or D22
Non-Naïve D1	Pos at D1	Pos at D1	Pos at D1	Any positive result at D1

SARS-CoV-2 naïve or non-naïve status was determined for all participants on serological samples using ELECSYS electrochemiluminescence immunoassays for anti-SARS-CoV-2 anti-S (S-ELECSYS; Elecsys Anti-SARS-CoV-2 S, Roche, Indianapolis, IN, USA) on D1 only and anti-nucleocapsid (N) (N-ELECSYS; Elecsys Anti-SARS-CoV-2 N, Roche) on D1 and D22, and on nasopharyngeal swabs using nucleic acid amplification tests (NAAT; Abbott RealTime SARS-CoV-2 assay, Abbott Molecular Inc., Des Plaines, IL, USA) on D1 and D22, following the manufacturer's instructions. SARS-CoV-2 naïve participants at D1 and D22 (naïve D1+D22) were those who tested negative for S-ELECSYS at D1 and negative for both N-ELECSYS and NAAT at both timepoints; the non-naïve subset of participants tested positive for at least one of the three tests at D1 and/or D22 (non-naïve D1/D22)

Methods 3. Measurement of SARS-CoV-2 neutralising antibody titres using a pseudovirus neutralisation assay

SARS-CoV-2 neutralising antibody (NAb) titres against the D614G variant and the Beta (B.1.351) variant were measured using a pseudovirus neutralisation (PsVN) assay performed at Monogram Biosciences LabCorp (South San Francisco, CA, USA). Pseudoviruses were prepared by co-transfecting HEK293 producer cells with an HIV-1 genomic vector and a SARS CoV-2 envelope expression vector. NAb activity was measured by assessing the inhibition of luciferase activity in HEK293 target cells expressing the ACE2 receptor following pre-incubation of the pseudovirions with serial dilutions of the serum specimen. The expression of luciferase activity in target cells is inhibited in the presence of anti- SARS-CoV-2 NAb. Data were displayed by plotting the percent inhibition of luciferase activity versus the log10 reciprocal of the serum/plasma dilution and NAb titers were reported as the reciprocal of the serum dilution conferring 50% inhibition (ID50) of pseudovirus infection. To ensure that the measured NAb activity was SARS-CoV-2 specific, each test specimen was also assessed using a non-specific pseudovirus (specificity control) that expresses a non-reactive envelope protein of one or more unrelated viruses.

Table S1. Participant demographic characteristics, by age group (safety analysis set)

	18–59 years			≥ 60 years		
	Low-dose (5 µg) n=121	**Medium-dose (10 µg) n=120**	**High-dose (15 µg) n=119**	**Low-dose (5 µg) n=119**	**Medium-dose (10 µg) n=120**	**High-dose (15 µg) n=122**
Sex						
Male	56 (46·3)	65 (54·2)	68 (57·1)	61 (51·3)	61 (50·8)	51 (41·8)
Female	65 (53·7)	55 (45·8)	51 (42·9)	58 (48·7)	59 (49·2)	71 (58·2)
Age, years						
Mean (SD)	41·8 (11·4)	41·8 (11·7)	40·3 (12·2)	66·0 (6·7)	65·1 (5·6)	65·6 (6·1)
Range	20·0; 59·0	18·0; 59·0	19·0; 59·0	60·0; 92·0	60·0; 88·0	60·0; 95·0
BMI, kg/m^2						
Mean (SD)	27·6 (5·8)	28·2 (6·2)	28·4 (6·6)	29·2 (5·4)	29·5 (5·6)	29.0 (5·4)
Country						
United States	112 (92·6)	113 (94·2)	109 (91·6)	80 (67·2)	80 (66·7)	87 (71·3)
Honduras	9 (7·4)	7 (5·8)	10 (8·4)	39 (32·8)	40 (33·3)	35 (28·7)
Race						
White	85 (70·2)	82 (68·3)	80 (67·2)	71 (59·7)	68 (56·7)	75 (61·5)
American Indian or Alaska Native	3 (2·5)	7 (5·8)	8 (6·7)	19 (16·0)	17 (14·2)	12 (9·8)
Black or African American	10 (8·3)	17 (14·2)	10 (8·4)	3 (2·5)	6 (5·0)	10 (8·2)
Asian	10 (8·3)	8 (6·7)	8 (6·7)	3 (2·5)	2 (1·7)	2 (1·6)
Native Hawaiian or other Pacific Islander	1 (0·8)	1 (0·8)	2 (1·7)	1 (0·8)	0	0
Multiple	2 (1·7)	0	4 (3·4)	3 (2·5)	2 (1·7)	0
Not reported	3 (2·5)	3 (2·5)	2 (1·7)	1 (0·8)	1 (0·8)	0
Unknown	7 (5·8)	2 (1·7)	5 (4·2)	18 (15·1)	24 (20·0)	23 (18·9)
Ethnicity						
Hispanic or Latino	25 (20·7)	25 (20·8)	28 (23·5)	43 (36·1)	43 (35·8)	39 (32·0)

Not Hispanic or Latino	95 (78·5)	95 (79·2)	91 (76·5)	75 (63·0)	77 (64·2)	82 (67·2)
Not reported or unknown	1 (0·8)	0	0	1 (0·8)	0	1 (0·8)
Baseline SARS-CoV-2 rapid serodiagnostic test						
Negative	109 (90·1)	108 (90·0)	108 (90·8)	110 (92·4)	110 (91·7)	111 (91·0)
Positive	12 (9·9)	12 (10·0)	11 (9·2)	9 (7·6)	10 (8·3)	11 (9·0)

Table S2. High-risk medical conditions of study participants (full analysis set)

	Low-dose (N=240) n (%)	Medium-dose (N=239) n (%)	High-dose (N=242) n (%)
At least one high-risk medical condition*	151 (62·9)	143 (59·8)	143 (59·1)
Obesity†	80 (33·3)	92 (38·5)	87 (36·0)
Hypertension	84 (35·0)	80 (33·5)	75 (31·0)
Type 2 diabetes	32 (13·3)	26 (10·9)	28 (11·6)
Smoking	21 (8·8)	15 (6·3)	19 (7·9)
Cancer	15 (6·3)	15 (6·3)	12 (5·0)
Moderate-to-severe asthma	8 (3·3)	8 (3·3)	13 (5·4)
Heart Conditions	9 (3·8)	5 (2·1)	7 (2·9)
Coronary artery disease or cardiomyopathies	8 (3·3)	4 (1·7)	6 (2·5)
Immunocompromised state from causes other than solid organ transplant	4 (1·7)	5 (2·1)	6 (2·5)
Chronic obstructive pulmonary disease	6 (2·5)	2 (0·8)	4 (1·7)
Hepatic disease	4 (1·7)	5 (2·1)	2 (0·8)
Cerebrovascular disease	2 (0·8)	5 (2·1)	2 (0·8)
Neurologic conditions	1 (0·4)	1 (0·4)	4 (1·7)
Chronic kidney disease	0	0	4 (1·7)
Cystic fibrosis	2 (0·8)	1 (0·4)	0
Immunocompromised state from solid organ transplant	1 (0·4)	0	1 (0·4)
Type 1 diabetes	0	1 (0·4)	1 (0·4)
Pulmonary fibrosis	1 (0·4)	0	0
Thalassemia	1 (0·4)	0	0
Sickle cell disease	0	0	0

n: number of subjects fulfilling the item listed

*High-risk conditions are those considered to be associated with an increased risk of severe COVID-19, as detailed at https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html; †Obesity: body mass index of 30 kg/m^2 or higher

Table S3: Safety overview after any injection by age stratum (safety analysis set)

	Low-dose (N=240)			Medium-dose (N=240)			High-dose (N=241)		
	n/M	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
All ages									
Immediate unsolicited AE	2/240	0.8	(0·1; 3·0)	1/240	0·4	(0; 2·3)	1/241	0·4	(0; 2·3)
Immediate unsolicited AR	1/240	0·4	(0; 2·3)	1/240	0·4	(0; 2·3)	0/241	0	(0; 1·5)
Up to 7 days after any vaccination									
Any solicited reaction	217/238	91·2	(86·8; 94·5)	213/237	89·9	(85·3; 93·4)	218/239	91·2	(86·9; 94·5)
Any grade 3 solicited reaction	52/238	21·8	(16·8 ; 27·6)	49/237	20·7	(15·7 ; 26·4)	45/239	18·8	(14·1 ; 24·4)
Solicited injection site reaction	201/238	84·5	(79·2; 88·8)	196/237	82·7	(77·3; 87·3)	200/239	83·7	(78·4; 88·1)
Grade 3 injection site reaction	20/238	8·4	(5·2 ; 12·7)	23/237	9·7	(6·3 ; 14·2)	17/239	7·1	(4·2 ; 11·1)
Solicited systemic reaction	191/238	80·3	(74·6; 85·1)	192/237	81·0	(75·4; 85·8)	185/239	77·4	(71·6; 82·5)
Grade 3 systemic reaction	45/238	18·9	(14·1 ; 24·5)	41/237	17·3	(12·7 ; 22·7)	41/239	17·2	(12·6 ; 22·5)
Up to 21 days after any vaccination									
Any unsolicited AE	87/240	36·3	(30·2; 42·7)	79/240	32·9	(27·0; 39·3)	89/241	36·9	(30·8; 43·4)
Any unsolicited non-serious AE	87/240	36·3	(30·2 ; 42·7)	79/240	32·9	(27·0; 39·3)	87/241	36·1	(30·0; 42·5)
Any grade 3 unsolicited AE	5/240	2·1	(0·7 ; 4·8)	6/240	2·5	(0·9; 5·4)	19/241	7·9	(4·8; 12·0)
Any unsolicited AR	47/240	19·6	(14·8; 25·2)	43/240	17·9	(13·3; 23·4)	35/241	14·5	(10·3; 19·6)
Any unsolicited non-serious AR	47/240	19·6	(14·8 ; 25·2)	43/240	17·9	(13·3; 23·4)	35/241	14·5	(10·3; 19·6)
Any grade 3 unsolicited AR	1/240	0·4	(0 ; 2·3)	3/240	1·3	(0·3; 3·6)	5/241	2·1	(0·7 ; 4·8)
Unsolicited non-serious injection site AR	13/240	5·4	(2·9; 9·1)	18/240	7·5	(4·5; 11·6)	9/241	3·7	(1·7; 7·0)
Unsolicited non-serious systemic AE	80/240	33·3	(27·4; 39·7)	67/240	27·9	(22·3; 34·1)	83/241	34·4	(28·5; 40·8)
Unsolicited non-serious systemic AR	38/240	15·8	(11·5; 21·1)	29/240	12·1	(8·2; 16·9)	27/241	11·2	(7·5; 15·9)
Up to D43*									
AE leading to study discontinuation	0/240	0	(0; 1·5)	0/240	0	(0; 1·5)	0/241	0	(0; 1·5)
SAE	0/240	0	(0; 1·5)	2/240	0·8	(0·1; 3·0)	2/241	0·8	(0·1; 3·0)
Grade 3 SAE	0/240	0	(0; 1·5)	1/240	0·4	(0; 2·3)	1/241	0·4	(0; 2·3)
Related SAE	0/240	0	(0; 1·5)	0/240	0	(0; 1·5)	0/241	0	(0; 1·5)
Death	0/240	0	(0; 1·5)	0/240	0	(0; 1·5)	0/241	0	(0; 1·5)

AESI	0/240	0	(0; 1·5)	0/240	0	(0; 1·5)	0/241	0	(0; 1·5)
MAAE	20/240	8·3	(5·2; 12·6)	11/240	4·6	(2·3; 8·1)	31/241	12·9	(8·9; 17·8)
18-59 years									
Immediate unsolicited AE	2/121	1·7	(0·2 ; 5·8)	1/120	0·8	(0 ; 4·6)	0/119	0	(0 ; 3·1)
Immediate unsolicited AR	1/121	0·8	(0 ; 4·5)	1/120	0·8	(0 ; 4·6)	0/119	0	(0 ; 3·1)
Up to 7 days after any vaccination									
Any solicited reaction	111/119	93·3	(87·2; 97·1)	110/119	92·4	(86·1; 96·5)	112/117	95·7	(90·3; 98·6)
Any grade 3 solicited reaction	35/119	29·4	(21·4; 38·5)	34/119	28·6	(20·7; 37·6)	28/117	23·9	(16·5; 32·7)
Solicited injection site reaction	107/119	89·9	(83·0; 94·7)	104/119	87·4	(80·1; 92·8)	109/117	93·2	(87·0; 97·0)
Grade 3 injection site reaction	16/119	13·4	(7·9; 20·9)	16/119	13·4	(7·9; 20·9)	11/117	9·4	(4·8; 16·2)
Solicited systemic reaction	105/119	88·2	(81·0; 93·4)	103/119	86·6	(79·1; 92·1)	94/117	80·3	(72·0; 87·1)
Grade 3 systemic reaction	31/119	26·1	(18·4; 34·9)	30/119	25·2	(17·7; 34·0)	24/117	20·5	(13·6; 29·0)
Up to 21 days after any vaccination									
Any unsolicited AE	50/121	41·3	(32·4; 50·6)	44/120	36·7	(28·1; 45·9)	44/119	37·0	(28·3; 46·3)
Any unsolicited non-serious AE	50/121	41·3	(32·4; 50·6)	44/120	36·7	(28·1; 45·9)	43/119	36·1	(27·5; 45·4)
Any grade 3 unsolicited AE	1/121	0·8	(0; 4·5)	3/120	2·5	(0·5; 7·1)	9/119	7·6	(3·5; 13·9)
Any unsolicited AR	30/121	24·8	(17·4; 33·5)	27/120	22·5	(15·4; 31·0)	17/119	14·3	(8·5; 21·9)
Any unsolicited non-serious AR	30/121	24·8	(17·4; 33·5)	27/120	22·5	(15·4; 31·0)	17/119	14·3	(8·5; 21·9)
Any grade 3 unsolicited AR	0/121	0	(0; 3·0)	2/120	1·7	(0·2; 5·9)	1/119	0·8	(0; 4·6)
Unsolicited non-serious injection site AR	7/121	5·8	(2·4; 11·6)	9/120	7·5	(3·5; 13·8)	5/119	4·2	(1·4; 9·5)
Unsolicited non-serious systemic AE	46/121	38·0	(29·3; 47·3)	39/120	32·5	(24·2; 41·7)	42/119	35·3	(26·8; 44·6)
Unsolicited non-serious systemic AR	25/121	20·7	(13·8; 29·0)	21/120	17·5	(11·2; 25·5)	12/119	10·1	(5·3; 17·8)
Up to D43*									
AE leading to study discontinuation	0/121	0	(0 ; 3·0)	0/120	0	(0 ; 3·0)	0/119	0	(0 ; 3·1)
SAE	0/121	0	(0 ; 3·0)	1/120	0·8	(0 ; 4·6)	1/119	0·8	(0 ; 4·6)
Grade 3 SAE	0/121	0	(0 ; 3·0)	0/120	0	(0 ; 3·0)	0/119	0	(0 ; 3·1)
Related SAE	0/121	0	(0 ; 3·0)	0/120	0	(0 ; 3·0)	0/119	0	(0 ; 3·1)
Death	0/121	0	(0 ; 3·0)	0/120	0	(0 ; 3·0)	0/119	0	(0 ; 3·1)
AESI	0/121	0	(0 ; 3·0)	0/120	0	(0 ; 3·0)	0/119	0	(0 ; 3·1)
MAAE	9/121	7·4	(3·5 ; 13·7)	5/120	4·2	(1·4; 9·5)	15/119	12·6	(7·2; 19·9)
≥60 years									

Immediate unsolicited AE	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	1/122	0·8	(0 ; 4·5)
Immediate unsolicited AR	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	0/122	0	(0 ; 3·0)
Up to 7 days after any vaccination									
Any solicited reaction	106/119	89·1	(82·0 ; 94·1)	103/118	87·3	(79·9 ; 92·7)	106/122	86·9	(79·6; 92·3)
Any grade 3 solicited reaction	17/119	14·3	(8·5 ; 21·9)	15/118	12·7	(7·3 ; 20·1)	17/122	13·9	(8·3; 21·4)
Solicited injection site reaction	94/119	79·0	(70·6 ; 85·9)	92/118	78·0	(69·4 ; 85·1)	91/122	74·6	(65·9; 82·0)
Grade 3 injection site reaction	4/119	3·4	(0·9 ; 8·4)	7/118	5·9	(2·4 ; 11·8)	6/122	4·9	(1·8; 10·4)
Solicited systemic reaction	86/119	72·3	(63·3 ; 80·1)	89/118	75·4	(66·6 ; 82·9)	91/122	74·6	(65·9; 82·0)
Grade 3 systemic reaction	14/119	11·8	(6·6 ; 19·0)	11/118	9·3	(4·7 ; 16·1)	17/122	13·9	(8·3; 21·4)
Up to 21 days after any vaccination									
Any unsolicited AE	37/119	31·1	(22·9 ; 40·2)	35/120	29·2	(21·2; 38·2)	45/122	36·9	(28·3; 46·1)
Any unsolicited non-serious AE	37/119	31·1	(22·9 ; 40·2)	35/120	29·2	(21·2; 38·2)	44/122	36·1	(27·6; 45·3)
Any grade 3 unsolicited AE	4/119	3·4	(0·9 ; 8·4)	3/120	2·5	(0·5; 7·1)	10/122	8·2	(4·0; 14·6)
Any unsolicited AR	17/119	14·3	(8·5 ; 21·9)	16/120	13·3	(7·8; 20·7)	18/122	14·8	(9·0 ; 22·3)
Any unsolicited non-serious AR	17/119	14·3	(8·5 ; 21·9)	16/120	13·3	(7·8; 20·7)	18/122	14·8	(9·0 ; 22·3)
Any grade 3 unsolicited AR	1/119	0·8	(0 ; 4·6)	1/120	0·8	(0; 4·0)	4/122	3·3	(0·9 ; 8·2)
Unsolicited injection site AR	6/119	5·0	(1·9 ; 10·7)	9/120	7·5	(3·5; 13·8)	4/122	3·3	(0·9 ; 8·2)
Unsolicited systemic AE	34/119	28·6	(20·7 ; 37·6)	28/120	23·3	(16·1; 312·9)	41/122	33·6	(25·3; 42·7)
Unsolicited systemic AR	13/119	10·9	(5·9 ; 18·0)	8/120	6·7	(2·9; 12·7)	15/122	12·3	(7·0 ; 19·5)
Up to D43*									
AE leading to study discontinuation	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	0/122	0	(0 ; 3·0)
SAE	0/119	0	(0 ; 3·1)	1/120	0·8	(0 ; 4·6)	1/122	0·8	(0 ; 4·5)
Grade 3 SAE	0/119	0	(0 ; 3·1)	1/120	0·8	(0 ; 4·6)	1/122	0·8	(0 ; 4·5)
Related SAE	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	0/122	0	(0 ; 3·0)
Death	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	0/122	0	(0 ; 3·0)
AESI	0/119	0	(0 ; 3·1)	0/120	0	(0 ; 3·0)	0/122	0	(0 ; 3·0)
MAAE	11/119	9·2	(4·7 ; 15·9)	6/120	5·0	(1·9 ; 10·6)	16/122	13·1	(7·7; 20·45)

*Includes events up to day 43, regardless of whether they were received after the first or second injection.
AE = adverse event. AESI = adverse event of special interest. AR = adverse reaction. n = number of participants experiencing the endpoint. M = number of participants with available data for the relevant endpoint. MAAE = medically-attended adverse event. SAE = serious adverse event.

Related SAEs: reported by an investigator as related to the vaccine. SAEs for which information on the relationship was missing, were considered as related

Table S4. Most frequently reported unsolicited adverse reactions occurring up to 21 days after any vaccination (MedDRA preferred terms) (safety analysis set)

	Low-dose (N=240)		Medium-dose (N=240)		High-dose (N=241)	
	n/M	n ARs	n/M	n ARs	n/M	n ARs
Fatigue	17/240	18	8/240	10	13/241	15
Nausea	7/240	7	5/240	5	2/241	2
Pruritus	0/240	0	4/240	5	0/241	0
Diarrhoea	3/240	3	2/240	2	1/241	1
Dizziness	2/240	2	2/240	2	3/241	3
Injection site rash	1/240	1	2/240	2	1/241	1
Decreased appetite	1/240	1	2/240	2	0/241	0
Lymphadenopathy	2/240	3	1/240	1	3/241	3

n = number of participants reporting the specified event. M = number of participants with available data for the relevant endpoint. n ARs = number of adverse reactions. SafAS = safety analysis set.

Adverse reactions were recorded using MedDRA preferred terms.

Table S5: Safety overview after any injection by SARS-CoV-2 positivity at baseline (D1) (safety analysis set)

	Low-dose (N=240)			Medium-dose (N=240)			High-dose (N=241)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
SARS-CoV-2 naïve at baseline (D1)*									
Immediate unsolicited AE	2/211	0·9	(0·1 ; 3·4)	1/210	0·5	(0 ; 2·6)	1/207	0·5	(0 ; 2·7)
Immediate unsolicited AR	1/211	0·5	(0 ;2·6)	1/210	0·5	(0 ; 2·6)	0/207	0	(0 ;1·8)
Up to 7 days after any vaccination									
Any solicited reactions	191/209	91·4	(86·7; 94·8)	189/208	90·9	(86·1 ; 94·4)	189/206	91·7	(87·1; 95·1)
Solicited injection site reaction	177/209	84·7	(79·1; 89·3)	175/208	84·1	(78·4 ; 88·8)	173/206	84·0	(78·2; 88·7)
Solicited systemic reaction	171/209	81·8	(75·9; 86·8)	170/208	81·7	(75·8 ; 86·7)	161/206	78·2	(71·9; 83·6)
Up to 21 days after any vaccination									
Any unsolicited AEs	81/211	38·4	(31·8; 45·3)	69/210	32·9	(26·5 ; 39·7)	81/207	39·1	(32·4; 46·1)
Any unsolicited ARs	45/211	21·3	(16·0; 27·5)	37/210	17·6	(12·7 ; 23·5)	34/207	16·4	(11·7; 22·2)
Any unsolicited non-serious AE	81/211	38·4	(31·8; 45·3)	69/210	32·9	(26·5 ; 39·7)	79/207	38·2	(31·5; 45·2)
Any unsolicited non-serious AR	45/211	21·3	(16·0; 27·5)	37/210	17·6	(12·7 ; 23·5)	34/207	16·4	(11·7; 22·2)
Unsolicited non-serious injection site AR	12/211	5·7	(3·0; 9·7)	16/210	7·6	(4·4 ; 12·1)	9/207	4·3	(2·0; 8·1)
Unsolicited non-serious systemic AE	75/211	35·5	(29·1; 42·4)	58/210	27·6	(21·7 ; 34·2)	75/207	36·2	(29·7; 43·2)
Unsolicited non-serious systemic AR	37/211	17·5	(12·7 ; 23·4)	25/210	11·9	(7·9 ; 17·1)	26/207	12·6	(8·4 ; 17·9)
Up to D43‡									
AE leading to study discontinuation	0/211	0	(0 ; 1·7)	0/210	0	(0 ; 1·7)	0/207	0	(0 ; 1·8)
SAE	0/211	0	(0 ; 1·7)	1/210	0·5	(0 ; 2·6)	2/207	1·0	(0·1 ; 3·4)
Related SAE	0/211	0	(0 ; 1·7)	0/210	0	(0 ; 1·7)	0/207	0	(0 ; 1·8)
Death	0/211	0	(0 ; 1·7)	0/210	0	(0 ; 1·7)	0/207	0	(0 ; 1·8)
AESI	0/211	0	(0 ; 1·7)	0/210	0	(0 ; 1·7)	0/207	0	(0 ; 1·8)
MAAE	20/211	9·5	(5·9 ; 14·3)	9/210	4·3	(2·0 ; 8·0)	28/207	13·5	(9·2 ; 19·0)
SARS-CoV-2 non-naïve at baseline (D1)†									
Immediate unsolicited AE	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
Immediate unsolicited AR	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
Up to 7 days after any vaccination									

Any solicited reaction	23/26	88·5	(69·8 ; 97·6)	22/27	81·5	(61·9 ; 93·7)	27/30	90·0	(73·5 ; 97·9)
Solicited injection site reaction	21/26	80·8	(60·6 ; 93·4)	20/27	74·1	(53·7 ; 88·9)	25/30	83·3	(65·3 ; 94·4)
Solicited systemic reaction	17/26	65·4	(44·3 ; 82·8)	20/27	74·1	(53·7 ; 88·9)	22/30	73·3	(54·1 ; 87·7)
Up to 21 days after any vaccination									
Any unsolicited AE	4/26	15·4	(4·4 ; 34·9)	10/28	35·7	(18·6 ; 55·9)	8/31	25·8	(11·9 ; 44·6)
Any unsolicited AR	1/26	3·8	(0·1 ; 19·6)	6/28	21·4	(8·3 ; 41·0)	1/31	3·2	(0·1 ; 16·7)
Any unsolicited non-serious AE	4/26	15·4	(4·4 ; 34·9)	10/28	35·7	(18·6 ; 55·9)	8/31	25·8	(11·9 ; 44·6)
Any unsolicited non-serious AR	1/26	3·8	(0·1 ; 19·6)	6/28	21·4	(8·3 ; 41·0)	1/31	3·2	(0·1 ; 16·7)
Unsolicited non-serious injection site AR	1/26	3·8	(0·1 ; 19·6)	2/28	7·1	(0·9 ; 23·5)	0/31	0	(0 ; 11·2)
Unsolicited non-serious systemic AE	3/26	11·5	(2·4 ; 30·2)	9/28	32·1	(15·9 ; 52·4)	8/31	25·8	(11·9 ; 44·6)
Unsolicited non-serious systemic AR	0/26	0	(0 ; 13·2)	4/28	14·3	(4·0 ; 32·7)	1/31	3·2	(0·1 ; 16·7)
Up to D43‡									
AE leading to study discontinuation	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
SAE	0/26	0	(0 ; 13·2)	1/28	3·6	(0·1 ; 18·3)	0/31	0	(0 ; 11·2)
Related SAE	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
Death	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
AESI	0/26	0	(0 ; 13·2)	0/28	0	(0 ; 12·3)	0/31	0	(0 ; 11·2)
MAAE	0/26	0	(0 ; 13·2)	2/28	7·1	(0·9 ; 23·5)	3/31	9·7	(2·0 ; 25·8)

*SARS-CoV-2 naïve at D1 i.e. tested negative for S-ELECSYS, N-ELECSYS, and NAAT on D1; †SARS-CoV-2 non-naïve at D1, i.e. tested positive for 1 or more of the tests on D1; ‡Includes events up to day 43, regardless of whether they were received after the first or second injection.

AE = adverse event. AESI = adverse event of special interest. AR = adverse reaction. n = number of participants experiencing the endpoint. M = number of participants with available data for the relevant endpoint. MAAE = medically-attended adverse event. SAE = serious adverse event.

Related SAEs: reported by an investigator as related to the vaccine. SAEs for which information on the relationship was missing, were considered as related .

Table S6. Safety overview after any injection by presence of at least one high-risk medical condition at baseline (D1) (safety analysis set)

	Low-dose (N=240)			Medium-dose (N=240)			High-dose (N=241)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
High-risk medical condition - yes									
Immediate unsolicited AE	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	1/142	0.7	(0 ; 3.9)
Immediate unsolicited AR	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	0/142	0	(0 ; 2.6)
Up to 7 days after any vaccination									
Any solicited reactions		88.0	(81.7 ; 92.7)	125/143	87.4	(80.8 ; 92.4)	122/140	87.1	(80.4 ; 92.2)
Solicited injection site reaction	117/150	78.0	(70.5 ; 84.3)	111/143	77.6	(69.9 ; 84.2)	107/140	76.4	(68.5 ; 83.2)
Solicited systemic reaction	111/150	74.0	(66.2 ; 80.8)	110/143	76.9	(69.1 ; 83.6)	103/140	73.6	(65.5 ; 80.7)
Up to 21 days after any vaccination									
Any unsolicited AEs	43/151	28.5	(21.4 ; 36.4)	42/144	29.2	(21.9 ; 37.3)	44/142	31.0	(23.5 ; 39.3)
Any unsolicited ARs	22/151	14.6	(9.4 ; 21.2)	19/144	13.2	(8.1 ; 19.8)	15/142	10.6	(6.0 ; 16.8)
Any unsolicited non-serious AE	43/151	28.5	(21.4 ; 36.4)	42/144	29.2	(21.9 ; 37.3)	42/142	29.6	(22.2 ; 37.8)
Any unsolicited non-serious AR	22/151	14.6	(9.4 ; 21.2)	19/144	13.2	(8.1 ; 19.8)	15/142	10.6	(6.0 ; 16.8)
Unsolicited non-serious injection site AR	8/151	5.3	(2.3 ; 10.2)	5/144	3.5	(1.1 ; 7.9)	5/142	3.5	(1.2 ; 8.0)
Unsolicited non-serious systemic AE	38/151	25.2	(18.5 ; 32.9)	39/144	27.1	(20.0 ; 35.1)	39/142	27.5	(20.3 ; 35.6)
Unsolicited non-serious systemic AR	16/151	10.6	(6.2 ; 16.6)	16/144	11.1	(6.5 ; 17.4)	10/142	7.0	(3.4 ; 12.6)
Up to D43[‡]									
AE leading to study discontinuation	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	0/142	0	(0 ; 2.6)
SAE	0/151	0	(0 ; 2.4)	2/144	1.4	(0.2 ; 4.9)	2/142	1.4	(0.2 ; 5.0)
Related SAE	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	0/142	0	(0 ; 2.6)
Death	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	0/142	0	(0 ; 2.6)
AESI	0/151	0	(0 ; 2.4)	0/144	0	(0 ; 2.5)	0/142	0	(0 ; 2.6)
MAAE	14/151	9.3	(5.2 ; 15.1)	7/144	4.9	(2.0 ; 9.8)	18/142	12.7	(7.7 ; 19.3)
High-risk medical condition - no									
Immediate unsolicited AE	2/89	2.2	(0.3 ; 7.9)	1/96	1.0	(0 ; 5.7)	0/99	0	(0 ; 3.7)
Immediate unsolicited AR	1/89	1.1	(0 ; 6.1)	1/96	1.0	(0 ; 5.7)	0/99	0	(0 ; 3.7)
Up to 7 days after any vaccination									

Any solicited reactions	85/88	96.6	(90.4 ; 99.3)	88/94	93.6	(86.6 ; 97.6)	96/99	97.0	(91.4 ; 99.4)
Solicited injection site reaction	84/88	95.5	(88.8 ; 98.7)	85/94	90.4	(82.6 ; 95.5)	93/99	93.9	(87.3 ; 97.7)
Solicited systemic reaction	80/88	90.9	(82.9 ; 96.0)	82/94	87.2	(78.8 ; 93.2)	82/99	82.8	(73.9 ; 89.7)
Up to 21 days after any vaccination									
Any unsolicited AEs	44/89	49.4	(38.7 ; 60.2)	37/96	38.5	(28.8 ; 49.0)	45/99	45.5	(35.4 ; 55.8)
Any unsolicited ARs	25/89	28.1	(19.1 ; 38.6)	24/96	25.0	(16.7 ; 34.9)	20/99	20.2	(12.8 ; 29.5)
Any unsolicited non-serious AE	44/89	49.4	(38.7 ; 60.2)	37/96	38.5	(28.8 ; 49.0)	45/99	45.5	(35.4 ; 55.8)
Any unsolicited non-serious AR	25/89	28.1	(19.1 ; 38.6)	24/96	25.0	(16.7 ; 34.9)	20/99	20.2	(12.8 ; 29.5)
Unsolicited non-serious injection site AR	5/89	5.6	(1.8 ; 12.6)	13/96	13.5	(7.4 ; 22.0)	4/99	4.0	(1.1 ; 10.0)
Unsolicited non-serious systemic AE	42/89	47.2	(36.5 ; 58.1)	28/96	29.2	(20.3 ; 39.3)	44/99	44.4	(34.5 ; 54.8)
Unsolicited non-serious systemic AR	22/89	24.7	(16.2 ; 35.0)	13/96	13.5	(7.4 ; 22.0)	17/99	17.2	(10.3 ; 26.1)
Up to D43‡									
AE leading to study discontinuation	0/89	0	(0 ; 4.1)	0/96	0	(0 ; 3.8)	0/99	0	(0 ; 3.7)
SAE	0/89	0	(0 ; 4.1)	0/96	0	(0 ; 3.8)	0/99	0	(0 ; 3.7)
Related SAE	0/89	0	(0 ; 4.1)	0/96	0	(0 ; 3.8)	0/99	0	(0 ; 3.7)
Death	0/89	0	(0 ; 4.1)	0/96	0	(0 ; 3.8)	0/99	0	(0 ; 3.7)
AESI	0/89	0	(0 ; 4.1)	0/96	0	(0 ; 3.8)	0/99	0	(0 ; 3.7)
MAAE	6/89	6.7	(2.5 ; 14.1)	4/96	4.2	(1.1 ; 10.3)	13/99	13.1	(7.2 ; 21.4)

AE = adverse event. AESI = adverse event of special interest. AR = adverse reaction. n = number of participants experiencing the endpoint. M = number of participants with available data for the relevant endpoint. MAAE = medically-attended adverse event. SAE = serious adverse event.

Related SAEs: reported by an investigator as related to the vaccine. SAEs for which information on the relationship was missing, were considered as related

Table S7: Neutralising antibody responses to D614G after the first injection (day 22), by age group (PPAS naïve D1+D22)

	Low-dose (5 µg) (N=201)		Medium-dose (10 µg) (N=207)		High-dose (15 µg) (N=203)	
	n/M or M	% or GMT/GMTR (95% CI)	n/M or M	% or GMT/GMTR (95% CI)	n/M or M	% or GMT/GMTR (95% CI)
Day 22						
All ages						
≥2-fold rise	35/155	22.6 (16.3 ; 30.0)	44/161	27.3 (20.6 ; 34.9)	51/155	32.9 (25.6 ; 40.9)
≥4-fold rise	28/155	18.1 (12.4 ; 25.0)	36/161	22.4 (16.2 ; 29.6)	42/155	27.1 (20.3 ; 34.8)
GMT	155	36.6 (29.7 ; 45.1)	161	39.5 (32.2 ; 48.4)	156	45.4 (36.8 ; 56.2)
GMTR	155	1.83 (1.49 ; 2.25)	161	1.97 (1.61 ; 2.42)	155	2.28 (1.85 ; 2.83)
18–59 years						
≥2-fold rise	19/74	25.7 (16.2 ; 37.2)	29/72	40.3 (28.9 ; 52.5)	35/74	47.3 (35.6 ; 59.3)
≥4-fold rise	14/74	18.9 (10.7 ; 29.7)	24/72	33.3 (22.7 ; 45.4)	30/74	40.5 (29.3 ; 52.6)
GMT	74	36.9 (27.7 ; 49.2)	72	52.2 (37.8 ; 72.1)	75	68.7 (48.3 ; 97.8)
GMTR	74	1.85 (1.39 ; 2.46)	72	2.61 (1.89 ; 3.61)	74	3.49 (2.45 ; 4.99)
≥60 years						
≥2-fold rise	16/81	19.8 (11.7 ; 30.1)	15/89	16.9 (9.8 ; 26.3)	16/81	19.8 (11.7 ; 30.1)
≥4-fold rise	14/81	17.3 (9.8 ; 27.3)	12/89	13.5 (7.2 ; 22.4)	12/81	14.8 (7.9 ; 24.4)
GMT	81	36.3 (26.7 ; 49.2)	89	31.5 (24.4 ; 40.6)	81	31.0 (24.9 ; 38.6)
GMTR	81	1.81 (1.34 ; 2.46)	89	1.57 (1.22 ; 2.03)	81	1.55 (1.24 ; 1.93)

Table S8. D614G neutralising antibody response after two injections in naïve participants by presence of high-risk medical condition (PPAS-naïve D1+D22)

	Low-dose N=168		Medium-dose N=177		High-dose N=176	
	M	**GMT (95% CI)**	**M**	**GMT (95% CI)**	**M**	**GMT (95% CI)**
Overall	165	2189 (1744, 2746)	173	2269 (1792, 2873)	172	2895 (2294, 3654)
With a high-risk medical condition						
All ages	99	2085 (1514, 2872)	104	2023 (1480, 2764)	98	2033 (1490, 2775)
18-59 years	34	3241 (2127, 4938)	37	3830 (2234, 6566)	32	4678 (2903, 7537)
≥60 years	65	1655 (1074, 2550)	67	1422 (987, 2048)	66	1358 (939, 1962)
Without a high-risk medical condition						
All ages	66	2354 (1725, 3213)	69	2699 (1875, 3884)	74	4622 (3323, 6428)
18-59 years	48	2766 (1956, 3912)	44	4056 (2680, 6136)	49	5469 (3651, 8193)
≥60 years	18	1532 (770, 3045)	25	1317 (700, 2478)	25	3323 (1844, 5987)

M = number of participants with available data for the relevant endpoint.

Table S9. D614G binding antibody profile at D36, overall, by age and by SARS-CoV-2 naïve status (PPAS)

Endpoint	Low-dose (5 µg) (N=201)		Medium-dose (10 µg) (N=207)		High-dose (15 µg) (N=203)	
	n/M or M	% or GMC/GMCR (95% CI)	n/M or M	% or GMC/GMCR (95% CI)	n/M or M	% or GMC/GMCR (95% CI)
PPAS-naïve D1+D22						
All ages						
≥2-fold rise (responders)*	153/153	100 (97·6, 100)	164/165	99·4 (96·7, 100)	158/159	99·4 (96·5, 100)
≥4-fold rise	161/162	99·4 (96·6, 100)	170/171	99·4 (96·8, 100)	170/171	99·4 (96·8, 100)
GMCs	168	15503 (13040, 18431)	177	17188 (14560, 20289)	176	17872 (14957, 21355)
GMCR	162	1463 (1224, 1748)	171	1692 (1422, 2014)	171	1733 (1437, 2090)
18–59 years						
≥2-fold rise (responders)*	74/74	100 (95·1, 100)	75/75	100 (95·2, 100)	78/78	100 (95·4, 100)
≥4-fold rise	79/79	100 (95·4, 100)	78/78	100 (95·4, 100)	81/81	100 (95·5, 100)
GMCs	83	21739 (18095; 26116)	82	25448 (20980, 30867)	81	26549 (22179, 31779)
GMCR	79	1950 (1595, 2384)	78	2427 (1953, 3016)	81	2684 (2231, 3230)
≥60 years						
≥2-fold rise (responders)*	79/79	100 (95·4, 100)	89/90	98·9 (94·0, 100)	80/81	98·8 (93·3, 100)
≥4-fold rise	82/83	98·8 (93·5, 100)	92/93	98·9 (94·2; 100)	89/90	98·9 (94·0, 100)
GMCs	85	11144 (8446, 14705)	95	12249 (9604, 15623)	95	12753 (9664, 16830)
GMCR	83	1112 (839, 1475)	93	1251 (974, 1606)	90	1169 (870, 1570)
PPAS non-naïve D1/D22						
All ages						
≥2-fold rise	28/28	100 (87·7, 100)	24/26	92·3 (74·9, 99·1)	23/23	100 (85·2, 100)
≥4-fold rise (responders)*	28/28	100 (87·7, 100)	24/26	92·3 (74·9, 99·1)	23/23	100 (85·2, 100)
GMCs	28	27565 (19544, 38879)	26	26293 (17728, 38996)	23	48699 (31012, 76475)

GMCR	28	131 (56·4, 303)	26	111 (45·5, 271)	23	284 (134, 603)
18–59 years						
≥2-fold rise	13/13	100 (75·3, 100)	14/16	87·5 (61·7, 98·4)	14/14	100 (76·8, 100)
≥4-fold rise (responders)*	13/13	100 (75·3, 100)	14/16	87·5 (61·7, 98·4)	14/14	100 (76·8, 100)
GMCs	13	34939 (20779, 58748)	16	32578 (21327, 49766)	14	50322 (25193, 101 000)
GMCR	13	195 (51·9, 732)	16	96·3 (27·8, 334)	14	371 (179, 769)
≥60 years						
≥2-fold rise	15/15	100 (78·2, 100)	10/10	100 (69·2, 100)	9/9	100 (66·4, 100)
≥4-fold rise (responders)*	15/15	100 (78·2, 100)	10/10	100 (69·2, 100)	9/9	100 (66·4, 100)
GMCs	15	22446 (13739, 36671)	10	18660 (8054, 43229)	9	46277 (24818, 86291)
GMCR	15	92·4 (27·9 ; 306)	10	139 (31·3 ; 621)	9	187 (31·2 ; 1124)

CI = confidence interval. GMC = geometric mean concentration. GMCR = geometric mean concentration ratio. LLOQ = lower limit of quantification. n = number of participants experiencing the endpoint. M = number of participants with available data for the relevant endpoint. PPAS = per protocol analysis set.

*Responders were defined in the naive participant subset as those who had ≥2-fold rise in antibody titres from baseline to D36 and in the non-naïve subset as those who had ≥4-fold rise in antibody titres from baseline to D36.

Table S10: Neutralising antibody responses to D614G after the first (day 22) and second (day 36) injections, by age group (PPAS non-naïve D1/D22)

	Low-dose (5 µg) (N=201)		Medium-dose (10 µg) (N=207)		High-dose (15 µg) (N=203)	
	n/M or M	% or GMT/GMTR (95% CI)	n/M or M	% or GMT/GMTR (95% CI)	n/M or M	% or GMT/GMTR (95% CI)
Day 22						
All ages						
≥2-fold rise	20/27	74.1 (53.7 ; 88.9)	13/22	59.1 (36.4 ; 79.3)	17/23	73.9 (51.6 ; 89.8)
≥4-fold rise	18/27	66.7 (46.0 ; 83.5)	12/22	54.5 (32.2 ; 75.6)	16/23	69.6 (47.1 ; 86.8)
GMT	27	3143 (836 ; 11815)	25	2338 (593 ; 9226)	23	7069 (1361; 36725)
GMTR	27	16.1 (6.84 ; 37.7)	22	9.32 (3.27 ; 26.6)	23	36.8 (11.5 ; 118)
18–59 years						
≥2-fold rise	10/12	83.3 (51.6 ; 97.9)	9/13	69.2 (38.6 ; 90.9)	10/14	71.4 (41.9 ; 91.6)
≥4-fold rise	8/12	66.7 (34.9 ; 90.1)	9/13	69.2 (38.6 ; 90.9)	10/14	71.4 (41.9 ; 91.6)
GMT	12	6082 (733 ; 50437)	15	4070 (714 ; 23200)	14	9094 (834 ; 99150)
GMTR	12	30.5 (6.94 ; 134)	13	16.9 (3.96 ; 71.7)	14	58.2 (10.7 ; 316)
≥60 years						
≥2-fold rise	10/15	66.7 (38.4 ; 88.2)	4/9	44.4 (13.7 ; 78.8)	7/9	77.8 (40.0 ; 97.2)
≥4-fold rise	10/15	66.7 (38.4 ; 88.2)	3/9	33.3 (7.5 ; 70.1)	6/9	66.7 (29.9 ; 92.5)
GMT	15	1853 (285 ; 12051)	10	1018 (78.4 ; 13219)	9	4777 (340 ; 67165)
GMTR	15	9.61 (3.30 ; 28.0)	9	3.96 (0.749 ; 21.0)	9	18.0 (3.21 ; 101)
Day 36						
All ages						
≥2-fold rise	28/28	100 (87·7, 100)	20/22	90·9 (70·8, 98·9)	23/23	100 (85·2, 100)
≥4-fold rise	27/28	96·4 (81·7, 99·9)	19/22	86·4 (65·1, 97·1)	22/23	95·7 (78·1, 99·9)
GMT	28	13637 (8187, 22717)	25	10216 (4610, 22641)	23	26647 (12318, 57643)
GMTR	28	75·6 (41·7, 137)	22	47·8 (19·0, 121)	23	139 (66·6, 288)
18–59 years						
≥2-fold rise	13/13	100 (75·3, 100)	12/13	92·3 (64·0, 99·8)	14/14	100 (76·8, 100)
≥4-fold rise	13/13	100 (75·3, 100)	12/13	92·3 (64·0, 99·8)	14/14	100 (76·8, 100)

GMT	13	15444 (6271, 38 036)	15	17973 (7274, 44 408)	14	29417 (8365, 103 000)
GMTR	13	92·5 (38·8, 221)	13	84·5 (23·2, 308)	14	188 (77·8, 456)
≥60 years						
≥2-fold rise	15/15	100 (78·2, 100)	8/9	88·9 (51·8, 99·7)	9/9	100 (66·4, 100)
≥4-fold rise	14/15	93·3 (68·1, 99·8)	7/9	77·8 (40·0, 97·2)	8/9	88·9 (51·8, 99·7)
GMT	15	12244 (6349, 23611)	10	4378 (971, 19736)	9	22848 (10576, 49361)
GMTR	15	63·5 (25·6, 157)	9	21·0 (5·23, 84·6)	9	86·1 (19·8, 374)

GMT = geometric mean titre; GMTR = geometric mean of individual titre ratios (D36/D1); M = number of participants with available data for the relevant endpoint; n = number of participants meeting criteria for ≥2- or 4-fold rise in GMTs**.**

Table S11. Neutralising antibody responses to the SARS-CoV-2 Beta variant 14 days after the second injection (D36) (PPAS naïve D1+D22 and PPAS non-naïve D1/D22)

	Low-dose (5 µg) (N=201)		Medium-dose (10 µg) (N=207)		High-dose (15 µg) (N=203)	
	M	**GMT (95% CI)**	**M**	**GMT (95% CI)**	**M**	**GMT (95% CI)**
PPAS-naïve D1+D22						
All ages	166	200 (156, 257)	173	191 (146, 249)	173	283 (223, 359)
18–59 years	83	255 (181, 359)	79	336 (231, 490)	81	526 (375, 737)
≥60 years	83	157 (109, 226)	94	118 (83·5, 168)	92	164 (122, 221)
PPAS non-naïve D1/D22						
All ages	28	1676 (774, 3628)	25	1775 (704, 4474)	23	2872 (1097, 7518)
18–59 years	13	2021 (522, 7835)	15	2752 (924, 8194)	14	2213 (476, 10 301)
≥60 years	15	1424 (522, 3885)	10	919 (148, 5724)	9	4307 (1540, 12044)

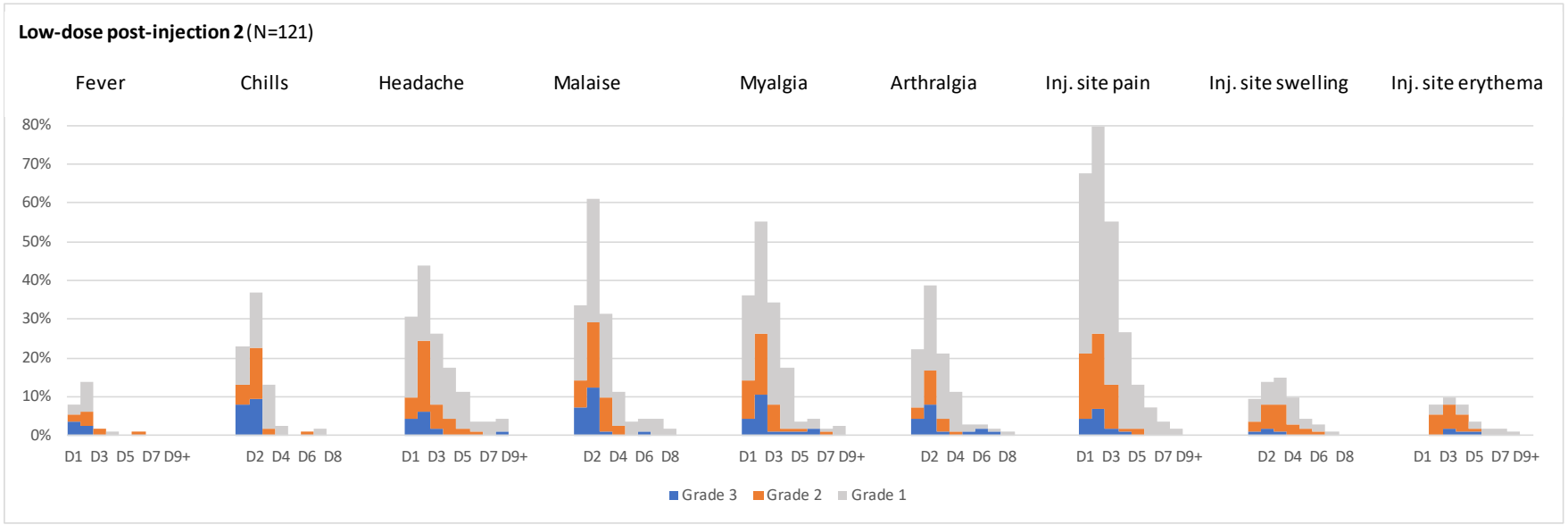
GMT = geometric mean titre. M = number of participants with available data for the relevant endpoint..

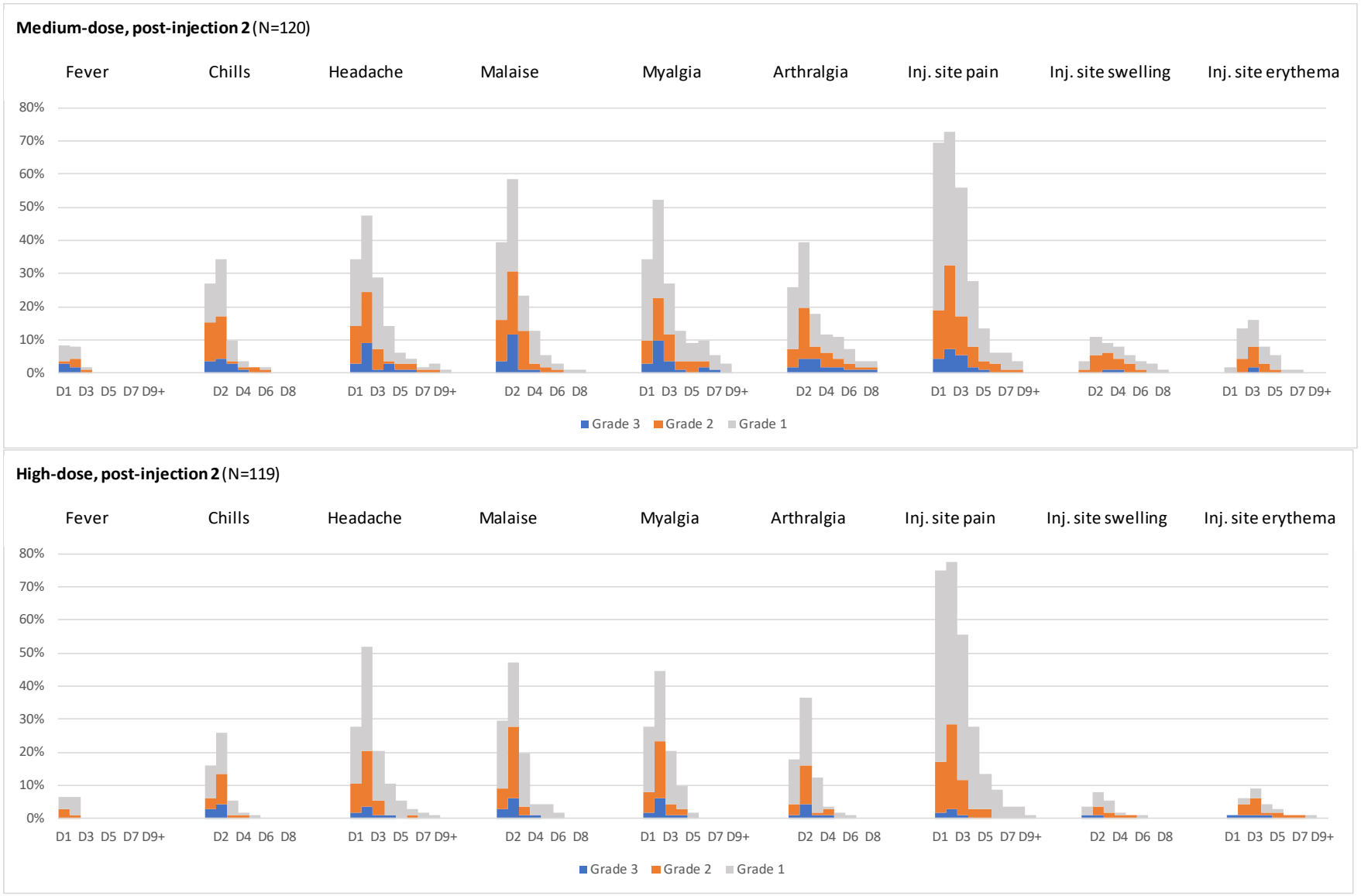
Table S12. Geometric means of fold-rise from baseline for individual cytokines after stimulation with S protein in whole blood (stimulated values minus negative control) (CMI analysis set)

		Low-dose (5 µg) (N=36)		Medium-dose (10 µg) (N=31)		High-dose (15 µg) (N=37)	
		M	Ratio (95% CI)	M	Ratio (95% CI)	M	Ratio (95% CI)
IFNγ	D22	34	6·48 (3·67 ; 11·4)	29	12·2 (6·50 ; 22·8)	33	11·1 (5·83 ; 21·1)
	D36	33	42·6 (25·2 ; 71·8)	29	38·9 (20·7 ; 73·3)	34	27·9 (16·7 ; 46·8)
IL-2	D22	34	36·9 (22·4 ; 60·8)	29	34·7 (19·2 ; 62·7)	33	32·9 (18·4 ; 58·8)
	D36	33	93·5 (66·2 ; 132)	29	49·9 (28·7 ; 86·6)	34	49·2 (31·0 ; 78·0)
IL-6	D22	34	7·10 (4·04 ; 12·5)	29	11·0 (5·33 ; 22·7)	33	10·2 (6·04 ; 17·3)
	D36	33	67·5 (33·0 ; 138)	29	71·6 (37·0 ; 138)	34	37·8 (16·8 ; 85·1)
TNF-α	D22	34	9·03 (5·01 ; 16·3)	29	11·4 (6·61 ; 19·7)	33	8·87 (4·97 ; 15·8)
	D36	33	48·9 (35·0 ; 68·3)	29	44·4 (29·0 ; 67·9)	34	32·2 (21·3 ; 48·8)
IL-4	D22	34	1·49 (1·18 ; 1·89)	29	2·18 (1·50 ; 3·17)	33	2·20 (1·60 ; 3·02)
	D36	33	9·19 (6·52 ; 13·0)	29	6·96 (4·72 ; 10·3)	34	7·24 (5·03 ; 10·4)
IL-5	D22	34	2·77 (2·00 ; 3·84)	29	4·24 (2·74 ; 6·55)	33	3·52 (2·48 ; 5·01)
	D36	33	20·0 (12·2 ; 32·9)	29	15·2 (8·75 ; 26·4)	34	13·3 (8·72 ; 20·1)
IL-10	D22	34	2·05 (1·48 ; 2·84)	29	2·89 (1·92 ; 4·36)	33	3·03 (2·09 ; 4·40)
	D36	33	9·95 (6·28 ; 15·7)	29	8·77 (4·66 ; 16·5)	34	10·6 (6·99 ; 16·1)
IL-13	D22	34	2·31 (1·62 ; 3·29)	29	3·84 (2·34 ; 6·28)	33	3·21 (2·24 ; 4·61)
	D36	33	8·94 (5·72 ; 14·0)	29	8·73 (5·41 ; 14·1)	34	7·89 (5·23 ; 11·9)
IL-17	D22	34	5·98 (3·68 ; 9·70)	29	8·69 (5·05 ; 15·0)	33	8·02 (4·73 ; 13·6)
	D36	33	23·3 (15·4 ; 35·4)	29	19·8 (11·2 ; 35·0)	34	20·0 (11·4 ; 34·9)
IL-21	D22	31	244 (108 ; 551)	26	379 (168 ; 858)	30	345 (151 ; 792)
	D36	30	4316 (2458 ; 7581)	25	2088 (934 ; 4667)	30	1277 (522 ; 3125)

Figure S1. Solicited injection site and solicited systemic adverse reactions occurring over the first seven days after the second vaccination for each antigen group, in younger adults (A; 18–59 years) and older adults (B; ≥60 years)

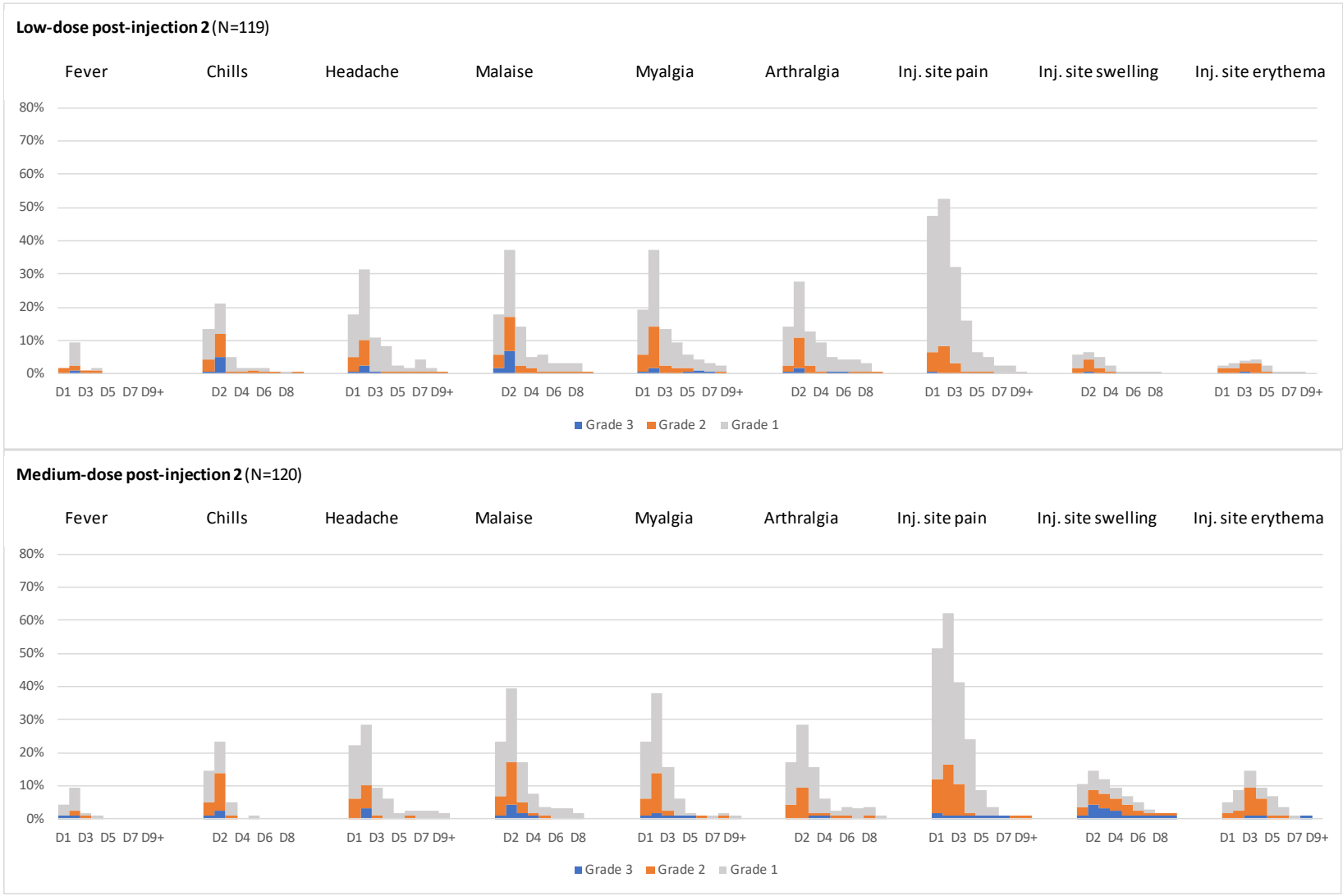
A. 18–59 years

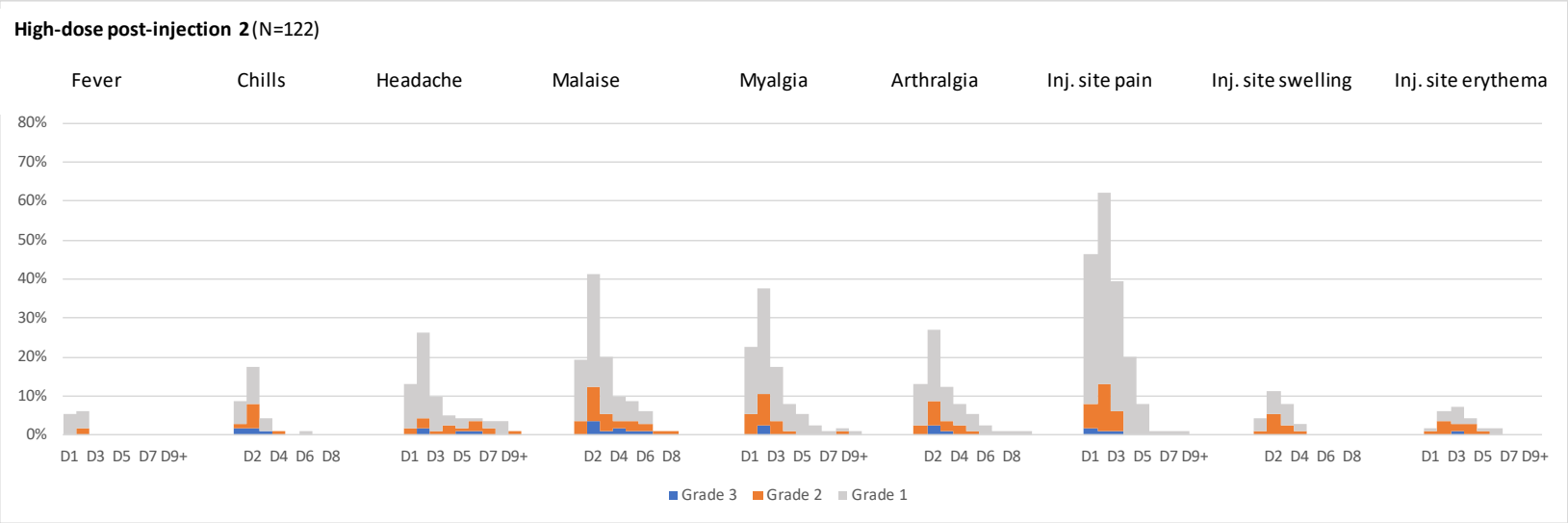




D = study day; Low-dose = 5 µg antigen dose; medium-dose = 10 µg antigen group; high-dose = 15 µg antigen group.

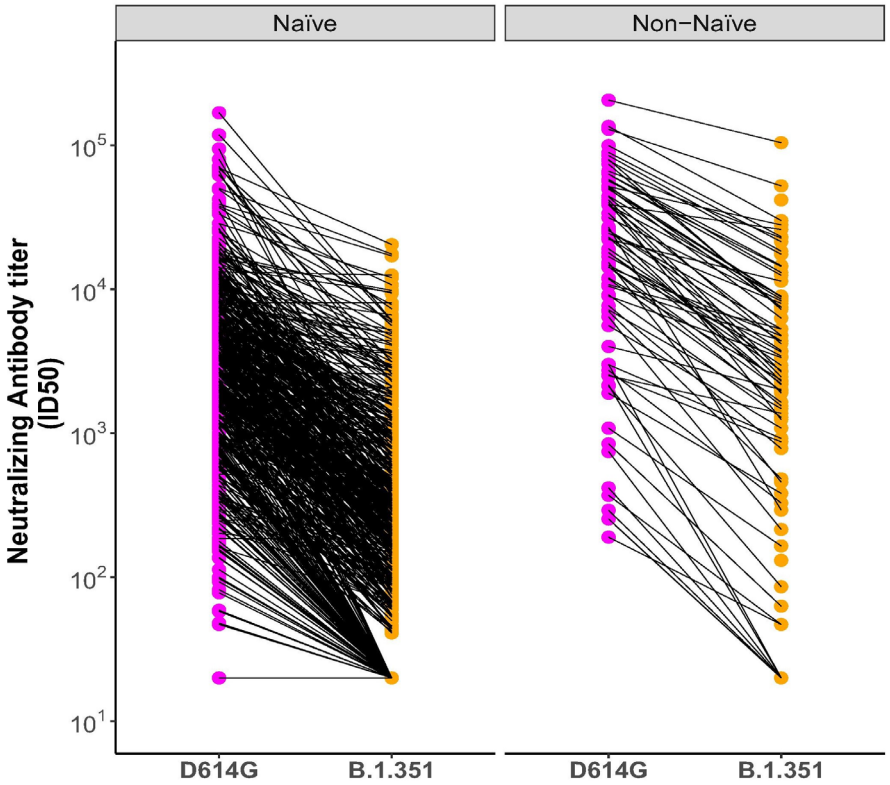
B. ≥ 60 years


Low-dose post-injection 2 (N=119)
Fever
Chills
Headache
Malaise
Myalgia
Arthralgia
Inj. site pain
Inj. site swelling
Inj. site erythema
80%
70%
60%
50%
40%
30%
20%
10%
0%
D1 D3 D5 D7 D9+
D2 D4 D6 D8
Grade 3
Grade 2
Grade 1
Medium-dose post-injection 2 (N=120)
Fever
Chills
Headache
Malaise
Myalgia
Arthralgia
Inj. site pain
Inj. site swelling
Inj. site erythema
80%
70%
60%
50%
40%
30%
20%
10%
0%
D1 D3 D5 D7 D9+
D2 D4 D6 D8
Grade 3
Grade 2
Grade 1



D = study day; Low-dose = 5 µg antigen dose; medium-dose = 10 µg antigen group; high-dose = 15 µg antigen group.

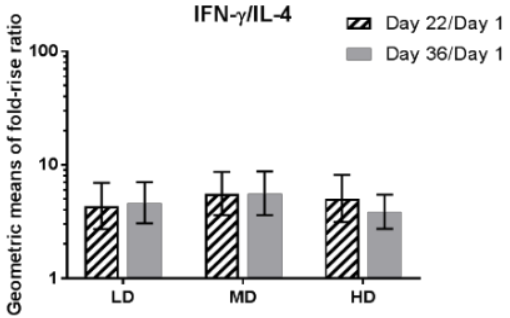
Figure S2. Neutralising antibody response to the Beta variant, 14 days after the second injection of CoV2 preS dTM-AS03 (all dose groups combined), by SARS-CoV-2 naïve status

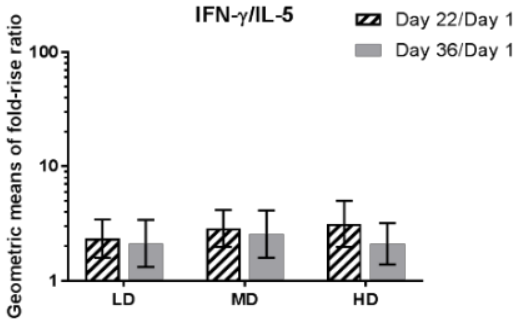


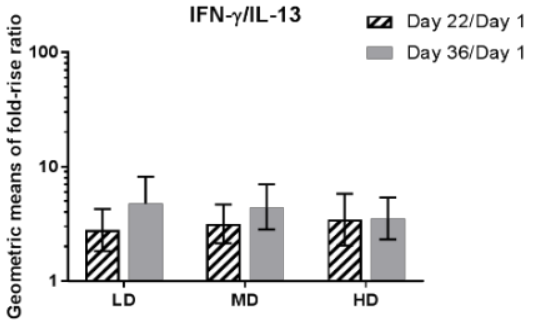
Naïve = the subset of PPAS participants who were SAR-CoV-2-naïve at D1 and D22; N=521; Non-naïve = the subset of PPAS participants who were SAR-CoV-2-non-naïve at D1 and/or D22, N=77
The lower limit of quantification (LLOQ) for the neutralising antibody assay was 1:40, with an upper limit of 1:191,429.

Figure S3. CMI analyses – ratios of fold-rises for IFN-γ (A), IL-2 (B) and TNF-α (C) to IL-4, IL-5 and IL-13 at Day 22 and Day 36 (CMIAS)
Footnote: CMI = cell mediated immunity. CMIAS = cell mediated immunity analysis set. HD = high-dose (15 µg). IFN = interferon. IL = interleukin. LD = Low-dose (5 µg). MD = medium-dose (10 µg). TNF = tumour necrosis factor.
Error bars denote 95% confidence intervals.

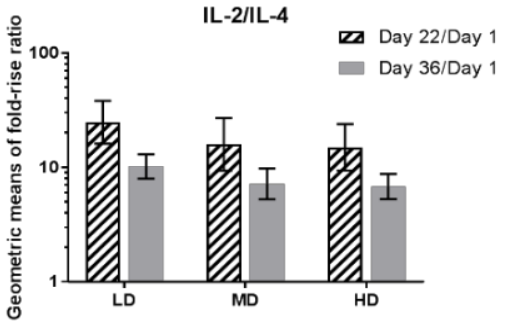
A

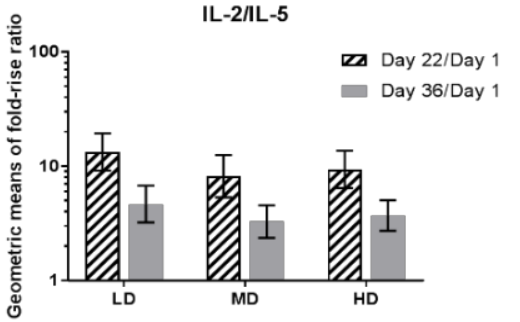

IFN-γ/IL-4
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD

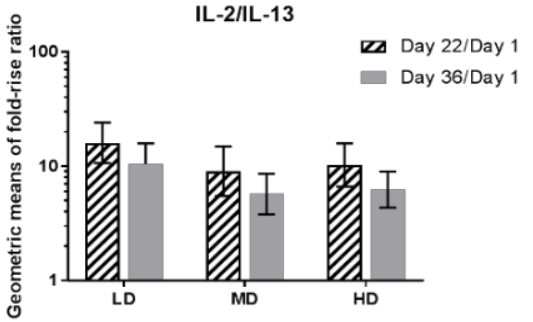

IFN-γ/IL-5
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD


IFN-γ/IL-13
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD

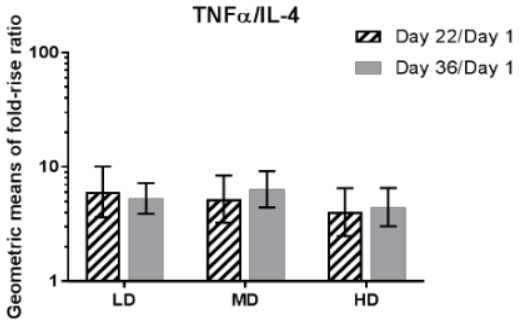
B

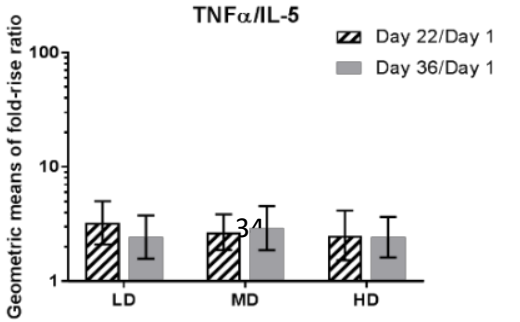

IL-2/IL-4
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD

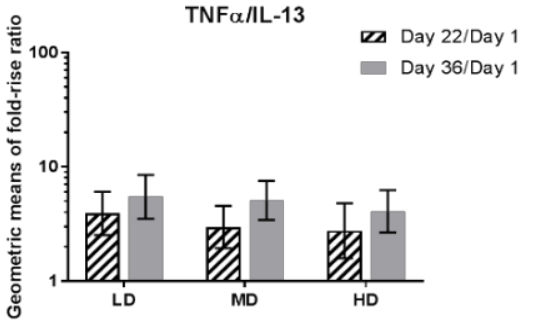

IL-2/IL-5
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD


IL-2/IL-13
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD

C


TNFα/IL-4
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD


TNFα/IL-5
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD


TNFα/IL-13
Day 22/Day 1
Day 36/Day 1
Geometric means of fold-rise ratio
100
10
1
LD
MD
HD