

ELECTRONIC SUPPLEMENTARY MATERIAL

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Association between reactogenicity and immunogenicity in a vaccinated cohort with two mRNA SARS-CoV-2 vaccines at a high-complexity reference hospital: a *post-hoc* analysis on immunology aspects of a prospective cohort study

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Measurement of antibodies and T-cell response. Analytical methods

Humoral immunogenicity

Levels of neutralizing and anti-spike antibodies (IgG + IgM) were measured on the Cobas platform (Roche©), based on semiquantitative measurement of antibody titres through serological enhanced “electrochemiluminescence”, on a scale that ranges from 0 to >10. Results >1.0 were considered positive antibody titres. IgG titres were measured on samples that tested positive in the Cobas platform in a subset of patients, as per local clinical practice protocols (Akashi Y et al, 2022). During the vaccination campaign the measurement method changed, and IgG titres were measured in the Atellica Analyzer (Siemens Healthineers©) (Florin L et al, 2021), with a quantitative scale that ranged from 0.5 to >150 U/ml. IgG were measured only in a subset of the total vaccinated population (N=322 vaccinees).

Cellular immunogenicity

SARS-CoV-2-specific T-cell response was measured by interferon-gamma ELISPOT assay measured from isolated PBMCs, as described by Egri N et al (Egri N et al., 2022).

In summary, venous blood samples were obtained from the forearm utilizing a butterfly needle connected to heparinized and serum-containing tubes. Peripheral blood mononuclear cells (PBMCs) were extracted from the blood samples through Ficoll-Paque density gradient centrifugation. Stimulation experiments were performed using 2×10^5 PBMCs cultured in X-VIVO™15 medium supplemented with 10% heat-inactivated AB serum and PepTivator® SARS-CoV-2 Prot_S and N peptide pools at a concentration of mg/ml (Miltenyi Bio-tec®). The diluent utilized was PBS+DMSO with a final DMSO concentration of 1%. For the ELISpot negative control, X-VIVO 15 medium with 20% DMSO to a final concentration of 1% was employed. Negative control wells were devoid of peptides, while positive control wells contained mAb CD3-2 from the kit. Cells were then cultured overnight (16–20 h) at 37°C with 5% CO₂ in precoated anti-IFN-g MSIP white plates (Human IFN-g ELISpotPRO kit (ALP) (Mabtech) Ref: 3420-2AST-2, Mabtech®). Following incubation, plates were washed five times with PBS (Sigma-Aldrich) and incubated for 2 h at room temperature with horseradish peroxidase (HRP)-conjugated anti-IFN-g detection antibody (1 mg/ml; clone mAb-7B6-1; Mabtech®).

After five additional washes with PBS, tetra-methylbenzidine (TMB) substrate was added, and spots were enumerated using an automated ELISpot Reader System (Autoimmun Diagnostika GmbH®). Positive peptide-specific responses were quantified by subtracting spots in unstimulated wells from peptide-stimulated wells, with results expressed as SFU (Spot Forming Units)/2x10⁵ PBMCs. SARS-CoV-2-specific spots were determined by spot increment, defined as stimulated spot numbers ≥ 6 SFU/2 $\times$ 10⁵ PBMCs. This threshold was established by calculating the mean $\pm$ 2 standard deviations in a cohort of healthy donors obtained prior to the onset of the SARS-CoV-2 pandemic. Spot counting was conducted automatically and was manually verified in all instances.

References:

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- Egri N, Olivé V, Hernández-Rodríguez J, & et al. (2022). CoVITEST: A Fast and Reliable Method to Monitor Anti-SARS-CoV-2 Specific T Cells From Whole Blood. *Front Immunol*, 13, 848586.

ii. Main analysis and sensitivity analyses

ii.i Main analysis

Table S1 Assessment of antibody positiveness (positive-negative titres)

Variable	Antibody positiveness											
	Negative antibody titres (n= 64)						Positive antibody titres (n= 151)					
	After 1 st vaccine dose	p- value	After 2 nd vaccine dose	p- value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p- value	After any dose	p- value
Proportions of AR												
Development of any AR (n, %)	43 (67.2)	0.891	37 (57.8)	0.408	52 (81.3)	0.368	100 (66.2)	0.891	78 (51.7)	0.408	130 (86.1)	0.368
Development of any mild AR (n, %)	19 (29.7)	0.071	8 (12.5)	0.905	26 (40.6)	0.100	28 (18.5)	0.071	18 (11.9)	0.905	44 (29.1)	0.100
Development of any moderate AR (n, %)	20 (31.3)	0.586	26 (40.6)	0.250	38 (59.4)	0.494	53 (35.1)	0.586	49 (32.5)	0.250	82 (54.3)	0.494
Development of any severe AR (n, %)	10 (15.6)	0.296	16 (25.0)	0.774	22 (34.4)	0.775	33 (21.9)	0.296	35 (23.2)	0.774	55 (36.4)	0.775
Maximum intensity												
Grade 1 (n, %)	13 (31.0)	0.339	4 (11.4)	0.890	6 (11.8)	0.497	21 (22.8)	0.339	11 (14.5)	0.890	22 (17.9)	0.497
Grade 2 (n, %)	19 (45.2)		15 (42.9)		23 (45.1)		38 (41.3)		30 (39.5)		46 (37.4)	
Grade 3 (n, %)	10 (23.8)		16 (45.7)		22 (43.1)		33 (35.9)		35 (46.1)		55 (44.7)	
Likert score Mean (SD)	4.79 (2.04)	0.106	6.09 (2.07)	0.858	5.92 (2.12)	0.872	5.44 (2.19)	0.106	6.22 (2.02)	0.858	5.92 (2.21)	0.872

Antibody titres according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody. Results are provided as absolute and relative (%) numbers for each variable. Statistically significant results are marked in bold type

Table S2 Assessment of antibody positiveness (positive-negative titres): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	31 (48.4)		56 (37.1)		0.121	
	23 (35.9)	11 (17.2)	47 (31.1)	21 (13.9)	0.491	0.537
Fatigue/asthenia <i>PT: Fatigue</i>	16 (25.0)		27 (17.9)		0.233	
	4 (6.3)	12 (18.8)	8 (5.3)	21 (13.9)	0.781	0.368
Fever <i>PT: Pyrexia</i>	17 (26.6)		46 (30.5)		0.566	
	4 (6.3)	13 (20.3)	20 (13.2)	35 (23.2)	0.136	0.645
Malaise <i>PT: Malaise</i>	4 (6.3)		24 (15.9)		0.055	
	1 (1.6)	3 (4.7)	4 (2.6)	19 (12.6)	0.629	0.081
Chills <i>PT: Chills</i>	3 (4.7)		11 (7.3)		0.480	
	0 (0)	3 (4.7)	4 (2.6)	7 (4.6)	0.189	0.987
Injection site redness <i>PT: Application site redness</i>	3 (4.7)		4 (2.6)		0.441	
	2 (3.1)	2 (3.1)	2 (1.3)	2 (1.3)	0.372	0.372

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	15 (23.4)		38 (25.2)		0.788	
	9 (14.1)	8 (12.5)	27 (17.9)	14 (9.3)	0.493	0.475
Muscle pain PT: Myalgia	12 (18.8)		29 (19.2)		0.938	
	2 (3.1)	10 (15.6)	7 (4.6)	24 (15.9)	0.613	0.961
Joint pain PT: Arthralgia	5 (7.8)		13 (8.6)		0.847	
	0 (0)	5 (7.8)	1 (0.7)	12 (7.9)	0.514	0.973
Shoulder pain PT: Musculoskeletal pain	3 (4.7)		6 (4.0)		0.811	
	2 (3.1)	1 (1.6)	4 (2.6)	1 (0.7)	0.770	0.530
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	5 (7.8)		10 (6.6)		0.754	
	3 (4.7)	2 (3.1)	9 (6.0)	2 (1.3)	0.710	0.372
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	1 (1.6)		2 (1.3)		0.892	
	0 (0)	1 (1.6)	0 (0)	2 (1.3)	NA	0.892

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Nervous system disorders						
Headache PT: Headache	19 (29.7)		40 (26.5)		0.631	
	8 (12.5)	13 (20.3)	19 (12.6)	23 (15.2)	0.987	0.362
Facial paralysis PT: Facial paralysis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Insomnia PT: Insomnia	2 (3.1)		2 (1.3)		0.372	
	0 (0)	2 (3.1)	0 (0)	2 (1.3)	NA	0.372
SOC: Gastrointestinal disorders						
Nausea PT: Nausea	2 (3.1)		5 (3.3)		0.944	
	1 (1.6)	1 (1.6)	4 (2.6)	1 (0.7)	0.629	0.530
Diarrhea PT: Diarrhoea	1 (1.6)		2 (1.3)		0.892	
	1 (1.6)	0 (0)	1 (0.7)	1 (0.7)	0.530	0.514
Vomiting PT: Vomiting	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Unsolicited adverse reactions						
SOC: <i>Musculoskeletal and connective tissue disorders</i>						
Other musculoskeletal disorders <i>PT: Musculoskeletal disorder</i>	3 (4.7)		4 (2.6)		0.441	
	1 (1.6)	2 (3.1)	0 (0)	4 (2.6)	0.124	0.846
SOC: <i>Skin and subcutaneous tissue disorders</i>						
Petechia, ecchymosis PT: <i>Ecchymosis</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Nervous system disorders</i>						
Cognitive alteration PT: <i>Cognitive disorder</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Alterations of smell and taste PT: <i>Parosmia</i>	0 (0)		1 (0.7)		0.514	
	0 (0)	0 (0)	0 (0)	1 (0.7)	NA	0.514
Paresthesia and hyperesthesia PT: <i>Dysaesthesia</i>	1 (1.6)		2 (1.3)		0.892	
	0 (0)	1 (1.6)	2 (1.3)	0 (0)	0.355	0.124
Presyncope, syncope and vasovagal syncope PT: <i>Syncope</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Sleepiness, hypersomnia PT: <i>Hypersomnia</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Instability sensation, vertigo, sickness PT: Dizziness	1 (1.6)		2 (1.3)		0.892	
	0 (0)	1 (1.6)	1 (0.7)	1 (0.7)	0.514	0.530
Tremor PT: Tremor	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Gastrointestinal disorders PT: Gastrointestinal disorder	0 (0)		1 (0.7)		0.514	
	0 (0)	0 (0)	1 (0.7)	0 (0)	0.514	NA
SOC: Respiratory, thoracic and mediastinal disorders						
Asthma PT: Asthma	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Rhinitis, nasal discharge PT: Rhinitis	0 (0)		1 (0.7)		0.514	
	0 (0)	0 (0)	0 (0)	1 (0.7)	NA	0.514

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Investigations</i>						
Hypertension, hypotension PT: <i>Blood pressure abnormal</i>	2 (3.1)		0 (0)		0.029	
	0 (0)	2 (3.1)	0 (0)	0 (0)	NA	0.029
SOC: <i>General disorders and administration site conditions</i>						
Influenza-like symptoms PT: <i>Influenza like illness</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Sensation of heat, sensation of cold PT: <i>Temperature regulation disorder</i>	0 (0)		2 (1.3)		0.355	
	0 (0)	0 (0)	1 (0.7)	1 (0.7)	0.514	0.514
Chest pain PT: <i>Chest pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Ear and labyrinth disorders						
PT: Ear pain	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Skin and subcutaneous tissue disorders						
General pruritus PT: Pruritus	2 (3.1)		0 (0)		0.029	
	1 (1.6)	1 (1.6)	0 (0)	0 (0)	0.124	0.124
Sweat PT: Cold sweat	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Immune system disorders						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: Hypersensitivity	1 (1.6)		1 (0.7)		0.530	
	0 (0)	1 (1.6)	1 (0.7)	0 (0)	0.514	0.124
SOC: Cardiac disorders						
Tachycardia PT: Tachycardia	0 (0)		1 (0.7)		0.514	
	0 (0)	0 (0)	0 (0)	1 (0.7)	NA	0.514

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Blood and lymphatic system disorders</i>						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	0 (0)		6 (4.0)		0.106	
	0 (0)	0 (0)	1 (0.7)	5 (3.3)	0.514	0.141
SOC: <i>Infections and infestations</i>						
Herpetic infection PT: <i>Herpes virus infection</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Distribution of proportions of solicited and unsolicited AR are displayed by elicited qualitative humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable.

Table S3 Assessment of antibody positiveness (positive-negative titres): severe solicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	3 (4.7)		15 (9.9)		0.204	
	3 (4.7)	0 (0)	13 (8.6)	3 (2.0)	0.316	0,256
Fatigue/astenia <i>PT: Fatigue</i>	9 (14.1)		10 (6.6)		0.079	
	3 (4.7)	6 (9.4)	1 (0.7)	9 (6.0)	0.046	0.369
Fever <i>PT: Pyrexia</i>	0 (0)		7 (4.6)		0.080	
	0 (0)	0 (0)	3 (2.0)	5 (3.3)	0.136	0.141
Malaise <i>PT: Malaise</i>	1 (1.6)		15 (9.9)		0.033	
	0 (0)	1 (1.6)	1 (0.7)	13 (8.6)	0.514	0.056
Chills <i>PT: Chills</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Injection site redness <i>PT: Application site redness</i>	0 (0)		1 (0.7)		0.514	
	0 (0)	0 (0)	1 (0.7)	0 (0)	0.514	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	8 (12.5)		15 (9.9)		0.578	
	6 (9.4)	2 (3.1)	10 (6.6)	5 (3.3)	0.482	0.944
Muscle pain PT: Myalgia	12 (18.8)		29 (19.2)		0.938	
	2 (3.1)	10 (15.6)	7 (4.6)	24 (15.9)	0.613	0.961
Joint pain PT: Arthralgia	3 (4.7)		10 (6.6)		0.586	
	0 (0)	3 (4.7)	0 (0)	10 (6.6)	NA	0.586
Shoulder pain PT: Musculoskeletal pain	0 (0)		2 (1.3)		0.355	
	0 (0)	0 (0)	1 (0.7)	0 (0)	0.514	NA
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	0 (0)		4 (2.6)		0.189	
	0 (0)	0 (0)	4 (2.6)	0 (0)	0.189	NA
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Nervous system disorders						
Headache PT: Headache	6 (9.4)		17 (11.3)		0.683	
	2 (3.1)	5 (7.8)	6 (4.0)	11 (7.3)	0.764	0.893

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited qualitative humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable

Table S4 Assessment of antibody titres (antibody titres above-below median):

Variable	Antibody titres below median* (n= 93)						Antibody titres above median* (n= 122)					
	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p-value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p-value	After any dose	p-value
Proportions of AR												
Development of any AR (n, %)	58 (62.4)	0.261	51 (54.8)	0.729	75 (80.6)	0.155	85 (69.7)	0.261	64 (52.5)	0.729	107 (87.7)	0.155
Development of any mild AR (n, %)	22 (23.7)	0.578	14 (15.1)	0.245	33 (35.5)	0.424	25 (20.5)	0.578	12 (9.8)	0.245	37 (30.3)	0.424
Development of any moderate AR (n, %)	28 (30.1)	0.299	34 (36.6)	0.653	53 (57.0)	0.762	45 (36.9)	0.299	41 (33.6)	0.653	67 (54.9)	0.762
Development of any severe AR (n, %)	14 (15.1)	0.113	24 (25.8)	0.530	33 (35.5)	0.930	29 (23.8)	0.113	27 (22.1)	0.530	44 (36.1)	0.930
Maximum intensity												
Grade 1 (n, %)	15 (27.3)	0.386	6 (12.2)	0.840	9 (12.3)	0.501	19 (24.1)	0.386	9 (14.5)	0.840	19 (18.8)	0.501
Grade 2 (n, %)	26 (47.3)		19 (38.8)		31 (42.5)		31 (39.2)		26 (41.9)		38 (37.6)	
Grade 3 (n, %)	14 (25.5)		24 (49.0)		33 (45.2)		29 (36.7)		27 (43.5)		44 (43.6)	
Likert score Mean (SD)	5.09 (2.15)	0.489	6.19 (2.06)	0.896	6.07 (2.13)	0.414	5.33 (2.17)	0.489	6.17 (2.02)	0.896	5.80 (2.21)	0.414

Antibody titres (in median titres $\leq$ median) according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody. Results are provided as absolute and relative (%) numbers for each variable. Statistically significant results are marked in bold type, * Median value of antibody titres (P25, P75)= 7.69 (0.73,10.00) on a semiquantitative scale ranging from 0 to >10

Table S5 Assessment of antibody titres (antibody titres above-below median): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: <i>General disorders and administration site conditions</i>						
Injection site pain <i>PT: Injection site pain</i>	39 (41.9)		48 (39.3)		0.701	
	29 (31.2)	16 (17.2)	41 (33.6)	16 (13.1)	0.707	0.404
Fatigue/asthenia <i>PT: Fatigue</i>	23 (24.7)		20 (16.4)		0.130	
	5 (5.4)	18 (19.4)	7 (5.7)	15 (12.3)	0.909	0.155
Fever <i>PT: Pyrexia</i>	24 (25.8)		39 (32.0)		0.326	
	5 (5.4)	19 (20.4)	19 (15.6)	29 (23.8)	0.019	0.560
Malaise <i>PT: Malaise</i>	9 (9.7)		19 (15.6)		0.203	
	1 (1.1)	8 (8.6)	4 (3.3)	14 (11.5)	0.288	0.491
Chills <i>PT: Chills</i>	7 (7.5)		7 (5.7)		0.598	
	1 (1.1)	6 (6.5)	3 (2.5)	4 (3.3)	0.457	0.274
Injection site redness <i>PT: Application site redness</i>	3 (3.2)		4 (3.3)		0.983	
	2 (2.2)	2 (2.2)	2 (1.6)	2 (1.6)	0.784	0.784

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	17 (18.3)		36 (29.5)		0.058	
	10 (10.8)	9 (9.7)	26 (21.3)	13 (10.7)	0.040	0.815
Muscle pain PT: Myalgia	17 (18.3)		24 (19.7)		0.797	
	2 (2.2)	15 (16.1)	7 (5.7)	19 (15.6)	0.193	0.912
Joint pain PT: Arthralgia	10 (10.8)		8 (6.6)		0.271	
	0 (0)	10 (10.8)	1 (0.8)	7 (5.7)	0.382	0.177
Shoulder pain PT: Musculoskeletal pain	5 (5.4)		4 (3.3)		0.447	
	4 (4.3)	1 (1.1)	2 (1.6)	1 (0.8)	0.240	0.847
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	5 (5.4)		10 (8.2)		0.421	
	3 (3.2)	2 (2.2)	9 (7.4)	2 (1.6)	0.189	0.784
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	1 (1.1)		2 (1.6)		0.727	
	0 (0)	1 (1.1)	0 (0)	2 (1.6)	NA	0.727

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Nervous system disorders						
Headache PT: Headache	29 (31.2)		30 (24.6)		0.283	
	13 (14.0)	19 (20.4)	14 (11.5)	17 (13.9)	0.583	0.206
Facial paralysis PT: Facial paralysis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Insomnia PT: Insomnia	2 (2.2)		2 (1.6)		0.784	
	0 (0)	2 (2.2)	0 (0)	2 (1.6)	NA	0.784
SOC: Gastrointestinal disorders						
Nausea PT: Nausea	2 (2.2)		5 (4.1)		0.425	
	1 (1.1)	1 (1.1)	4 (3.3)	1 (0.8)	0.288	0.847
Diarrhea PT: Diarrhoea	1 (1.1)		2 (1.6)		0.727	
	1 (1.1)	0 (0)	1 (0.8)	1 (0.8)	0.847	0.382
Vomiting PT: Vomiting	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Unsolicited adverse reactions						
SOC: Musculoskeletal and connective tissue disorders						
Other musculoskeletal disorders PT: Musculoskeletal disorder	4 (4.3)		3 (2.5)		0.451	
	1 (1.1)	3 (3.2)	0 (0)	3 (2.5)	0.251	0.735
SOC: Skin and subcutaneous tissue disorders						
Petechia, ecchymosis PT: Ecchymosis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Nervous system disorders						
Cognitive alteration PT: Cognitive disorder	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Alterations of smell and taste PT: Parosmia	0 (0)		1 (0.8)		0.382	
	0 (0)	0 (0)	0 (0)	1 (0.8)	NA	0.382
Paresthesia and hyperesthesia PT: Dysaesthesia	1 (1.1)		2 (1.6)		0.727	
	0 (0)	1 (1.1)	2 (1.6)	0 (0)	0.215	0.251
Presyncope, syncope and vasovagal syncope PT: Syncope	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Sleepiness, hypersomnia PT: Hypersomnia	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Instability sensation, vertigo, sickness PT: Dizziness	1 (1.1)		2 (1.6)		0.727	
	0 (0)	1 (1.1)	1 (0.8)	1 (0.8)	0.382	0.847
Tremor PT: Tremor	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Gastrointestinal disorders PT: Gastrointestinal disorder	1 (1.1)		0 (0)		0.251	
	1 (1.1)	0 (0)	0 (0)	0 (0)	0.251	NA
SOC: Respiratory, thoracic and mediastinal disorders						
Asthma PT: Asthma	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Rhinitis, nasal discharge PT: Rhinitis	0 (0)		1 (0.8)		0.382	
	0 (0)	0 (0)	0 (0)	1 (0.8)	NA	0.382

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Investigations</i>						
Hypertension, hypotension PT: <i>Blood pressure abnormal</i>	2 (2.2)		0 (0)		0.104	
	0 (0)	2 (2.2)	0 (0)	0 (0)	NA	0.104
SOC: <i>General disorders and administration site conditions</i>						
Influenza-like symptoms PT: <i>Influenza like illness</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Sensation of heat, sensation of cold PT: <i>Temperature regulation disorder</i>	1 (1.1)		1 (0.8)		0.847	
	1 (1.1)	0 (0)	0 (0)	1 (0.8)	0.251	0.382
Chest pain PT: <i>Chest pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Ear and labyrinth disorders						
PT: Ear pain	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Skin and subcutaneous tissue disorders						
General pruritus PT: Pruritus	2 (2.2)		0 (0)		0.104	
	1 (1.1)	1 (1.1)	0 (0)	0 (0)	0.251	0.251
Sweat PT: Cold sweat	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Immune system disorders						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: Hypersensitivity	1 (1.1)		1 (0.8)		0.847	
	0 (0)	1 (1.1)	1 (0.8)	0 (0)	0.382	0.251
SOC: Cardiac disorders						
Tachycardia PT: Tachycardia	0 (0)		1 (0.8)		0.382	
	0 (0)	0 (0)	0 (0)	1 (0.8)	NA	0.382

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Blood and lymphatic system disorders</i>						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	0 (0)		6 (4.9)		0.030	
	0 (0)	0 (0)	1 (0.8)	5 (4.1)	0.382	0.048
SOC: <i>Infections and infestations</i>						
Herpetic infection PT: <i>Herpes virus infection</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited quantitative humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, *Median value of antibody titres (P25, P75)= 7.69 (0.73,10.00) on a semiquantitative scale ranging from 0 to >10

Table S6 Assessment of antibody titres (antibody titres above-below median): severe solicited AR

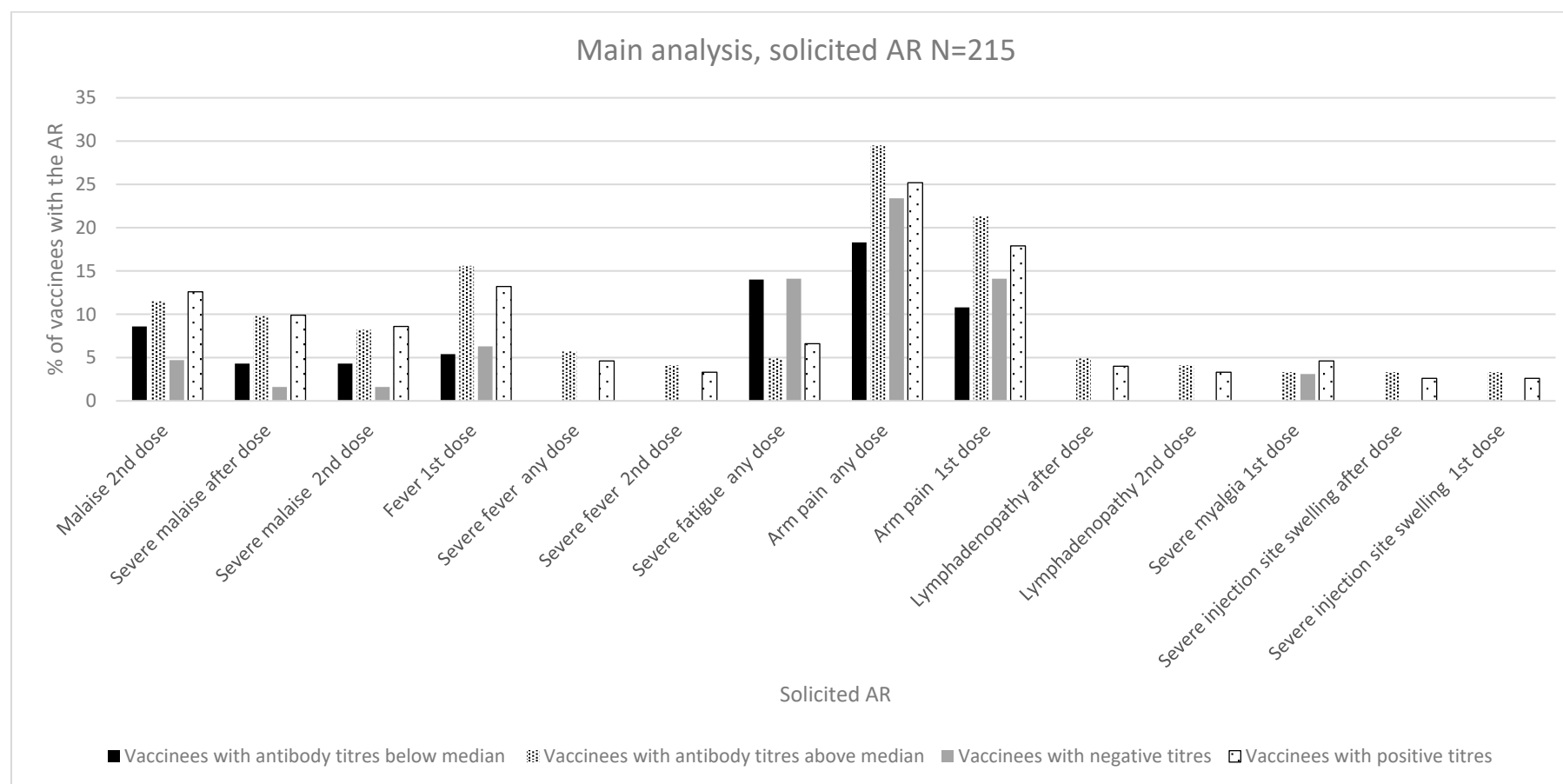
Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	6 (6.5)		12 (9.8)		0.375	
	6 (6.5)	0 (0)	10 (8.2)	3 (2.5)	0.629	0.128
Fatigue/asthenia <i>PT: Fatigue</i>	13 (14.0)		6 (4.9)		0.020	
	3 (3.2)	10 (10.8)	1 (0.8)	5 (4.1)	0.196	0.058
Fever <i>PT: Pyrexia</i>	0 (0)		7 (5.7)		0.019	
	0 (0)	0 (0)	3 (2.5)	5 (4.1)	0.128	0.048
Malaise <i>PT: Malaise</i>	4 (4.3)		12 (9.8)		0.126	
	0 (0)	4 (4.3)	1 (0.8)	10 (8.2)	0.382	0.251
Injection site redness <i>PT: Application site redness</i>	0 (0)		1 (0.8)		0.382	
	0 (0)	0 (0)	1 (0.8)	0 (0)	0.382	NA
SOC: Musculoskeletal and connective tissue disorders						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Arm pain PT: Pain in extremity	8 (8.6)		15 (12.3)		0.385	
	6 (6.5)	2 (2.2)	10 (8.2)	5 (4.1)	0.629	0.425
Muscle pain PT: Myalgia	7 (7.5)		11 (9.0)		0.696	
	0 (0)	7 (7.5)	4 (3.3)	8 (6.6)	0.078	0.782
Joint pain PT: Arthralgia	8 (8.6)		5 (4.1)		0.170	
	0 (0)	8 (8.6)	0 (0)	5 (4.1)	NA	0.170
Shoulder pain PT: Musculoskeletal pain	1 (1.1)		1 (0.8)		0.847	
	1 (1.1)	0 (0)	0 (0)	1 (0.8)	0.251	0.251
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	0 (0)		4 (3.3)		0.078	
	0 (0)	0 (0)	4 (3.3)	0 (0)	0.078	NA
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Nervous system disorders						
Headache	11 (11.8)		12 (9.8)		0.640	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 93)		Antibody titres above median* (n= 122)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
<i>PT:</i> <i>Headache</i>	3 (3.2)	9 (9.7)	5 (4.1)	7 (5.7)	0.738	0.276

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited qualitative humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, * Median value of antibody titres (P25, P75)= 7.69 (0.73,10.00) on a semiquantitative scale ranging from 0 to >10

Figure S1: Summary of results of immunogenicity and reactogenicity of the main population



Bar diagram of results of main analysis. Immunogenicity is expressed as antibody positiveness (positive-negative titres) and antibody titres (antibody titres below-above median) data (%). Reactogenicity results are represented as % of vaccinees developing each solicited AR

ii.ii Sensitivity analysis 1

Table S7: Characteristics of subpopulation 1

Covariates	Total population (N= 3563)
Age N Mean (SD) Median (P25, P75) min, max	3563 41.84 (12.79) 42.00 (30.00, 53.00) 18.00, 81.00
Gender Male (n, %) Female (n, %)	976 (27.4) 2587 (72.6)
Occupational SARS-CoV-2 contact In contact with SARS-CoV-2 patients Without contact with SARS-CoV-2 patients	1501 (42.1) 1957 (54.9)
^aPrevious SARS-CoV-2 infection Yes No	444 (12.5) 3119 (87.5)
Comorbidities ^b Any comorbidity Arterial hypertension Diabetes mellitus Heart failure Chronic bronchitis Asthma Rheumatic/immune-mediated disease	1305 (36.6) 141 (4.0) 53 (1.5) 13 (0.4) 12 (0.3) 126 (3.5) 33 (0.9)
Drug allergies	302 (8.5)
Food allergies	146 (4.1)
Type of administered vaccine BNT16b2 First dose: Second dose: mRNA-1273 First dose: Second dose:	2698 (75.7) 2167 (60.8) 865 (24.3) 773 (21.7)
^cPopulation type HCP SOTR	3460 103
Humoral immunogenicity (semiquantitative ab titres) Positive Negative	3487 (97.9) 76 (2.1)
IgG titres Positive Negative	326 322 (98.8) 4 (1.2)
Cellular immunogenicity Positive Negative	59 51 (86) 8 (14)

Covariables of studied population. ^aDiagnosis by RCP, antigen test and antibody positive serology; ^bNumber of vaccinees with at least one comorbidity; ^cHCPs: Healthcare professionals; SOTR: solid-organ transplant recipients. Results are provided as absolute and relative (%) numbers for each variable

Table S8: Assessment of antibody positiveness (positive-negative titres)

Variable	Antibody positiveness											
	Negative antibody titres (n= 76)						Positive antibody titres (n= 3487)					
	After 1 st vaccine dose	p- value	After 2 nd vaccine dose	p- value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p- value	After any dose	p- value
Proportions of AR												
Development of any AR (n, %)	56 (73.7)	0.074	45 (59.2)	0.156	64 (84.2)	0.810	2222 (63.7)	0.074	2335 (67.0)	0.156	2971 (85.2)	0.810
Development of any mild AR (n, %)	21 (27.6)	0.063	17 (22.4)	0.308	29 (38.2)	0.198	667 (19.1)	0.063	622 (17.8)	0.308	1089 (31.2)	0.198
Development of any moderate AR (n, %)	26 (34.2)	0.950	27 (35.5)	0.113	42 (55.3)	0.321	1181 (33.9)	0.950	1557 (44.7)	0.113	2123 (60.9)	0.321
Development of any severe AR (n, %)	17 (22.4)	0.520	13 (17.1)	0.017	25 (32.9)	0.207	677 (19.4)	0.520	1036 (29.7)	0.017	1397 (40.1)	0.207
Maximum intensity												
Grade 1 (n, %)	18 (33.3)	0.164	12 (27.3)	0.003	15 (23.8)	0.020	480 (22.9)	0.164	261 (11.6)	0.003	350 (12.2)	0.020
Grade 2 (n, %)	19 (35.2)		19 (43.2)		23 (36.5)		943 (44.9)		949 (42.3)		1132 (39.3)	
Grade 3 (n, %)	17 (31.5)		13 (29.5)		25 (39.7)		677 (32.2)		1036 (46.1)		1397 (48.5)	
Likert score												
Mean (SD)	4.96 (2.41)	0.241	4.95 (2.37)	0.001	5.48 (2.47)	0.031	5.34 (2.46)	0.241	6.10 (2.06)	0.004	6.15 (2.36)	0.031

Antibody titres according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable

Table S9: Assessment of antibody positiveness (positive-negative titres): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain	35 (46.1)		1348 (38.7)		0.190	
PT: Injection site pain	30 (39.5)	13 (17.1)	1058 (30.3)	603 (17.3)	0.090	0.970
Fatigue/asthenia	17 (22.4)		988 (28.3)		0.253	
PT: Fatigue	7 (9.2)	11 (14.5)	223 (14.6)	782 (22.4)	0.940	0.100
Fever	17 (22.4)		1095 (31.4)		0.090	
PT: Pyrexia	9 (11.8)	11 (14.5)	216 (6.2)	974 (27.9)	0.050	0.010
Malaise	7 (9.2)		622 (17.8)		0.050	
PT: Malaise	3 (3.9)	4 (5.3)	138 (4.0)	517 (14.8)	0.990	0.020
Chills	5 (6.6)		448 (12.8)		0.100	
PT: Chills	3 (3.9)	2 (2.6)	83 (2.4)	385 (11.0)	0.380	0.020
Injection site redness	2 (2.6)		155 (4.4)		0.450	
PT: Application site redness	1 (1.3)	1 (1.3)	90 (2.6)	72 (2.1)	0.490	0.650
SOC: Musculoskeletal and connective tissue disorders						
	24 (31.6)		1048 (30.1)		0.770	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	Arm pain PT: Pain in extremity	17 (22.4)	13 (17.1)	690 (19.8)	548 (15.7)	0.580
Muscle pain PT: Myalgia	5 (6.6)		709 (20.3)		0.003	
	2 (2.6)	4 (5.3)	117 (3.4)	621 (17.8)	0.730	0.004
Joint pain PT: Arthralgia	4 (5.3)		328 (9.4)		0.220	
	0 (0)	4 (5.3)	32 (0.9)	307 (8.8)	0.400	0.280
Shoulder pain PT: Musculoskeletal pain	8 (10.5)		106 (3.0)		0.002	
	1 (1.3)	7 (9.2)	61 (1.7)	52 (1.5)	0.770	<0.001
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	5 (6.6)		246 (7.1)		0.870	
	5 (6.6)	0 (0)	144 (4.1)	124 (3.6)	0.290	0.090
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		73 (2.1)		0.200	
	0 (0)	0 (0)	40 (1.1)	39 (1.1)	0.350	0.350
SOC: Nervous system disorders						
Headache PT: Headache	11 (14.5)		967 (27.7)		0.010	
	5 (6.6)	8 (10.5)	330 (9.5)	750 (21.5)	0.390	0.020

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
Facial paralysis PT: Facial paralysis	0 (0)		1 (0)		0.880	
	0 (0)	0 (0)	1 (0)	0 (0)	0.880	NA
Insomnia PT: Insomnia	0 (0)		35 (1.0)		0.380	
	0 (0)	0 (0)	9 (0.3)	26 (0.7)	0.660	0.450
SOC: Gastrointestinal disorders						
Nausea PT: Nausea	2 (2.6)		164 (4.7)		0.400	
	0 (0)	2 (2.6)	53 (1.5)	119 (3.4)	0.280	0.710
Diarrhea PT: Diarrhoea	3 (3.9)		107 (3.1)		0.660	
	1 (1.3)	2 (2.6)	35 (1.0)	73 (2.1)	0.790	0.750
Vomiting PT: Vomiting	2 (2.6)		61 (1.7)		0.560	
	0 (0)	2 (2.6)	15 (0.4)	50 (1.4)	0.570	0.390
Unsolicited adverse reactions						
SOC: Musculoskeletal and connective tissue disorders						
Other musculoskeletal disorders PT: Musculoskeletal disorder	0 (0)		90 (2.6)		0.160	
	0 (0)	0 (0)	32 (0.9)	62 (1.8)	0.400	0.240
SOC: Skin and subcutaneous tissue disorders						
Petechia, ecchymosis	0 (0)		14 (0.4)		0.580	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	PT: <i>Ecchymosis</i>	0 (0)	0 (0)	10 (0.3)	4 (0.1)	0.640
SOC: <i>Nervous system disorders</i>						
Cognitive alteration <i>PT:</i> <i>Cognitive disorder</i>	1 (1.3)		5 (0.1)		0.010	
	1 (1.3)	0 (0)	3 (0.1)	2 (0.1)	0.002	0.830
Alterations of smell and taste <i>PT:</i> <i>Parosmia</i>	0 (0)		8 (0.2)		0.680	
	0 (0)	0 (0)	5 (0.1)	3 (0.1)	0.740	0.800
Paresthesia and hyperesthesia <i>PT:</i> <i>Dysaesthesia</i>	0 (0)		27 (0.8)		0.440	
	0 (0)	0 (0)	13 (0.4)	16 (0.5)	0.590	0.550
Presyncope, syncope and vasovagal syncope <i>PT:</i> <i>Syncope</i>	0 (0)		7 (0.2)		0.700	
	0 (0)	0 (0)	2 (0.1)	5 (0.1)	0.830	0.740
Sleepiness, hypersomnia <i>PT:</i> <i>Hypersomnia</i>	0 (0)		16 (0.5)		0.550	
	0 (0)	0 (0)	3 (0.1)	13 (0.4)	0.800	0.590
Instability sensation, vertigo, sickness <i>PT:</i> <i>Dizziness</i>	4 (5.3)		86 (2.5)		0.120	
	0 (0)	4 (5.3)	30 (0.9)	58 (1.7)	0.420	0.020
Tremor	0 (0)		7 (0.2)		0.70	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	<i>PT:</i> <i>Tremor</i>	0 (0)	0 (0)	2 (0.1)	5 (0.1)	0.830
SOC: <i>Gastrointestinal disorders</i>						
Gastrointestinal disorders <i>PT:</i> <i>Gastrointestinal disorder</i>	1 (1.3)		35 (1.0)		0.790	
	0 (0)	1 (1.3)	12 (0.3)	22 (0.6)	0.610	0.460
SOC: <i>Respiratory, thoracic and mediastinal disorders</i>						
Asthma <i>PT:</i> <i>Asthma</i>	0 (0)		4 (0.1)		0.770	
	0 (0)	0 (0)	1 (0)	2 (0.1)	0.880	0.830
Rhinitis, nasal discharge <i>PT:</i> <i>Rhinitis</i>	0 (0)		26 (0.7)		0.450	
	0 (0)	0 (0)	11 (0.3)	16 (0.5)	0.620	0.550
SOC: <i>Investigations</i>						
Hypertension, hypotension <i>PT:</i> <i>Blood pressure abnormal</i>	1 (1.3)		12 (0.3)		0.160	
	0 (0)	1 (1.3)	4 (0.1)	7 (0.2)	0.770	0.040
SOC: <i>General disorders and administration site conditions</i>						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
Influenza-like symptoms PT: <i>Influenza like illness</i>	0 (0)		47 (1.3)		0.310	
	0 (0)	0 (0)	16 (0.5)	32 (0.9)	0.550	0.400
Sensation of heat, sensation of cold PT: <i>Temperature regulation disorder</i>	1 (1.3)		5 (0.1)		0.010	
	1 (1.3)	0 (0)	2 (0.1)	5 (0.1)	0.002	0.740
Chest pain PT: <i>Chest pain</i>	0 (0)		8 (0.2)		0.680	
	0 (0)	0 (0)	0 (0)	8 (0.2)	NA	0.68
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		4 (0.1)		0.770	
	0 (0)	0 (0)	0 (0)	4 (0.1)	NA	0.77
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	0 (0)		11 (0.3)		0.620	
	0 (0)	0 (0)	5 (0.1)	7 (0.2)	0.740	0.700
SOC: <i>Ear and labyrinth disorders</i>						
PT: <i>Ear pain</i>	0 (0)		3 (0.1)		0.800	
	0 (0)	0 (0)	1 (0)	2 (0.1)	0.880	0.830
SOC: <i>Skin and subcutaneous tissue disorders</i>						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
General pruritus PT: <i>Pruritus</i>	1 (1.3)		7 (0.2)		0.040	
	0 (0)	1 (1.3)	4 (0.1)	3 (0.1)	0.770	0.002
Sweat PT: <i>Cold sweat</i>	0 (0)		16 (0.5)		0.550	
	0 (0)	0 (0)	2 (0.1)	14 (0.4)	0.830	0.580
SOC: Immune system disorders						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: <i>Hypersensitivity</i>	1 (1.3)		49 (1.4)		0.950	
	0 (0)	1 (1.3)	24 (0.7)	31 (0.9)	0.470	0.700
SOC: Cardiac disorders						
Tachycardia PT: <i>Tachycardia</i>	0 (0)		11 (0.3)		0.620	
	0 (0)	0 (0)	5 (0.1)	6 (0.2)	0.740	0.720
SOC: Blood and lymphatic system disorders						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	4 (5.3)		142 (4.1)		0.600	
	2 (2.6)	2 (2.6)	39 (1.1)	107 (3.1)	0.220	0.830
SOC: Infections and infestations						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
Herpetic infection PT:	0 (0)		10 (0.3)		0.640	
<i>Herpes virus infection</i>	0 (0)	0 (0)	6 (0.2)	4 (0.1)	0.720	0.770

Distribution of proportions of solicited and unsolicited AR are displayed by elicited immunogenicity (humoral and cellular) and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable

Table S10: Assessment of antibody positiveness (positive-negative titres): severe solicited AR

Severe adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	11 (14.5)		338 (9.7)		0.170	
	10 (13.2)	1 (1.3)	229 (6.6)	138 (4.0)	0.020	0.240
Fatigue/asthenia <i>PT: Fatigue</i>	7 (9.2)		483 (13.9)		0.250	
	1 (1.3)	6 (7.9)	114 (3.3)	389 (11.2)	0.340	0.370
Fever <i>PT: Pyrexia</i>	2 (2.6)		110 (3.2)		0.800	
	0 (0)	2 (2.6)	19 (0.5)	92 (2.6)	0.520	0.990
Malaise <i>PT: Malaise</i>	1 (1.3)		305 (8.7)		0.020	
	0 (0)	1 (1.3)	53 (1.5)	258 (7.4)	0.280	0.040
Injection site redness <i>PT: Application site redness</i>	1 (1.3)		39 (1.1)		0.870	
	0 (0)	1 (1.3)	21 (0.6)	20 (0.6)	0.500	0.400
SOC: Musculoskeletal and connective tissue disorders						
Arm pain <i>PT: Pain in extremity</i>	5 (6.6)		392 (11.2)		0.200	
	4 (5.3)	1 (1.3)	238 (6.8)	187 (5.4)	0.590	0.120

Severe adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Muscle pain <i>PT:</i> <i>Myalgia</i>	3 (3.9)		333 (9.5)		0.100	
	1 (1.3)	2 (2.6)	45 (1.3)	296 (8.5)	0.980	0.070
Joint pain <i>PT:</i> <i>Arthralgia</i>	2 (2.6)		184 (5.3)		0.310	
	0 (0)	2 (2.6)	17 (0.5)	171 (4.9)	0.540	0.360
Shoulder pain <i>PT:</i> <i>Musculoskeletal pain</i>	1 (1.3)		28 (0.8)		0.620	
	0 (0)	1 (1.3)	11 (0.3)	16 (0.5)	0.620	0.280
SOC: Injury, poisoning and procedural complications						
Injection site swelling <i>PT:</i> <i>Application site swelling</i>	1 (1.3)		70 (2.0)		0.670	
	1 (1.3)	0 (0)	43 (1.2)	33 (0.9)	0.950	0.390
SOC: Vaccination site pruritus						
Injection site pruritus <i>PT:</i> <i>Vaccination site pruritus</i>	0 (0)		18 (0.5)		0.530	
	0 (0)	0 (0)	8 (0.2)	11 (0.3)	0.680	0.620

Severe adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres		Positive antibody titres			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Nervous system disorders						
Headache PT: Headache	3 (3.9)		419 (12.0)		0.030	
	1 (1.3)	2 (2.6)	115 (3.3)	331 (9.5)	0.340	0.040

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited immunogenicity (humoral and cellular) and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable

Table S11: Assessment of antibody titres (antibody titres above-below median):

Variable	Antibody titres below median* (n= 440)						Antibody titres above median * (n= 3123)					
	After 1 st vaccine dose	p- value	After 2 nd vaccine dose	p- value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p- value	After any dose	p- value
Proportions of AR												
Development of any AR (n, %)	295 (67.0)	0.147	291 (66.1)	0.753	382 (86.8)	0.302	1983 (63.5)	0.147	2089 (66.9)	0.753	2653 (85.0)	0.302
Development of any mild AR (n, %)	102 (23.2)	0.028	99 (22.5)	0.008	168 (38.2)	0.001	586 (18.8)	0.028	540 (17.3)	0.008	950 (30.4)	0.001
Development of any moderate AR (n, %)	147 (33.4)	0.825	188 (42.7)	0.436	257 (58.4)	0.280	1060 (33.9)	0.825	1396 (44.7)	0.436	1908 (61.1)	0.280
Development of any severe AR (n, %)	90 (20.5)	0.581	108 (24.5)	0.016	163 (37.0)	0.190	604 (19.3)	0.581	941 (30.1)	0.016	1259 (40.3)	0.190
Maximum intensity												
Grade 1 (n, %)	75 (26.9)	0.223	47 (17.0)	0.006	62 (16.9)	0.017	423 (22.6)	0.223	226 (11.2)	0.006	303 (11.8)	0.017
Grade 2 (n, %)	114 (40.9)		121 (43.8)		142 (38.7)		848 (45.2)		847 (42.1)		1013 (39.3)	
Grade 3 (n, %)	90 (32.3)		108 (39.1)		163 (44.4)		604 (32.2)		941 (46.7)		1259 (48.9)	
Likert score Mean (SD)	5.27 (2.21)	0.685	5.64 (2.14)	0.003	5.91 (2.17)	0.067	5.34 (2.50)	0.685	6.14 (2.05)	0.003	6.16 (2.38)	0.067

Antibody titres (in median titres </> median) according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, * Median value of antibody titres (P25, P75)= 10.00 (10.00, 10.00) on a semiquantitative scale ranging from 0 to >10

Table S12: Assessment of antibody titres (antibody titres above-below median): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	192 (43.6)		1191 (38.1)		0.030	
	145 (33.0)	82 (18.6)	943 (30.2)	534 (17.1)	0.240	0.420
Fatigue/asthenia <i>PT: Fatigue</i>	112 (25.5)		893 (28.6)		0.170	
	41 (9.3)	85 (19.3)	279 (8.9)	708 (22.7)	0.790	0,110
Fever <i>PT: Pyrexia</i>	139 (31.6)		973 (31.2)		0.850	
	37 (8.4)	114 (25.9)	188 (6.0)	871 (27.9)	0.050	0.380
Malaise <i>PT: Malaise</i>	68 (15.5)		561 (18.0)		0.200	
	16 (3.6)	56 (12.7)	125 (4.0)	465 (14.9)	0.710	0.230
Chills <i>PT: Chills</i>	45 (10.2)		408 (13.1)		0.090	
	10 (2.3)	35 (8.0)	76 (2.4)	352 (11.3)	0.840	0.040
Injection site redness <i>PT: Application site redness</i>	17 (3.9)		140 (4.5)		0.550	
	10 (2.3)	8 (1.8)	81 (2.6)	65 (2.1)	0.700	0.720

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	126 (28.6)		946 (30.3)		0.480	
	84 (19.1)	69 (15.7)	623 (19.9)	492 (15.8)	0.670	0.970
Muscle pain PT: Myalgia	94 (21.4)		620 (19.9)		0.460	
	17 (3.9)	79 (18.0)	102 (3.3)	546 (17.5)	0.510	0.810
Joint pain PT: Arthralgia	43 (9.8)		289 (9.3)		0.730	
	5 (1.1)	38 (8.6)	27 (0.9)	273 (8.7)	0.570	0.940
Shoulder pain PT: Musculoskeletal pain	21 (4.8)		93 (3.0)		0.040	
	8 (1.8)	13 (3.0)	54 (1.7)	46 (1.5)	0.890	0.020
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	37 (8.4)		214 (6.9)		0.230	
	25 (5.7)	14 (3.2)	124 (4.0)	110 (3.5)	0.090	0.720

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	11 (2.5)		62 (2.0)		0.480	
	6 (1.4)	5 (1.1)	34 (1.1)	34 (1.1)	0.610	0.930
SOC: Nervous system disorders						
Headache PT: Headache	118 (26.8)		860 (27.5)		0.750	
	38 (8.6)	89 (20.2)	297 (9.5)	669 (21.4)	0.560	0.570
Facial paralysis PT: Facial paralysis	0 (0)		1 (0)		0.710	
	0 (0)	0 (0)	1 (0)	0 (0)	0.710	NA
Insomnia PT: Insomnia	7 (1.6)		28 (0.9)		0.170	
	1 (0.2)	6 (1.4)	8 (0.3)	20 (0.6)	0.910	0.100
SOC: Gastrointestinal disorders						
Nausea PT: Nausea	25 (5.7)		141 (4.5)		0.280	
	13 (3.0)	12 (2.7)	40 (1.3)	109 (3.5)	0.010	0.410

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Diarrhea PT: Diarrhoea	13 (3.0)		97 (3.1)		0.860	
	3 (0.7)	10 (2.3)	33 (1.1)	65 (2.1)	0.460	0.790
Vomiting PT: Vomiting	8 (1.8)		55 (1.8)		0.930	
	1 (0.2)	7 (1.6)	14 (0.4)	45 (1.4)	0.500	0.810
Unsolicited adverse reactions						
SOC: Musculoskeletal and connective tissue disorders						
Other musculoskeletal disorders PT: Musculoskeletal disorder	10 (2.3)		80 (2.6)		0.720	
	3 (0.7)	7 (1.6)	29 (0.9)	55 (1.8)	0.610	0.800
SOC: Skin and subcutaneous tissue disorders						
Petechia, ecchymosis PT: Ecchymosis	1 (0.2)		13 (0.4)		0.560	
	1 (0.2)	0 (0)	9 (0.3)	4 (0.1)	0.820	0.450
SOC: Nervous system disorders						
Cognitive alteration PT: Cognitive disorder	1 (0.2)		5 (0.2)		0.750	
	1 (0.2)	0 (0)	3 (0.1)	2 (0.1)	0.440	0.600

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Alterations of smell and taste PT: Parosmia	2 (0.5)		6 (0.2)		0.280	
	1 (0.2)	1 (0.2)	4 (0.1)	2 (0.1)	0.600	0.270
Paresthesia and hyperesthesia PT: Dysaesthesia	5 (1.1)		22 (0.7)		0.330	
	2 (0.5)	3 (0.7)	11 (0.4)	13 (0.4)	0.740	0.440
Presyncope, syncope and vasovagal syncope PT: Syncope	1 (0.2)		6 (0.2)		0.880	
	0 (0)	1 (0.2)	2 (0.1)	4 (0.1)	0.560	0.600
Sleepiness, hypersomnia PT: Hypersomnia	0 (0)		16 (0.5)		0.130	
	0 (0)	0 (0)	3 (0.1)	13 (0.4)	0.520	0.180
Instability sensation, vertigo, sickness PT: Dizziness	8 (1.8)		82 (2.6)		0.310	
	2 (0.5)	7 (1.6)	28 (0.9)	55 (1.8)	0.340	0.800
Tremor PT: Tremor	0 (0)		7 (0.2)		0.320	
	0 (0)	0 (0)	2 (0.1)	5 (0.1)	0.600	0.400
SOC: Gastrointestinal disorders						

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Gastrointestinal disorders PT: Gastrointestinal disorder	7 (1.6)		29 (0.9)		0.190	
	1 (0.2)	5 (1.1)	11 (0.4)	18 (0.6)	0.670	0.170
SOC: Respiratory, thoracic and mediastinal disorders						
Asthma PT: Asthma	1 (0.2)		3 (0.1)		0.440	
	1 (0.2)	0 (0)	0 (0)	2 (0.1)	0.010	0.600
Rhinitis, nasal discharge PT: Rhinitis	2 (0.5)		24 (0.8)		0.47	
	2 (0.5)	0 (0)	9 (0.3)	16 (0.5)	0.560	0.130
SOC: Investigations						

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Hypertension, hypotension PT: <i>Blood pressure abnormal</i>	3 (0.7)		10 (0.3)		0.240	
	0 (0)	3 (0.7)	4 (0.1)	5 (0.2)	0.450	0.030
SOC: General disorders and administration site conditions						
Influenza-like symptoms PT: <i>Influenza like illness</i>	4 (0.9)		43 (1.4)		0.420	
	2 (0.5)	3 (0.7)	14 (0.4)	29 (0.9)	0.990	0.610
Sensation of heat, sensation of cold PT: <i>Temperature regulation disorder</i>	3 (0.7)		10 (0.3)		0.240	
	0 (0)	3 (0.7)	4 (0.1)	5 (0.2)	0.450	0.030
Chest pain PT: <i>Chest pain</i>	0 (0)		8 (0.3)		0.290	
	0 (0)	0 (0)	0 (0)	8 (0.3)	NA	0.290
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		4 (0.1)		0.450	
	0 (0)	0 (0)	0 (0)	4 (0.1)	NA	0.450
	2 (0.5)		9 (0.3)		0.560	

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	0 (0)	2 (0.5)	5 (0.2)	5 (0.2)	0.400	0.190
SOC: Ear and labyrinth disorders						
PT: <i>Ear pain</i>	0 (0)		3 (0.1)		0.520	
	0 (0)	0 (0)	1 (0)	2 (0.1)	0.710	0.600
SOC: Skin and subcutaneous tissue disorders						
General pruritus PT: <i>Pruritus</i>	2 (0.5)		6 (0.2)		0.280	
	1 (0.2)	1 (0.2)	3 (0.1)	3 (0.1)	0.440	0.440
Sweat PT: <i>Cold sweat</i>	2 (0.5)		14 (0.4)		0.990	
	0 (0)	2 (0.5)	2 (0.1)	12 (0.4)	0.600	0.830
SOC: Immune system disorders						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: <i>Hypersensitivity</i>	8 (1.8)		42 (1.3)		0.430	
	1 (0.2)	7 (1.6)	23 (0.7)	25 (0.8)	0.220	0.100

Adverse reactions (PT MedDRA term)	Development of any AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres below median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
SOC: <i>Cardiac disorders</i>						
Tachycardia PT: <i>Tachycardia</i>	0 (0)		11 (0.4)		0.210	
	0 (0)	0 (0)	5 (0.2)	6 (0.2)	0.400	0.360
SOC: <i>Blood and lymphatic system disorders</i>						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	20 (4.5)		126 (4.0)		0.610	
	7 (1.6)	14 (3.2)	34 (1.1)	95 (3.0)	0.360	0.870
SOC: <i>Infections and infestations</i>						
Herpetic infection PT: <i>Herpes virus infection</i>	1 (0.2)		9 (0.3)		0.820	
	1 (0.2)	0 (0)	5 (0.2)	4 (0.1)	0.750	0.450

Distribution of proportions of non-severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity (mean Ab titres $\leq$ Q2) and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, *Median value of antibody titres (P25, P75)= 10.00 (10.00, 10.00) on a semiquantitative scale ranging from 0 to >10

Table S13: Assessment of antibody titres (antibody titres above-below median): severe solicited AR

Adverse reactions (PT MedDRA term)	Development of any severe AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres above median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	47 (10.7)		302 (9.7)		0.500	
	33 (7.5)	14 (3.2)	206 (6.6)	125 (4.0)	0.480	0.410
Fatigue/astenia <i>PT: Fatigue</i>	49 (11.1)		441 (14.1)		0.090	
	11 (2.5)	40 (9.1)	104 (3.3)	355 (11.4)	0.360	0.150
Fever <i>PT: Pyrexia</i>	10 (2.3)		102 (3.3)		0.260	
	2 (0.5)	8 (1.8)	17 (0.5)	86 (2.8)	0.810	0.250
Malaise <i>PT: Malaise</i>	32 (7.3)		274 (8.8)		0.290	
	7 (1.6)	25 (5.7)	46 (1.5)	234 (7.5)	0.850	0.170
Chills <i>PT: Chills</i>	NA		NA		NA	
	NA	NA	NA	NA	NA	NA
Injection site redness <i>PT: Application site redness</i>	6 (1.4)		34 (1.1)		0.610	
	4 (0.9)	2 (0.5)	17 (0.5)	19 (0.6)	0.350	0.690

Adverse reactions (PT MedDRA term)	Development of any severe AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres above median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	43 (9.8)		354 (11.3)		0.330	
	30 (6.8)	15 (3.4)	212 (6.8)	173 (5.5)	0.980	0.060
Muscle pain PT: Myalgia	35 (8.0)		301 (9.6)		0.260	
	5 (1.1)	29 (6.6)	41 (1.3)	269 (8.6)	0.760	0.150
Joint pain PT: Arthralgia	25 (5.7)		161 (5.2)		0.640	
	3 (0.7)	22 (5.0)	14 (0.4)	151 (4.8)	0.510	0.880
Shoulder pain PT: Musculoskeletal pain	3 (0.7)		26 (0.8)		0.740	
	2 (0.5)	1 (0.2)	9 (0.3)	16 (0.5)	0.560	0.420
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	12 (2.7)		59 (1.9)		0.240	
	10 (2.3)	2 (0.5)	34 (1.1)	31 (1.0)	0.030	0.270

Adverse reactions (PT MedDRA term)	Development of any severe AR				^a p-value	
	Antibody titres below median* (n=440)		Antibody titres above median* (n=3123)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		18 (0.6)		0.110	
	0 (0)	0 (0)	8 (0.3)	11 (0.4)	0.290	0.210
SOC: Nervous system disorders						
Headache PT: Headache	39 (8.9)		383 (12.3)		0.040	
	11 (2.5)	28 (6.4)	105 (3.4)	305 (9.8)	0.340	0.020

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity (mean Ab titres $\leq$ Q2) and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, *Median value of antibody titres (P25, P75)= 10.00 (10.00, 10.00) on a semiquantitative scale ranging from 0 to >10

Table S14: Cellular immunogenicity assessment

Variable	Negative cellular immunogenicity (n= 8)						Positive cellular immunogenicity (n= 51)					
	After 1 st vaccine dose	p- value	After 2 nd vaccine dose	p- value	After any dose	p- value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p- value	After any dose	p- value
Proportions of AR												
Development of any AR (n, %)	6 (75.0)	0.715 9	6 (75.0)	0.715 9	6 (75.0)	0.135 5	35 (68.6)	0.7159	35 (68.6)	0.7159	47 (92.2)	0.1355
Development of any mild AR (n, %)	1 (12.5)	0.815 7	3 (37.5)	0.194 6	4 (50.0)	0.246 6	8 (15.7)	0.8157	9 (17.6)	0.1946	15 (29.4)	0.2466
Development of any moderate AR (n, %)	3 (37.5)	0.989 4	4 (50.0)	0.716 2	5 (62.5)	0.989 4	19 (37.3)	0.9894	22 (43.1)	0.7162	32 (62.7)	0.9894
Development of any severe AR (n, %)	3 (37.5)	0.256 3	1 (12.5)	0.169 1	3 (37.5)	0.478 3	10 (19.6)	0.2563	19 (37.3)	0.1691	26 (51.0)	0.4783
Maximum intensity												
Grade 1 (n, %)	1 (16.7)	0.639 4	1 (20.0)	0.342 3	1 (16.7)	0.906 7	7 (21.2)	0.6394	5 (14.3)	0.3423	5 (10.9)	0.9067
Grade 2 (n, %)	2 (33.3)		3 (60.0)		2 (33.3)		16 (48.5)		11 (31.4)		15 (32.6)	
Grade 3 (n, %)	3 (50.0)		1 (20.0)		3 (50.0)		10 (30.3)		19 (54.3)		26 (56.5)	
Likert score Mean (SD)	5.67 (1.97)	0.755	5.20 (2.28)	0.256	5.48 (2.47)	0.467	5.32 (1.89)	0.755	6.32 (1.85)	0.256	6.45 (1.73)	0.467

Cellular immunogenicity according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable

Table S15: Cellular immunogenicity assessment: solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	1 (12.5)		23 (45.1)		0.080	
	0 (0)	1 (12.5)	17 (33.3)	14 (27.5)	0.050	0.370
Fatigue/asthenia <i>PT: Fatigue</i>	3 (37.5)		14 (27.5)		0.560	
	2 (25.0)	3 (37.5)	3 (5.9)	12 (23.5)	0.070	0.400
Fever <i>PT: Pyrexia</i>	2 (25.0)		17 (33.3)		0.639	
	1 (12.5)	2 (25.0)	5 (9.8)	13 (25.5)	0.810	0.980
Malaise <i>PT: Malaise</i>	2 (25.0)		10 (19.6)		0.720	
	0 (0)	2 (25.0)	2 (3.9)	9 (17.6)	0.570	0.620
Chills <i>PT: Chills</i>	1 (12.5)		7 (13.7)		0.925	
	1 (12.5)	0 (0)	5 (9.8)	2 (3.9)	0.810	0.570
Injection site redness <i>PT: Application site redness</i>	0 (0)		2 (3.9)		0.570	
	0 (0)	0 (0)	1 (2.0)	1 (2.0)	0.690	0.690

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Musculoskeletal and connective tissue disorders</i>						
Arm pain <i>PT:</i> <i>Pain in extremity</i>	3 (37.5)		15 (29.4)		0.640	
	3 (37.5)	1 (12.5)	8 (15.7)	7 (13.7)	0.140	0.930
Muscle pain <i>PT:</i> <i>Myalgia</i>	1 (12.5)		13 (25.5)		0.420	
	1 (12.5)	0 (0)	2 (3.9)	12 (23.5)	0.300	0.120
Joint pain <i>PT:</i> <i>Arthralgia</i>	0 (0)		7 (13.7)		0.260	
	0 (0)	0 (0)	0 (0)	7 (13.7)	NA	0.260
Shoulder pain <i>PT:</i> <i>Musculoskeletal pain</i>	1 (12.5)		1 (2.0)		0.130	
	1 (12.5)	0 (0)	0 (0)	1 (2.0)	0.010	0.700
SOC: <i>Injury, poisoning and procedural complications</i>						
Injection site swelling <i>PT:</i> <i>Application site swelling</i>	0 (0)		4 (7.8)		0.410	
	0 (0)	0 (0)	3 (5.9)	2 (3.9)	0.480	0.570

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Nervous system disorders						
Headache PT: Headache	3 (37.5)		16 (31.4)		0.730	
	2 (25.0)	2 (25.0)	6 (11.8)	12 (23.5)	0.310	0.930
Facial paralysis PT: Facial paralysis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Insomnia PT: Insomnia	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Nausea PT: Nausea	0 (0)		3 (5.9)		0.480	
	0 (0)	0 (0)	1 (2.0)	2 (3.9)	0.700	0.600
Diarrhea PT: Diarrhoea	1 (12.5)		0 (0)		0.010	
	1 (12.5)	78 (2.2)	0 (0)	0 (0)	0.010	NA
Vomiting PT: Vomiting	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Unsolicited adverse reactions						
SOC: <i>Musculoskeletal and connective tissue disorders</i>						
Other musculoskeletal disorders <i>PT: Musculoskeletal disorder</i>	1 (12.5)		1 (2.0)		0.130	
	0 (0)	1 (12.5)	0 (0)	1 (2.0)	NA	0.130
SOC: <i>Skin and subcutaneous tissue disorders</i>						
Petechia, ecchymosis PT: <i>Ecchymosis</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Nervous system disorders</i>						
Cognitive alteration <i>PT: Cognitive disorder</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Alterations of smell and taste <i>PT: Parosmia</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Paresthesia and hyperesthesia <i>PT: Dysaesthesia</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Presyncope, syncope and vasovagal syncope PT: Syncope	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Sleepiness, hypersomnia PT: Hypersomnia	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Instability sensation, vertigo, sickness PT: Dizziness	0 (0)		2 (3.9)		0.57	
	0 (0)	0 (0)	1 (2.0)	1 (2.0)	0.700	0.700
Tremor PT: Tremor	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Gastrointestinal disorders PT: Gastrointestinal disorder	1 (12.5)		0 (0)		0.010	
	1 (12.5)	25 (0.7)	0 (0)	0 (0)	0.010	NA
SOC: Respiratory, thoracic and mediastinal disorders						
Asthma PT: Asthma	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Rhinitis, nasal discharge PT: Rhinitis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Investigations						
Hypertension, hypotension PT: Blood pressure abnormal	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: General disorders and administration site conditions						
Influenza-like symptoms PT: Influenza like illness	0 (0)		1 (2.0)		0.700	
	0 (0)	0 (0)	1 (2.0)	0 (0)	0.700	NA
Sensation of heat, sensation of cold PT: Temperature regulation disorder	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Chest pain PT: Chest pain	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Hiporexia, anorexia PT: Decreased appetite	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Ear and labyrinth disorders</i>						
PT: <i>Ear pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Skin and subcutaneous tissue disorders</i>						
General pruritus PT: <i>Pruritus</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Sweat PT: <i>Cold sweat</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Immune system disorders</i>						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: <i>Hypersensitivity</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA

Adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: <i>Cardiac disorders</i>						
Tachycardia PT: <i>Tachycardia</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Blood and lymphatic system disorders</i>						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	0 (0)		2 (3.9)		0.570	
	0 (0)	0 (0)	1 (2.0)	1 (2.0)	0.700	0.700
SOC: <i>Infections and infestations</i>						
Herpetic infection PT: <i>Herpes virus infection</i>	0 (0)		1 (2.0)		0.700	
	0 (0)	0 (0)	1 (2.0)	0 (0)	0.700	NA

Distribution of proportions of non-severe solicited and unsolicited AR are displayed by elicited cellular immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant. Results are provided as absolute and relative (%) numbers for each variable

Table S16: Cellular immunogenicity assessment: severe solicited AR

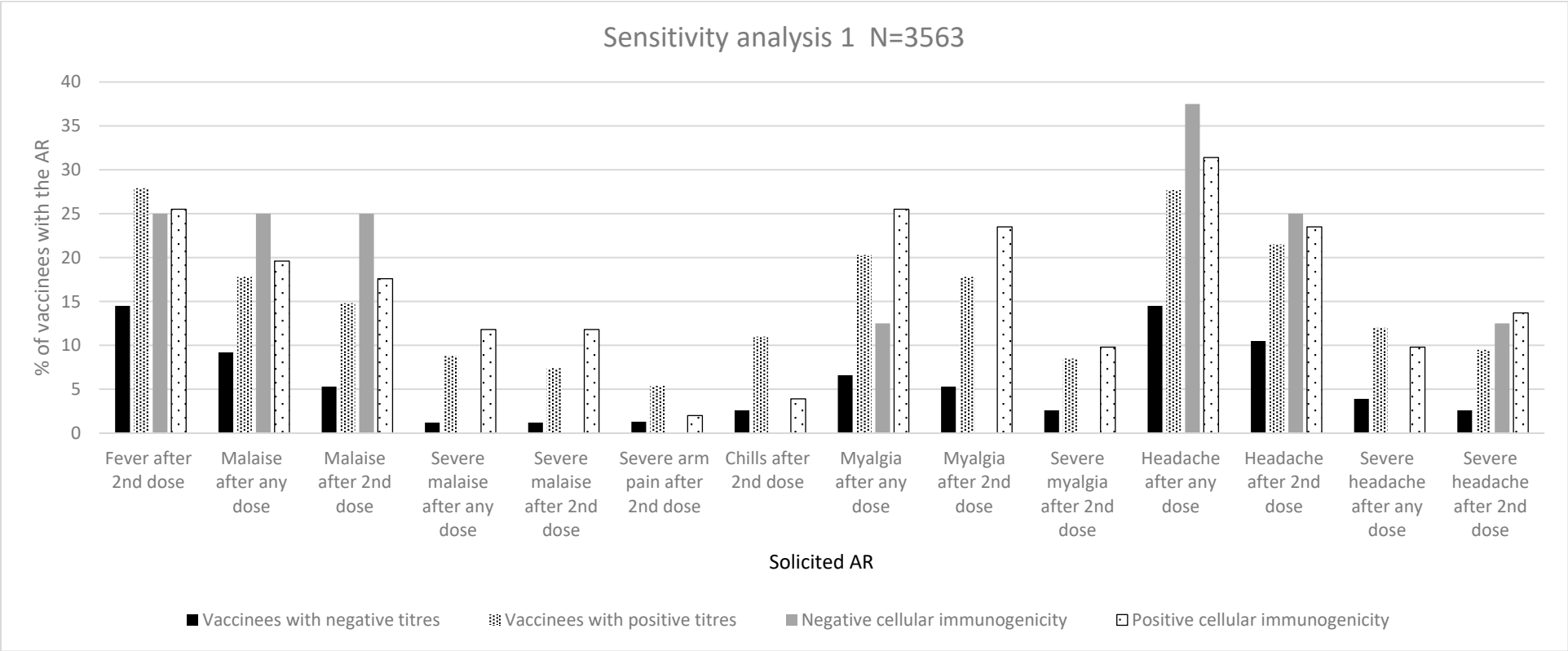
Severe adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	0 (0)		7 (13.7)		0.260	
	0 (0)	0 (0)	2 (3.9)	5 (9.8)	0,570	0.350
Fatigue/astenia <i>PT: Fatigue</i>	1 (12.5)		10 (19.6)		0.630	
	1 (12.5)	0 (0)	2 (3.9)	9 (17.6)	0.300	0.200
Fever <i>PT: Pyrexia</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)		
Malaise <i>PT: Malaise</i>	0 (0)		6 (11.8)		0.310	
	0 (0)	0 (0)	0 (0)	6 (11.8)	NA	0.310
Injection site redness <i>PT: Application site redness</i>	0 (0)		1 (2.0)		0.700	
	0 (0)	0 (0)	1 (2.0)	0 (0)	0.70	NA
SOC: Musculoskeletal and connective tissue disorders						

Severe adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Arm pain PT: <i>Pain in extremity</i>	2 (25.0)		5 (9.8)		0.220	
	2 (25.0)	0 (0)	4 (7.8)	1 (2.0)	0.140	0.700
Muscle pain PT: <i>Myalgia</i>	0 (0)		6 (11.8)		0.310	
	0 (0)	0 (0)	1 (2.0)	5 (9.8)	0.700	0.350
Joint pain PT: <i>Arthralgia</i>	0 (0)		5 (9.8)		0.350	
	0 (0)	0 (0)	0 (0)	5 (9.8)	NA	0.350
Shoulder pain PT: <i>Musculoskeletal pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Injury, poisoning and procedural complications</i>						

Severe adverse reactions (PT MedDRA term)	Cellular immunogenicity				^a p-value	
	Negative		Positive			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Injection site swelling <i>PT:</i> <i>Application site swelling</i>	0 (0)		2 (3.9)		0.570	
	0 (0)	0 (0)	2 (3.9)	0 (0)	0.570	NA
<i>SOC: Vaccination site pruritus</i>						
Injection site pruritus <i>PT:</i> <i>Vaccination site pruritus</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
<i>SOC: Nervous system disorders</i>						
Headache <i>PT:</i> <i>Headache</i>	1 (12.5)		8 (15.7)		0.820	
	0 (0)	1 (12.5)	1 (2.0)	7 (13.7)	0.700	0.930

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited cellular immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant. Results are provided as absolute and relative (%) numbers for each variable

Figure S2: Summary of results of immunogenicity and reactogenicity of sensitivity analysis 1



Bar diagram of results of main analysis. Immunogenicity is expressed as antibody positiveness (positive-negative titres) and cellular immunogenicity (positive-negative) data (%). Reactogenicity results are represented as % of vaccinees developing each solicited AR

ii.iii Sensitivity analysis 2

Table S17: Characteristics of subpopulation 2

Covariates	Total population (N=597)
Age N Mean (SD) Median (P25, P75) min, max	3563 39.42 (12.69) 38.00 (28.00 , 50.00) 18.00 , 69.00
Gender Male (n, %) Female (n, %)	173 (29.0) 424 (71.0)
Occupational SARS-CoV-2 contact In contact with SARS-CoV-2 patients Without contact with SARS-CoV-2 patients	282 (47.2) 315 (52.8)
^aPrevious SARS-CoV-2 infection Yes No	269 (45.1) 328 (54.9)
Comorbidities ^b Any comorbidity Arterial hypertension Diabetes mellitus Heart failure Chronic bronchitis Asthma Rheumatic/immune-mediated disease	212 (35.5) 25 (4.2) 9 (1.5) 2 (0.3) 2 (0.3) 19 (3.2) 6 (1.0)
Drug allergies	49 (8.2)
Food allergies	25 (4.2)
Type of administered vaccine BNT16b2 First dose: Second dose: mRNA-1273 First dose: Second dose:	446 (74.7) 341 (57.1) 151 (25.3) 120 (20.1)
Humoral immunogenicity (semiquantitative ab titres) Positive Negative	324 (54) 273 (46)
IgG titres Positive Negative	164 (99.4) 2 (1.2)

Covariables of studied population. ^aDiagnosis by RCP, antigen test and antibody positive serology; ^bNumber of vaccinees with at least one comorbidity. Results are provided as absolute and relative (%) numbers for each variable

Table S18: Assessment of antibody positiveness (positive-negative titres)

Variable	Antibody positiveness											
	Negative antibody titres (n= 273)						Positive antibody titres (n= 324)					
	After 1 st vaccine dose	p- value	After 2 nd vaccine dose	p- value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p- value	After any dose	p- value
Proportions of AR												
Development of any AR (n, %)	189 (69.2)	0.221	187 (68.5)	0.008	238 (87.2)	0.445	239 (73.8)	0.221	188 (58.0)	0.008	289 (89.2)	0.445
Development of any mild AR (n, %)	68 (24.9)	0.296	60 (22.0)	0.100	108 (39.6)	0.115	69 (21.3)	0.296	54 (16.7)	0.100	108 (33.3)	0.115
Development of any moderate AR (n, %)	99 (36.3)	0.099	126 (46.2)	0.052	165 (60.4)	0.690	139 (42.9)	0.099	124 (38.3)	0.052	201 (62.0)	0.690
Development of any severe AR (n, %)	53 (19.4)	0.017	72 (26.4)	0.411	99 (36.3)	0.204	90 (27.8)	0.017	76 (23.5)	0.411	134 (41.4)	0.204
Maximum intensity												
Grade 0 (n, %)	93 (34.1)	0.050	98 (35.9)	0.265	45 (16.5)	0.587	101 (31.2)	0.050	142 (43.8)	0.265	47 (14.5)	0.587
Grade 1 (n, %)	48 (17.6)		26 (9.5)		35 (12.8)		39 (12.0)		25 (7.7)		35 (10.8)	
Grade 2 (n, %)	79 (28.9)		77 (28.2)		94 (34.4)		94 (29.0)		81 (25.0)		108 (33.3)	
Grade 3 (n, %)	53 (19.4)		72 (26.4)		99 (36.3)		90 (27.8)		76 (23.5)		134 (41.4)	
Likert score Mean (SD)	3.37 (2.99)	0.083	3.63 (3.31)	0.001	4.93 (2.99)	0.772	3.83 (3.21)	0.083	3.01 (3.23)	0.001	5.03 (2.95)	0.772

Antibody titres according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody; in bold type: statistically significant. Results are provided as absolute and relative (%) numbers for each variable

Table S19: Assessment of antibody positiveness (positive-negative titres): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	134 (49.1)		119 (36.7)		0.002	
	103 (37.7)	50 (18.3)	92 (28.4)	50 (15.4)	0.015	0.347
Fatigue/asthenia <i>PT: Fatigue</i>	31 (11.4)		23 (7.1)		0.071	
	21 (7.7)	11 (4.0)	20 (6.2)	5 (1.5)	0.465	0.061
Fever <i>PT: Pyrexia</i>	91 (33.3)		121 (37.3)		0.308	
	16 (5.9)	82 (30.0)	73 (22.5)	79 (24.4)	<0.001	0.121
Malaise <i>PT: Malaise</i>	37 (13.6)		76 (23.5)		0.002	
	5 (1.8)	34 (12.5)	36 (11.1)	49 (15.1)	<0.001	0.348
Chills <i>PT: Chills</i>	27 (9.9)		45 (13.9)		0.135	
	2 (0.7)	25 (9.2)	25 (7.7)	24 (7.4)	<0.001	0.438

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Injection site redness PT: Application site redness	15 (5.5)		11 (3.4)		0.211	
	10 (3.7)	6 (2.2)	8 (2.5)	3 (0.9)	0.395	0.204
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	81 (29.7)		90 (27.8)		0.610	
	49 (17.9)	47 (17.2)	73 (22.5)	31 (9.6)	0.167	0.006
Muscle pain PT: Myalgia	66 (24.2)		81 (25.0)		0.816	
	9 (3.3)	58 (21.2)	36 (11.1)	55 (17.0)	0.003	0.185
Joint pain PT: Arthralgia	25 (9.2)		27 (8.3)		0.722	
	0 (0)	25 (9.2)	10 (3.1)	20 (6.2)	0.034	0.169
Shoulder pain PT: Musculoskeletal pain	7 (2.6)		10 (3.1)		0.702	
	5 (1.8)	2 (0.7)	4 (1.2)	5 (1.5)	0.551	0.359
SOC: Injury, poisoning and procedural complications						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Injection site swelling PT: Application site swelling	31 (11.4)		23 (7.1)		0.071	
	21 (7.7)	11 (4.0)	20 (6.2)	5 (1.5)	0.465	0.061
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	8 (2.9)		4 (1.2)		0.141	
	5 (1.8)	3 (1.1)	2 (0.6)	2 (0.6)	0,170	0.520
SOC: Nervous system disorders						
Headache PT: Headache	79 (28.9)		92 (28.4)		0.884	
	24 (8.8)	61 (22.3)	48 (14.8)	60 (18.5)	0.024	0.247
Facial paralysis PT: Facial paralysis	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Insomnia PT: Insomnia	6 (2.2)		5 (1.5)		0.554	
	1 (0.4)	5 (1.8)	1 (0.3)	4 (1.2)	0.903	0.551
SOC: Gastrointestinal disorders						
Nausea	16 (5.9)		16 (4.9)		0.6181	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
PT: Nausea	8 (2.9)	8 (2.9)	11 (3.4)	5 (1.5)	0.747	0.247
Diarrhea PT: Diarrhoea	8 (2.9)		9 (2.8)		0.911	
	3 (1.1)	5 (1.8)	4 (1.2)	5 (1.5)	0.878	0.785
Vomiting PT: Vomiting	7 (2.6)		3 (0.9)		0.120	
	1 (0.4)	6 (2.2)	1 (0.3)	2 (0.6)	0.903	0.094
Unsolicited adverse reactions						
SOC: Musculoskeletal and connective tissue disorders						
Other musculoskeletal disorders PT: Musculoskeletal disorder	7 (2.6)		15 (4.6)		0.182	
	2 (0.7)	5 (1.8)	9 (2.8)	7 (2.2)	0.064	0.775
SOC: Skin and subcutaneous tissue disorders						
Petechia, ecchymosis PT: Ecchymosis	0 (0)		1 (0.3)		0.358	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.358	NA
SOC: Nervous system disorders						
Cognitive alteration PT: Cognitive disorder	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Alterations of smell and taste	1 (0.4)		1 (0.3)		0.903	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
PT: Parosmia	1 (0.4)	0 (0)	0 (0)	1 (0.3)	0.276	0.358
Paresthesia and hyperesthesia PT: Dysaesthesia	3 (1.1)		4 (1.2)		0.878	
	1 (0.4)	2 (0.7)	3 (0.9)	1 (0.3)	0.404	0.466
Presyncope, syncope and vasovagal syncope PT: Syncope	1 (0.4)		0 (0)		0.276	
	0 (0)	1 (0.4)	0 (0)	0 (0)	NA	0.276
Sleepiness, hypersomnia PT: Hypersomnia	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Instability sensation, vertigo, sickness PT: Dizziness	6 (2.2)		3 (0.9)		0.204	
	2 (0.7)	5 (1.8)	2 (0.6)	2 (0.6)	0.863	0.170
Tremor PT: Tremor	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Gastrointestinal disorders PT: Gastrointestinal disorder	5 (1.8)		2 (0.6)		0.170	
	1 (0.4)	4 (1.5)	1 (0.3)	0 (0)	0.903	0.029
SOC: Respiratory, thoracic and mediastinal disorders						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Asthma PT: Asthma	1 (0.4)		0 (0)		0.276	
	1 (0.4)	0 (0)	0 (0)	0 (0)	0.276	NA
Rhinitis, nasal discharge PT: Rhinitis	2 (0.7)		2 (0.6)		0.863	
	2 (0.7)	0 (0)	1 (0.3)	1 (0.3)	0.466	0.358
SOC: Investigations						
Hypertension, hypotension PT: Blood pressure abnormal	2 (0.7)		0 (0)		0.123	
	0 (0)	2 (0.7)	0 (0)	0 (0)	NA	0.123
SOC: General disorders and administration site conditions						
Influenza-like symptoms PT: Influenza like illness	5 (1.8)		4 (1.2)		0.551	
	2 (0.7)	4 (1.5)	2 (0.6)	2 (0.6)	0.863	0.301
Sensation of heat, sensation of cold PT: Temperature regulation disorder	0 (0)		1 (0.3)		0.358	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.358	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Chest pain PT: <i>Chest pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	2 (0.7)		0 (0)		0.123	
	0 (0)	2 (0.7)	0 (0)	0 (0)	NA	0.123
SOC: <i>Ear and labyrinth disorders</i>						
PT: <i>Ear pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Skin and subcutaneous tissue disorders</i>						
General pruritus PT: <i>Pruritus</i>	2 (0.7)		0 (0)		0.123	
	1 (0.4)	0 (0)	1 (0.4)	0 (0)	0.276	0.276
Sweat	2 (0.7)		1 (0.3)		0.466	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
	PT: <i>Cold sweat</i>	0 (0)	2 (0.7)	1 (0.3)	0 (0)	0.358
SOC: <i>Immune system disorders</i>						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: <i>Hypersensitivity</i>	6 (2.2)		4 (1.2)		0.361	
	0 (0)	6 (2.2)	3 (0.9)	1 (0.3)	0.111	0.033
SOC: <i>Cardiac disorders</i>						
Tachycardia PT: <i>Tachycardia</i>	0 (0)		2 (0.6)		0.194	
	0 (0)	0 (0)	1 (0.3)	1 (0.3)	0.358	0.358
SOC: <i>Blood and lymphatic system disorders</i>						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	16 (5.9)		9 (2.8)		0.061	
	6 (2.2)	11 (4.0)	3 (0.9)	6 (1.9)	0.204	0.111
SOC: <i>Infections and infestations</i>						
Herpetic infection PT: <i>Herpes virus infection</i>	1 (0.4)		1 (0.3)		0.903	
	1 (0.4)	0 (0)	1 (0.3)	0 (0)	0.903	NA

Distribution of proportions of non-severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant. Results are provided as absolute and relative (%) numbers for each variable

Table S20: Assessment of antibody positiveness (positive-negative titres): severe solicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	26 (9.5)		30 (9.3)		0.912	
	17 (6.2)	8 (2.9)	20 (6.2)	11 (3.4)	0.978	0.747
Fatigue/asthenia <i>PT: Fatigue</i>	34 (12.5)		40 (12.3)		0.968	
	9 (3.3)	27 (9.9)	14 (4.3)	26 (8.0)	0.517	0.425
Fever <i>PT: Pyrexia</i>	7 (2.6)		17 (5.2)		0.096	
	0 (0)	7 (2.6)	11 (3.4)	7 (2.2)	0.002	0.746
Malaise <i>PT: Malaise</i>	17 (6.2)		42 (13.0)		0.006	
	3 (1.1)	14 (5.1)	18 (5.6)	26 (8.0)	0.003	0.159
Injection site redness <i>PT: Application site redness</i>	5 (1.7)		2 (0.6)		0.170	
	4 (1.4)	1 (0.3)	2 (0.6)	0 (0)	0.301	0.276

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	28 (10.3)		35 (10.8)		0.829	
	19 (7.0)	11 (4.0)	28 (8.6)	8 (2.5)	0.447	0.279
Muscle pain PT: Myalgia	23 (8.0)		36 (11.7)		0.273	
	3 (1.0)	20 (6.9)	18 (5.8)	21 (6.8)	0.003	0.684
Joint pain PT: Arthralgia	14 (5.1)		17 (5.2)		0.948	
	0 (0)	14 (5.1)	6 (1.9)	13 (4.0)	0.024	0.513
Shoulder pain PT: Musculoskeletal pain	1 (0.4)		2 (0.6)		0.666	
	1 (0.4)	0 (0)	1 (0.3)	0 (0)	0.903	NA
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	9 (3.3)		9 (2.8)		0.712	
	8 (2.9)	1 (0.4)	8 (2.5)	1 (0.3)	0.728	0.903
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		1 (0.3)		0.358	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.358	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Negative antibody titres (n= 273)		Positive antibody titres (n= 324)			
	After any dose		After any dose			
	After 1 st dose	After 2 nd dose	After 1 st dose	After 2 nd dose		
SOC: Nervous system disorders						
Headache PT: Headache	24 (8.8)		40 (12.3)		0.162	
	6 (2.2)	19 (7.0)	20 (6.2)	21 (6.5)	0.018	0.816

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant. Results are provided as absolute and relative (%) numbers for each variable

Table S21: Assessment of antibody titres (antibody titres above-below median):

Variable	Antibody titres below median* (n= 288)						Antibody titres above median* (n= 309)					
	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p-value	After any dose	p-value	After 1 st vaccine dose	p-value	After 2 nd vaccine dose	p-value	After any dose	p-value
Proportions of AR												
Development of any AR (n, %)	200 (69.4)	0.239	193 (67.0)	0.040	249 (86.5)	0.183	228 (73.8)	0.239	182 (58.9)	0.040	278 (90.0)	0.183
Development of any mild AR (n, %)	70 (24.3)	0.446	62 (21.5)	0.144	111 (38.5)	0.247	67 (21.7)	0.446	52 (16.8)	0.144	105 (34.0)	0.247
Development of any moderate AR (n, %)	103 (35.8)	0.048	129 (44.8)	0.163	172 (59.7)	0.443	135 (43.7)	0.048	121 (39.2)	0.163	194 (62.8)	0.443
Development of any severe AR (n, %)	60 (20.8)	0.085	75 (26.0)	0.494	107 (37.2)	0.364	83 (26.9)	0.085	73 (23.6)	0.494	126 (40.8)	0.364
Maximum intensity												
Grade 1 (n, %)	50 (26.2)	0.072	27 (14.9)	0.935	36 (15.1)	0.719	37 (17.5)	0.072	24 (13.6)	0.935	34 (12.8)	0.719
Grade 2 (n, %)	81 (42.4)		79 (43.6)		96 (40.2)		92 (43.4)		79 (44.9)		106 (39.8)	
Grade 3 (n, %)	60 (31.4)		75 (41.4)		107 (44.8)		83 (39.2)		73 (41.5)		126 (47.4)	
Likert score		0.083		0.570		0.592		0.083		0.570		0.592
N	189		175		236		206		163		259	
Mean (SD)	5.28 (2.18)		5.87 (2.13)		6.06 (2.15)		5.65 (2.09)		5.77 (2.02)		5.97 (2.07)	
Median	5.00 (3.00,		6.00 (4.00,		6.00 (4.00,		6.00 (4.00,		6.00 (4.00,		6.00 (4.00,	
(P25, P75)	7.00)		8.00)		8.00)		7.00)		7.00)		8.00)	
min,Max	{1.00, 10.00}		{2.00,10.00}		{1.00,10.00}		{0.00,10.00}		{2.00,10.00}		{0.00,10.00}	

Antibody titres (in titres above and below median) according to proportions (rate) of AR and intensity of AR. AR: adverse reaction; Ab: antibody; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, Median value of antibody titres (P25, P75)= 2.53 (0.47 , 10.00) on a semiquantitative scale ranging from 0 to >10

Table S22: Assessment of antibody titres (antibody titres above-below median): solicited and unsolicited AR

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain <i>PT: Injection site pain</i>	141 (49.0)		112 (36.2)		0.002	
	110 (38.2)	52 (18.1)	85 (27.5)	48 (15.5)	0.005	0.410
Fatigue/astenia <i>PT: Fatigue</i>	74 (25.7)		86 (27.8)		0.556	
	24 (8.3)	58 (20.1)	43 (13.9)	53 (17.2)	0.031	0.350
Fever <i>PT: Pyrexia</i>	95 (33.0)		117 (37.9)		0.213	
	19 (6.6)	83 (28.8)	70 (22.7)	78 (25.2)	<0.001	0.325
Malaise <i>PT: Malaise</i>	41 (14.2)		72 (23.3)		0.004	
	7 (2.4)	37 (12.8)	34 (11.0)	46 (14.9)	<0.001	0.472
Chills <i>PT: Chills</i>	29 (10.1)		43 (13.9)		0.149	
	4 (1.4)	25 (8.7)	23 (7.4)	24 (7.8)	0.004	0.685

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Injection site redness PT: Application site redness	15 (5.2)		11 (3.6)		0.324	
	10 (3.5)	6 (2.1)	8 (2.6)	3 (1.0)	0.528	0.265
SOC: Musculoskeletal and connective tissue disorders						
Arm pain PT: Pain in extremity	85 (29.5)		86 (27.8)		0.650	
	52 (18.1)	49 (17.0)	70 (22.7)	29 (9.4)	0.164	0.006
Muscle pain PT: Myalgia	68 (23.6)		79 (25.6)		0.580	
	9 (3.1)	60 (20.8)	36 (11.7)	53 (17.2)	<0.001	0.251
Joint pain PT: Arthralgia	28 (9.7)		24 (7.8)		0.397	
	1 (0.3)	27 (9.4)	9 (2.9)	18 (5.8)	0.015	0.101
Shoulder pain PT: Musculoskeletal pain	9 (3.1)		8 (2.6)		0.694	
	6 (2.1)	3 (1.0)	3 (1.0)	4 (1.3)	0.265	0.774
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	31 (10.8)		23 (7.4)		0.158	
	21 (7.3)	11 (3.8)	20 (6.5)	5 (1.6)	0.693	0.096
SOC: Vaccination site pruritus						
Injection site pruritus PT:	8 (2.8)		4 (1.3)		0.200	
	5 (1.7)	3 (1.0)	2 (0.6)	2 (0.6)	0.217	0.597

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
<i>Vaccination site pruritus</i>						
<i>SOC: Nervous system disorders</i>						
Headache <i>PT:</i> <i>Headache</i>	83 (28.8)		88 (28.5)		0.927	
	26 (9.0)	64 (22.2)	46 (14.9)	57 (18.4)	0.028	0.252
Facial paralysis <i>PT:</i> <i>Facial paralysis</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Insomnia <i>PT:</i> <i>Insomnia</i>	6 (2.1)		5 (1.6)		0.673	
	1 (0.3)	5 (1.7)	1 (0.3)	4 (1.3)	0.960	0.658
<i>SOC: Gastrointestinal disorders</i>						
Nausea <i>PT:</i> <i>Nausea</i>	17 (5.9)		15 (4.9)		0.570	
	9 (3.1)	8 (2.8)	10 (3.2)	5 (1.6)	0.938	0.332
Diarrhea <i>PT:</i> <i>Diarrhoea</i>	9 (3.1)		8 (2.6)		0.694	
	3 (1.0)	6 (2.1)	4 (1.3)	4 (1.3)	0.774	0.453
Vomiting	7 (2.4)		3 (1.0)		0.165	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
PT: Vomiting	1 (0.3)	6 (2.1)	1 (0.3)	2 (0.6)	0.960	0.127
Unsolicited adverse reactions						
SOC: Musculoskeletal and connective tissue disorders						
Other musculoskeletal disorders PT: Musculoskeletal disorder	8 (2.8)		14 (4.5)		0.256	
	3 (1.0)	5 (1.7)	8 (2.6)	7 (2.3)	0.160	0.645
SOC: Skin and subcutaneous tissue disorders						
Petechia, ecchymosis PT: Ecchymosis	0 (0)		1 (0.3)		0.334	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.334	NA
SOC: Nervous system disorders						
Cognitive alteration PT: Cognitive disorder	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Alterations of smell and taste PT: Parosmia	1 (0.3)		1 (0.3)		0.960	
	1 (0.3)	0 (0)	0 (0)	1 (0.3)	0.300	0.334
Paresthesia and hyperesthesia	3 (1.0)		4 (1.3)		0.774	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
PT: Dysaesthesia	1 (0.3)	2 (0.7)	3 (1.0)	1 (0.3)	0.351	0.522
Presyncope, syncope and vasovagal syncope PT: Syncope	1 (0.3)		0 (0)		0.300	
	0 (0)	1 (0.3)	0 (0)	0 (0)	NA	0.300
Sleepiness, hypersomnia PT: Hypersomnia	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Instability sensation, vertigo, sickness PT: Dizziness	6 (2.1)		3 (1.0)		0.265	
	2 (0.7)	5 (1.7)	2 (0.6)	2 (0.6)	0.944	0.217
Tremor PT: Tremor	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: Gastrointestinal disorders						
Gastrointestinal disorders PT: Gastrointestinal disorder	6 (2.1)		1 (0.3)		0.046	
	1 (0.3)	4 (1.4)	1 (0.3)	0 (0)	0.960	0.038
SOC: Respiratory, thoracic and mediastinal disorders						

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Asthma PT: Asthma	1 (0.3)		0 (0)		0.300	
	1 (0.3)	0 (0)	0 (0)	0 (0)	0.300	NA
Rhinitis, nasal discharge PT: Rhinitis	2 (0.7)		2 (0.6)		0.944	
	2 (0.7)	0 (0)	1 (0.3)	1 (0.3)	0.522	0.334
SOC: Investigations						
Hypertension, hypotension PT: Blood pressure abnormal	2 (0.7)		0 (0)		0.142	
	0 (0)	2 (0.7)	0 (0)	0 (0)	NA	0.142
SOC: General disorders and administration site conditions						
Influenza-like symptoms PT: Influenza like illness	5 (1.7)		4 (1.3)		0.658	
	2 (0.7)	4 (1.4)	2 (0.6)	2 (0.6)	0.944	0.364
Sensation of heat, sensation of cold PT: Temperature regulation disorder	0 (0)		1 (0.3)		0.334	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.334	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Chest pain PT: <i>Chest pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Hiporexia, anorexia PT: <i>Decreased appetite</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Inflammation in extremities other than the vaccinated arm PT: <i>Inflammation</i>	2 (0.7)		0 (0)		0.142	
	0 (0)	2 (0.7)	0 (0)	0 (0)	NA	0.142
SOC: <i>Ear and labyrinth disorders</i>						
PT: <i>Ear pain</i>	0 (0)		0 (0)		NA	
	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
SOC: <i>Skin and subcutaneous tissue disorders</i>						
General pruritus PT: <i>Pruritus</i>	2 (0.7)		0 (0)		0.142	
	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0.300	0.300

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
Sweat PT: <i>Cold sweat</i>	2 (0.7)		1 (0.3)		0.522	
	0 (0)	2 (0.7)	1 (0.3)	0 (0)	0.334	0.142
SOC: Immune system disorders						
Immediate hypersensitivity, delayed hypersensitivity, exanthema, urticaria, rash PT: <i>Hypersensitivity</i>	6 (2.1)		4 (1.3)		0.453	
	0 (0)	6 (2.1)	3 (1.0)	1 (0.3)	0.094	0.046
SOC: Cardiac disorders						
Tachycardia PT: <i>Tachycardia</i>	0 (0)		2 (0.6)		0.171	
	0 (0)	0 (0)	1 (0.3)	1 (0.3)	0.334	0.334
SOC: Blood and lymphatic system disorders						
Lymphadenopathy PT: <i>Lymphadenopathy</i>	16 (5.6)		9 (2.9)		0.107	
	6 (2.1)	11 (3.8)	3 (1.0)	6 (1.9)	0.265	0.168
SOC: Infections and infestations						
Herpetic infection PT:	1 (0.3)		1 (0.3)		0.960	
	1 (0.3)	0 (0)	1 (0.3)	0 (0)	0.960	NA

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose		After any dose			
	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose		
<i>Herpes virus infection</i>						

Distribution of proportions of non-severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, Median value of antibody titres (P25, P75)= 2.53 (0.47 , 10.00) on a semiquantitative scale ranging from 0 to >10

Table S23: Assessment of antibody titres (antibody titres above-below median): severe solicited AR

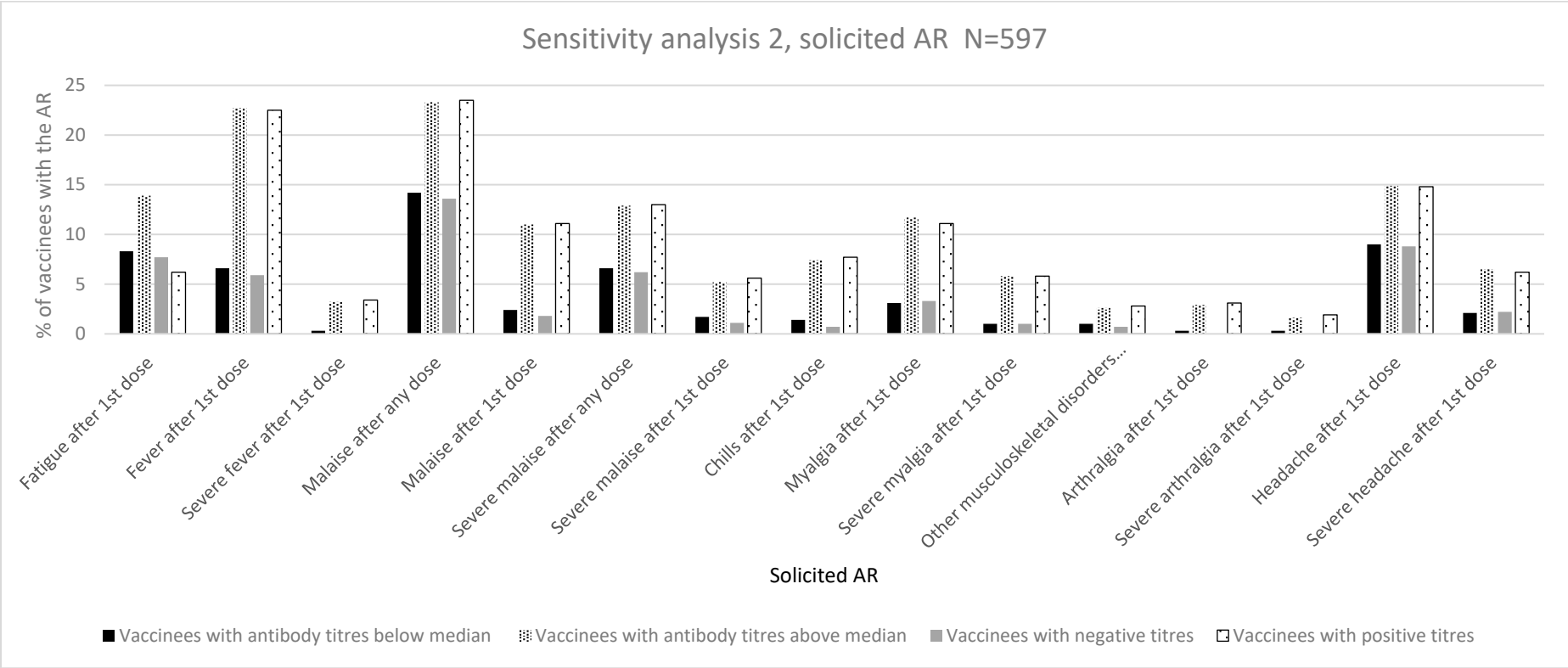
Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose	After any dose	After any dose	After any dose		
Solicited adverse reactions						
SOC: General disorders and administration site conditions						
Injection site pain PT: Injection site pain	31 (10.8)		25 (8.1)		0.263	
	22 (7.6)	8 (2.8)	15 (4.9)	11 (3.6)	0.159	0.587
Fatigue/asthenia PT: Fatigue	35 (12.2)		39 (12.6)		0.862	
	10 (3.5)	27 (9.4)	13 (4.2)	26 (8.4)	0.641	0.680
Fever PT: Pyrexia	8 (2.8)		16 (5.2)		0.136	
	1 (0.3)	7 (2.4)	10 (3.2)	7 (2.3)	0.009	0.894
Malaise PT: Malaise	19 (6.6)		40 (12.9)		0.009	
	5 (1.7)	15 (5.2)	16 (5.2)	25 (8.1)	0.023	0.159
Injection site redness PT: Application site redness	5 (1.7)		2 (0.6)		0.217	
	4 (1.4)	1 (0.3)	2 (0.6)	0 (0)	0.364	0.300
SOC: Musculoskeletal and connective tissue disorders						
Arm pain	30 (10.4)		33 (10.7)		0.917	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose	After any dose	After any dose	After any dose		
PT: Pain in extremity	20 (6.9)	12 (4.2)	27 (8.7)	7 (2.3)	0.416	0.186
Muscle pain PT: Myalgia	23 (8.0)		36 (11.7)		0.134	
	3 (1.0)	20 (6.9)	18 (5.8)	21 (6.8)	0.002	0.943
Joint pain PT: Arthralgia	16 (5.6)		15 (4.9)		0.700	
	1 (0.3)	15 (5.2)	5 (1.6)	12 (3.9)	0.120	0.436
Shoulder pain PT: Musculoskeletal pain	2 (0.7)		1 (0.3)		0.522	
	2 (0.7)	0 (0)	0 (0)	0 (0)	0.142	NA
SOC: Injury, poisoning and procedural complications						
Injection site swelling PT: Application site swelling	9 (3.1)		9 (2.9)		0.880	
	8 (2.8)	1 (0.3)	8 (2.6)	1 (0.3)	0.887	0.960
SOC: Vaccination site pruritus						
Injection site pruritus PT: Vaccination site pruritus	0 (0)		1 (0.3)		0.334	
	0 (0)	0 (0)	1 (0.3)	0 (0)	0.334	NA
SOC: Nervous system disorders						
Headache	26 (9.0)		38 (12.3)		0.200	

Adverse reactions (PT MedDRA term)	Humoral immunogenicity				^a p-value	
	Humoral immunogenicity		Humoral immunogenicity			
	Antibody titres below median* (n= 288)		Antibody titres above median* (n= 309)			
	After any dose	After any dose	After any dose	After any dose		
	<i>PT:</i> <i>Headache</i>	6 (2.1)	21 (7.3)	20 (6.5)	19 (6.1)	0.009

Distribution of proportions of severe solicited and unsolicited AR are displayed by elicited humoral immunogenicity and dose; ^achi-square test; AR: adverse reaction; SOC: System Organ Class; PT: Preferred term; NA: not applicable, p-value not calculable because of absence of valid values in both comparison groups; in bold type: statistically significant results. Results are provided as absolute and relative (%) numbers for each variable, Median value of antibody titres (P25, P75)= 2.53 (0.47 , 10.00) on a semiquantitative scale ranging from 0 to >10

Figure S3: Summary of results of immunogenicity and reactogenicity of sensitivity analysis 2



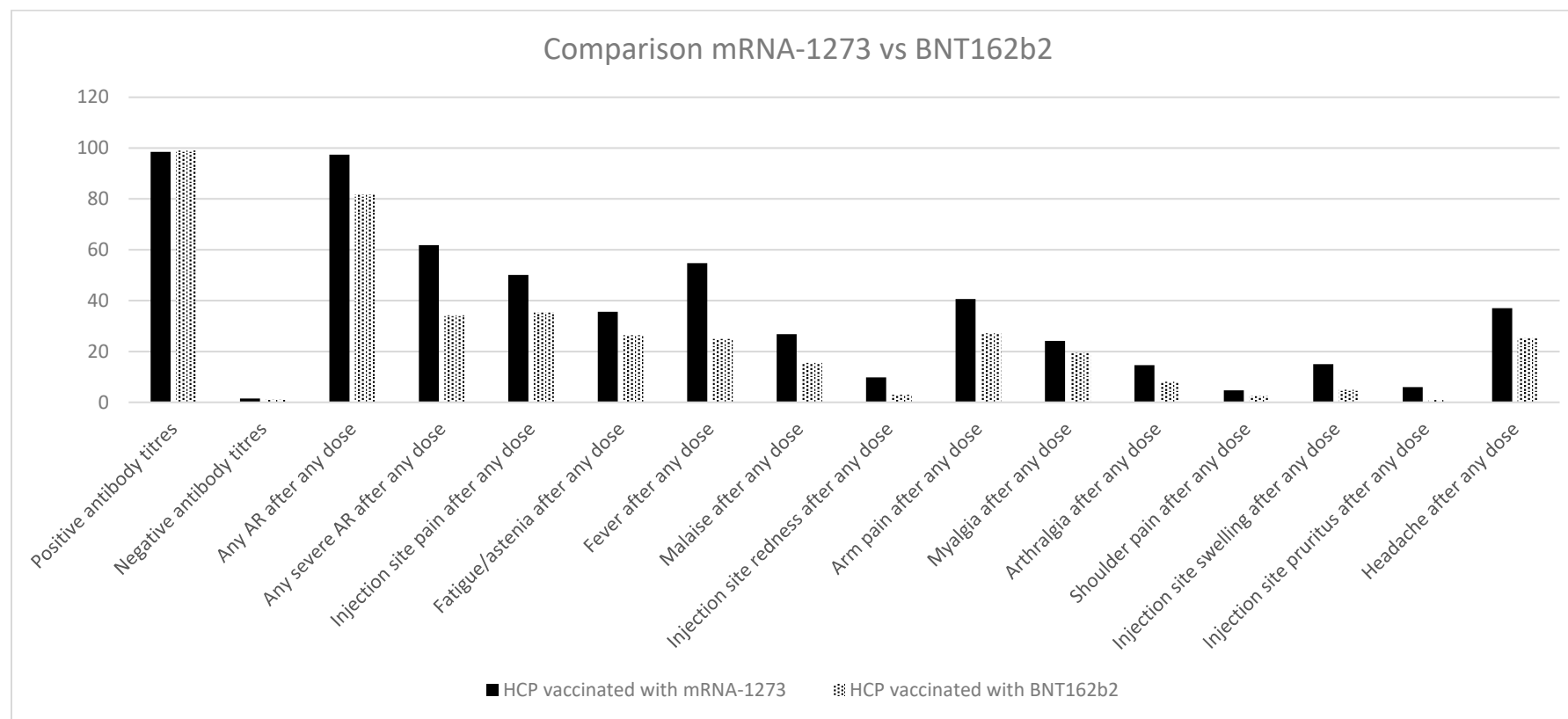
Bar diagram of results of main analysis. Immunogenicity is expressed as antibody positiveness (positive-negative titres) and cellular immunogenicity (positive-negative) data (%). Reactogenicity results are represented as % of vaccinees developing each solicited AR

Table S24: Reactogenicity and immunogenicity by vaccine and population types

Subpopulation 1		Vaccine type (mRNA-1273 vs BNT162b2)		Population type (HCP vs SOTR)		HCP		SOTR	
N=3563		mRNA-1273 All vaccinees N=865	BNT162b2 All vaccinees N=2698	HCP N=3460	SOTR N=103	HCP vaccinated with mRNA-1273 N=762	HCP vaccinated with BNT162b2 N=2698	SOTR vaccinated with mRNA-1273 N=103	SOTR vaccinated with BNT162b2
Immunogenicity (n, %)									
Qualitative immunogenicity	Positive titres	810 (94)	2677 (99)	3428 (99)	59 (57)	746 (98.5)	2665 (99)	59 (57)	NA
	Negative titres	55 (6)	21 (1)	32 (1)	44 (43)	11 (1.5)	21 (1)	44 (43)	NA
Reactogenicity (n, %)									
Any AR after any dose		832 (96.2)	2203 (81.7)	2945 (85.1)	90 (87.4)	742 (97.4)	2203 (81.7)	90 (87.4)	NA
Any severe AR after any dose		500 (57.8)	922 (34.2)	1393 (40.3)	29 (28.2)	471 (61.8)	922 (34.2)	29 (28.2)	NA
Injection site pain		431 (49.8)	952 (35.3)	1334 (38.6)	49 (47.6)	382 (50.1)	952 (35.3)	49 (47.6)	NA
Fatigue/asthenia		292 (33.8)	713 (26.4)	984 (28.4)	21 (20.4)	271 (35.6)	713 (26.4)	21 (20.4)	NA
Fever		439 (50.8)	673 (24.9)	1090 (31.5)	22 (21.4)	417 (54.7)	673 (24.9)	22 (21.4)	NA
Malaise		212 (24.5)	417 (15.5)	621 (17.9)	8 (7.8)	204 (26.8)	417 (15.5)	8 (7.8)	NA
Injection site redness		77 (8.9)	80 (3.0)	155 (4.5)	2 (1.9)	75 (9.8)	80 (3.0)	2 (1.9)	NA
Arm pain		341 (39.4)	731 (27.1)	1040 (30.1)	32 (31.1)	309 (40.6)	731 (27.1)	32 (31.1)	NA
Myalgia		191 (22.1)	523 (19.4)	707 (20.4)	7 (6.8)	184 (24.1)	523 (19.4)	7 (6.8)	NA
Arthralgia		114 (13.2)	218 (8.1)	329 (9.5)	3 (2.9)	111 (14.6)	218 (8.1)	3 (2.9)	NA
Shoulder pain		46 (5.3)	68 (2.5)	104 (3.0)	10 (9.7)	36 (4.7)	68 (2.5)	10 (9.7)	NA
Injection site swelling		120 (13.9)	131 (4.9)	245 (7.1)	6 (5.8)	114 (15.0)	131 (4.9)	6 (5.8)	NA
Injection site pruritus		49 (5.7)	24 (0.9)	70 (2.0)	3 (2.9)	46 (6.0)	24 (0.9)	3 (2.9)	NA
Headache		297 (34.3)	681 (25.2)	963 (27.8)	15 (14.6)	282 (37.0)	681 (25.2)	15 (14.6)	NA

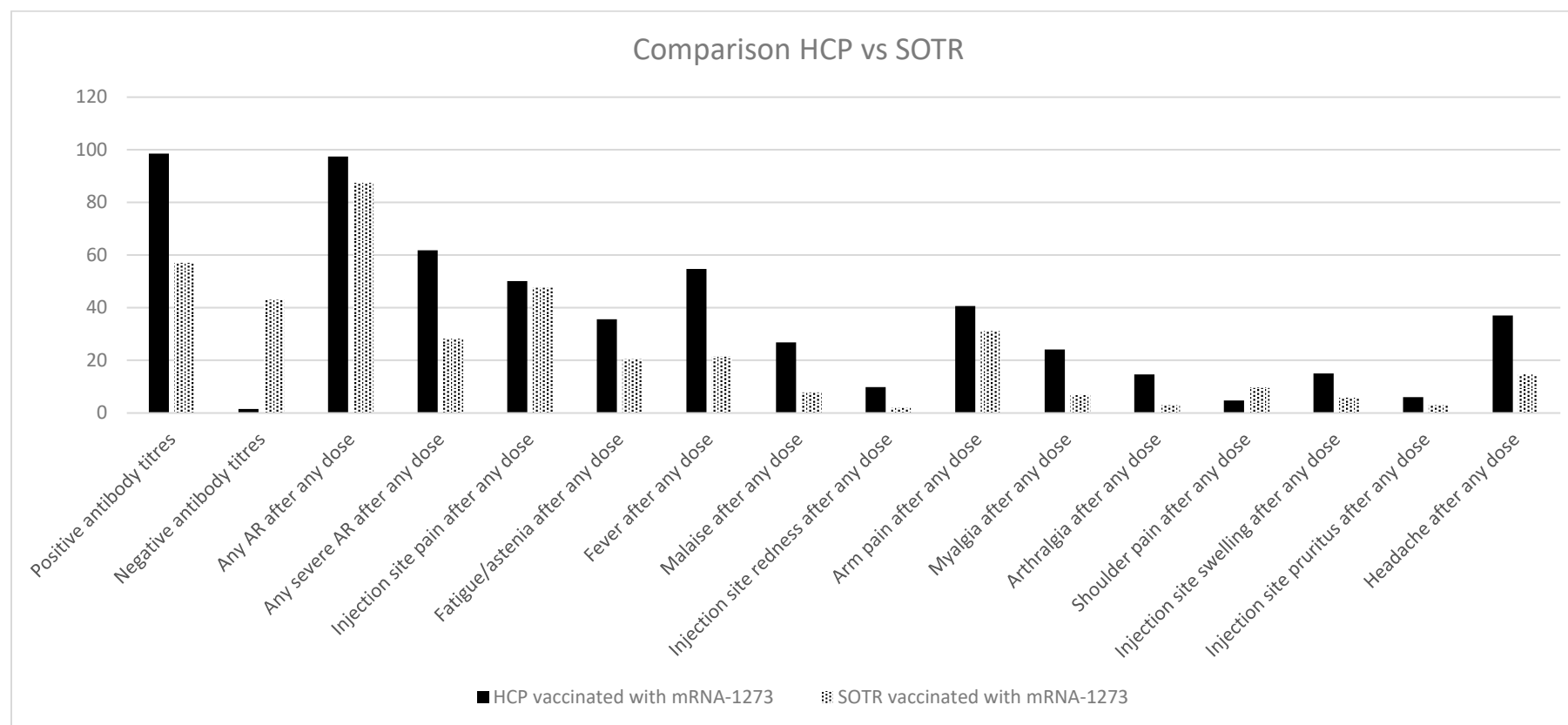
HCP: health-care professional; SOTR: solid-organ transplant recipient; NA: not applicable because all SOTR were vaccinated with mRNA-1273

Figure S4: Comparison of vaccine types



HCP: health-care professional; SOTR: solid-organ transplant recipient; AR: adverse reaction; positive/negative antibody titres: % of vaccinees with positive or negative titres; any AR, any severe AR and solicited AR: % of vaccinees with at least one event

Figure S5: Comparison of population types



HCP: health-care professional; SOTR: solid-organ transplant recipient; AR: adverse reaction; positive/negative antibody titres: % of vaccinees with positive or negative titres; any AR, any severe AR and solicited AR: % of vaccinees with at least one event

Table S25 STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No*
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	

		(c) Explain how missing data were addressed		
		(d) If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10	
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10	
		(b) Indicate number of participants with missing data for each variable of interest		
Outcome data	15*	Report numbers of outcome events or summary measures	10-12	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12	
		(b) Report category boundaries when continuous variables were categorized		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12	

Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Pages where the different items of the STROBE checklist are described

Reference: <https://www.strobe-statement.org/>