THE LANCET
Infectious Diseases

Supplementary appendix

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

Supplement to: Goepfert PA, Fu B, Chabanon A-L, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study. *Lancet Infect Dis* 2021; published online April 19. https://doi.org/10.1016/S1473-3099(21)00147-X.

Interim safety and immunogenicity results for SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: a randomised, placebo-controlled, dose-ranging study

Paul A Goepfert MD, Professor,[1] Bo Fu PhD,[2] Anne-Laure Chabanon PharmD PhD,[3] Matthew I Bonaparte PhD,[2] Matthew G Davis MD,[4] Brandon J Essink MD,[5] Ian Frank MD, Professor,[6] Owen Haney PharmD,[2] Helene Janosczyk, MA,[2] Michael C Keefer MD, Professor,[7] Marguerite Koutsoukos PhD,[8] Murray A Kimmel DO,[9] Roger Masotti, MS,[2] Stephen J Savarino MD,[2] Lode Schuerman MD,[8] Howard Schwartz MD,[10] Lawrence D Sher, MD,[11] Jon Smith PhD,[2] Fernanda Tavares-Da-Silva MD,[8] Sanjay Gurunathan MD,[2] Carlos A DiazGranados MD,[2] Guy De Bruyn MD[2]

1. Department of Medicine, University of Alabama at Birmingham

2. Sanofi Pasteur, Swiftwater, PA, USA

3. Sanofi Pasteur, Lyon, France

4. Rochester Clinical Research, Rochester, NY, USA

5. Meridian Clinical Research, Omaha, NE, USA

6. Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

7. University of Rochester, School of Medicine and Dentistry, Rochester, NY, USA

8. GlaxoSmithKline Vaccines, Wavre, Belgium

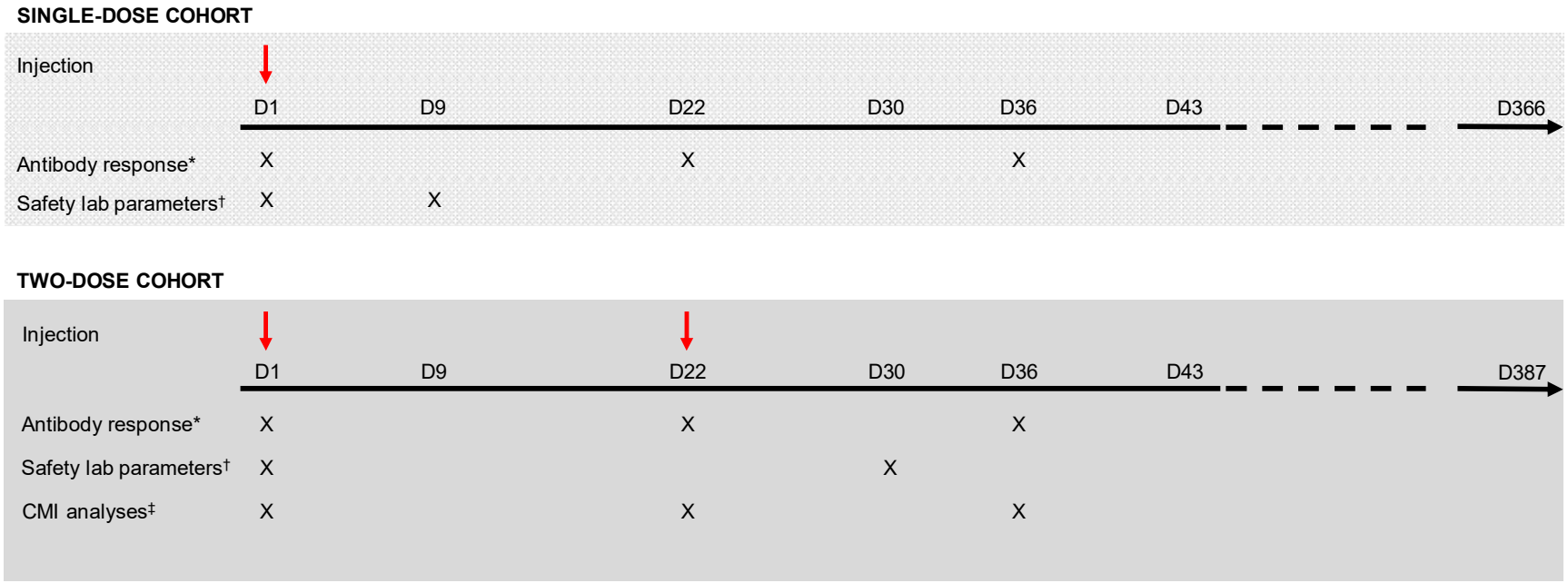
9. Optimal Research LLC, Melbourne, FL, USA

10. Research Centers of America, Hollywood, FL, USA

11. Peninsula Research Associates, Rolling Hills Estates, CA, USA

Appendix

Appendix 1. Study design for (A) the single-dose and (B) the two-dose schedule



CMI, cell-mediated immunity; D, study day; red arrows indicate the first or second study injections.

*Serum samples (30 mL) were used to determine SARS-CoV-2 neutralising and binding antibody responses at the specified timepoints; †Assessments included serum chemistries, haematology, urinalysis and microscopy; ‡Whole blood samples (10 mL) from a subset of participants in the 18–49 years age stratum in the two-dose cohort were used for cell-mediated immunity analyses.

Appendix 2. Planned group sizes allocated to each treatment group

Single-dose cohort				
	Dose Level*	**Adjuvant**	**Number of participants**	
			Sentinel Safety† (N=30)	**Total (N=150)**
18–49 years	LD	AF03	6	20
	LD	AS03	6	20
	HD	AF03	6	20
	HD	AS03	6	20
	Placebo	None	6	20
50 years of age and older	LD	AF03	N/A	10
	LD	AS03	N/A	10
	HD	AF03	N/A	10
	HD	AS03	N/A	10
	Placebo	None	N/A	10

Two-dose cohort			
	Dose Level*	**Adjuvant**	**Number of participants (N=290)**
18–49 years	LD	AF03	20
	LD	AS03	60
	HD	AF03	20
	HD	AS03	60

	HD	None	20
	Placebo	None	20
50 years of age and older	LD	AF03	10
	LD	AS03	30
	HD	AF03	10
	HD	AS03	30
	Placebo	None	10

HD, high dose; LD, low dose; N, total participants; N/A, not available (participants aged ≥ 50 years were not allocated to this study arm).

*The targeted dose levels were not met; effective dose levels were 1·3 µg (low-dose) and 2·6 µg (high-dose) of functional vaccine antigen, CoV2 preS, instead of 5 and 15ug, respectively.

†Sentinel safety cohort: Participants in the 18–49 years age stratum from the single-dose cohort were included in the sentinel safety cohort.

Note: A subset of 87 participants in the two-dose cohort (60 participants 18–49 years of age [18 per group in AS03-adjuvanted vaccines; 6 per group in all other study groups]) and 27 participants ≥ 50 years of age [9 per group in AS03-adjuvanted groups; 3 per group in all other study groups, with the exception of the unadjuvanted group]), were randomly assigned to a cellular-mediated immune (CMI) subset.

Appendix 3.

Generation of the SARS-CoV-2 recombinant prefusion S protein, preS dTM

Sanofi Pasteur has developed a candidate SARS-CoV-2 recombinant protein vaccine containing purified recombinant prefusion S protein (preS dTM). The preS dTM was produced from a Sanofi Pasteur proprietary cell culture technology based on the insect cell baculovirus expression vector system. The preS dTM sequence was based on the Wuhan YP_009724390.1 strain S sequence, modified to improve the conformation, stability, trimerization and trimerisation and to facilitate the purification. The modifications comprised the introduction of two proline mutations in the C-terminal region of S2 domain, which was previously shown to stabilise the protein in a prefusion conformation.(Pallesen, Wang et al. 2017, Wrapp, Wang et al. 2020) Briefly, the modified sequence was cloned into a baculovirus transfer plasmid, which was then used to generate a recombinant baculovirus containing the gene of interest. The recombinant baculovirus was first amplified in expresSF+ insect cells prior to infecting a large scale expresSF+ insect cells culture in suspension. After incubation, the recombinant protein was purified from the supernatant using several affinity and chromatography columns.

Purity was determined by SDS-PAGE and scanning densitometry. Spike protein bands were identified by Western Blotting, with Affinity Purified SARS-CoV-2 Spike Rabbit Polyclonal Antibody. Purity was calculated as the percentage of spike protein band density relative to the all other bands. The release specification for purity of the S-protein trimer was ≥90% purity. This specification was met for the clinical material evaluated in this trial using this method. The release specification and method was proposed and approved by US FDA. Conversely, the specification for HCP was <10%.

The AF03 (Sanofi Pasteur) and AS03 (GlaxoSmithKline) adjuvants

One dose of the AF03 adjuvant (Sanofi Pasteur) emulsion19 contained 12·5 mg squalene, 1·85 mg sorbitan monooleate (Dehymuls S SMO™), 2·38 mg Macrogol cetostearyl ether (Kolliphor CS12™) and 2·31 mg mannitol in phosphate-buffered saline (PBS), and was presented in a 0·7 mL monodose vial (single dose, 0·25mL per dose). One dose of the AS03 Adjuvant System20 (GlaxoSmithKline) contained 11·86 mg α-tocopherol, 10·69 mg squalene and 4.·86 mg polysorbate-80 (Tween®80) in PBS, and was presented in a 3·15 mL multidose vial (10 doses, 0·25 mL per dose).

Appendix 4 - Immunogenicity Analyses

Microneutralisation assay

The microneutralisation assay was performed at Sanofi Pasteur Global Clinical Immunology, Swiftwater, PA, USA. Serial two-fold dilutions of heat inactivated serum samples (56°C for 30 minutes) were incubated with a challenge dose targeting 50% tissue culture infectious dose ($TCID_{50}$) of SARS-CoV-2 (strain USA-WA1/2020 [BEI Resources; catalog# NR-52281]) at 37°C with 5% CO_2 for 1 hour. The serum-virus mixtures were inoculated into wells of a 96-well microplate with preformed Vero E6 (ATCC® CRL-1586™) cell monolayers and adsorbed at 37°C with 5% CO_2 for 0·5 hour. Additional assay media was added to all wells without removing the existing inoculum and incubated at 37°C with 5% CO_2 for 2 days. After washing and fixation of the Vero E6 cell monolayers, SARS-CoV-2 antigen production in cells was detected by successive incubations with an anti-SARS-CoV nucleoprotein mouse monoclonal antibody (Sino Biological catalog# 40143-MM05), HRP IgG conjugate (Jackson ImmunoResearch Laboratories, catalog #115-035-062), and SeraCare SureBlue® TMB substrate. The resulting optical density (OD) was measured at 450/630 nm using a Molecular Devices microplate reader. The reduction in SARS-CoV-2 infectivity, as compared to that in the virus control wells, constitutes a positive neutralisation reaction indicating the presence of neutralising antibodies in the serum sample. The 50% neutralisation titre (MN_{50}) was defined as the reciprocal of the serum dilution for which the virus infectivity was reduced by 50% relative to the virus control on each plate. The MN_{50} for each sample was interpolated by calculating the slope and intercept using the last dilution with an OD below the 50% neutralisation point and the first dilution with an OD above the 50% neutralisation point; MN_{50} titre = (OD of 50% neutralisation point - intercept)/slope. The Lower Limit of Quantitation (LLOQ) of the assay was a titer of 10.

Enzyme-linked immunosorbent assay

The SARS-CoV-2 anti-S protein IgG antibodies were measured using an indirect ELISA performed at Nexelis, Laval, Quebec, Canada. Microtitre plates were coated with recombinant SARS-CoV-2 S protein antigen (SARS-CoV-2 S-antigen with 2P mutations in pre-fusion trimer conformation produced in HEK293 cell line, GeneArt, Regensburg, Germany) diluted in coating buffer and incubated overnight (17–21 hours) at 2–8°C. The plates were blocked following the addition of 5% Skim Milk in 1X PBS+ 0·05% Tween-20 blocking buffer to all wells, then incubated for 1 hour at room temperature. Following incubation, the plates were washed with 1X PBS + 0·05% Tween-20 (PBST). The pre-diluted controls, reference, and test samples were then serially diluted in the wells of the pre-coated test plates. Following incubation for 1 hour at room temperature, the plates were washed with PBST, and goat anti-human IgG HRP enzyme conjugate was added to all wells. The plates were incubated for 1 hour at room temperature, washed with PBST and TMB substrate solution was added to all wells. The plates were incubated for substrate development for 30 minutes, stopped by the addition of a stop solution (2N H_2SO_4) to all wells. The OD of the microtitre plates were read at 450/620 nm using an assay specific SoftMax Pro template. The average OD value for the plate blank was then subtracted from the ODs within each plate. The sample IgG concentrations were then extrapolated for the blanks, controls, and test samples based on the reference standard curve, which was included on each assay plate within a run. The LLOQ of the assay was established at 18·9 EU/ml.

CMI analyses

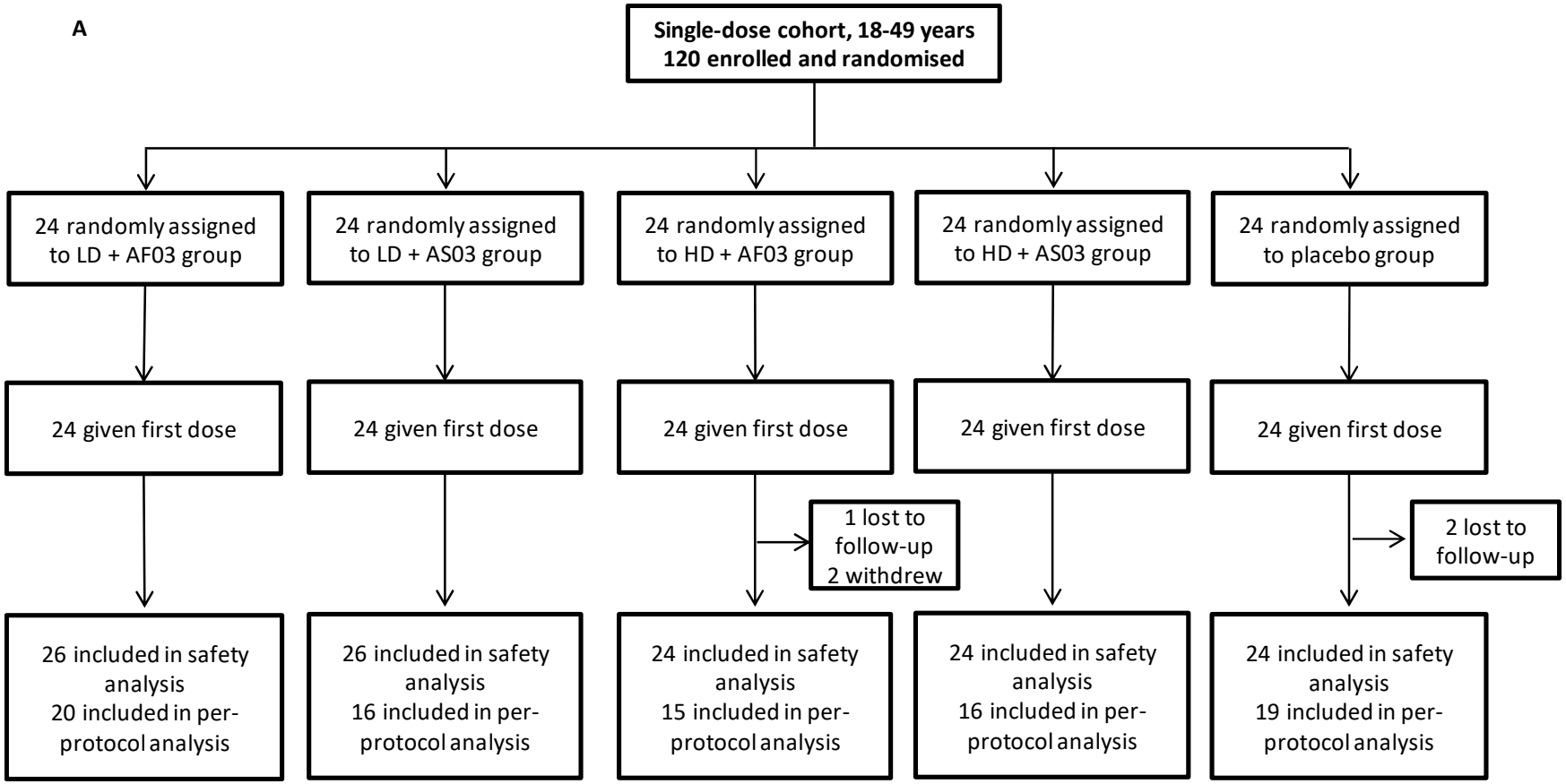
The TruCulture OptiMAP™ assay (Myriad RBM) is microsphere-based and consists of using antigen-specific antibodies optimized in a capture-sandwich format. All incubations were performed at room temperature. Five µL of a diluted mixture of capture-antibody microspheres were mixed with 5 µL blocker and 10 µL standard, pre-diluted sample, or control in a hard-bottom microtitre plate. TruCulture samples were diluted to the appropriate dilution. The plate was incubated for 1 hour. Ten µL biotinylated detection antibody was added to each well, thoroughly mixed, and incubated for 1 hour. Ten µL diluted Streptavidin-phycoerythrin was added to each well, thoroughly mixed, and incubated for 60 minutes. A filter-membrane microtitre plate was pre-wetted by adding 100 µL wash buffer followed by aspiration via a vacuum manifold device. The reaction contents of the hard-bottom plate were then transferred to the respective wells of the filter plate. All wells were vacuum aspirated, and the contents were washed twice with 100 µL wash buffer. After the last wash, 100 µL wash buffer was added to each well, and the washed microspheres were resuspended with thorough mixing. The plate was then analysed on a Luminex platform. Cytokine concentrations were automatically calculated by adapted

software (Myriad RBM) using a standard curve. GM-CSF, IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, TNFα were acquired initially and data for IFN-γ, IL-2, and TNFα are analysed here. IFN-γ is considered the most relevant Th1 polarising cytokine. IL-2 and TNFα are also commonly classified as Th1 cytokines, although they have pleiotropic effects.

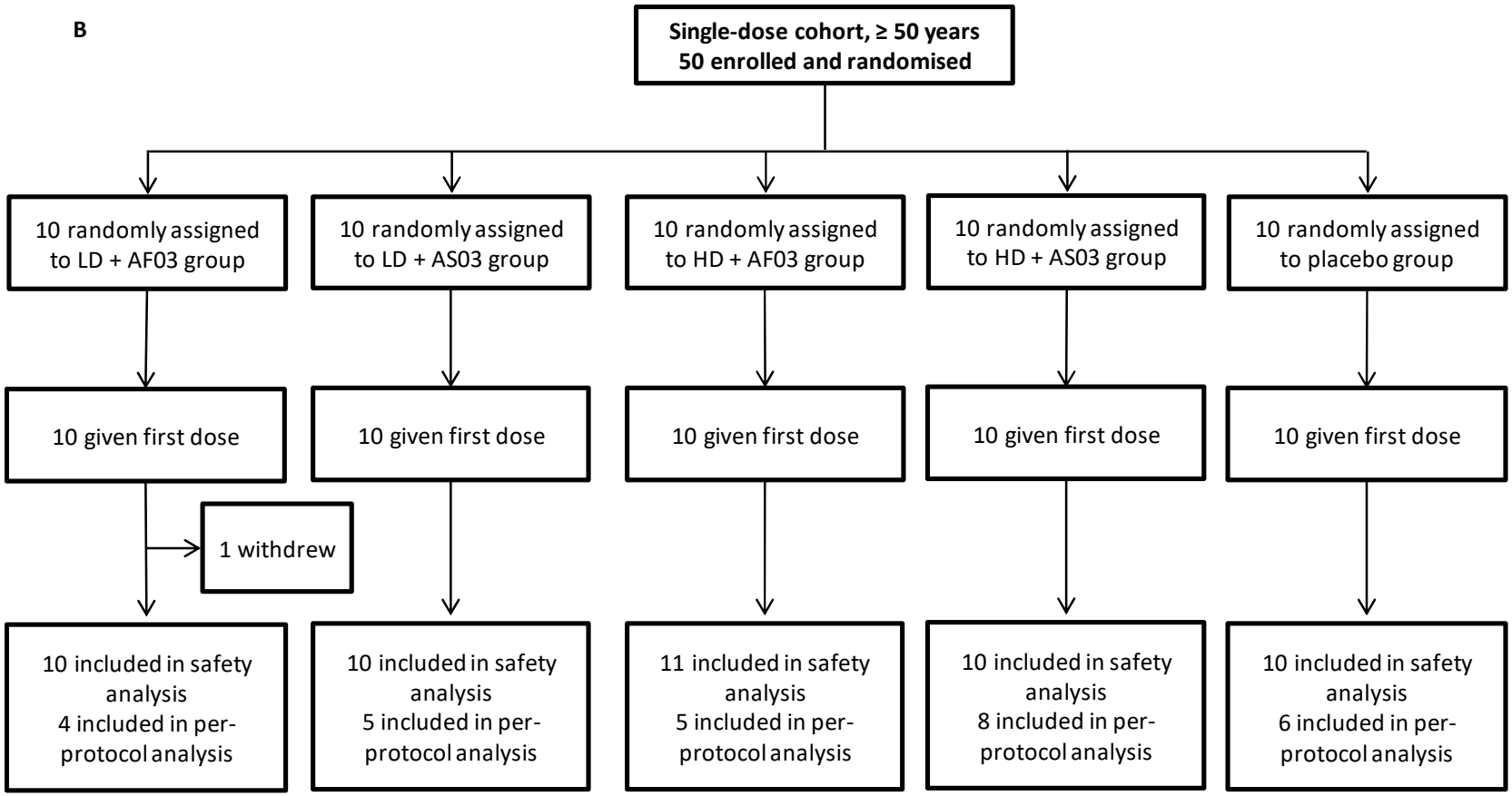
Computation of cytokine fold-rise ratios

Specific cytokine production was firstly calculated at each timepoint by subtracting cytokine concentration measured in negative control (N) samples from antigen stimulated samples (S). The fold-rise for the individual cytokines at D36/D1 and D22/D1 was calculated by dividing the (S-N) measurement post-vaccination (D22 or D36) by the pre-vaccination (D1) measurement; the fold-rise for individual cytokines were then used to compute the fold-rise ratios and 95% CI for cytokine pairs.

Supplementary Appendix 5: Participant flow through the study for those randomised to receive a single dose in the (A) 18-49 years and (B) ≥ 50 years age strata.



B


Single-dose cohort, ≥ 50 years
50 enrolled and randomised
10 randomly assigned to LD + AF03 group
10 randomly assigned to LD + AS03 group
10 randomly assigned to HD + AF03 group
10 randomly assigned to HD + AS03 group
10 randomly assigned to placebo group
10 given first dose
10 given first dose
10 given first dose
10 given first dose
10 given first dose
1 withdrew
10 included in safety analysis
4 included in per-protocol analysis
10 included in safety analysis
5 included in per-protocol analysis
11 included in safety analysis
5 included in per-protocol analysis
10 included in safety analysis
8 included in per-protocol analysis
10 included in safety analysis
6 included in per-protocol analysis

Appendix 6. Numbers (%) of participants with solicited injection site reactions and systemic reactions (overall and Grade 3 severity), after each dose in the two-dose cohort (A) and single-dose cohort (B), by age group.

A. Two-dose cohort

		LD + AF03 N=26		LD + AS03 N=80		HD + AF03 N=26		HD + AS03 N=85		HD N=18		Placebo N=29	
		n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
Post dose 1													
18–49 years													
Pain	Overall	11/16	68.8 (41.3 ; 89.0)	37/51	72.5 (58.3 ; 84.1)	9/17	52.9 (27.8 ; 77.0)	44/54	81.5 (68.6 ; 90.7)	2/18	11.1 (1.4 ; 34.7)	3/18	16.7 (3.6 ; 41.4)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	0/17	0 (0 ; 19.5)	0/54	0 (0 ; 6.6)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Erythema	Overall	1/16	6.3 (0.2 ; 30.2)	0/51	0 (0 ; 7.0)	0/17	0 (0 ; 19.5)	2/54	3.7 (0.5 ; 12.7)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	0/17	0 (0 ; 19.5)	0/54	0 (0 ; 6.6)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Swelling	Overall	0/16	0 (0 ; 20.6)	1/51	2.0 (0 ; 10.4)	0/17	0 (0 ; 19.5)	4/54	7.4 (2.1 ; 17.9)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	0/17	0 (0 ; 19.5)	0/54	0 (0 ; 6.6)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Fever	Overall	1/16	6.3 (0.2 ; 30.2)	1/50	2.0 (0.1 ; 10.6)	1/17	5.9 (0.1 ; 28.7)	2/54	3.7 (0.5 ; 12.7)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
	Grade 3	0/16	0 (0 ; 20.6)	0/50	0 (0 ; 7.1)	0/17	0 (0 ; 19.5)	0/54	0 (0 ; 6.6)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Headache	Overall	2/16	12.5 (1.6 ; 38.3)	13/51	25.5 (14.3 ; 39.6)	5/17	29.4 (10.3 ; 56.0)	22/54	40.7 (27.6 ; 55.0)	4/18	22.2 (6.4 ; 47.6)	6/18	33.3 (13.3 ; 59.0)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	0/17	0 (0 ; 19.5)	1/54	1.9 (0 ; 9.9)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Malaise	Overall	4/16	25.0 (7.3 ; 52.4)	13/51	25.5 (14.3 ; 39.6)	5/17	29.4 (10.3 ; 56.0)	14/54	25.9 (15.0 ; 39.7)	1/18	5.6 (0.1 ; 27.3)	3/18	16.7 (3.6 ; 41.4)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	1/17	5.9 (0.1 ; 28.7)	0/54	0 (0 ; 6.6)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
Myalgia	Overall	5/16	31.3 (11.0 ; 58.7)	16/51	31.4 (19.1 ; 45.9)	6/17	35.3 (14.2 ; 61.7)	23/54	42.6 (29.2 ; 56.8)	2/18	11.1 (1.4 ; 34.7)	1/18	5.6 (0.1 ; 27.3)
	Grade 3	0/16	0 (0 ; 20.6)	0/51	0 (0 ; 7.0)	1/17	5.9 (0.1 ; 28.7)	1/54	1.9 (0 ; 9.9)	0/18	0 (0 ; 18.5)	0/18	0 (0 ; 18.5)
50 years and older													
Pain	Overall	5/10	50.0 (18.7 ; 81.3)	16/28	57.1 (37.2 ; 75.5)	4/9	44.4 (13.7 ; 78.8)	20/31	64.5 (45.4 ; 80.8)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Erythema	Overall	0/10	0 (0 ; 30.8)	1/28	3.6 (0.1 ; 18.3)	1/9	11.1 (0.3 ; 48.2)	2/31	6.5 (0.8 ; 21.4)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Swelling	Overall	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	1/31	3.2 (0.1 ; 16.7)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Fever	Overall	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)

Headache	Overall	1/10	10.0 (0.3 ; 44.5)	7/28	25.0 (10.7 ; 44.9)	2/9	22.2 (2.8 ; 60.0)	12/31	38.7 (21.8 ; 57.8)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Malaise	Overall	0/10	0 (0 ; 30.8)	3/28	10.7 (2.3 ; 28.2)	1/9	11.1 (0.3 ; 48.2)	10/31	32.3 (16.7 ; 51.4)	0/0	(NC ; NC)	2/11	18.2 (2.3 ; 51.8)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Myalgia	Overall	0/10	0 (0 ; 30.8)	6/28	21.4 (8.3 ; 41.0)	3/9	33.3 (7.5 ; 70.1)	9/31	29.0 (14.2 ; 48.0)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	1/9	11.1 (0.3 ; 48.2)	0/31	0 (0 ; 11.2)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Post dose 2													
18–49 years													
Pain	Overall	13/16	81.3 (54.4 ; 96.0)	44/51	86.3 (73.7 ; 94.3)	14/17	82.4 (56.6 ; 96.2)	49/54	90.7 (79.7 ; 96.9)	2/17	11.8 (1.5 ; 36.4)	2/18	11.1 (1.4 ; 34.7)
	Grade 3	0/16	0 (0 ; 20.6)	3/51	5.9 (1.2 ; 16.2)	1/17	5.9 (0.1 ; 28.7)	3/54	5.6 (1.2 ; 15.4)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
Erythema	Overall	2/16	12.5 (1.6 ; 38.3)	10/51	19.6 (9.8 ; 33.1)	3/17	17.6 (3.8 ; 43.4)	27/54	50.0 (36.1 ; 63.9)	1/17	5.9 (0.1 ; 28.7)	1/18	5.6 (0.1 ; 27.3)
	Grade 3	0/16	0 (0 ; 20.6)	2/51	3.9 (0.5 ; 13.5)	0/17	0 (0 ; 19.5)	15/54	27.8 (16.5 ; 41.6)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
Swelling	Overall	3/16	18.8 (4.0 ; 45.6)	8/51	15.7 (7.0 ; 28.6)	3/17	17.6 (3.8 ; 43.4)	18/54	33.3 (21.1 ; 47.5)	1/17	5.9 (0.1 ; 28.7)	0/18	0 (0 ; 18.5)
	Grade 3	0/16	0 (0 ; 20.6)	1/51	2.0 (0 ; 10.4)	0/17	0 (0 ; 19.5)	9/54	16.7 (7.9 ; 29.3)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
Fever	Overall	2/16	12.5 (1.6 ; 38.3)	18/50	36.0 (22.9 ; 50.8)	5/17	29.4 (10.3 ; 56.0)	15/54	27.8 (16.5 ; 41.6)	0/16	0 (0 ; 20.6)	0/18	0 (0 ; 18.5)
	Grade 3	0/16	0 (0 ; 20.6)	3/50	6.0 (1.3 ; 16.5)	1/17	5.9 (0.1 ; 28.7)	5/54	9.3 (3.1 ; 20.3)	0/16	0 (0 ; 20.6)	0/18	0 (0 ; 18.5)
Headache	Overall	8/16	50.0 (24.7 ; 75.3)	39/52	75.0 (61.1 ; 86.0)	13/17	76.5 (50.1 ; 93.2)	31/54	57.4 (43.2 ; 70.8)	3/17	17.6 (3.8 ; 43.4)	3/18	16.7 (3.6 ; 41.4)
	Grade 3	0/16	0 (0 ; 20.6)	8/52	15.4 (6.9 ; 28.1)	1/17	5.9 (0.1 ; 28.7)	3/54	5.6 (1.2 ; 15.4)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
Malaise	Overall	8/16	50.0 (24.7 ; 75.3)	38/51	74.5 (60.4 ; 85.7)	13/17	76.5 (50.1 ; 93.2)	39/54	72.2 (58.4 ; 83.5)	0/17	0 (0 ; 19.5)	2/18	11.1 (1.4 ; 34.7)
	Grade 3	0/16	0 (0 ; 20.6)	10/51	19.6 (9.8 ; 33.1)	3/17	17.6 (3.8 ; 43.4)	10/54	18.5 (9.3 ; 31.4)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
Myalgia	Overall	8/16	50.0 (24.7 ; 75.3)	40/52	76.9 (63.2 ; 87.5)	13/17	76.5 (50.1 ; 93.2)	38/54	70.4 (56.4 ; 82.0)	2/17	11.8 (1.5 ; 36.4)	2/18	11.1 (1.4 ; 34.7)
	Grade 3	2/16	12.5 (1.6 ; 38.3)	8/52	15.4 (6.9 ; 28.1)	3/17	17.6 (3.8 ; 43.4)	6/54	11.1 (4.2 ; 22.6)	0/17	0 (0 ; 19.5)	0/18	0 (0 ; 18.5)
50 years and older													
Pain	Overall	6/10	60.0 (26.2 ; 87.8)	26/28	92.9 (76.5 ; 99.1)	5/9	55.6 (21.2 ; 86.3)	29/31	93.5 (78.6 ; 99.2)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	1/31	3.2 (0.1 ; 16.7)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Erythema	Overall	0/10	0 (0 ; 30.8)	9/28	32.1 (15.9 ; 52.4)	1/9	11.1 (0.3 ; 48.2)	10/31	32.3 (16.7 ; 51.4)	0/0	(NC ; NC)	0/10	0 (0 ; 30.8)
	Grade 3	0/10	0 (0 ; 30.8)	1/28	3.6 (0.1 ; 18.3)	0/9	0 (0 ; 33.6)	5/31	16.1 (5.5 ; 33.7)	0/0	(NC ; NC)	0/10	0 (0 ; 30.8)
Swelling	Overall	0/10	0 (0 ; 30.8)	7/28	25.0 (10.7 ; 44.9)	1/9	11.1 (0.3 ; 48.2)	8/31	25.8 (11.9 ; 44.6)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	2/31	6.5 (0.8 ; 21.4)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Fever	Overall	2/10	20.0 (2.5 ; 55.6)	10/28	35.7 (18.6 ; 55.9)	0/9	0 (0 ; 33.6)	8/30	26.7 (12.3 ; 45.9)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/28	0 (0 ; 12.3)	0/9	0 (0 ; 33.6)	2/30	6.7 (0.8 ; 22.1)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Headache	Overall	5/10	50.0 (18.7 ; 81.3)	18/28	64.3 (44.1 ; 81.4)	3/9	33.3 (7.5 ; 70.1)	22/31	71.0 (52.0 ; 85.8)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
	Grade 3	1/10	10.0 (0.3 ; 44.5)	1/28	3.6 (0.1 ; 18.3)	0/9	0 (0 ; 33.6)	3/31	9.7 (2.0 ; 25.8)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Malaise	Overall	5/10	50.0 (18.7 ; 81.3)	21/28	75.0 (55.1 ; 89.3)	5/9	55.6 (21.2 ; 86.3)	25/31	80.6 (62.5 ; 92.5)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)

	Grade 3	1/10	10.0 (0.3 ; 44.5)	3/28	10.7 (2.3 ; 28.2)	0/9	0 (0 ; 33.6)	4/31	12.9 (3.6 ; 29.8)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)
Myalgia	Overall	4/10	40.0 (12.2 ; 73.8)	20/28	71.4 (51.3 ; 86.8)	5/9	55.6 (21.2 ; 86.3)	27/31	87.1 (70.2 ; 96.4)	0/0	(NC ; NC)	1/11	9.1 (0.2 ; 41.3)
	Grade 3	0/10	0 (0 ; 30.8)	3/28	10.7 (2.3 ; 28.2)	0/9	0 (0 ; 33.6)	3/31	9.7 (2.0 ; 25.8)	0/0	(NC ; NC)	0/11	0 (0 ; 28.5)

B. Single-dose cohort

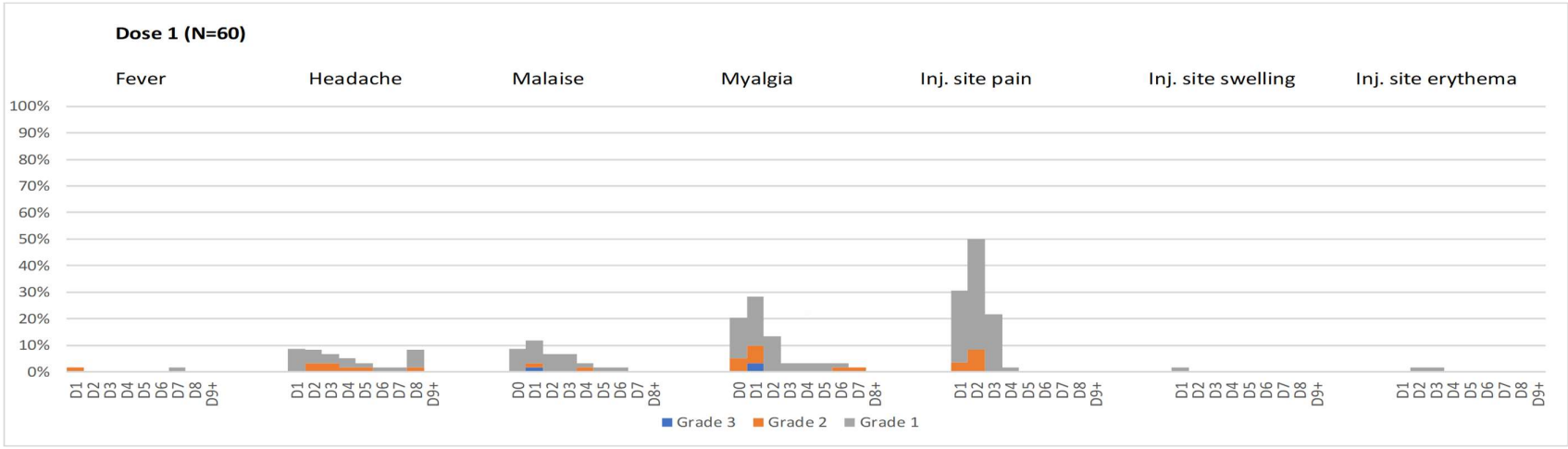
		LD + AF03 N=36		LD + AS03 N=36		HD + AF03 N=35		HD + AS03 N=34		Placebo N=34	
		n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
Post dose 1											
18–49 years											
Pain	Overall	14/26	53.8 (33.4 ; 73.4)	23/26	88.5 (69.8 ; 97.6)	16/23	69.6 (47.1 ; 86.8)	22/24	91.7 (73.0 ; 99.0)	5/23	21.7 (7.5 ; 43.7)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/23	0 (0 ; 14.8)
Erythema	Overall	1/26	3.8 (0.1 ; 19.6)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	3/24	12.5 (2.7 ; 32.4)	0/23	0 (0 ; 14.8)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/23	0 (0 ; 14.8)
Swelling	Overall	1/26	3.8 (0.1 ; 19.6)	2/26	7.7 (0.9 ; 25.1)	1/23	4.3 (0.1 ; 21.9)	2/24	8.3 (1.0 ; 27.0)	0/23	0 (0 ; 14.8)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/23	0 (0 ; 14.8)
Fever	Overall	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/22	0 (0 ; 15.4)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/22	0 (0 ; 15.4)
Headache	Overall	8/26	30.8 (14.3 ; 51.8)	10/26	38.5 (20.2 ; 59.4)	3/23	13.0 (2.8 ; 33.6)	8/24	33.3 (15.6 ; 55.3)	5/23	21.7 (7.5 ; 43.7)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/23	0 (0 ; 14.8)
Malaise	Overall	4/26	15.4 (4.4 ; 34.9)	9/26	34.6 (17.2 ; 55.7)	7/23	30.4 (13.2 ; 52.9)	6/24	25.0 (9.8 ; 46.7)	4/23	17.4 (5.0 ; 38.8)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	1/24	4.2 (0.1 ; 21.1)	0/23	0 (0 ; 14.8)
Myalgia	Overall	5/26	19.2 (6.6 ; 39.4)	10/26	38.5 (20.2 ; 59.4)	9/23	39.1 (19.7 ; 61.5)	11/24	45.8 (25.6 ; 67.2)	4/23	17.4 (5.0 ; 38.8)
	Grade 3	0/26	0 (0 ; 13.2)	0/26	0 (0 ; 13.2)	0/23	0 (0 ; 14.8)	0/24	0 (0 ; 14.2)	0/23	0 (0 ; 14.8)
50 years and older											
Pain	Overall	4/10	40.0 (12.2 ; 73.8)	7/10	70.0 (34.8 ; 93.3)	5/11	45.5 (16.7 ; 76.6)	6/10	60.0 (26.2 ; 87.8)	0/10	0 (0 ; 30.8)
	Grade 3	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
Erythema	Overall	1/10	10.0 (0.3 ; 44.5)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
	Grade 3	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
Swelling	Overall	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
	Grade 3	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)

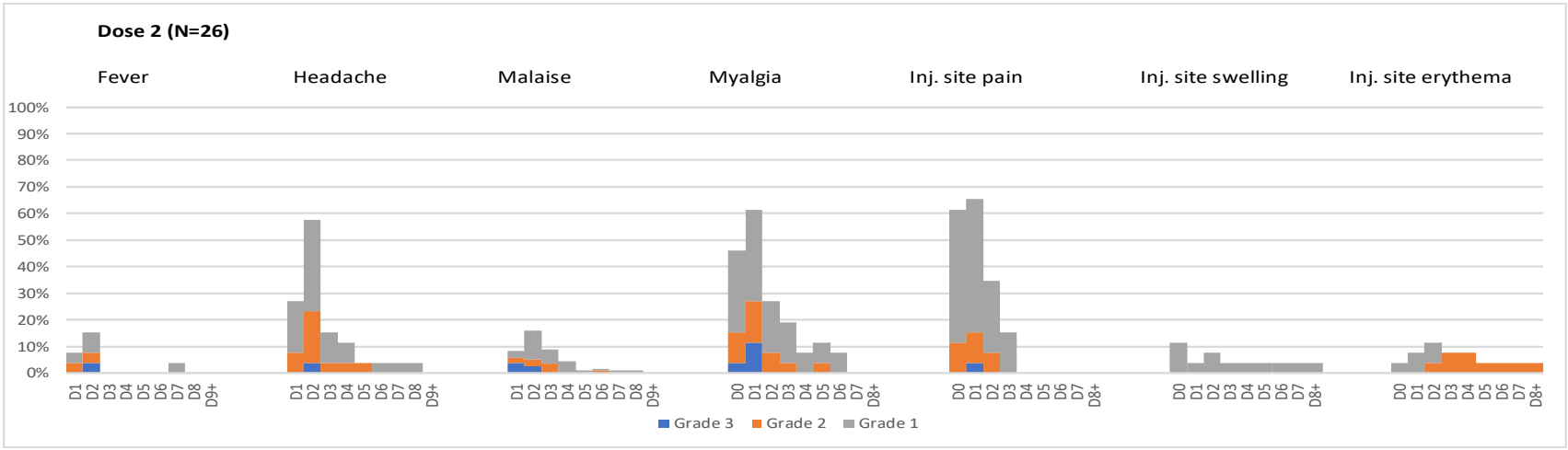
Fever	Overall	0/9	0 (0 ; 33.6)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
	Grade 3	0/9	0 (0 ; 33.6)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
Headache	Overall	2/10	20.0 (2.5 ; 55.6)	3/10	30.0 (6.7 ; 65.2)	1/11	9.1 (0.2 ; 41.3)	3/10	30.0 (6.7 ; 65.2)	1/10	10.0 (0.3 ; 44.5)
	Grade 3	0/10	0 (0 ; 30.8)	1/10	10.0 (0.3 ; 44.5)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
Malaise	Overall	2/10	20.0 (2.5 ; 55.6)	2/10	20.0 (2.5 ; 55.6)	2/11	18.2 (2.3 ; 51.8)	2/10	20.0 (2.5 ; 55.6)	1/10	10.0 (0.3 ; 44.5)
	Grade 3	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)
Myalgia	Overall	1/10	10.0 (0.3 ; 44.5)	2/10	20.0 (2.5 ; 55.6)	4/11	36.4 (10.9 ; 69.2)	4/10	40.0 (12.2 ; 73.8)	2/10	20.0 (2.5 ; 55.6)
	Grade 3	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)	0/11	0 (0 ; 28.5)	0/10	0 (0 ; 30.8)	0/10	0 (0 ; 30.8)

M, number of participants included; n, number of participants reporting the specified event;

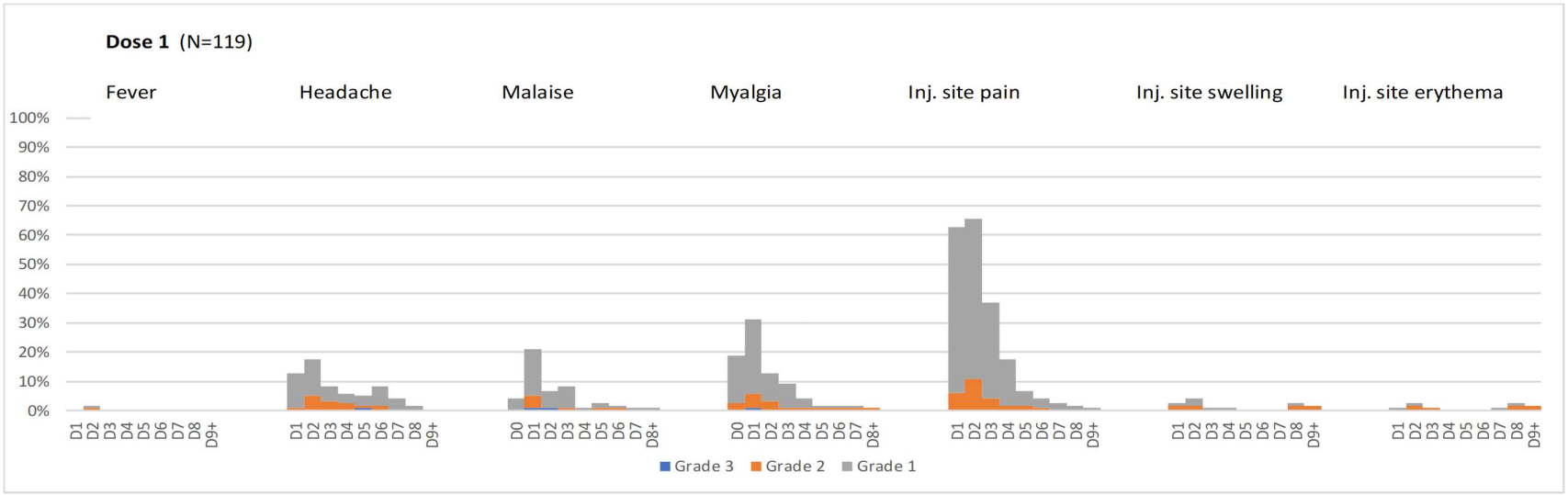
Appendix 7: Solicited systemic and injection site reactions over time for the adjuvanted high-dose vaccine groups

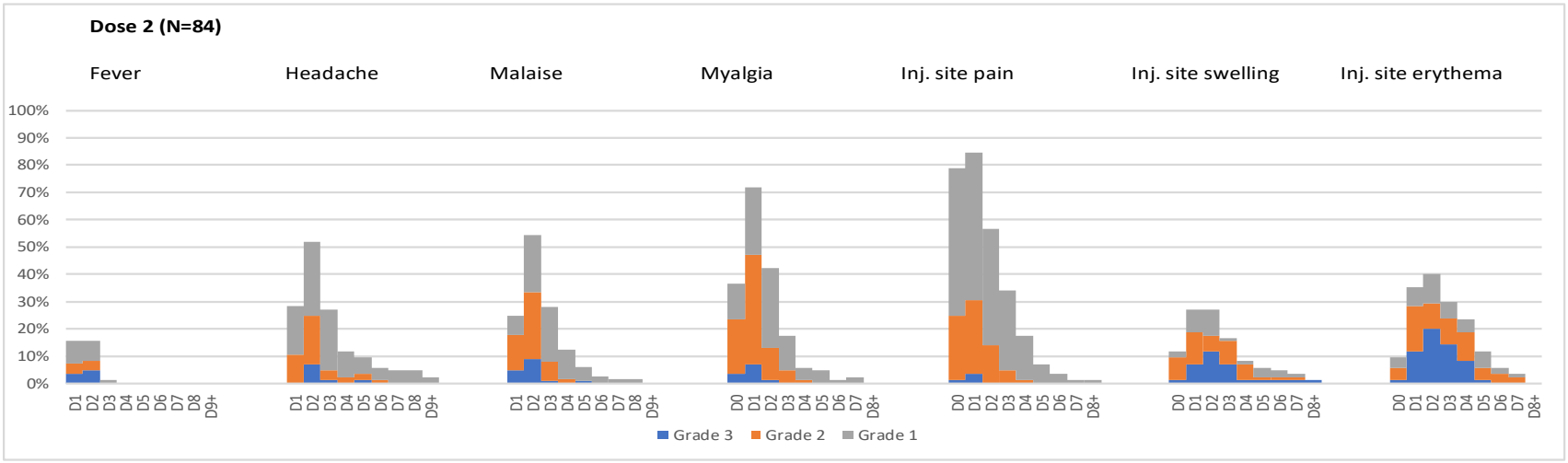
HD+AF03 group





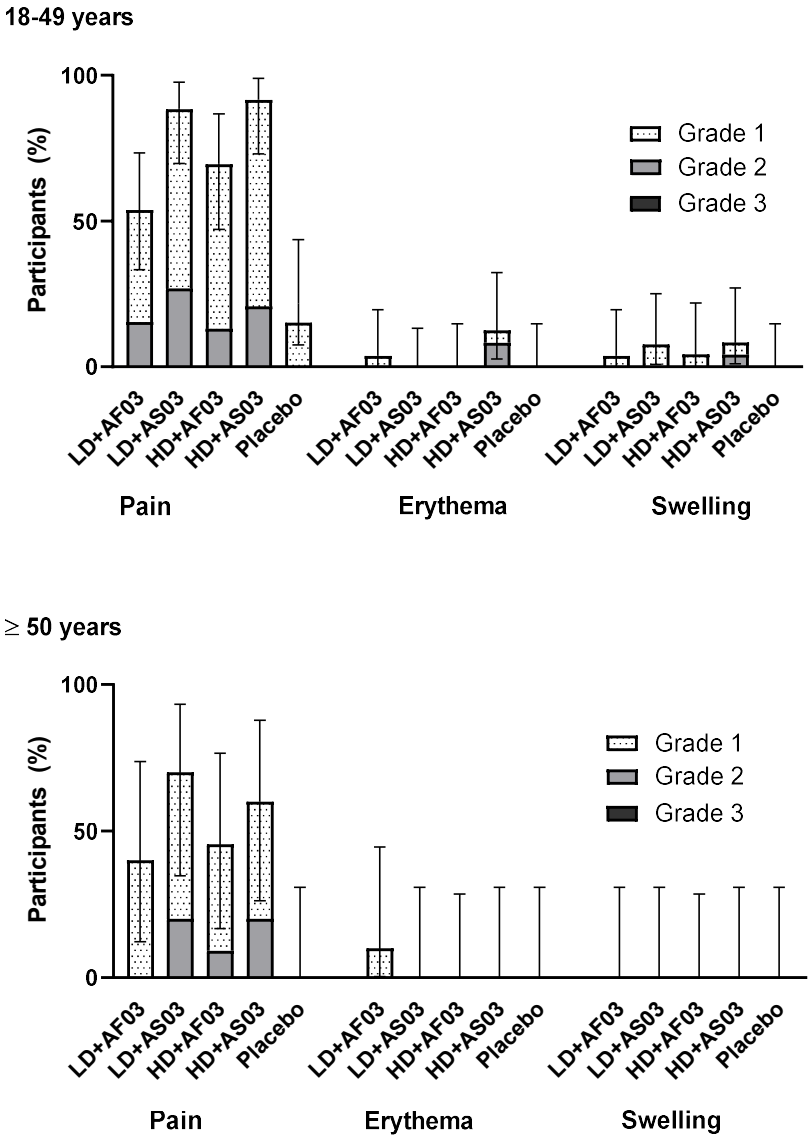
HD+AS03 group



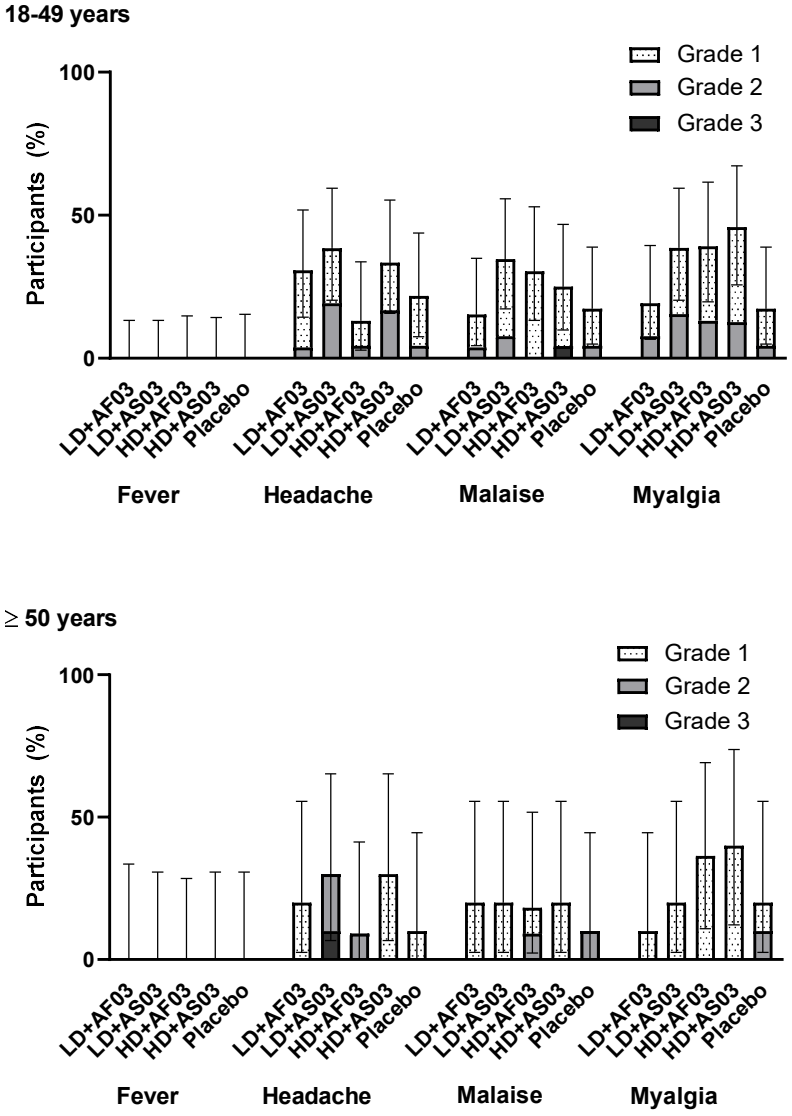


Appendix 8. Solicited injection site reactions (A) and solicited systemic reactions (B) after a single dose, by age strata (single-dose cohort, SafAS)

A.



B.


18-49 years
Grade 1
Grade 2
Grade 3
Participants (%)
100
50
0
LD+AF03
LD+AS03
HD+AF03
HD+AS03
Placebo
Fever
Headache
Malaise
Myalgia
≥ 50 years
Grade 1
Grade 2
Grade 3
Participants (%)
100
50
0
LD+AF03
LD+AS03
HD+AF03
HD+AS03
Placebo
Fever
Headache
Malaise
Myalgia

Appendix 9. Summary of unsolicited adverse events within 21 days after any dose for both age strata combined within (A) the two-dose cohort and (B) the single-dose cohort (SafAS).

A. Two-dose cohort

	LD + AF03 N=26			LD + AS03 N=80			HD + AF03 N=26			HD + AS03 N=85			HD N=18			Placebo N=29		
	n	% (95% CI)	AEs	n	% (95% CI)	AEs	n	% (95% CI)	AEs	n	% (95% CI)	AEs	n	% (95% CI)	AEs	n	% (95% CI)	AEs
Unsolicited AE	12	46·2 (26·6; 66·6)	29	34	42·5 (31·5; 54·1)	79	11	42·3 (23·4; 63·1)	33	50	58·8 (47·6; 69·4)	108	5	27·8 (9·7; 53·5)	9	9	31·0 (15·3; 50·8)	13
Grade 3	1	3·8 (0·1; 19·6)	5	4	5·0 (1·4; 12·3)	5	1	3·8 (0·1; 19·6)	2	3	3·5 (0·7; 10·0)	6	1	5·6 (0·1; 27·3)	1	0	0 (0; 11·9)	0
Unsolicited AR	6	23·1 (9·0; 43·6)	6	21	26·3 (17·0; 37·3)	42	5	19·2 (6·6; 39·4)	9	37	43·5 (32·8; 54·7)	70	1	5·6 (0·1; 27·3)	1	3	10·3 (2·2; 27·4)	4
Grade 3	0	0 (0; 13·2)	0	1	1·3 (0; 6·8)	1	0	0 (0; 13·2)	0	3	3·5 (0·7; 10·0)	6	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
Unsolicited injection site AR	3	11·5 (2·4; 30·2)	3	6	7·5 (2·8; 15·6)	7	2	7·7 (0·9; 25·1)	2	20	23·5 (15·0; 34·0)	24	1	5·6 (0·1; 27·3)	1	1	3·4 (0·1; 17·8)	1
Grade 3	0	0 (0; 13·2)	0	0	0 (0; 4·5)	0	0	0 (0; 13·2)	0	0	0 (0; 4·2)	0	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
Unsolicited systemic AE	11	42·3 (23·4; 63·1)	26	32	40·0 (29·2; 51·6)	72	11	42·3 (23·4; 63·1)	31	42	49·4 (38·4; 60·5)	84	5	27·8 (9·7; 53·5)	8	8	27·6 (12·7; 47·2)	12
Grade 3	1	3·8 (0·1; 19·6)	5	4	5·0 (1·4; 12·3)	5	1	3·8 (0·1; 19·6)	2	3	3·5 (0·7; 10·0)	6	1	5·6 (0·1; 27·3)	1	0	0 (0; 11·9)	0
Unsolicited systemic AR	3	11·5 (2·4; 30·2)	3	18	22·5 (13·9; 33·2)	35	4	(4·4; 34·9)	7	26	30·6 (21·0; 41·5)	46	0	0 (0; 18·5)	0	2	6·9 (0·8; 22·8)	3
Grade 3	0	0 (0; 13·2)	0	1	1·3 (0; 6·8)	1	0	(0; 13·2)	0	3	3·5 (0·7; 10·0)	6	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
SAE	0	0 (0; 13·2)	0	0	0 (0; 4·5)	0	0	(0; 13·2)	0	1	1·2 (0; 6·4)	1	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
Grade 3	0	0 (0; 13·2)	0	0	0 (0; 4·5)	0	0	(0; 13·2)	0	0	0 (0; 4·2)	0	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
AESI	0	0 (0; 13·2)	0	0	0 (0; 4·5)	0	0	(0; 13·2)	0	0	0 (0; 4·2)	0	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
Grade 3	0	0 (0; 13·2)	0	0	0 (0; 4·5)	0	0	(0; 13·2)	0	0	0 (0; 4·2)	0	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0
MAAE	1	3·8 (0·1; 19·6)	1	5	6·3 (2·1; 14·0)	8	2	(0·9; 25·1)	3	3	3·5 (0·7; 10·0)	5	0	0 (0; 18·5)	0	1	3·4 (0·1; 17·8)	1
Grade 3	0	0 (0; 13·2)	0	1	1·3 (0; 6·8)	1	0	(0; 13·2)	0	0	(0; 4·2)	0	0	0 (0; 18·5)	0	0	0 (0; 11·9)	0

B. Single-dose cohort

	LD + AF03 N=36			LD + AS03 N=36			HD + AF03 N=35			HD + AS03 N=34			Placebo N=34		
	n	**% (95% CI)**	**AEs**	**n**	**% (95% CI)**	**AEs**	**n**	**% (95% CI)**	**AEs**	**n**	**% (95% CI)**	**AEs**	**n**	**% (95% CI)**	**AEs**
Unsolicited AE	10	27·8 (14·2; 45·2)	15	9	25·0 (12·1; 42·2)	17	9	25·7 (12·5; 43·3)	18	10	29·4 (15·1; 47·5)	14	8	23·5 (10·7; 41·2)	12
Grade 3	0	0 (0; 9·7)	0	1	2·8 (0·1; 14·5)	1	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Unsolicited AR	5	13·9 (4·7; 29·5)	6	3	8·3 (1·8; 22·5)	3	4	11·4 (3·2; 26·7)	7	3	8·8 (1·9; 23·7)	3	1	2·9 (0·1; 15·3)	1
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Unsolicited injection site AR	2	5·6 (0·7; 18·7)	3	0	0 (0; 9·7)	0	1	2·9 (0·1; 14·9)	1	2	5·9 (0·7; 19·7)	2	0	0 (0; 10·3)	0
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Unsolicited systemic AE	8	22·2 (10·1; 39·2)	12	9	25·0 (12·1; 42·2)	17	9	25·7 (12·5; 43·3)	17	9	26·5 (12·9; 44·4)	12	8	23·5 (10·7; 41·2)	12
Grade 3	0	0 (0; 9·7)	0	1	2·8 (0·1; 14·5)	1	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Unsolicited systemic AR	3	8·3 (1·8; 22·5)	3	3	8·3 (1·8; 22·5)	3	3	8·6 (1·8; 23·1)	6	1	2·9 (0·1; 15·3)	1	1	2·9 (0·1; 15·3)	1
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
SAE	1	2·8 (0·1; 14·5)	1	0	0 (0; 9·7)	0	1	2·9 (0·1; 14·9)	1	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
AESI	0	0 (0; 9·7)	0	1	2·8 (0·1; 14·5)	1	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0
MAAE	2	5·6 (0·7; 18·7)	3	3	8·3 (1·8; 22·5)	4	1	2·9 (0·1; 14·9)	1	1	2·9 (0·1; 15·3)	1	3	8·8 (1·9; 23·7)	3
Grade 3	0	0 (0; 9·7)	0	0	0 (0; 9·7)	0	0	0 (0; 10·0)	0	0	0 (0; 10·3)	0	0	0 (0; 10·3)	0

Numbers presented are numbers of participants experiencing at least one of the specified items, or the number of adverse events specified (column, AEs).
AESI, adverse event of special interest; AR, adverse reaction; HD, high-dose; LD, high-dose; MAAE, medically attended adverse event; (S)AE, serious adverse event

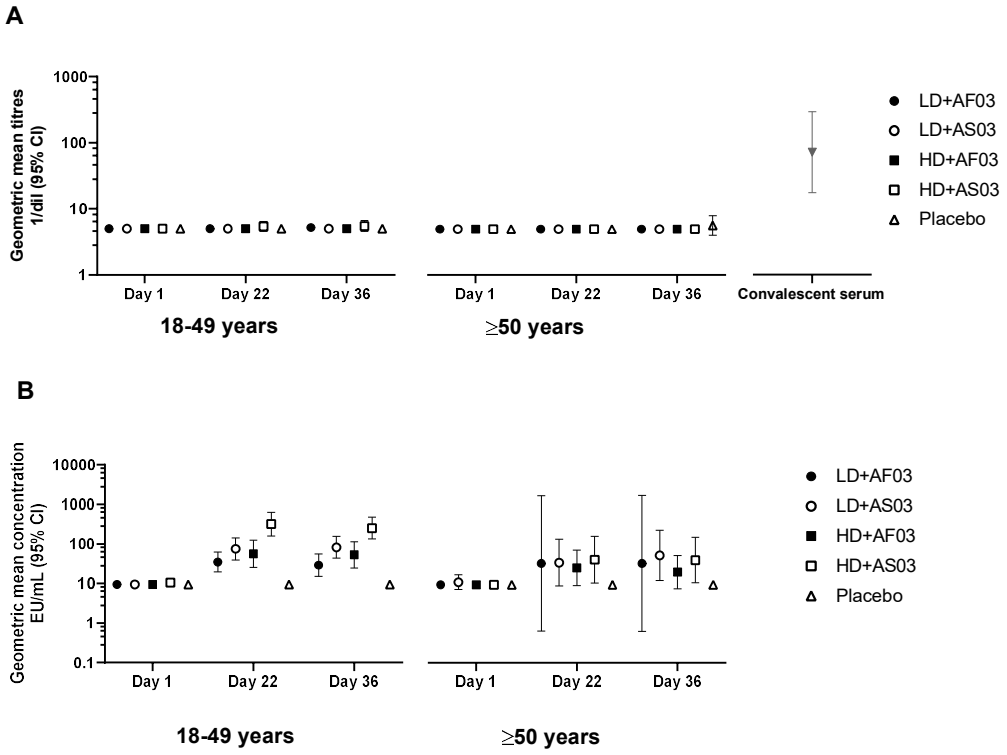
Appendix 10.

Description of unsolicited adverse events occurring within 21 days after any dose for both age strata

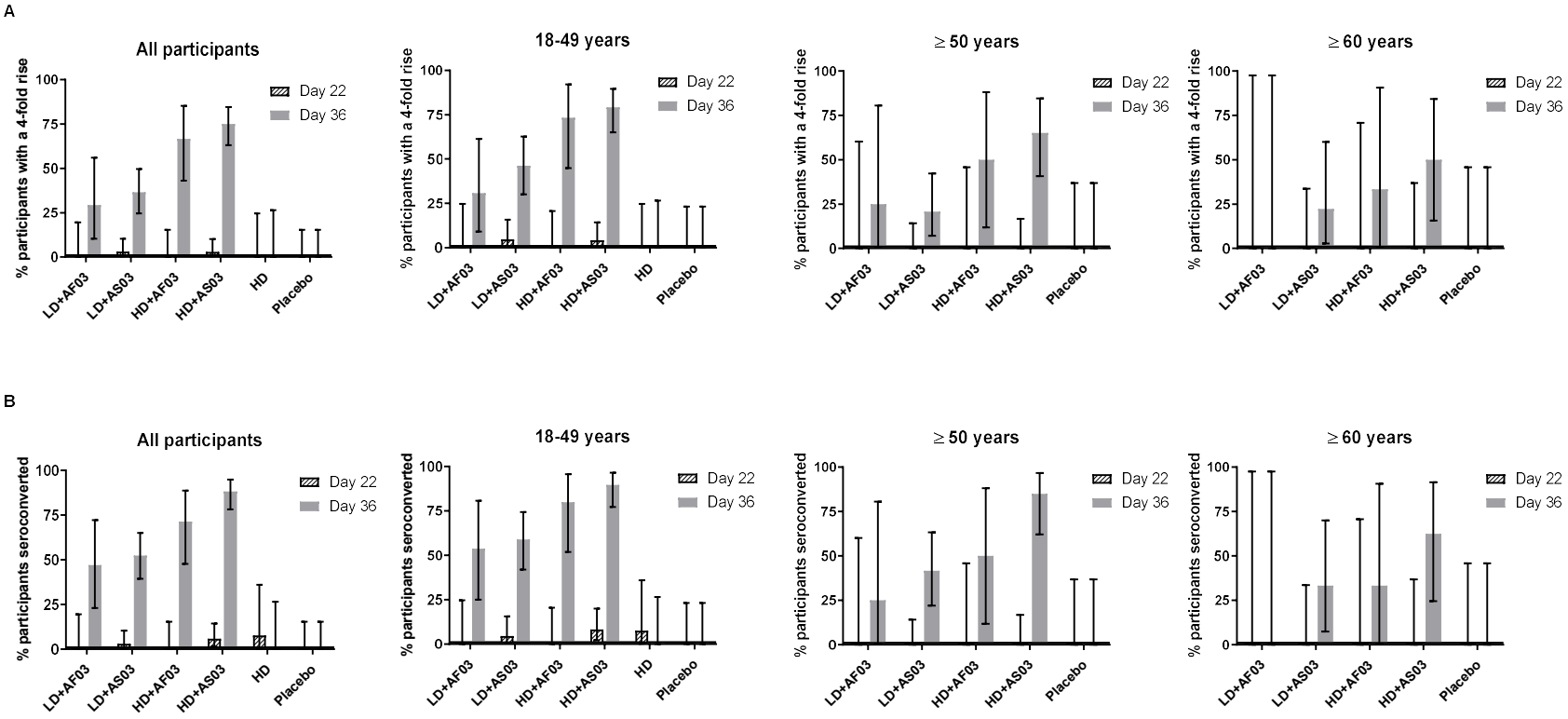
- "General disorders and administration site conditions" (18.9% and 6.3% in Pooled Vaccine and Pooled Placebo groups, respectively; 22.2% and 16.9% in Pooled High Dose and Pooled Low Dose groups, respectively; 22.6%, 13.8%, and 5.6% in Pooled AS03, Pooled AF03, and High Dose Without Adjuvant groups, respectively)
- "Nervous system disorders" (9.6% and 6.3% in Pooled Vaccine and Pooled Placebo groups, respectively; 11.1% and 7.3% in Pooled High Dose and Pooled Low Dose groups, respectively; 9.8%, 8.1%, and 16.7% in Pooled AS03, Pooled AF03, and High Dose Without Adjuvant groups, respectively)
- "Gastrointestinal disorders" (9.3% and 3.2% in Pooled Vaccine and Pooled Placebo groups, respectively; 11.1% and 7.3% in Pooled High Dose and Pooled Low Dose groups, respectively; 10.6%, 6.5%, and 11.1% in Pooled AS03, Pooled AF03, and High Dose Without Adjuvant groups, respectively)
- "Musculoskeletal and connective tissue disorders" (6.9% and 4.8% in Pooled Vaccine and Pooled Placebo groups, respectively; 8.3% and 6.2% in Pooled High Dose and Pooled Low Dose groups, respectively; 7.7%, 6.5%, and 0% in Pooled AS03, Pooled AF03, and High Dose Without Adjuvant groups, respectively)
- "Respiratory, thoracic and mediastinal disorders" (5.6% and 4.8% in Pooled Vaccine and Pooled Placebo groups, respectively; 5.0% and 6.7% in Pooled High Dose and Pooled Low Dose groups, respectively; 4.3%, 8.9%, and 0% in Pooled AS03, Pooled AF03, and High Dose Without Adjuvant groups, respectively)

Appendix 11. Neutralising antibody titres (microneutralisation assay; A) and binding antibody responses (ELISA; B) after single dose, by age strata (single-dose cohort; PPAS-IAS)

Footnote: Neutralising antibody titres are additionally shown for a panel of 93 convalescent serum samples, as indicated, in (A).

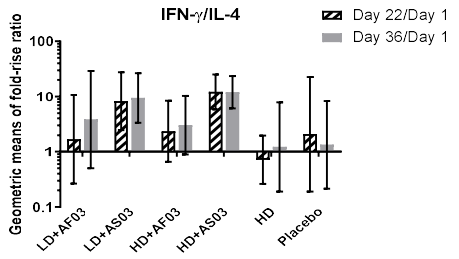


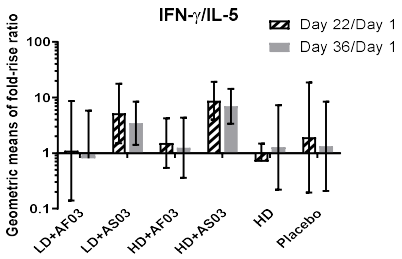
Appendix 12. Percentages of participants with (A) a 4-fold rise in neutralising antibody titres, relative to D1, and (B) seroconversion, overall and by age strata at Day 22 and Day 36, two dose cohort (PPAS-IAS)

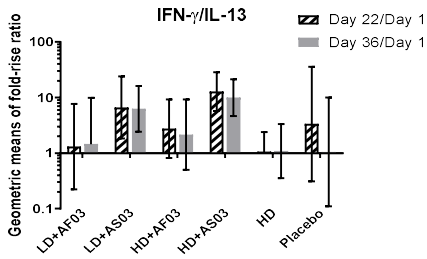


Appendix 13. CMI analyses – ratios of fold-rises for IFN-γ (A), IL-2 (B) and TNFα (C) to IL-4, IL-5 and IL-13 at Day 22 and Day 36 (PPAS-CMI)

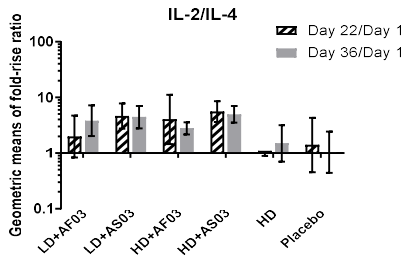
A

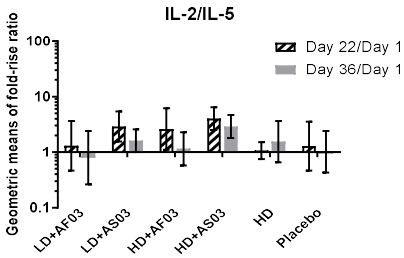


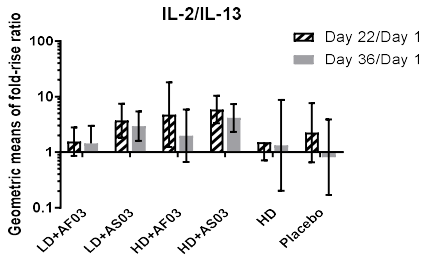




B







C