Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study

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Summary

Background The literature on first generation COVID-19 vaccines show they were less effective against new SARS-CoV-2 variants of concern including Omicron (BA.1, BA.2, BA.4 and BA.5 subvariants). New vaccines developed against variant strains may provide cross-protection against emerging variants when used as boosters and facilitate vaccination across a range of countries, healthcare settings and populations. However, there are no data on such vaccines when used as a primary series.

Methods A global Phase 3, multi-stage efficacy study (NCT04904549) among adults (≥18 years) was conducted in 53 research centres in eight countries (United States, Honduras, Japan, Colombia, Kenya, India, Ghana, Nepal). Participants were randomized 1:1 to receive two intramuscular injections of a monovalent SARS-CoV-2 recombinant protein vaccine with AS03-adjuvant (10 μg of the spike (S) protein from the ancestral D614 strain) or placebo on Day 1 (D01) and Day 22 (D22). The primary efficacy endpoint was prevention of virologically confirmed SARS-CoV-2 infection with symptoms of COVID-19-like illness (CLI) ≥14 days after the second

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injection (post-dose 2 [PD2]) in participants who were SARS-CoV-2 naïve on D01 + D22. Safety and reactogenicity were also evaluated.

Findings Between May 26 and November 7, 2021, 10,114 participants received ≥1 study injection, and 9441 participants received both injections. 2108 (20.8%) participants were SARS-CoV-2 naïve at D01 and D22. The primary endpoint was analysed in a subset of the full analysis set (the modified full analysis set PD2 [mFAS-PD2], excluding participants who did not complete the vaccination schedule or received vaccination despite meeting one of the contraindication criteria, had onset of symptomatic COVID-19 between the first injection and before 14 days after the second injection, or participants who discontinued before 14 days after the second injection [n = 9377; vaccine, n = 4702; placebo, n = 4675]). Data were available for 2051 SARS-CoV-2 naïve and 7159 non-naïve participants. At the cut-off date (January 28, 2022), symptomatic COVID-19 was reported in 169 naïve participants (vaccine, n = 81; placebo, n = 88) ≥14 days PD2, with a vaccine efficacy (VE) of 15.3% (95% CI, −15.8; 38.2). VE regardless of D01/D22 serostatus was 32.9% (95% CI, 15.3; 47.0) and VE in non-naïve participants was 52.7% (95% CI, 31.2; 67.9). Viral genome sequencing was performed up to the data cut-off point and identified the infecting strain in 99/169 adjudicated cases in the PD2 naïve population (Delta [25], Omicron [72], other variants [3], one participant had infection with both Delta and Omicron variants and has been included in the totals for both Delta and Omicron). The vaccine was well-tolerated with an acceptable safety profile.

Interpretation In the context of changing circulating viral variants, it is challenging to induce protection in naïve individuals with a two-dose priming schedule based on the parental D614 strain. However, while the primary endpoint of this trial was not met, the results show that a monovalent D614 vaccine can still be of value in individuals previously exposed to SARS-CoV-2.

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Keywords: SARS-CoV-2; Vaccine; Efficacy; Monovalent

Research in context

Evidence before this study

PubMed was searched from database inception up to 20 December 2022, with no language restrictions, for studies that reported the efficacy, effectiveness and safety of recombinant protein candidates against SARS-CoV2 using the search terms "efficacy OR effectiveness OR safety", "vaccine", "clinical trial", "SARS-CoV2", and "recombinant AND protein", and "adjuvant". In the retrieved articles, first generation COVID-19 vaccines were less effective against new SARS-CoV-2 variants of concern including Omicron (BA.1, BA.2, BA.4 and BA.5 subvariants). Vaccines developed against variant strains may provide cross-protection against emerging variants when used as boosters; however, there are no data on these vaccines when used as a primary series.

Added value of this study

In this study, we report that vaccine efficacy (VE) against symptomatic COVID-19 was not demonstrated for the CoV2 preS dTM-AS03 monovalent (D614) vaccine in the naïve population (VE 15.3%, 95% confidence interval (CI), −15.8: 38.2). However, after two doses VE was demonstrated in the non-naïve population (52.7%, 95% CI, 31.2; 67.9). Although this study was not powered to assess strain-specific efficacy, we show some level of protection against the Delta strain in participants regardless of prior infection (VE 72.9%, 95% CI, 35.5; 90.1). This is comparable to estimates of VE against the Delta variant with other D614-based COVID-19 vaccines, which have varied from 44% to 95%. An acceptable safety profile was demonstrated, and no safety concerns were identified during the study conduct in the adult and older-adult populations.

Implications of all the available evidence

The D614 monovalent vaccine demonstrated efficacy to prevent symptomatic COVID-19 disease in non-naive participants, which is relevant in the current environment where most of the population has already been exposed to SARS-CoV-2, either through vaccination or natural infection.

Introduction

Since coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, countries have been struggling to contain the ensuing pandemic and its impact on health and the global economy.[1] As of March 2023, the World Health Organization estimates that over 6.85 million deaths have been caused by COVID-19 since the start of the pandemic, while massive vaccination programs have resulted in over 13 billion vaccine doses being administered worldwide.[2] Indeed, modelling estimates (based on 2020/2021 excess death rates) have indicated that vaccination has saved up to 20 million lives globally, representing a reduction of 63% in total deaths.[3]

The epidemiological context of COVID-19 has changed since 2019. Firstly, a large proportion of the global population has survived previous infection. Secondly, while most currently available vaccines were developed using the Spike (S) sequence from the ancestral D614 Wuhan-Hu-1 strain, current evidence suggests that these may be less effective against emerging variants (including Beta, Gamma, Delta and Omicron).[4–9] The addition of new vaccines to the current armamentarium will extend the options to facilitate protection across different regions, healthcare settings and populations in the context of the ongoing pandemic, regardless of prior infection, and with the threat of rapidly evolving SARS-CoV-2 virus strains. Using a baculovirus expression vector system to express stabilised SARS-CoV-2 pre-fusion S antigen (preS dTM) from the ancestral D614 strain, Sanofi has developed a monovalent SARS-CoV-2 recombinant protein vaccine with the GSK AS03 adjuvant system (CoV2 preS dTM-AS03).[10] Interim results of a Phase 2 dose-ranging study showed an acceptable safety and reactogenicity, and robust immunogenicity of two doses administered 21 days apart in SARS-CoV-2 naïve and non-naïve adults.[11]

Based on those Phase 2 data, a 10 μg antigen dose was selected for evaluation in this Phase 3 efficacy trial in the context of primary vaccination. Here, we present the efficacy, safety and immunogenicity data of a two-dose primary vaccination series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine.

Methods

Study design

This Phase 3, parallel, international, randomized, double-blind, placebo-controlled study was designed as a multi-stage platform trial comprising two stages (NCT04904549). In Stage 1, which is reported here, the efficacy, safety and immunogenicity of a prototype monovalent vaccine containing the ancestral D614 recombinant S protein with the GSK AS03 adjuvant (CoV2 preS dTM-AS03 [D614]) was assessed in 53 clinical research centres across eight countries (Colombia, Ghana, Honduras, India, Japan, Kenya, Nepal and the United States) (Supplementary Appendix Section 1.1). Stage 2, which assessed the clinical efficacy and safety of a bivalent vaccine containing stabilized SARS-CoV-2 pre-fusion S proteins from both the ancestral D614 and the Beta (B.1.351) variant (CoV2 preS dTM-AS03 [D614 + B.1.351]) is reported elsewhere.[12]

The study was conducted in compliance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol and amendments were approved by applicable Independent Ethics Committees/Institutional Review Boards and per local regulations. All participants provided written informed consent before any investigations or vaccinations were performed. An independent data and safety monitoring board[13] provided study oversight and reviewed unblinded data.

Participants

We recruited adults aged ≥18 years with no prior COVID-19 vaccination. The inclusion and exclusion criteria are reported in Supplementary Appendix Section 1.2. The investigators ensured that trial participants were aware that approved/authorized COVID-19 vaccines were already available in some of the countries and regions included in the study, and the participants were encouraged to obtain the approved/authorized vaccine as applicable. Participants were only enrolled in the trial if they expressed no interest in receiving one of the approved/authorized vaccines. At every opportunity, participants were advised on the availability and benefits of these vaccines. Furthermore, participants were permitted to receive an authorized vaccine outside of the study protocol, while being offered the option to continue in the study for safety and immunogenicity follow-up visits. The study also included participants with a potentially high risk for severe COVID-19 (Supplementary Appendix Section 1.3) as well as other subpopulations at risk.

Randomization and masking

Participants were randomized (1:1) using an interactive response system (IRT), to receive either the monovalent vaccine or placebo (saline). Participants were stratified by age (18–59 years/≥60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity and study site, using permuted sub-block randomization with a block size of eight (four vaccine and four placebo). All participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff, and those administering the study intervention were blinded to group assignments; only those preparing the study intervention were unblinded, but they were not involved in study outcome assessments. A subset of participants was also allocated to the random immunogenicity subcohort (RIS), either by random allocation at enrolment or in a supplemental ad hoc selection (in the US and Japan).

Procedures

The recombinant protein antigen CoV2 preS dTM and the AS03 adjuvant system (GSK Vaccines, Rixensart, Belgium) have been described previously.[10,11,14] Participants in the vaccine group received two 0.5 mL injections of the monovalent vaccine, and participants in the placebo group received two 0.5 mL injections of 0.9% normal saline. Each 0.5 mL injection of the monovalent CoV2 preS dTM- AS03-adjuvanted vaccine contained 10 μg recombinant protein antigen CoV2 preS dTM (D614 strain). Vaccinations were administered on study days 01 and 22 by intramuscular injection into the deltoid region by qualified and trained personnel.

Blood samples and nasopharyngeal swabs were collected before each vaccination to establish whether participants had previous or ongoing SARS-CoV-2 infection (naïve [naïve at D0 and D22] or non-naïve [non-naïve at D0 or D22]). Active and passive COVID-19-like illness (CLI) surveillance was conducted: participants were contacted once a week to determine whether they had any symptoms of a CLI (Supplementary Appendix Section 1.4) or if they had a positive COVID-19 test from another source at any time during the study. If the participant reported CLI symptoms, nasopharyngeal and anterior nasal swabs were collected at the participant's first visit after symptom onset and 2–4 days later for virological confirmation using nucleic acid amplification test (NAAT). Further anterior nasal swabs were collected from participants with laboratory confirmed NAAT and SARS-CoV-2 infection at 7–9 days and 12–14 days after the first illness visit. Participants with a positive result for SARS-CoV-2 in any specimen were requested to continue recording their daily COVID-19 symptoms until the end of their illness or for up to 30 days from symptom onset. If symptoms persisted for >30 days, participants were asked to record the date the symptoms resolved. An independent, blinded adjudication committee reviewed potential cases to determine whether the case definitions for symptomatic and/or severe COVID-19 were met. Viral genomic sequencing was performed on respiratory samples from the cases to identify the SARS-CoV-2 variant, as previously described.[15,16]

Outcomes

The primary efficacy endpoint was the occurrence of symptomatic COVID-19 (virologically confirmed SARS-CoV-2 infection accompanied by protocol-defined CLI [Supplementary Appendix Section 1.4]) ≥14 days after the second injection in participants who were SARS-CoV-2 naïve at Day 01 and Day 22.

Secondary efficacy endpoints included the occurrence of symptomatic disease regardless of serostatus (at D01 + D22) and in non-naïve individuals; and efficacy against moderate or worse COVID-19, or hospitalized COVID-19 ≥14 days PD2 in all participants and according to prior infection status. The efficacy endpoints are defined in Supplementary Appendix Section 1.5.

Pre-defined exploratory efficacy endpoints included efficacy by age category (18–59 years and ≥60 years) and participants with high-risk medical conditions. The occurrence of symptomatic or severe COVID-19 ≥14 days after the first injection and the occurrence of asymptomatic infection in SARS-CoV-2 naïve participants were also assessed.

The neutralizing antibody profiles against the D614G variant at Day 01, Day 22 and Day 43 were assessed in all participants assigned to the RIS. The levels of neutralizing antibodies in serum samples were assessed using a validated SARS-CoV-2 pseudovirus neutralization assay (Monogram Biosciences, South San Francisco, CA, USA), as previously described.[17] Briefly, pseudotyped virus particles—comprising vesicular stomatitis virus, the S glycoprotein of SARS-CoV-2 (minus the last 19 amino acids of the cytoplasmic tail) and a luciferase reporter—were initially incubated for ~60 min with seven two-fold serial dilutions of heat-inactivated human serum samples at a target working dilution (75,000 to 300,000 relative luminescence units [RLUs]/well) in a 96-well plate. The serum–virus particles were then transferred to 96-well plates that were seeded with Vero-E6 cells and incubated for ~20 h in addition to the luciferase substrate. The plate(s) were then read on a luminescence plate reader. The intensity of the luminescence, quantified in RLUs, was inversely proportional to the level of neutralizing antibodies present in the serum. The neutralizing titre of a serum sample was calculated as the reciprocal serum dilution corresponding to the 50% neutralization antibody titre (NT50) for that sample.

Adverse events (AEs) were reported to investigators by participants during each study visit or during any follow-up contact. All participants receiving at least one injection of the study vaccine or placebo provided safety data throughout the duration of the study, including the incidence of immediate unsolicited systemic AEs (occurring within 30 min of each dose), serious adverse events (SAEs), adverse events of special interest (AESIs) and medically attended adverse events (MAAEs) (Supplementary Appendix Section 1.6). Reactogenicity was also assessed by collecting data on solicited injection site reactions (SISRs) and solicited systemic reactions (SSRs) occurring within 7 days after each vaccination and unsolicited AEs occurring within 21 days after each vaccination. SAEs, AESIs and MAAEs were assessed during the entire study period.

Statistical analyses

Calculations for determining the sample size are reported in Supplementary Appendix Section 1.7. The primary efficacy analysis was conducted in the modified full analysis set post-dose 2 (mFAS-PD2). This

comprised participants receiving both injections who did not meet any of the vaccine contraindications and did not discontinue within 14 days PD2. Participants with symptomatic COVID-19 with onset between the first injection (post-dose 1 [PD1]) and 14 days PD2 were excluded from the mFAS-PD2 analysis. The mFAS-PD1 consisted of participants who did not meet any of the vaccine contraindications, did not discontinue within 14 days PD1, and did not develop symptomatic COVID-19 with onset between the first injection and 14 days PD1.

Safety outcomes were assessed in the safety analysis set (SafAS), which included all randomized participants who received ≥1 injection of study vaccine or placebo. Safety outcomes are reported as the proportion of participants reporting an event, with 95% confidence interval (CI) calculated using the Clopper–Pearson method. The reactogenicity safety analysis set (RSafAS) was a subset of the SafAS that comprised approximately 4500 participants (the first 4000 participants recruited [2000 in each arm], as well as all participants from Japan, as required by the local regulatory authority).

Immunogenicity was assessed in the immunogenicity analysis set (IAS), which included patients allocated to the RIS who had completed both study doses and met no other predefined exclusion criteria/protocol deviations. Participants were defined as responders if they had baseline values below the lower limit of quantification with a quantifiable neutralization titre post-vaccination, or if they had baseline values above the lower limit of quantification with a four-fold increase in neutralizing antibody titres post-vaccination. The ratios of GMTs/GMCs were obtained between groups with the two-sided 95% CIs calculated using normal approximation of log-transformed titers/concentrations. Full descriptions of the analysis sets are reported in Supplementary Appendix Section 1.8.

The calculation for the point estimate of vaccine efficacy (VE; primary efficacy endpoint) was based on the incidence rate per 1000 person-years in mFAS-PD2 participants who were SARS-CoV-2 naïve at Day 01 and Day 22. The primary endpoint analyses (VE) is calculated as: 1 – the ratio of {(the number cases in the vaccine/total person-years at risk in the vaccine group)/(the number cases in the placebo/total person-years at risk in the placebo group)}. We also computed the VE with cumulative incidence (i), as supportive analysis. CUMI was computed as the number of cases divided by the number of participants at risk. The 95% CI is computed by using the Clopper-Pearson method. As supportive analysis, VE was also estimated using survival analysis based on a stratified Cox proportional hazard model with score-based 95% CI.

For the primary efficacy objective to be met, the VE was required to be >50%, and the lower bound of the 95% CI was required to be >30%. The CI for incidence rate (by person-years) was calculated using the Poisson method. The CI for the VE was calculated using an exact binomial method. Survival analyses (Kaplan–Meier curves) were estimated, with 95% CI calculated using the Hall–Wellner confidence band. Statistical analyses were performed using SAS® Version 9.4 or later.

Role of funding

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Results

Participants

Between May 26, 2021, and November 7, 2021, 10,139 participants were randomized to receive the vaccine (n = 5061) or placebo (n = 5078), with 10,114 (99.8%) participants receiving one dose and 9441 (93.1%) participants completing both doses (Fig. 1). In total, 743 participants (350 in the vaccine group and 393 in the placebo group) discontinued the study PD1 (n = 371) or PD2 (n = 372) (Supplementary Appendix Section 2.1). The mFAS-PD2 subset comprised 9377 participants (4702 in the vaccine group and 4675 in the placebo group), for whom available data on serostatus confirmed that 2051 were naïve at Day 01 and Day 22 (1039 in the vaccine group and 1012 in the placebo group; primary efficacy analysis population) and 7159 were non-naïve at Day 01 or Day 22 (3572 in the vaccine group and 3587 in the placebo group). Participants were censored from the mFAS-PD2 for the following reasons: 698 participants (6.9%) did not did not complete the vaccination schedule of two vaccinations (341 [6.7%] in the vaccine group and 387 [7.0%] in the placebo group); 32 participants (0.3%) had the onset of a symptomatic COVID-19 episode between the first injection and 14 days after the second injection (6 [0.1%] in the vaccine group and 26 [0.5%] in the placebo group); five participants (<0.1%) received the second injection despite meeting the defined contraindication criteria (two participants [<0.1%] in the vaccine group and three participants [<0.1%] in the placebo group; 29 participants (0.3%) discontinued from the study before 14 days after the second injection (11 [0.2%] in the vaccine group and 18 [0.4%] in the placebo group). Two participants (one in the vaccine group and one in the placebo group) were censored from the mFAS-PD2

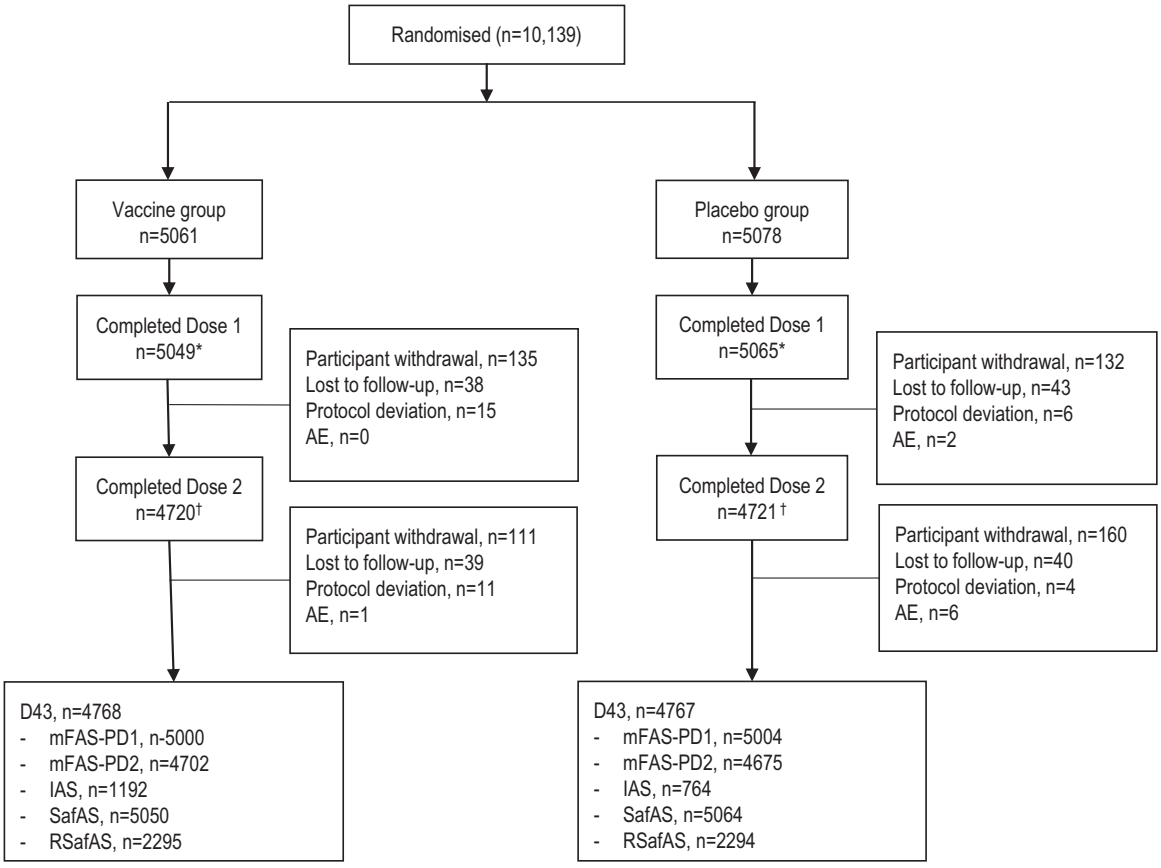

Fig. 1: CONSORT diagram for patient flow through the study. *Among the randomized participants, 12 participants in the vaccine group and 13 participants in the placebo group did not receive any injection. †According to the study protocol, participants were permitted to miss an injection and still attend the later visits; these participants were not considered to have discontinued from the study, and are not included in the figure.

because of both the onset of symptomatic COVID-19 between the first injection and 14 day after the second injection and because of discontinuation from the study before 14 days after the second injection. The mFAS-PD1 subset comprised 10,004 participants, and the IAS comprised 1956 participants (Fig. 1). The disposition of the participants in the study populations as randomized are reported in the Supplementary Appendix Section 2.2.

Demographic characteristics are reported for the 10,114 (99.8%) participants who received ≥1 study injection (SafAS), based on first visit data (Table 1). The demographics were comparable across treatment groups. The mean (SD) age was 37.9 (13.9) years, 56.6% were male, and 73.8% of participants had evidence of prior infection (non-naïve) at enrolment. High-risk medical conditions were present in 31.6% of participants (Table 1). The demographics and baseline characteristics of the mFAS-PD2 naïve population are reported in Supplementary Appendix Section 2.3.

To the data cut-off date (January 28, 2022), the longest duration of follow-up PD1 was 248 days (median 165 days; SafAS) and 227 days (median 139 days; mFAS-PD2) PD2 (Supplementary Appendix Section 2.4 and 2.5). The proportion of patients with ≥2 months' follow-up at the cut-off date was 96.1% (9719/10,114) PD1 and 98.5% (9237/9377) PD2.

To the data cut-off date, a total of 308 participants reported a confirmed symptomatic case of COVID-19 ≥14 days after the second injection. Of these, 169 cases were in naïve participants, 133 cases were in non-naïve participants, and for six the serostatus was unknown. The distribution of symptomatic COVID-19 cases over time highlights that, between August and November 2021, most of the reported cases were likely due to the Delta variant (Fig. 2). By December 2021 and January 2022, the circulating variant type had mostly switched from Delta to Omicron (mainly BA.1, with some BA.2 subvariants). There were few symptomatic cases early in the study and most cases were reported during the global Omicron wave (Fig. 2).

	Vaccine group (N = 5050)	Placebo group (N = 5064)	Total (N = 10,114)
Sex, n (%)			
Male	2838 (56.2)	2889 (57.0)	5727 (56.6)
Female	2212 (43.8)	2175 (43.0)	4387 (43.4)
Age, years			
Mean (SD)	37.9 (13.8)	37.8 (13.9)	37.9 (13.9)
Median (min; max)	36.0 (26.0; 47.0)	36.0 (26.0; 47.0)	36.0 (26.0; 47.0)
Age categories, n (%)			
18–59 years	4636 (91.8)	4644 (91.7)	9280 (91.8)
≥60 years	414 (8.2)	420 (8.3)	834 (8.2)
BMI, mean (SD); median (Q1; Q3)	25.0 (5.46); 23.9 (21.2; 27.7)	25.0 (5.41); 23.9 (21.2; 27.6)	25.0 (5.43); 23.9 (21.2; 27.6)
Race, n (%)			
White	114 (2.3)	116 (2.3)	230 (2.3)
Asian	2219 (43.9)	2226 (44.0)	4445 (43.9)
Black or African American	1057 (20.9)	1052 (20.8)	2109 (20.9)
American Indian or Alaska Native	1641 (32.5)	1645 (32.5)	3286 (32.5)
Native Hawaiian or other Pacific Islander	1 (<0.1)	3 (<0.1)	4 (<0.1)
Multiple	8 (0.2)	6 (0.1)	14 (0.1)
Not reported	1 (<0.1)	3 (<0.1)	4 (<0.1)
Unknown	9 (0.2)	13 (0.3)	22 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	1673 (33.1)	1677 (33.1)	3350 (33.1)
Not Hispanic or Latino	3362 (66.6)	3364 (66.4)	6726 (66.5)
Not reported	2 (<0.1)	5 (<0.1)	7 (<0.1)
Unknown	13 (0.3)	18 (0.4)	31 (0.3)
Country, n (%)			
United States	207 (4.1)	215 (4.2)	422 (4.2)
Honduras	719 (14.2)	722 (14.3)	1441 (14.2)
Colombia	929 (18.4)	929 (18.3)	1858 (18.4)
Japan	147 (2.9)	152 (3.0)	299 (3.0)
India	1822 (36.1)	1826 (36.1)	3648 (36.1)
Ghana	917 (18.2)	914 (18.0)	1831 (18.1)
Kenya	64 (1.3)	64 (1.3)	128 (1.3)
Nepal	245 (4.9)	242 (4.8)	487 (4.8)
Prior SARS-CoV-2 infection, n (%)			
Naïve at Day 01	1277 (25.3)	1277 (25.2)	2554 (25.3)
Non-naïve at Day 01	3721 (73.7)	3740 (73.9)	7461 (73.8)
Undetermined at Day 01	52 (1.0)	47 (0.9)	99 (1.0)
Naïve at Day 01 and Day 22	1058 (21.0)	1050 (20.7)	2108 (20.8)
Non-naïve at Day 01 or Day 22	3851 (76.3)	3876 (76.5)	7727 (76.4)
Undetermined at Day 01 or Day 22	141 (2.8)	138 (2.7)	279 (2.8)
High-risk medical condition			
Yes	1578 (31.2)	1621 (32.0)	3199 (31.6)
No	2472 (68.8)	3443 (68.0)	6915 (38.4)

BMI, body mass index; Q, quarter (of year); SafAS, safety analysis set; SD standard deviation.

Table 1: **Demographics and clinical characteristics at baseline in the participants who received at least one injection (SafAS).**

Efficacy

Primary efficacy

In the mFAS-PD2, 81 naïve participants in the vaccine group (7.8%) and 88 in the placebo group (8.7%) had confirmed symptomatic COVID-19 ≥14 days after the second injection, with a VE of 15.3% (95% CI, –15.8, 38.2), which did not meet the primary efficacy objective (Fig. 3). The Kaplan–Meier curve showed a cross-over of the curves, with a higher number of cases accumulating in the vaccine group compared with the placebo group from around 165 days from 14 days PD2 (Fig. 4). Survival analysis based on the stratified Cox proportional hazard model is reported in Supplementary Appendix Section 2.6.

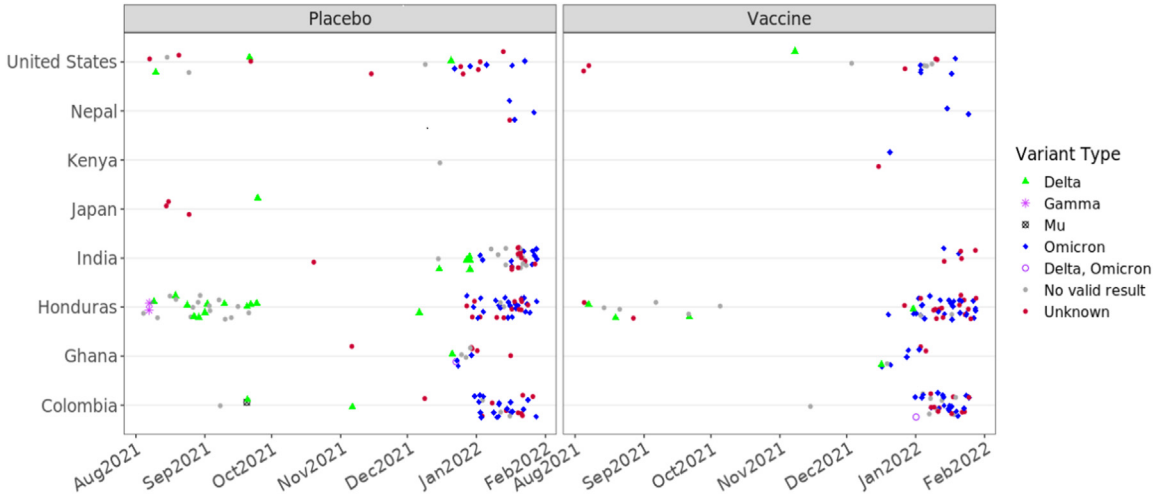

Fig. 2: Variant distribution by country and calendar time in all participants regardless of prior SARS-CoV-2 infection.

Secondary efficacy

Regardless of serostatus, in the mFAS-PD2 126 (2.7%) participants in the vaccine group and 182 (3.9%) participants in the placebo group had confirmed symptomatic COVID-19 (VE 32.9%, 95% CI, 15.3; 47.0). In the mFAS-PD2 non-naïve participants, 43 (1.2%) participants in the vaccine group and 90 (2.5%) participants in the placebo group had confirmed symptomatic COVID-19 ≥14 days after the second injection (VE 52.7%, 95% CI, 31.2; 67.9) (Fig. 3). In the Kaplan–Meier analysis, the curves diverged until the analysis cut-off, with more cases accumulating in the placebo group than in the vaccine group (Fig. 4). Efficacy results in naïve, non-naïve and all participants in mFAS-PD2 are shown in Supplementary Appendix Section 2.7.

A total of 13 cases of confirmed severe COVID-19 were reported ≥14 days after the second injection: eight among naïve participants (vaccine n = 3; placebo n = 5; VE 44.8%, 95% CI, –183.7; 91.4) and four in non-naïve participants (vaccine n = 2, placebo n = 2; VE 1.0%, 95% CI, –1266.1; 92.8); serostatus data were not available for one patient in the placebo group. Five cases of hospitalized symptomatic COVID-19 were reported ≥14 days after the second injection, all of which were in naïve participants in the placebo group. A total of 35 cases of symptomatic COVID-19 with severity of moderate or worse were reported ≥14 days after the second injection: 26 in naïve participants (vaccine n = 8; placebo n = 18) and eight in non-naive participants (vaccine n = 3; placebo n = 5) (Supplementary Appendix Section 2.7); serostatus data were not available for one patient in the placebo group.

Exploratory efficacy

In the mFAS-PD1, the VE against symptomatic COVID-19 was 34.1% (95% 12.7; 50.4) in the naïve participants and 52.2% (95% CI, 31.9; 66.9) in the non-naïve participants (Supplementary Appendix Section 2.8).

Approximately 32% of the participants had a high-risk medical condition at the time of recruitment. In the mFAS-PD2, the VE against symptomatic COVID-19 PD2 in naïve participants with a high-risk medical condition was 26.7% (95% CI, –13.4; 53.0 [39 participants in the vaccine group and 51 participants in the placebo group]) compared with those without high-risk medical conditions, in whom the VE against symptomatic COVID-19 was 0.4% (95% CI, –59.4; 37.5 [42 participants in the vaccine group and 37 participants in the placebo group]) (Fig. 3).

The VE against asymptomatic SARS-CoV-2 infection in the naïve participants in mFAS-PD2 was –1.4% (95% –37.1; 25.0); the VE could not be calculated for the non-naïve participants (Supplementary Appendix Section 2.9).

When assessed by age group, in naïve participants aged 18–59 years there were 74 participants with symptomatic COVID-19 in the vaccine group and 81 participants with symptomatic COVID-19 in the placebo group (VE 17.9%, 95% CI -14.0; 40.9), whereas in the ≥60-year group there were only seven cases in each arm (VE -5.0, 95% CI, –251; 68.6). For non-naïve participants aged 18–59 years the VE was 52.7% (95% CI, 30.3; 68.4 [40 participants in the vaccine group and 84 participants in the placebo group]) and in those ≥60 years there were three participants with a case of symptomatic COVID-19 in the vaccine group and six participants in the placebo group, with a VE of 52.6% (95% CI, –121.9; 92.3) (Fig. 3; Supplementary Appendix Section 2.10).

Viral variants

Of the 169 participants (173 episodes) with adjudicated cases of symptomatic COVID-19 in the PD2 naïve

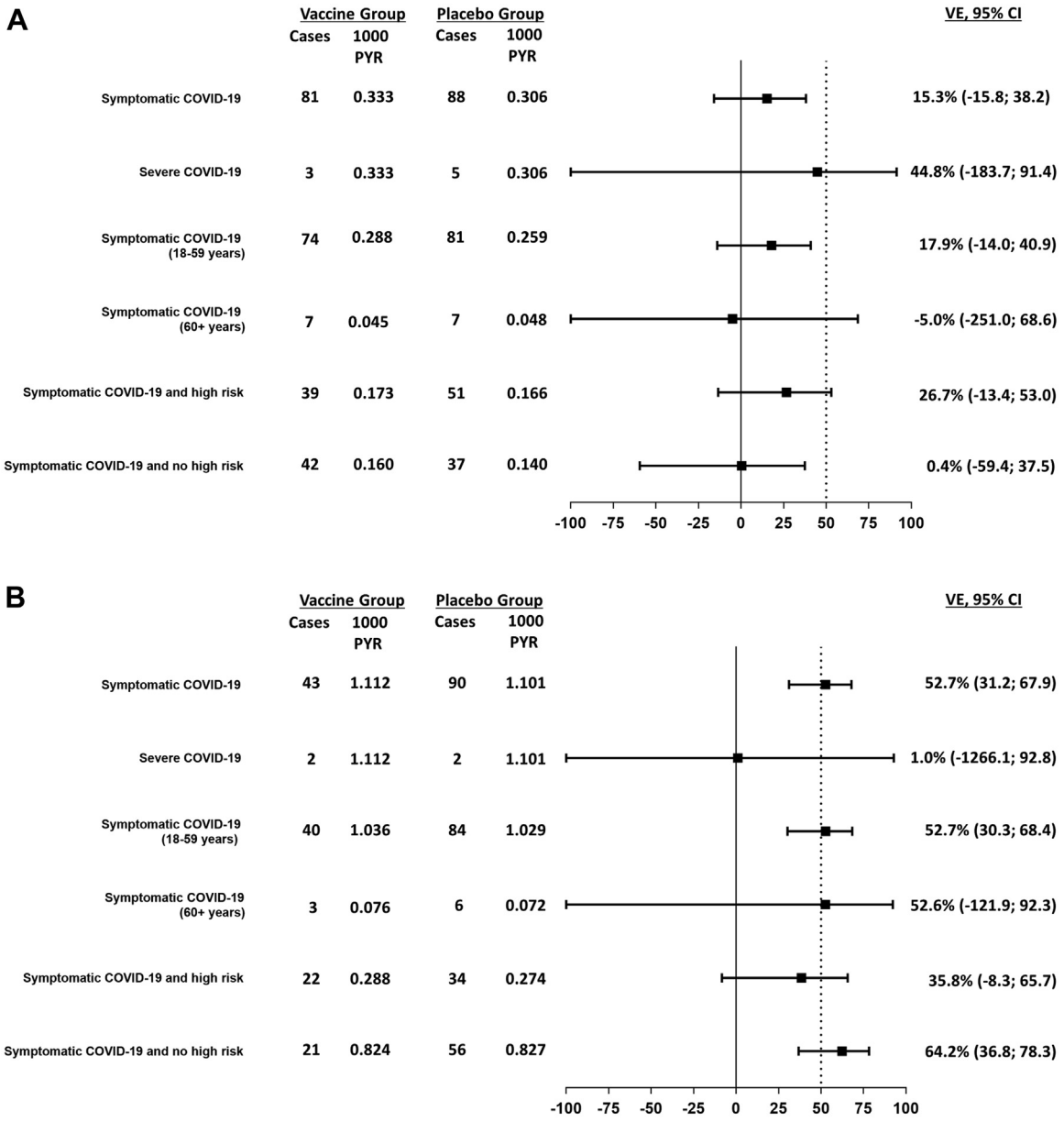

Fig. 3: Forest plots for efficacy outcomes against symptomatic disease in the mFAS-PD2 naïve participants at Day 01 and Day 22 all variants (A); in the mFAS-PD2 non-naïve participants at Day 01 or Day 22 all variants (B).

population, viral genomic sequencing was performed up to the cut-off date and identified the causative strain in 99 cases: Delta, n = 25; Omicron BA.1 and BA.2 sub-variants, n = 72; Gamma, n = 2; and Mu, n = 1. One participant had infection with both Delta and Omicron variants and has been included in the totals for both Delta and Omicron. In the naïve participants PD2, symptomatic COVID-19 due to the delta variant was reported by seven participants in the vaccine group and 18 participants in the placebo group (VE 64.2%, 95% CI, 10.2; 87.4). Symptomatic COVID-19 due to the Omicron variant was reported by 44 participants in the vaccine group and 28 participants in the placebo group (VE -44.5%, 95% CI, –141.1; 12.0). The variant was unknown in 70 participants (for 36 no valid result could be obtained [14 in the vaccine group and 22 in the placebo group] and 34 could not be tested [17 in each treatment arm]). Kaplan–Meier curves for both Omicron and Delta variants in the mFAS-PD2 naïve population are provided in the Supplementary Appendix Section 2.11.

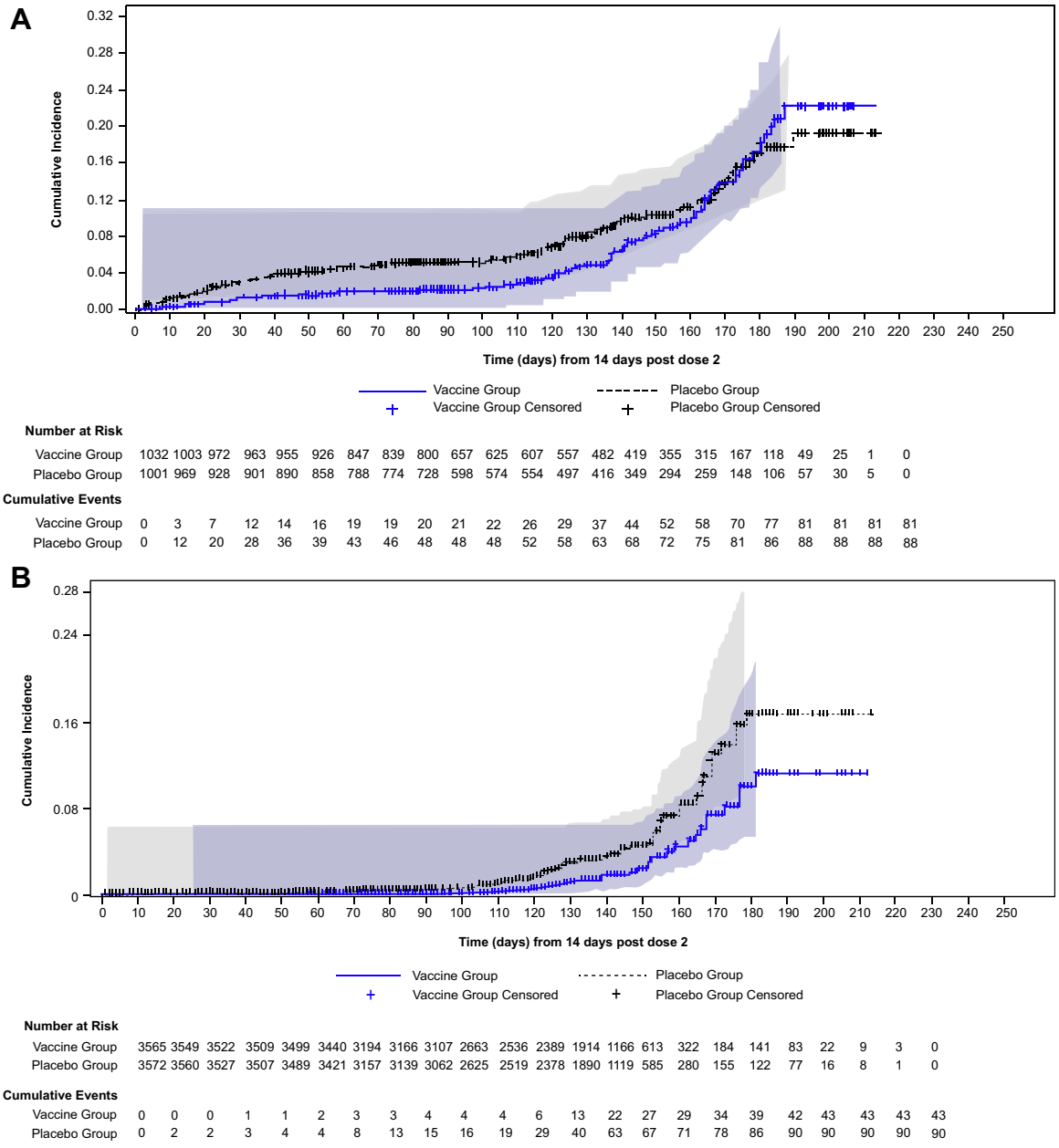

Fig. 4: Kaplan–Meier cumulative incidence of symptomatic COVID-19 in the mFAS-PD2 naïve participants at Day 01 and Day 22 (A) and non-naïve participants at Day 01 or Day 22 (B). The shaded areas indicate the confidence interval bands.

In the non-naïve participants PD2, symptomatic COVID-19 due to the Delta variant was reported by no participants in the vaccine group and seven participants in the placebo group (VE 100%, 95% CI, 31.3; 100.0). Symptomatic COVID-19 due to the Omicron variant was reported by 16 participants in the vaccine group and 34 participants in the placebo group (VE 53.4%, 95% CI, 13.2; 76.0). Variants were unknown in 22 participants in the vaccine group and 32 participants in the placebo group. The number of cases PD1 in non-naïve participants was similar to those for PD2 (Delta variant: no participants in the vaccine group and eight participants in the placebo group [VE 100%, 95% CI, 41.7; 100.0]; Omicron variant: 16 participants in the vaccine group and 32 participants in the placebo group [VE 50.2%, 95% CI, 6.6; 74.5]). The Kaplan–Meier curves for the non-

naïve populations are shown in Supplementary Appendix Section 2.12. VE by variant and naïve/non-naïve status is reported in Supplementary Appendix Section 2.13. It is noted that the distribution of variants among participants differed between the mFAS-PD1 and mFAS-PD2 data sets, especially in the naïve subpopulation.

For Omicron cases in naïve participants, no increase in severe outcomes, hospitalization or mortality was observed in the vaccine group compared with the placebo group (data not shown). Two cases of severe COVID-19 due to Omicron were reported in the naïve vaccine group compared with no cases in the naïve placebo group; neither case required admission to hospital. Furthermore, symptoms of Grade 3 intensity were reported in 23% of the Omicron cases in the naïve vaccine group compared with 73% of the Omicron cases in the naïve placebo group. The clinical presentation of COVID-19 cases due to the Omicron variant (intensity, number and duration of symptoms) was similar between naïve participants in the vaccine and placebo groups. In naïve participants with COVID-19 due to the Omicron variant, a higher proportion of participants in the placebo group had ten or more symptoms and symptoms that lasted for longer than 10 days compared with the vaccine group. In addition, the viral load in symptomatic cases due to the Omicron variant was similar in the vaccine and placebo groups for the naive participants (Supplementary Appendix Section 2.14).

Immunogenicity

Immunogenicity was assessed in 1956 of the 2270 participants included in the IAS. The most common reasons for exclusion (more than one reason possible per participant) were: not collecting a blood sample at Day 43 (n = 147); not completing the 2-dose regimen (n = 146); and not receiving vaccine in the proper time window (n = 112). At Day 43, higher neutralization antibody titres against the D614G variant were measured in non-naïve participants compared with naïve participants. In the vaccine group, the geometric mean titre (GMT) against the D614G variant was 1409 (95% CI, 1180; 1682) in naïve participants and 9109 (95% CI, 7164; 11,583) in the non-naïve participants (Table 2). The GMT ratios at Day 43 for vaccine/placebo were 37.95 (95% CI, 29.56; 48.72) for all participants, 62.40 (95% CI, 51.13; 76.15) for naïve participants and 13.91 (95% CI, 9.63; 20.10) for non-naïve participants (Table 2). At Day 43 (21 days PD2), the proportion of responders with D614G neutralizing antibodies was 96.7% (95% CI, 93.9; 98.4) for naïve participants and 77.6% (95% CI, 72.3; 82.3) for non-naïve participants.

Safety

Safety was assessed in the SafAS (10,114 participants: vaccine, n = 5050; placebo, n = 5064) who received ≥1 study injection; reactogenicity was assessed in a subset of participants from the SafAS who had reported reactogenicity data (4589 participants: vaccine, n = 2295; placebo, n = 2294) (Fig. 1).

In the SafAS, immediate unsolicited AEs (after any injection) were experienced by approximately 0.1% of participants in either the vaccine or placebo groups, all of which were non-serious (Table 3). In total, one of 5050 AEs in the vaccine group and nine of 5064 AEs in the placebo group led to study discontinuation (Table 3). There were no deaths in the vaccine group and nine deaths in the placebo group; none were considered related to the study interventions according to the assessments of the principal investigators. Two deaths in the placebo group were associated with symptomatic COVID-19. Up until the data cut-off, there were 145 SAEs reported by 118 participants; four SAEs (in three participants) in the vaccine group and no SAEs in the placebo group were considered as 'related' to the study interventions by the investigator. However, as these events lacked evidence for a causal relationship to the study intervention and were isolated reports at receipt with no similar events received after their occurrence, the four SAEs in the vaccine group were assessed as 'not related' by the study sponsor (Supplementary Appendix Section 2.15). After the data cut-off date and upon further review of medical records, the Grade 3 SAEs of psychotic disorder and seizure in one participant were re-assessed as 'not related' by the investigator. The proportion of patients experiencing an AESI up to the analysis cut-off date was <0.1% in the vaccine group and 0.1% in the placebo group (Table 3). Two AESIs, that were also immune-mediated diseases (pIMDs), occurred within 21 days after the last injection and were assessed as related to the study intervention (one case of rapidly progressive glomerulonephritis in the vaccine group, and one case of Bell's palsy in the placebo group) (Supplementary Appendix Section 2.15). Three additional pIMDs were reported by three participants but were not considered related to the study intervention by the investigator (one case of Bell's palsy, one case of gouty arthritis and one case of gout in the placebo group). There were no reported cases of thrombosis with thrombocytopenia syndrome, myocarditis, pericarditis or Guillain-Barré syndrome. MAAEs were reported with similar frequencies in the vaccine group (7.8%) compared with the placebo group (8.4%) (Table 3).

In the RSafAS, solicited reactions after any injection were seen in 56.7% of the vaccine group and 35.7% of the placebo group (Table 3). The majority of these solicited reactions (~80%) lasted between 1 and 3 days; only 4% lasted beyond the solicited period (>7 days). Pain was the most frequently reported solicited injection site reaction, with headache, myalgia and malaise the most commonly reported solicited systemic reactions (Fig. 5). The proportions of participants reporting solicited

Prior infection status	Time point/ratio	Vaccine group (N = 1192)		Placebo group (N = 764)		Ratio (vaccine/placebo)
		N	GMT/GMTR (95% CI)	N	GMT/GMTR (95% CI)	GMTR (95% CI)
All	D01	711	75.0 (65.0; 86.5)	522	81.0 (68.3; 96.0)	0.93 (0.74; 1.15)
	D22	665	601 (464; 780)	492	81.8 (68.4; 98.0)	7.35 (5.36; 10.08)
	D43	651	3536 (3010; 4155)	487	93.2 (76.8; 113)	37.95 (29.56; 48.72)
	D22/D01	625	6.79 (5.51; 8.36)	476	1.08 (1.00; 1.17)	
	D43/D01	621	45.0 (37.3; 54.3)	473	1.16 (1.02; 1.32)	
	D43/D22	623	6.09 (4.98; 7.45)	472	1.06 (0.95; 1.18)	
Naïve D01	D01	361	20.2 (19.8; 20.7)	287	20.3 (19.9; 20.7)	1.00 (0.97; 1.03)
	D22	327	35.0 (30.2; 40.5)	284	20.6 (19.8; 21.5)	1.70 (1.46; 1.97)
	D43	333	1461 (1233; 1732)	283	23.4 (21.2; 25.9)	62.34 (51.19; 75.93)
	D22/D01	326	1.73 (1.50; 2.00)	283	1.02 (0.98; 1.06)	
	D43/D01	332	73.1 (61.8; 86.4)	283	1.16 (1.05; 1.27)	
	D43/D22	313	39.4 (33.1; 46.9)	281	1.12 (1.03; 1.22)	
Non-naïve D01	D01	335	326 (264; 403)	229	476 (376; 604)	0.68 (0.50; 0.94)
	D22	327	11,221 (8823; 14,271)	202	592 (461; 760)	18.95 (13.41; 26.77)
	D43	310	9239 (7243; 11,786)	202	654 (499; 858)	14.12 (9.74; 20.48)
	D22/D01	289	32.7 (23.3; 45.9)	187	1.18 (0.97; 1.45)	
	D43/D01	282	24.9 (17.5; 35.4)	188	1.18 (0.88; 1.57)	
	D43/D22	302	0.842 (0.685; 1.03)	189	0.97 (0.77; 1.22)	
Naïve D01 and D22	D01	328	20.3 (19.8; 20.8)	258	20.1 (19.9; 20.3)	1.01 (0.98; 1.04)
	D22	297	32.8 (28.6; 37.7)	256	20.3 (19.9; 20.7)	1.62 (1.41; 1.86)
	D43	300	1409 (1180; 1682)	254	22.6 (20.6; 24.7)	62.40 (51.13; 76.15)
	D22/D01	296	1.62 (1.42; 1.85)	255	1.01 (0.99; 1.03)	
	D43/D01	299	70.4 (59.2; 83.9)	254	1.12 (1.02; 1.23)	
	D43/D22	283	40.6 (34.0; 48.4)	253	1.11 (1.02; 1.21)	
Non-naïve D01 or D22	D01	344	303 (246; 374)	233	456 (360; 578)	0.66 (0.48; 0.92)
	D22	335	10,452 (8183; 13,350)	205	577 (450; 742)	18.10 (12.76; 25.67)
	D43	318	9109 (7164; 11,583)	206	655 (500; 857)	13.91 (9.63; 20.10)
	D22/D01	297	32.6 (23.3; 45.6)	190	1.20 (0.98; 1.47)	
	D43/D01	290	26.6 (18.8; 37.6)	192	1.24 (0.93; 1.67)	
	D43/D22	310	0.895 (0.724; 1.11)	192	1.00 (0.79; 1.26)	

CI, confidence interval; D, day; GMT, geometric mean titre; GMTR, geometric mean titre ratio; IAS, immunogenicity analysis set.

Table 2: **Summary of geometric mean titres and geometric mean titre ratios in each group, and geometric mean titre ratios between groups for neutralizing antibodies against the D614G variant (in the IAS).**

reactions in the 18–59 years age group were 56.0% in the vaccine group and 36.3% in the placebo group, and 62.3% and 30.8% respectively in the ≥60 years age group. The proportions of participants who reported a Grade 3 solicited reaction PD1 were 3.0% in the vaccine group and 1.7% in the placebo group; the proportions PD2 were 4.0% in the vaccine group and 1.5% in the placebo group. The proportion of participants reporting a solicited reaction of any grade was slightly lower PD2 (39.4% in the vaccine group and 19.3% in the placebo group) compared with PD1 (46.8% in the vaccine group and 28.0% in the placebo group) and intensities were similar after both vaccinations. An overview of the safety data PD1 and PD2 is reported in Supplementary Appendix Section 2.16.

The proportions of participants reporting a solicited reaction or non-serious unsolicited AEs after any injection was greater in the naïve participants (vaccine/placebo groups) than in the non-naïve participants (solicited reactions: 68.2%/40.3% vs 52.2%/33.6%; non-serious unsolicited AEs: 10.6%/9.5% vs 4.9%/5.2%) (Supplementary Appendix Section 2.17).

No difference in adverse pregnancy outcomes was observed between the vaccine and placebo groups, based on the limited available data (pregnancy was an exclusion criterion and contraception was required for females of child-bearing potential). To the analysis cut-off date, 51 participants reported a pregnancy, and pregnancy-associated SAEs occurred in two participants in the vaccine group (one abortion and one ectopic pregnancy), and five participants in the placebo group (five abortions); none of these events were considered related to the study intervention. Limited data regarding pregnancy outcomes did not reveal any safety concern for the study vaccine.

There was no evidence of vaccine-associated enhanced disease (VAED). There was no indication of an increased risk of severity of COVID-19 (severe cases,

Population	Vaccine (N = 5050)		Placebo (N = 5064)	
	n/M	% (95% CI)	n/M	% (95% CI)
Patients experiencing at least one of the following within 30 min after any injection				
SafAS				
Immediate unsolicited AE	7/5050	0.1 (0.1; 0.3)	6/5064	0.1 (0; 0.3)
Immediate unsolicited AR	7/5050	0.1 (0.1; 0.3)	2/5064	<0.1 (0; 0.1)
Patients experiencing at least one solicited reaction within 7 days after an injection				
RSafAS				
Solicited reaction	1298/2288	56.7 (54.7; 58.8)	812/2277	35.7 (33.7; 37.7)
Grade 3 solicited reaction	139/2288	6.1 (5.1; 7.1)	66/2277	2.9 (2.2; 3.7)
Solicited injection site reaction	1023/2286	44.8 (42.7; 46.8)	490/2266	21.6 (19.9; 23.4)
Grade 3 solicited injection site reaction	53/2286	2.3 (1.7; 3.0)	15/2266	0.7 (0.4; 1.1)
Solicited systemic reaction	1060/2288	46.3 (44.3; 48.4)	666/2276	29.3 (27.4; 31.2)
Grade 3 solicited systemic reaction	115/2288	5.0 (4.2; 6.0)	64/2276	2.8 (2.2; 3.6)
Patients experiencing at least one of the following up to analysis cut-off date				
SafAS				
AE leading to study termination	1/5050	<0.1 (0; 0.1)	9/5064	0.2 (0.1; 0.3)
SAE	42/5050	0.8 (0.6; 1.1)	76/5064	1.5 (1.2; 1.9)
Related SAE	3/5050	<0.1 (0; 0.2)	0/5064	0 (0; 0.1)
Death	0/5050	0 (0; 0.1)	9/5064	0.2 (0.1; 0.3)
AESI	1/5050	<0.1 (0; 0.1)	7/5064	0.1 (0.1; 0.3)
MAAE	394/5050	7.8 (7.1; 8.6)	427/5064	8.4 (7.7; 9.2)
COVID-19-associated MAAE	101/5050	2.0 (1.6; 2.4)	134/5064	2.6 (2.2; 3.1)
Virologically confirmed SARS-CoV-2 infection and/or symptomatic COVID-19 (regardless of adjudication)	344/5050	6.8 (6.1; 7.5)	433/5064	8.6 (7.8; 9.4)

AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; MAAE, medically attended adverse event; SAE, serious adverse event; RSafAS, reactogenicity safety analysis set; SafAS: safety analysis set. M: Number of participants with available data for the relevant endpoint (for solicited AEs) and for corresponding subgroup for unsolicited AEs. n: number of participants experiencing the endpoint listed. The denominator for the reactogenicity subset was 4589 (i.e., participants of the subset who received at least one study injection).

***Table 3*: Summary of safety outcomes in patients who received at least one injection (SafAS/RSafAS).**

hospitalisations, or deaths) in the vaccine group compared with the placebo group, neither in all participants or the naïve and non-naïve groups. There were no fatal or hospitalized cases of COVID-19 due to the Omicron variant in the naïve vaccine recipients and no evidence of vaccine-associated enhanced disease. Virologically confirmed SARS-CoV-2 infection and/or symptomatic COVID-19 was reported in 6.8% (95% CI, 6.1, 7.5) of participants in the vaccine group compared with 8.6% (95% CI, 7.8, 9.4) of participants in the placebo group (Table 3).

Discussion

In this analysis of the CoV2 preS dTM-AS03 monovalent (D614) vaccine, the vaccine showed an acceptable safety profile and was well-tolerated. The efficacy against symptomatic COVID-19 in the naïve population could not be demonstrated against the SARS-CoV-2 variants circulating at the time, according to the FDA-defined criteria for the demonstration of efficacy for COVID-19 vaccines (lower bound of the 95% CI > 30%[18]); however, efficacy was observed ≥14 days PD2 in the non-naïve population, which may have been driven mainly by the efficacy against the Delta variant.

We estimated that a sample size of 7112 SARS-CoV-2 naïve participants would be powered independently to demonstrate the primary objective of VE against symptomatic COVID-19 in SARS-CoV-2 naïve adults under the assumption of a VE >70%, which is much greater than the VE observed for the primary endpoint in a context of circulating variants of concern. However, only 2051 naive participants were available for analysis in the mFAS-PD2. This was due to the global epidemiological context at the time the study was conducted, where the majority of adults had already been infected, as described in the published literature.[19–22] The high proportion of non-naive participants identified in the study (>75% of participants) reflects the epidemiology of the disease and underlines the importance of demonstrating efficacy in this non-naïve population.

During this period, multiple variants of concern (VoCs) were circulating, including the Alpha, Gamma, Mu, Delta and Omicron variants. The timing of this study allowed assessment of the vaccine against infection with the Delta and Omicron variants. At the beginning of this study, the predominant SARS-CoV-2 variant was Delta, with a shift at the end of the study period to Omicron (mainly BA.1 and some BA.2). The situation reported here reflects the wider global epidemiological picture for the duration of this study. Until mid-December 2021, the Delta variant was the predominant SARS-CoV-2 variant in the USA, accounting

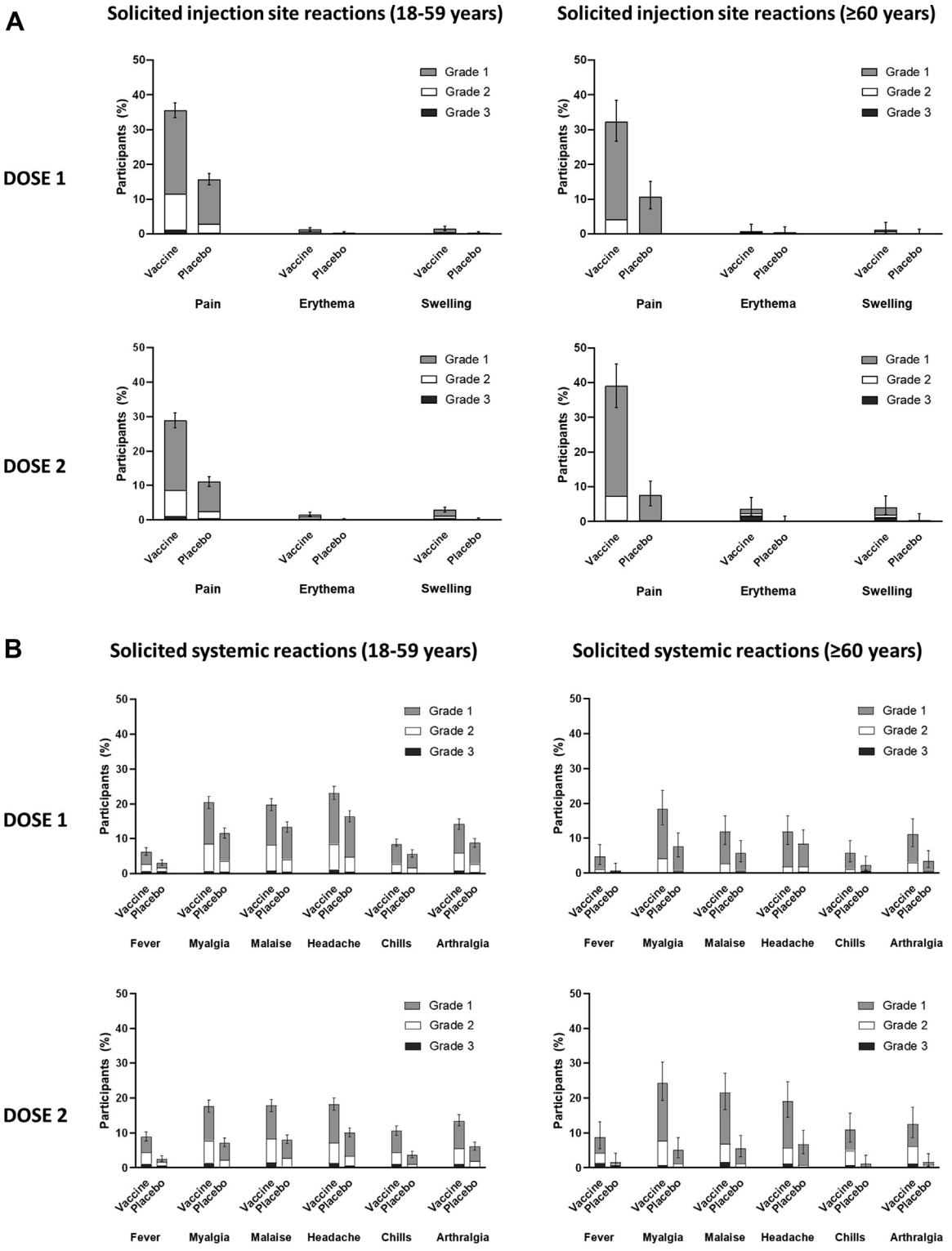

Fig. 5: Proportion of participants with solicited injection site reactions within 7 days of each study injection in participants aged 18–59 years and participants aged ≥60 years (A); the proportion of participants with solicited systemic reactions within 7 days of each study injection in participants aged 18–59 years and participants aged ≥60 years (B).

for >99% of cases and leading to an increase in hospitalizations in some states.[23] The Omicron variant, which emerged towards the end of 2021, was responsible for the majority of the later cases included in the analysis, occurring ≥4 months post-immunization, which corresponds to the time when vaccine effectiveness against mild symptomatic Omicron infection begins to wane for other registered vaccines.[24,25]

VE was not observed in naïve individuals, which is in agreement with Anderson et al., 2021, who reported that one dose of the mRNA vaccine, BNT162b2, elicits stronger antibody responses in individuals previously exposed to COVID-19 compared with two doses of BNT162b2 in those without prior infection.[25] Furthermore, in the context where high numbers of the population have been vaccinated but the virus is still circulating, it may be that non-naïve participants displayed 'hybrid' immunity to SARS-CoV-2, due to the combination of vaccination and infection,[26] which is thought to confer greater protection than infection or vaccination alone, although the data on this are currently limited.

Although this study was not powered to assess efficacy for each circulating strain, we demonstrated protection against the Delta strain in participants regardless of prior infection (VE 72.9%, 95% CI, 35.5; 90.1) and in the naïve participants (VE 64.2%, 95% CI, 10.2; 57.4). These VEs are comparable to estimates of VE to the Delta variant with other COVID-19 vaccines, which have varied from 44% to 95%.[26–29] Only seven cases were reported in the non-naive participants, all of which were in the placebo group.

Our results show a lack of efficacy in the naïve participants against the Omicron variant, as described with other vaccines,[25] which resulted in a reduction in our primary efficacy outcome. In naïve participants, an imbalance in symptomatic COVID-19 Omicron cases was observed in vaccinated (44 cases) versus placebo recipients (28 cases). Two severe cases of Omicron were reported in the vaccine group among naïve participants, although neither required hospitalization. The absence of efficacy may be associated with a combination of different factors, including the limited protection of the monovalent D614 formulation against Omicron, as seen with other authorized vaccines,[25] and the waning immunity due to the length of time between administration of the two doses of the study vaccine and the start of the Omicron wave (i.e., most Omicron cases occurred between 4 and 6 months PD2).

The clinical presentation of Omicron cases (number, intensity and duration of symptoms) was similar for naïve participants in the vaccine and placebo groups, with no evidence of an increased risk of severe COVID-19 in the vaccine group compared to the placebo group. In addition, the viral load of symptomatic Omicron cases was similar in both the vaccine and placebo groups. In contrast, in non-naïve participants, the results show that two doses of the D614 monovalent vaccine offer efficacy against symptomatic COVID-19 for both Delta (VE: 100.0%, 95% CI, 31.3; 100) and Omicron (VE: 53.4%, 95% CI, 13.2; 76.0) variants. As participants aged >60 years were among the first to be eligible for authorized COVID-19 vaccines at the time of the study, they accounted for only 8% of recruited participants. For this reason, the number of symptomatic COVID-19 cases observed in this age group was limited and vaccine efficacy could not be accurately estimated. Efficacy estimates in non-naïve participants was mainly driven by efficacy in the younger age group (18–59 years); however, a favorable case-split (three vaccine vs. six placebo) was observed in the older age group (≥60 years) and the VE point estimate observed in older adults is in line with the VE point estimate observed in younger participants.

The safety profile of this vaccine was acceptable, with no cases of myocarditis, pericarditis or thrombosis with thrombocytopenia syndrome reported during the safety follow-up, whereas these have previously been reported after vaccination with other SARS-CoV-2 vaccines,[30,31] although these rare side effects would not be expected in a study of this size.[32,33] The reactogenicity was mostly mild-to-moderate and transient. There was no indication that reactogenicity was increasing following the second vaccine dose compared to the first dose, nor that pre-existing antibodies in the non-naïve participants would result in higher reactogenicity. Interestingly, the incidence of solicited reactions in this study was lower than in the Phase 2 study.[12] This could potentially be due to several reasons: the use of a placebo control in this study (i.e., participants in the Phase 2 study were aware they were receiving an active product and, consequently, may have been more likely to report reactogenicity), differences in participating countries, enrolment at different time periods during the pandemic, and the influence of serostatus at baseline: in our study reactogenicity tended to be higher in naïve participants, and over 90% of participants enrolled in the Phase 2 study were naïve.

Our study has limitations. VE could not be accurately calculated in adults aged ≥60 years because of limited numbers enrolled in this age category, likely due to the uptake of available vaccines for emergency use in older adults during the study period, and due to the study enrolling more participants from countries with overall younger populations. Furthermore, VE could not be reliably estimated for hospitalized or severe cases, again owing to the limited number of cases. The high neutralizing antibody titres against the D614G strain reported here should be interpreted with caution in the current epidemiological context where other variants are now circulating. Participants were permitted to receive influenza vaccination at any time in relation to the study intervention to allow them to be protected against flu. Although there is an increasing body of evidence of that cross-protection of the influenza vaccine against

COVID-19 may affect the effectiveness of the COVID-19 vaccines,[34] this has not been investigated in this study, and there are no data on this for the monovalent vaccine. Finally, we note that there can be selection bias in population analysis. Pre-planning the application of methods such as instrumental variance analysis and G-estimation may be used in future pandemics. In conclusion, although the primary endpoint (efficacy against symptomatic COVID-19 disease ≥14 days after the second injection in participants who were SARS-CoV-2 naïve on D01 + D22) was not met, the CoV2 preS dTM-AS03 D614 monovalent vaccine demonstrated efficacy to prevent symptomatic COVID-19 disease in non-naive participants, and suggested efficacy against the Omicron variant, although the VE for Omicron is based on a small number of patients. This is relevant in the current environment where most of the population has already been exposed to COVID-19, either through vaccination or natural infection. The vaccine showed an acceptable safety profile with no safety concerns identified during the study conduct in the adult or older adult populations, including in those with high-risk medical conditions.

Contributors

GHD, SRW, AC, JA, ASB, BF, MAC, M-HG, MK, MK-J, RM, MLR, LS, TT, CAD, LC, KMN, SG, SSa and CDG contributed substantially to the conception and design of the work reported in this article. GHD, NR, SRW, AC, NG, MA, JA, ASB, TB, MIB, BF, M-HG, MK-J, MJ, NLM, RM, HR, MLR, FS, TT, JT, CAD, RMC, SG, AU, RS, SK, SSa, MC and SSr contributed substantially to data acquisition for the work reported in this article. GHD, NR, SRW, AC, NG, MA, JA, ASB, TB, MB, MAC, BF, M-HG, MK-J, MJ, JJK, MK, NLM, HR, MLR, FS, LS, TT, JT, CAD, RMC, KMN, RS, SG, SSa, MC and SSr contributed substantially to data analysis or interpretation of data for the work reported in this article. All authors were involved in the drafting or critically revising of the manuscript, and all authors approved the final version and are accountable for the accuracy and integrity of the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication. Three authors (AC, BF and DG) have accessed and verified the data. Three authors (AC, BF and DG) have accessed and verified the data.

Data sharing statement

Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

Declaration of interests

GHD, JA, MIB, MC, M-HG, JA, CAD, RMC, MC and SSa are Sanofi employees. JA, MIB, M-HG, JA, CAD, RMC, MC, CAD, SSr and SSa hold stock or stock options in Sanofi. SSr and SSa are the named inventors on a patent associated with the vaccine reported in this manuscript. RMC has received institutional funding from BARDA for the present study; has received support for attending meetings and/or travel from Sanofi; and holds patents planned, issued or pending from Sanofi. NR has received institutional funding from the National Institutes of Health; and institutional grants or contracts from Merck, Sanofi, Quidel, Pfizer and Lilly. SRW has received institutional funding from Sanofi and the National Institute of Allergy and Infectious Diseases/National Institutes of Health; and institutional grants or contracts from Janssen Vaccines/Johnson & Johnson, Moderna Tx, Pfizer, Vir Biotechnology and Worcester HIV Vaccine; has participated on data safety monitoring or advisory boards for Janssen Vaccines/Johnson & Johnson; and his spouse holds stock/stock options in Regeneron Pharmaceuticals. NG has received institutional grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). LS, MAC and MK are employees of the GSK group of companies and own shares in the GSK group of companies. MJ and JJK have received institutional support from Sanofi and the NIAID/NIH with respect to this study. MLR has received institutional support/contracts for the present manuscript from WRAIR IPA and the US Medical Research and Development Command. MA, and MKJ are employees of the NIAID, which funded aspects of the current study; The NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI 68614HVTN), the Statistics and Data Management Center (UM1 AI 68635), the HVTN Laboratory Center (UM1 AI 68618), the HIV Prevention Trials Network Leadership and Operations Center (UM1 AI 68619), the AIDS Clinical Trials Group Leadership and Operations Center (UM1 AI 68636), and the Infectious Diseases Clinical Research Consortium leadership group 5 (UM1 AI 148684-03). One of the sites in Kenya in this study received funding from NIAID. LC has received grant funding from the NIAD/NIH. The Center for Vaccine Development and Global Health (CVD) receives grants from Pfizer to conduct clinical trials of COVID-19 vaccines: KMN receives no salary support for this grant. KMN receives grants from NIH to participate in overall organization of COVID vaccine trials and for participation in vaccine trials. ASB has received honorarium for the conduct of this trial as Principal Investigator from Sanofi Healthcare India Private Limited. TT, SK, BF, AC, KPA, TB, RM, NLM, HR, FS, JT, SG, KS, AU and RS have no interests to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102168.

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