Efficacy of a bivalent (D614 + B.1.351) SARS-CoV-2 Protein Vaccine

*Gustavo H. Dayan MD[1], *Nadine Rouphael MD[2], *Stephen R. Walsh MD[3], Aiying Chen PhD[1], Nicole Grunenberg MD[4], Mary Allen MS[5], Johannes Antony PhD[6], Kwaku Poku Asante PhD[7], Amit Suresh Bhate MD[8], Tatiana Beresnev MD[5], Matthew I Bonaparte PhD[1], Maria Angeles Ceregido PhD[9], Dmytro Dobrianskyi MD[10], Bo Fu PhD[1], Marie-Helene Grillet MD[11], Maryam Keshtkar-Jahromi MD[12,13], Michal Juraska PhD[4], Jia Jin Kee MD[4], Hannah Kibuuka MD[14], Marguerite Koutsoukos PhD[9], Roger Masotti MS[1], Nelson L. Michael MD[15], Humberto Reynales PhD[16], Merlin L. Robb MD[17], Sandra M. Villagómez Martínez MD[18], Fredrick Sawe MBChB[19], Lode Schuerman MD[9], Tina Tong DrPH[5], John Treanor MD[20], T. Anh Wartel MD[21], ‡Carlos A. Diazgranados MD[1], Roman M. Chicz PhD[22], Sanjay Gurunathan MD[1], ‡Stephen Savarino MD[1], Saranya Sridhar DPhil[23], the VAT00008 study team†

*Authors contributed equally to the study.

‡Affiliation at time of study

†VAT00008 Study Team

Karina Abalos, Jose Accini, Naveena Aloysia, John Humphrey Amuasi, Nana Akosua Ansah, David Benkeser, Aude Berge, Hanna Beyko, Oleksandra Bilotkach, Thomas Breuer, Alberto Cadena Bonfanti, Elisabeth Bukusi, Richard Canter, Jaime Augusto Carrillo, Mederic Celle, Danaya Chansinghakul, Florence Coux, Chandan Das, Santa Kumar Das, Louis Devlin, Luis Espinoza, Michael Fay, Dean Follmann, Carina Frago, Agnes Garinga, Peter B Gilbert, Claudia Gonzalez, Maria Angelica Granados, Lea Guillery, Ying Huang, Kathy Hudzina, Manish Jain, Piush Kanodia, Nitin Khandelwal, Cissy Kityo Mutuluuza, Francis Kiweewa, Noah Kiwanuka, Chalit Kosolsak, Darshna Kukian, Jitendra Singh Kushwaha, Thelma Laot, Eduardo Lopez-Medina, Hugo Macareno Arroyo, Kishorchandra Mandaliya, Stephanie Mamod, Somnath Mangarule, Javier Martínez, Lisa Menard, Sandra Mendoza, Satyajit Mohapatra, Catherine Moreau, Nelly Mugo, Videlis Nduba, Fernando Noriega, Patricia ahirya Ntege, Brenda Okech, Maria Otero, Samuel Gurrion Ouma, Janet Oyieko, Mercedes Paredes, Erwin

Pardo, Svitlana Postol, David Pekala, Penny Peng, Marie-Laure Py, Enrique Rivas, Rafael Rivero, Edith Rodriguez, Mansoor Saleh, Pedro Sánchez, Nessryne Sater, Jinen Shah, Rajeev Shrestha, Abraham Siika, Chandramani Singh, Veer Bahadur Singh, Dipesh Tamrakar, Fernanda Tavares Da-Silva, Lucas Otieno Tina, Hector Velasquez, Deo Wabwire, Anne Wajja, Elodie Zaworski, Nianxian Zhang.

Affiliations

1. Sanofi, Swiftwater, PA, USA
2.Emory University Hop eClininc, Atlanta, GA, USA
3.Harvard Medical School, Boston, MA, USA
4.Fred Hutchinson Cancer Center, Seattle, WA, USA
5. National Institute of Allergy and Infectious Diseases / National Institutes of Health, Bethedsa, MA, USA
6. Sanofi, Frankfurt, Germany
7. Research and Development Division, Ghana Health Service, Kintampo North Municipality, Ghana
8 . Jeevan Rekha Hospital, Belgavi, India
9. GSK, Wavre, Belgium
10. Medical Centre, Medical Clinic Blagomed LLC, Kyiv, Ukraine
11. Sanofi, Lyon, France
12. National Institute of Health, Rockville, Maryland
13. John Hopkins University School of Medicine, Baltimore, Maryland
14. Makerere University Walter Reed Project, Kampala, Uganda
15. Walter Reed Army Institute of Research, MD, USA
16. Centro de Attencion e Investigation Medica S.A.S. – Caimed Chía, Chía, Colombia
17. The Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MA, USA
18. Hospital de Temixco en acuerdo con el Instituto Nacional de Pediatria, México
19. Kenya Medical Research Institute — US Army Medical Research, Kisumu, Kenya
20. Tunnell Government Services in support of Biomedical Advanced Research and Development Authority (BARDA), Administration for Strategic Preparedness and Response (ASPR), Department of Health and Human Services (HHS), Washington, DC, USA
21. International Vaccine Institute, Seoul, South Korea
22. Sanofi, Cambridge, MA, USA
23. Sanofi, Reading, UK

Corresponding Author: Gustavo H. Dayan (Gustavo.Dayan@sanofi.com)

Abstract

Background

COVID-19 vaccines with alternative strain compositions are needed to provide broad protection against newly emergent SARS-CoV-2 variants of concern.

Methods

We conducted a global Phase 3, multi-stage efficacy study (NCT04904549) among adults aged ≥18 years. Participants were randomized 1:1 to receive two intramuscular injections 21 days apart of a bivalent SARS-CoV-2 recombinant protein vaccine with AS03-adjuvant (5 µg of ancestral (D614) and 5 µg of B.1.351 [beta] variant spike protein) or placebo. Symptomatic COVID-19 was defined as laboratory-confirmed COVID-19 with COVID-19-like illness (CLI) symptoms. The primary efficacy endpoint was the prevention of symptomatic COVID-19 ≥14 days after the second injection (post-dose 2 [PD2]).

Results

Between 19 Oct 2021 and 15 Feb 2022, 12,924 participants received ≥1 study injection. 75% of participants were SARS-CoV-2 non-naïve. 11,416 participants received both study injections (efficacy-evaluable population [vaccine, n=5,736; placebo, n=5,680]). Up to 15 March 2022, 121 symptomatic COVID-19 cases were reported (32 in the vaccine group and 89 in the placebo group) ≥14 days PD2 with a vaccine efficacy (VE) of 64.7% (95% confidence interval [CI] 46.6; 77.2%). VE was 75.1% (95% CI 56.3; 86.6%) in non-naïve and 30.9% (95% CI -39.3; 66.7%) in naïve participants. Viral genome sequencing identified the infecting strain in 68 cases (Omicron [BA.1 and BA.2 subvariants]: 63; Delta: 4; Omicron and Delta: 1). The vaccine was well-tolerated and had an acceptable safety profile.

Conclusions

A bivalent vaccine conferred heterologous protection against symptomatic infection with newly emergent Omicron (BA.1 and BA.2) in non-naïve adults 18–59 years of age.

ClinicalTrials.gov: NCT04904549

Introduction

First-generation COVID-19 vaccines were developed using the Spike (S) sequence from the SARS-CoV-2 ancestral Wuhan-Hu-1 (D614) strain.[1] However, these vaccines are less effective against new emergent SARS-CoV-2 variants of concern (VOCs; including Omicron [BA.1, BA.2, BA.4 and BA.5] variants) [2-7] Vaccines with variant strains have been developed to provide cross-protection against emerging variants. One strategy for variant vaccine composition is inclusion of the prevalent circulating strain, with mRNA Omicron-containing bivalent vaccines authorized as boosters based on demonstrated induction of antibodies to circulating Omicron variants.[8,9] However, there are no data on whether an alternative non-Omicron variant vaccine provides cross-protective efficacy against Omicron variants.

Sanofi and GSK have developed a bivalent vaccine containing stabilized SARS-CoV-2 pre-fusion S proteins from both the ancestral D614 and the Beta (B.1.351) variant, with the GSK AS03 adjuvant system (CoV2 preS dTM-AS03 [D614 + B.1.351]). This bivalent vaccine is being evaluated as a two-injection primary series in previously unvaccinated individuals and as a booster vaccine based on preclinical studies showing induction of cross-neutralizing antibody responses against a broad panel of VOCs.[10,11] For the first time, we describe the clinical efficacy and safety of two injections of the bivalent vaccine as a primary series during a period of Omicron circulation.

Methods

Trial Design

This Phase 3, parallel, international, randomized, modified double-blind, placebo-controlled study was designed as a multi-stage platform trial with two stages (NCT04904549). Stage 1 evaluated the efficacy of the prototype vaccine, containing the ancestral D614 recombinant S protein (CoV2 preS dTM-AS03 [D614]) (manuscript in preparation). Stage 2, reported here, evaluated the efficacy and safety of a primary series of two injections of the bivalent vaccine, administered 21 days apart. Stage 2 was conducted in 54 clinical research centers across eight countries: Colombia, Ghana, India, Kenya, Mexico, Nepal, Uganda and Ukraine **(Supplementary Appendix Section 1.1)**. Participant enrollment started on 19 October 2021 and finished on 15 February 2022. Eligible participants were randomized 1:1 to receive either the bivalent vaccine or placebo (saline) (**Supplementary Appendix 1.2**).

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. Approval was received by the following Independent Ethics Committees/Institutional Review Boards. Colombia: Comité de Ética en Investigación CAIMED (approved); Comité de Ética en Investigación de la Fundación del Caribe para la Investigación Biomédica (approved); Comité de Ética en Investigación VITA (approved); Corporación Científica Pediátrica Comité de Etica en Investigación Biomédica (approved); Comité de Ética en investigación de la División Ciencias de la Salud de la Universidad del Norte (approved); Comité de Ética en Investigación Clínica de la Costa (approved). Ghana: Kwame Nkrumah University of Science and Technology Committee on Human Research, Publication and Ethics (approved); Kintampo Health Research Centre Institutional Ethics Committee (approved); Navrongo Health Research Centre Institutional Review Board (approved); Ghana Health Service Ethics Review Committee (approved).

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All participants provided informed consent. An independent data and safety monitoring board[12] provided study oversight and reviewed unblinded data.

Participants

Adults aged ≥18 years who had not received a prior COVID-19 vaccine were eligible for inclusion; full details of the inclusion and exclusion criteria are reported in the **Supplementary Appendix Section 1.3**. Efforts were made to make participants aware of the availability of approved/authorized COVID-19 vaccines (**Supplementary Appendix Section 1.4**). Participants with a potentially high risk for severe COVID-19 (**Supplementary Appendix Section 1.5**) and other subpopulations at risk of COVID-19 infection, including ethnic and racial minorities, were included.

Interventions and assessments

The recombinant protein antigen CoV2 preS dTM and the AS03 Adjuvant System (GSK Vaccines, Rixensart, Belgium) have been described previously.[13-15] Briefly, CoV2 preS dTM, stabilized in its prefusion form, is produced using the baculovirus expression system technology. Each 0.5 mL injection of the bivalent vaccine formulation contained 5 µg of the ancestral D614 and 5 µg of the B.1.351 variant Spike protein antigen. The injection protocol is reported in **Supplementary Appendix Section 1.6**. Vaccinations were administered on study days 1 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 or non-naïve). Testing procedures and criteria for determination of prior SARS-CoV-2 infection are described in the **Supplementary Appendix Section 1.7**.

Surveillance for COVID-19-like illness (CLI) was both active and passive: participants were contacted once a week to determine whether they had any symptoms of a CLI (**Supplementary Appendix Section 1.8**) or if they had a positive COVID-19 test from another source at any time during the

study. In the event of 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 NAAT (**Supplementary Appendix Section 1.9**). An independent 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.[16, 17]

Efficacy endpoints

The primary efficacy objective was to assess in all participants, regardless of prior infection, the clinical efficacy of the bivalent vaccine for prevention of symptomatic COVID-19 ≥14 days after the second injection (post-dose 2 [PD2]). Secondary efficacy endpoints included the occurrence of symptomatic disease in naïve and non-naïve individuals; and severe, moderate or worse, or hospitalized COVID-19 ≥14 days PD2 in all participants and according to prior infection status. Additional reported analyses and all endpoints are defined in **Supplementary Appendix Sections 1.10** and **1.11**.

Safety

Participants were directed to report any adverse events (AEs) during their study visits or during any follow-up contact with the investigators. Safety data were collected from all participants receiving at least one injection of the study vaccine or placebo (**Supplementary Appendix Section 1.12**) throughout the duration of the study. Solicited injection site reactions (SISRs) and solicited systemic reactions (SSRs) occurring within 7 days after each vaccination and non-serious unsolicited AEs occurring within 21 days after each vaccination were collected in a subset of approximately 4,000 participants (the first 4000 participants recruited [2000 in each arm], as well as all participants ≥60 years of age).

Statistical Analyses

The data cut-off date for the analyses reported here was 15 March 2022. Calculations for determining this sample size are reported in **Supplementary Appendix Section 1.13**; descriptions of the analysis sets are reported in **Supplementary Section 1.14**.

Efficacy analyses were conducted on the modified full analysis set PD2 (mFAS-PD2), comprising participants who received both injections (excluding participants with onset of symptomatic COVID-19 between the first injection [post-dose 1 (PD1)] and 14 days PD2) who did not meet any vaccine contraindications and did not discontinue the study within 14 days PD2. These participants were further divided based on prior infection status PD1 and PD2.

For the primary endpoint, the point estimate of vaccine efficacy (VE) was calculated based on the incidence rate per 1000 person-years per group in the mFAS-PD2 population, regardless of prior infection status. The primary objective was met if the VE point estimate was >50% and the lower bound of the confidence interval (CI) was >30%. Survival analyses (Kaplan-Meier curves with 95% CI) were also performed. Sensitivity analyses were conducted assuming that unsequenced cases were due to the Omicron variant, which was the prevalent variant circulating at the time of the study. Safety outcomes were assessed in the safety analysis set (SafAS), comprising all randomized participants who received ≥1 injection of study vaccine or placebo. Statistical analyses were performed using SAS® Version 9.4 or later.

Results

Participants

Between 19 October 2021 and 15 February 2022, 13,506 participants were randomized. Owing to the ongoing war in Ukraine, data completeness could not be confirmed for the four Ukrainian sites; therefore, none of the 504 participants from these sites were included in the main analyses, although sensitivity analyses including these data were performed.

In the current analysis, 13,002 participants were randomized to receive the study vaccine (n=6,512) or placebo (n=6,490) up to the cut-off date of 15 March 2022 (**Figure 1**). Of those, 414 participants (3.2%) discontinued the study, 89 of whom discontinued PD2 (**Supplementary Appendix Section 2.1**). The main analysis sets are presented in **Supplementary Appendix 2.2.**

A total of 12,924 participants received ≥1 study injection (SafAS), for whom demographic characteristics are reported based on first visit samples (**Table 1**). Patient demographics were comparable across treatment groups. The mean (SD) age was 36.1 (12.9) years and 58.4% were male (**Table 1**). 75% of participants had evidence of prior infection (non-naïve) at enrollment. High-risk medical conditions were present in 32.2% of participants (**Table 1** and **Supplementary Appendix Section 2.3**).

In both treatment groups, the longest duration of follow-up was 148 days (median 85 days) PD1 and 118 days (median 58 days) PD2 (**Supplementary Appendix Sections 2.4 and 2.5**). The proportion of patients with ≥2 months' follow-up at the data cut-off date was 67.4% (8,706/12,924) PD1 and 47.2% (5,453/11,543) PD2. Variant distribution according to time and country is shown in **Figure 2**.

Efficacy

The mFAS-PD2 set comprised 11,416 participants (5736 [50.2%] in the vaccine group; 5680 [49.8%] in the placebo group). 121 symptomatic COVID-19 episodes were reported ≥14 days PD2 (32 in the vaccine vs 89 in the placebo group), with an overall VE of 64.7% (95% CI 46.6; 77.2%) which met the primary efficacy endpoint (**Figure 3**). Similar results were reported in the sensitivity analysis including Ukrainian participants (**Supplementary Appendix Section 2.6**). The cumulative incidence rate of symptomatic COVID-19 was higher in the placebo group than in the vaccine group starting from 14 days after the second dose (**Figure 4**).

Five participants (three vaccine recipients, two placebo recipients) reported severe COVID-19, and 12 participants reported moderate or worse symptomatic COVID-19 (five vaccine recipients, seven

placebo recipients) occurring from 14 days PD2 in mFAS-PD2 participants. Two placebo recipients in the mFAS-PD2 were hospitalized with COVID-19, and there were no deaths associated with COVID-19 reported in the study.

VE against symptomatic COVID-19 infection in non-naïve participants was 75.1% (95% CI: 56.3%; 86.6%), while in naïve participants the point estimate for VE was 30.9% (95% CI -39.3%; 66.7%) (**Figure 3)**. The cumulative incidence was higher in the placebo group than in the vaccine group starting from 14 days PD2 in non-naïve participants and after approximately 30 days PD2 in naïve participants **(Figure 4).** The overall VE against symptomatic COVID-19 was 60.3% (95% CI 47.1%; 70.5%) PD1 (**Supplementary Appendix Section 2.7**). The higher cumulative incidence in the placebo group started within 14 days PD1 in naïve, non-naïve and all participants in the mFAS-PD1 population (**Supplementary Appendix 2.8**).

Efficacy results against symptomatic disease in all participants and subgroups are shown in **Figure 3** and **Supplementary Appendix Section 2.9**. Efficacy against asymptomatic SARS-CoV-2 infection (assessed in naïve participants only) was 1.2 (95% CI -31.0; 25.5) with 100 cases in the vaccine group and 107 cases in the placebo group (**Supplementary Appendix Section 2.10)**.

Viral variants

Of the 121 adjudicated cases, the causative viral strain was sequenced in 68 cases (56%), with the majority (63/68) corresponding to the BA.1 and BA.2 subvariants of Omicron and the others corresponding to Delta (4/68). One participant had mixed infection with the Omicron and Delta variants and was included in the analysis for both variants. Results for the other 53 adjudicated cases (approximately 44%) were not available for different reasons (**Supplementary Appendix Section 2.11**).

Among the 68 sequenced cases, 64 were Omicron (14 in the vaccine recipients and 50 in the placebo recipients), with the Omicron-specific VE estimated as 72.5% (95% CI: 49.5; 86.0) (**Figure 3**). Kaplan-

Meier analyses showed higher cumulative incidence in the placebo group compared with the vaccine group 14 days PD2 (**Supplementary Appendix Section 2.12**). There was also a favorable case split relating to the Delta variant: no Delta-related COVID-19 cases in the vaccine group versus five cases in the placebo group.

The VE against symptomatic COVID-19 caused by the Omicron or undefined variants (sensitivity analyses) was 63.1% (95% CI 43.9; 76.2%) in all participants, 73.8% (95% CI 53.9; 85.9) in non-naïve participants and 27.6% (95% CI -47.3; 65.3) in naïve participants (**Supplementary Appendix Section 2.13**).

Safety

A summary of safety outcomes in patients who received at least one injection of vaccine or placebo (SafAS population) are reported in **Table 2** and **Supplementary Appendix Sections 2.14** and **2.15**.

For both the vaccine and placebo groups, immediate unsolicited AEs and adverse reactions (ARs) ≤30 minutes after any injection were reported by <0.1%. In the reactogenicity subset (N=4,823), solicited reactions (SISRs and SSRs) ≤7 days after any injection occurred in 57.8% vaccine recipients and 40.9% placebo recipients (**Figure 5**).

Grade 3 solicited reactions were reported by 8.1% of vaccine recipients and 4.9% of the placebo recipients within 7 days after any injection, with comparable frequency PD1 and PD2 in the vaccine group (**Table 2; Figure 5; Supplementary Appendix Section 2.14**).

The proportion of MAAEs reported was similar in the vaccine (5.7%) and placebo (6.0%) groups. The proportion of AESIs, SAEs and deaths were <1% in both study arms; no AE, AESI, SAE or death was deemed to be treatment related. There were no reported cases of thrombosis with thrombocytopenia syndrome, myocarditis, pericarditis, Bell's Palsy, or Guillain–Barré syndrome.

Discussion

This is the first report of an efficacy trial conducted with a variant COVID-19 vaccine. In this Phase 3 study evaluating a bivalent vaccine as a primary series during the period of predominant Omicron (BA.1 and BA.2) circulation, the primary objective of demonstrating efficacy against symptomatic COVID-19 of >50%, with a lower bound of the 95% confidence interval >30%, in all participants was met.

The epidemiological context for this efficacy trial is markedly different from those conducted at the pandemic's onset.[18,19] A large proportion of participants had serological evidence of previous infection representative of the epidemiological situation at the time of the study. Thus, the VE against symptomatic COVID-19 in non-naïve participants of 75% observed in this study starting 14 days PD1 is of particular relevance. This also suggests the potential use of the vaccine as a booster dose at this stage of the pandemic when most of the population have already been exposed to the virus or have been vaccinated. Lower VE was observed in naïve individuals, albeit the number of participants in this sub-group was limited. These are consistent with observations in other efficacy trials[20,21] and the high antibody titres observed in animal studies.[11]

During the surveillance period, two major variants were circulating: Omicron (BA.1 and BA.2 subvariants) and to a lesser extent Delta, with no cases of BA.4 and BA.5. Thus, the data reported here is the first assessment of clinical efficacy of a COVID-19 vaccine against the Omicron variant. Since sequencing results were unavailable in approximately 44% of the cases in the mFAS-PD2, we conducted sensitivity analyses that assumed these cases were caused by Omicron variants, and VE was also demonstrated.

Primary immunization with two doses of prototype vaccines provided limited protection against symptomatic disease caused by the Omicron variant. We demonstrated efficacy against Omicron with two doses of a Beta-containing variant as opposed to previous reports of high efficacy against Omicron following three doses of mRNA vaccines.[22] A BNT162b2 or mRNA-1273 booster after a primary course substantially increased protection, but that protection waned over time.[23] Variant-

updated COVID-19 vaccines[24] and booster vaccines incorporating Omicron subvariants are under development or are authorized for use. Their use has been endorsed by global regulators provided that novel COVID-19 booster vaccines containing alternative variants still confer adequate protection against Omicron and other VOCs. Our Beta strain-containing vaccine confers protection against newly emergent variants, thus providing clinical evidence that broad cross-protection can be conferred by such vaccines, and challenges the current paradigm of variant-chasing vaccine strain composition.

While the exact mechanism of cross-protection is unknown, it may be primarily related to the B1.3.5.1 component of the bivalent vaccine. Substitutions in the Beta variant spike at positions K417N, E484K, N501Y may provide new antibody epitopes which are well-positioned to provide cross-neutralizing immunogenicity against a wide array of variants including contemporary circulating strains.[15] The results of this study in Omicron-confirmed cases suggests the potential for a Beta variant containing variant vaccine to be used as a part of a booster program, and a beta variant containing vaccine (VidPrevtyn Beta) has now been recommended as a booster in adults previously vaccinated with a mRNA or adenoviral vector COVID-19 vaccine.[25] Results from a booster study in individuals previously primed with the CoV2 preS dTM-AS03 (D614) vaccine or with other approved mRNA and adenovirus-vectored vaccines, confirmed that a booster with an CoV2 preS dTM-AS03 (B.1.351, Beta) vaccine delivered an immune response comparable to that of the bivalent (ancestral + Beta variant) booster (in press).

The number of severe COVID-19 cases or hospitalizations was limited; however, all hospitalized cases were observed in the placebo group. The few severe and hospitalized cases may have been due to the Omicron variant leading to milder COVID-19 disease versus other variants, particularly as most participants had already experienced a prior SARS-CoV-2 infection.[26] Additionally, most participants in this study were younger adults aged 18–59 years with lower risk of severe COVID-19

than older people.[27,28] Of note, the VE in participants aged 18–59 years with risk factors for severe COVID 19 was similar to that in the same age group without risk factors.

The bivalent vaccine showed an acceptable reactogenicity profile in this study; after both doses, AEs were mostly mild to moderate and transient, regardless of participant age or prior infection. Injection-site and systemic reactions were each reported by less than half of participants in the reactogenicity subset. These rates may indicate potentially less reactogenicity compared with mRNA-based licensed vaccines, although these vaccines have not been evaluated together in the context of a single trial.[29,30] No cases of myocarditis, pericarditis or thrombosis with thrombocytopenia syndrome were reported during the observed 2–3 months of safety follow-up, which have previously been reported after vaccination with other vaccines.[31-41]

Our study has limitations. Due to the limited number of older adults (≥60 years) enrolled in the trial, VE could not be accurately estimated in this age group. This was most likely due to the roll-out of vaccines authorized for emergency use in this age category available at the time of the study. The limited number of hospitalized and severe cases prevented any conclusions for VE against these outcomes. The short duration of follow-up (median length of follow up PD2 was 58 days) also precluded conclusions on the durability of the vaccine's protection and long-term safety. Because immunogenicity results were not available, correlates of protection could not be assessed. While sequencing was attempted on all primary endpoint cases, results were only available in approximately 56% of primary endpoints. We observed a higher rate of missing sequence data in the vaccine group (56%) compared to the placebo group (39%). One explanation for this observation is the potential impact of the vaccine on reducing viral load. Although the higher rate of missing data in the vaccine group may bias the variant-specific efficacy estimates, sensitivity analyses confirmed efficacy against Omicron.

Conclusions

Our results demonstrate the clinical efficacy of a beta variant containing vaccine to protect against different SARS-CoV-2 variants, including Omicron (BA.1 and BA.2), and an acceptable safety profile in adults <60 years old. These data show that vaccines developed with an antigen from a non-predominant strain can confer cross- protection against newly emergent variants.

Statements

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, MIB, BF, M-HG, CAG, RMC, SS are Sanofi employees. MIB, BF, M-HG, CAG, RMC, SS hold stock or stock options in Sanofi. SS hold patents pending on COVID-19 vaccine. 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. M-HG has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events 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 Immunology/National Institutes of Health; and institutional grants or contracts from Janssen Vaccines/Johnson & Johnson, Moderna Tx, 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 funding from Sanofi, GSK and the National Institute of Allergy and Immunology/National Institutes of Health; and is in receipt of grants or contracts from the NIH/NIAID/DAIDS. MA is an employee of the NIAID, which funded aspects of the current study. MAC and MK are employees of GSK and owns shares in the GSK group of companies. LS is an employee of the GSK group of

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Tables and Figures

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

	Vaccine group (N=6,472)	Placebo group (N=6,450)	Total (N=12,924*)
Sex, n (%)			
Male	3789 (58.5)	3751 (58.2)	7542 (58.4)
Female	2683 (41.5)	2699 (41.8)	5382 (41.6)
Age,years			
Mean (SD)	36.1 (13.0)	36.0 (12.9)	36.1 (12.9)
Median (min; max)	34.0 (18.0; 93.0)	34.0 (18.0; 93.0)	34.0 (18.0; 93.0)
Age categories, n (%)			
18-59 years	6078 (93.9)	6067 (94.1)	12,147 (94.0)
≥60 years	394 (6.1)	383 (5.9)	777 (6.0)
BMI, mean (SD); median (Q1; Q3)	23.8 (4.61); 22.9 (20.7; 25.8)	23.8 (4.41) 22.9 (20.8; 25.8)	23.8 (4.51) 22.9 (20.7; 25.8)
Race, n (%)			
American Indian or Alaskan native	408 (6.3)	402 (6.2)	811† (6.3)
Asian	2562 (39.6)	2567 (39.8)	5129 (39.7)
Black or African American	2873 (44.4)	2854 (44.2)	5727 (44.3)
White	36 (0.6)	38 (0.6)	74 (0.6)
Multiracial	5 (<0.1)	6 (<0.1)	11 (<0.1)
Not reported	95 (1.5)	82 (1.3)	177 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	1056 (16.3)	1051 (16.3)	2109† (16.3)
Not Hispanic or Latino	5381 (83.1)	5372 (83.3)	10,753 (83.2)
Not reported	15 (0.2)	13 (0.2)	28 (0.2)
Country, n (%) (%)			
Mexico	495 (7.6)	493 (7.6)	989 (7.7)
Colombia	537 (8.3)	532 (8.2)	1070 (8.3)
India	1661 (25.7)	1672 (25.9)	3333 (25.8)
Uganda	212 (3.3)	206 (3.2)	418 (3.2)
Ghana	597 (9.2)	598 (9.3)	1195 (9.2)
Kenya	2066 (31.9)	2052 (31.8)	4118 (31.9)
Nepal	904 (14.0)	897 (13.9)	1801 (13.9)
Prior SARS-CoV-2 infection, n (%)			
Naïve at Day 1	588 (9.1)	588 (9.1)	1176 (9.1)
Non-naïve at Day 1	4860 (75.1)	4831 (74.9)	9693 (75.0)
Undetermined at Day 1	1024 (15.8)	1031 (16.0)	2055 (15.9)
Naïve at Day 22	333 (5.1)	350 (5.4)	683 (4.3)
Non-naïve at Day 22	5478 (84.6)	5486 (85.1)	10,966 (94.8)
Undetermined at Day 22	661 (10.2)	614 (9.5)	1275 (0.9)
High-risk medical condition			

Yes	2095 (32.4)	2070 (32.1)	4165 (32.2)
No	4377 (67.6)	4380 (67.9)	8759 (67.8)

*Two participants received a vaccine at V1 but whether they received the vaccine or the placebo is unknown. Therefore there is a difference of 2 participants in the total number of participants of the SafAS.

†One of the 2 participants who had missing information about the vaccine/placebo was American Indian or Alaska Native. For the other participant, the race was unknown although the ethnicity was Hispanic or Latino.

Table 2: Summary of safety outcomes in patients who received at least one injection (SafAS)

Population	Vaccine (N=6472)		Placebo (N=6450)	
	n/M	% (95% CI)	n/M	% (95% CI)
Patients experiencing at least one of the following within 30 minutes after any injection				
SafAS				
Immediate unsolicited AE	4/6472	<0.1 (0–0.2)	7/6450	0.1 (0–0.2)
Immediate unsolicited AR	4/6472	<0.1 (0–0.2)	6/6450	<0.1 (0–0.2)
Patients experiencing at least one solicited reaction within 7 days after an injection				
RSafAS				
Solicited reaction	1398/2420	57.8 (55.8–59.7)	983/2403	40.9 (38.9–42.9)
Grade 3 solicited reaction	196/2420	8.1 (7.0–9.3)	118/2403	4.9 (4.1–5.9)
Solicited injection site reaction	1130/2419	46.7 (44.7–48.7)	645/2403	26.8 (25.1–28.7)
Grade 3 solicited injection site reaction	98/2419	4.1 (3.3–4.9)	43/2403	1.8 (1.3–2.4)
Solicited systemic reaction	1100/2420	45.5 (43.5–47.5)	823/2403	34.2 (32.4–36.2)
Grade 3 solicited systemic reaction	172/2420	7.1 (6.1–8.2)	109/2403	4.5 (3.7–5.4)
Patients experiencing at least one of the following up to analysis cut-off date				
SafAS				
AE leading to study termination	5/6472	<0.1 (0–0.2)	5/6450	<0.1 (0–0.2)
SAE	30/6472	0.5 (0.3–0.7)	26/6450	0.4 (0.3–0.6)
Related SAE	0/6472	0 (0–0.1)	0/6450	0 (0–0.1)
Death*	4/6472	<0.1 (0–0.2)	6/6450	<0.1 (0–0.2)
AESI	1/6472	<0.1 (0–0.1)	1/6450	<0.1 (0–0.1)
Related AESI	0/6472	0 (0–0.1)	0/6450	0 (0–0.1)
MAAE	366/6472	5.7 (5.1–6.2)	385/6450	6.0 (5.4–6.6)
Related MAAE	11/6472	0.2 (0.1–0.3)	7/6450	0.1 (0.1–0.2)
COVID-19-associated MAAE	67/6472	1.0 (0.8–1.3)	86/6450	1.3 (1.1–1.6)
Virologically confirmed SARS-CoV-2 infection and/or symptomatic COVID-19 (regardless of adjudication)**	928/6472	14.3 (13.5–15.2)	1181/6450	18.3 (17.4–19.3)

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 reatogenicity subset was 4823 (i.e., the first 2000 participants recruited to each trial arm and all participants ≥60 years of age).

*Four deaths in the vaccine group due to angioedema (after carbimazole and propranolol administration), acute respiratory distress syndrome (negative Covid-19 test), chronic kidney disease, and gunshot wound. Six deaths in the placebo group due to hepatic failure, inguinal hernia, desmoid fibromatosis tumor, esophageal carcinoma, enterocolitis hemorrhagic, and septic shock tumor. None of the deaths were considered related to the treatment.

**Cases collected for safety purposes; not necessarily laboratory-confirmed.
AE, adverse event; AESI, adverse events of special interest; MAAE, medically attended adverse events SAE, serious adverse event. RSafAS, reactogenicity safety analysis set. SafAS: safety analysis set.

Figure Legends

Figure 1: CONSORT diagram for patient flow through the study

Figure 2: Variant distribution by country and calendar time in all participants, regardless of prior SARS-CoV-2 infections (mFAS-PD2)

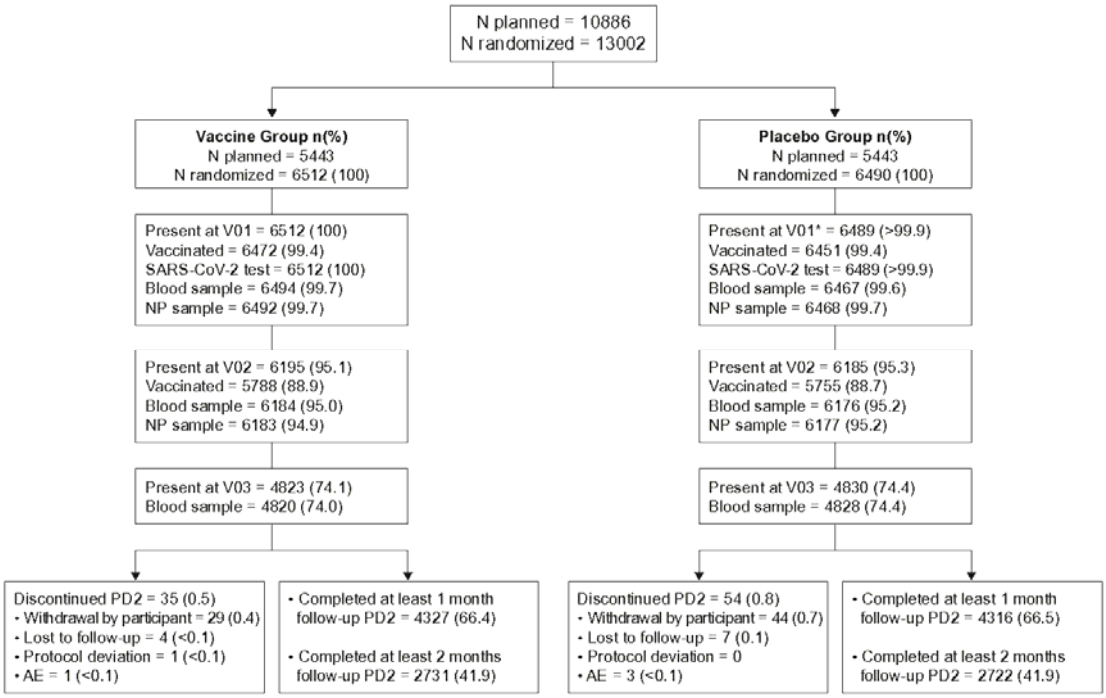
Figure 3: Forest plots for efficacy outcomes against symptomatic disease in all participants and subgroups caused by (A) all variants and (B) for the Omicron variant

Figure 4: Kaplan-Meier cumulative incidence of symptomatic COVID-19 in the mFAS-PD2 population (overall, naïve and non-naïve populations)

Figure 5: (A) 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; (B) 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

Figures

Figure 1.



Data are presented as number (%). *V1 for one participant did not appear in the database during the data extraction dated 09 June 2022 because the site was entering additional data for V01 at the time the data extraction was performed. However, this participant was included in mFAS-PD1, mFAS-PD2, mFAS-PD2 Non-naïve-D01/D22 analysis sets because both V01 and V02 were performed. Abbreviations: AE, adverse event. NP, nasopharyngeal. PD2, post dose 2. V, visit.

Figure 2.

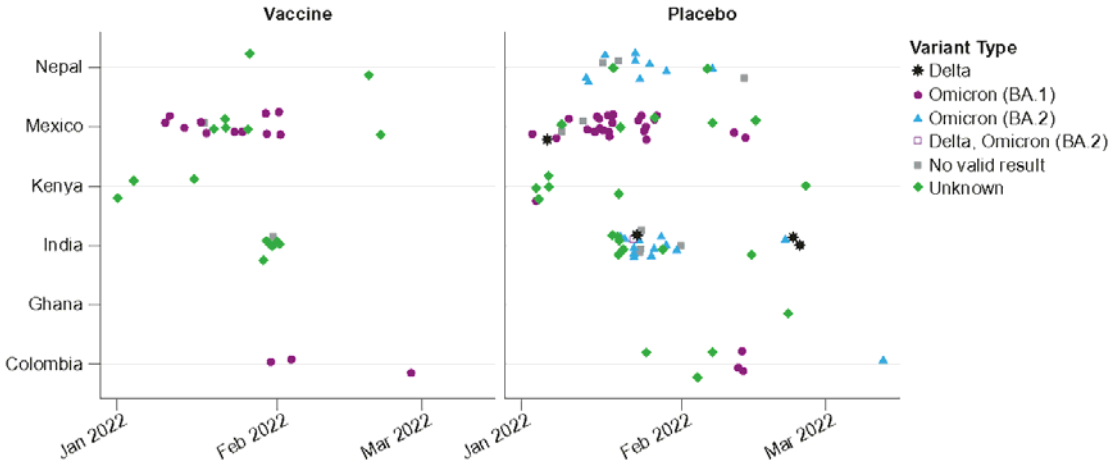
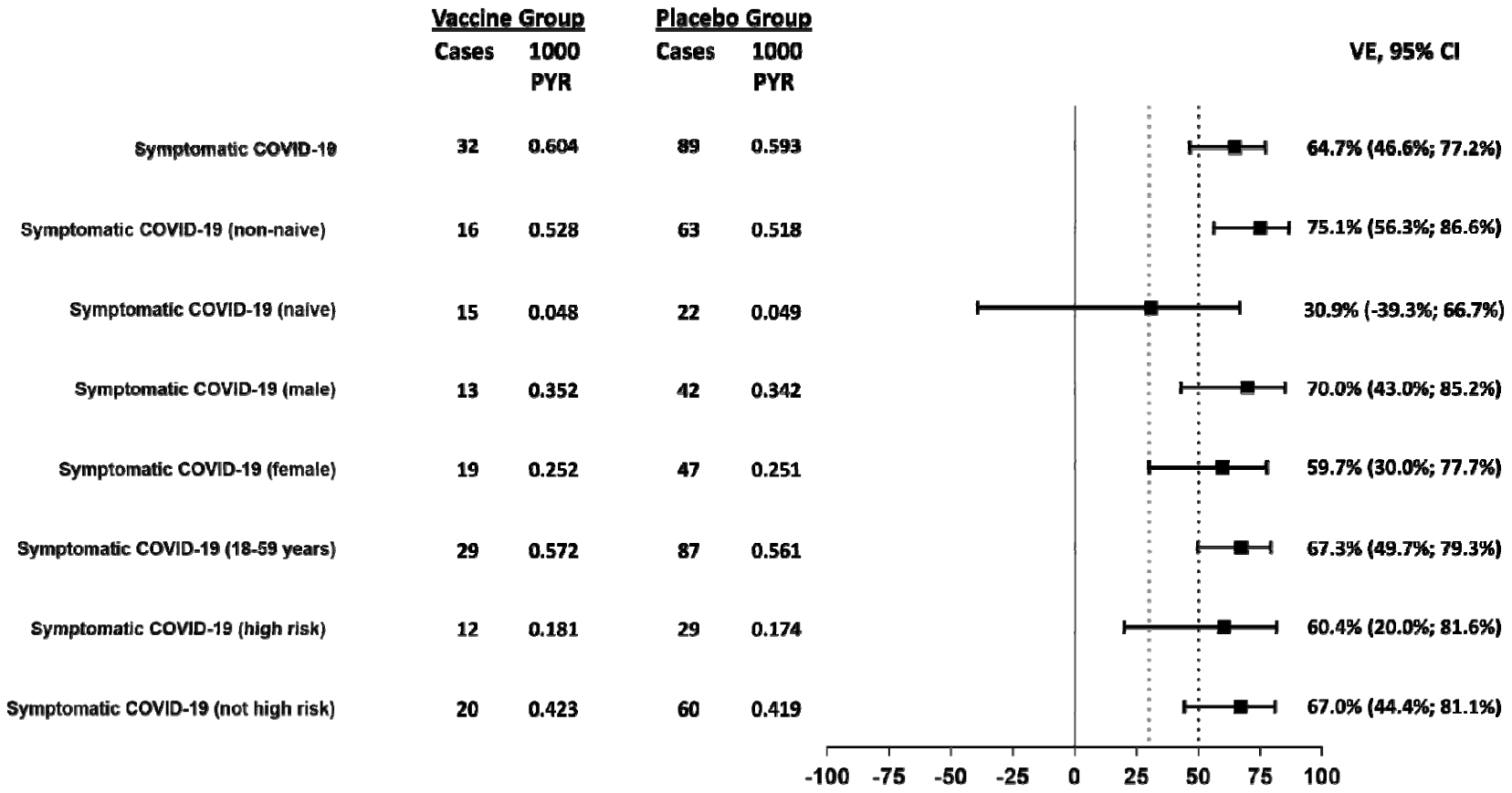
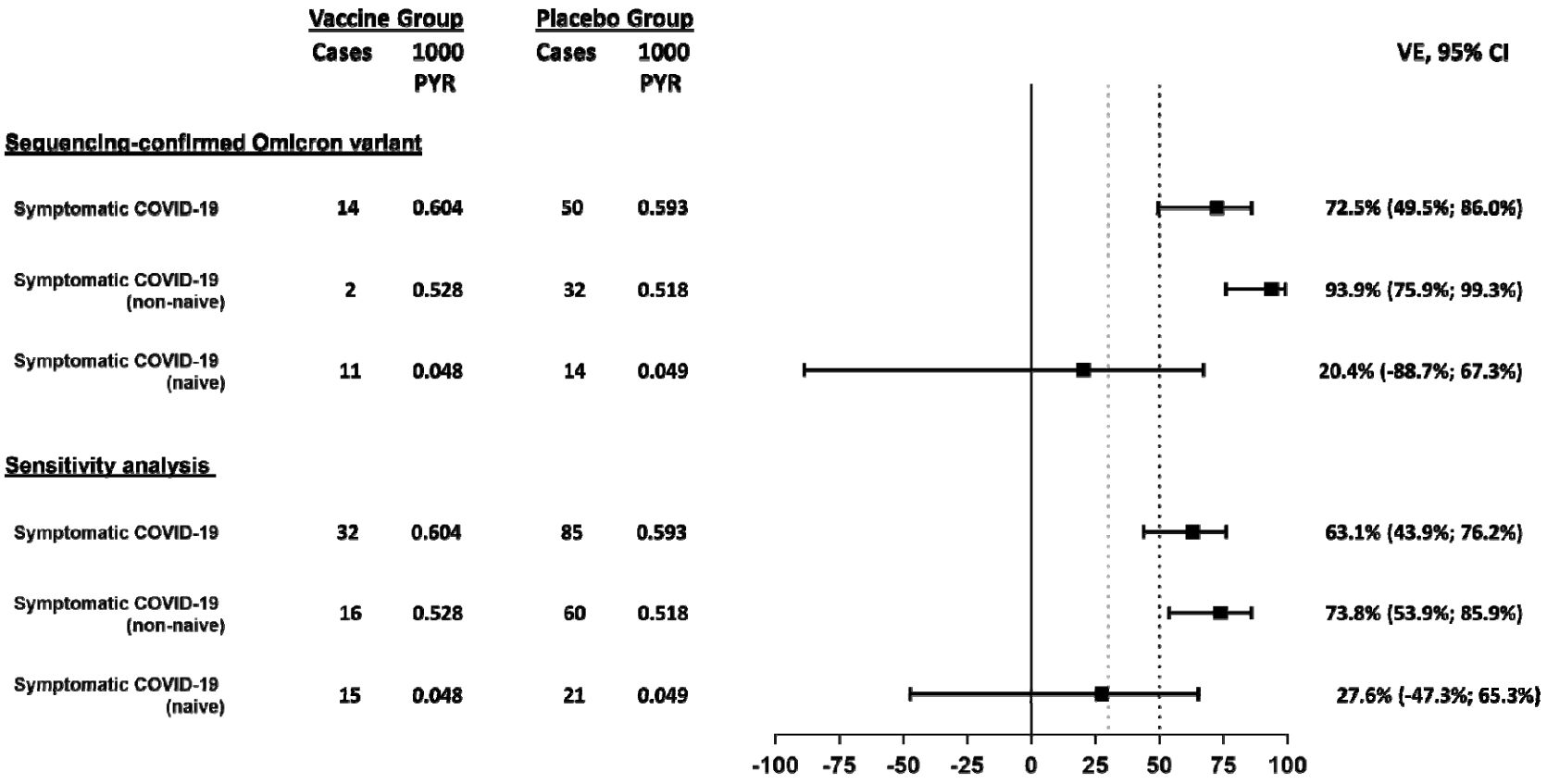


Figure 3.

A.



B.



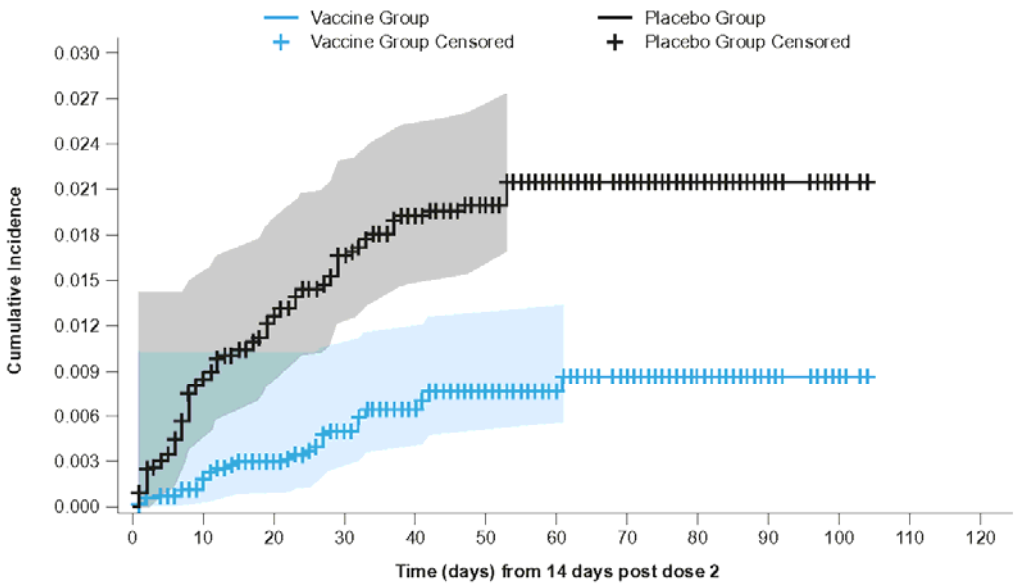
A. Efficacy outcomes overall and by subgroups for the mFAS-PD2 analysis subset. The success criteria for demonstration of efficacy was defined as a point estimate >50% (black dotted line) and a lower bound confidence interval >30% (grey dotted line).

Outcomes with too few cases to reliably calculate vaccine efficacy (severe COVID-19, moderate or worse COVID-19, hospitalization, and symptomatic COVID-19 in participants aged ≥60 years) are not shown.

B. Vaccine efficacy is shown for all sequence-confirmed Omicron cases and for the sensitivity analysis, which included sequence confirmed cases and cases for which there were no sequencing results, assuming that the latter group were caused by the Omicron variant as this was the variant that was responsible for most of the symptomatic COVID-19 cases at the time of the study. The success criteria for demonstration of efficacy was defined as a point estimate >50% (black dotted line) and a lower bound confidence interval >30% (grey dotted line). Owing to the low number of cases due to the Delta variant, these are not shown in the Forest plot.

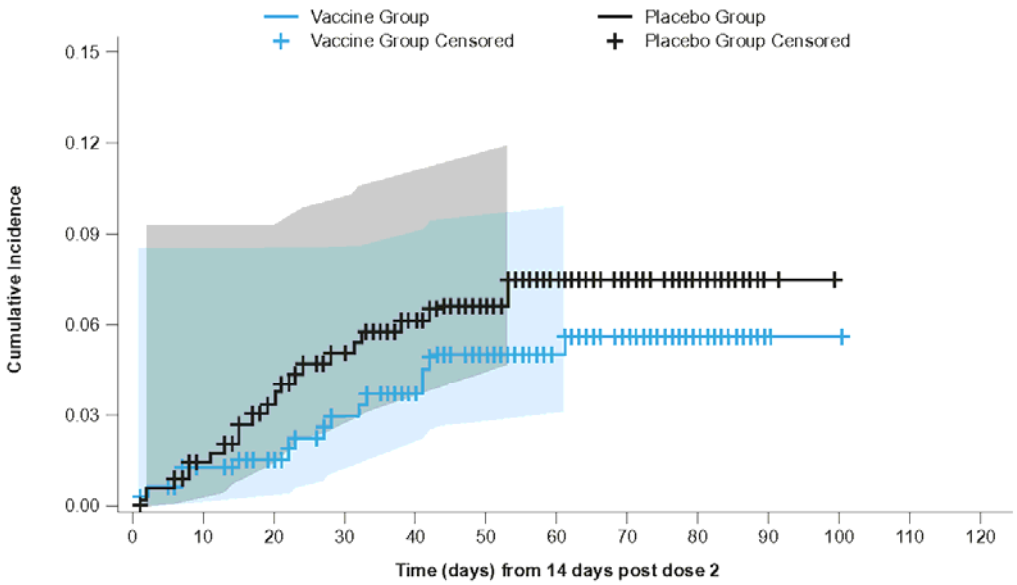
Figure 4.

A. Overall



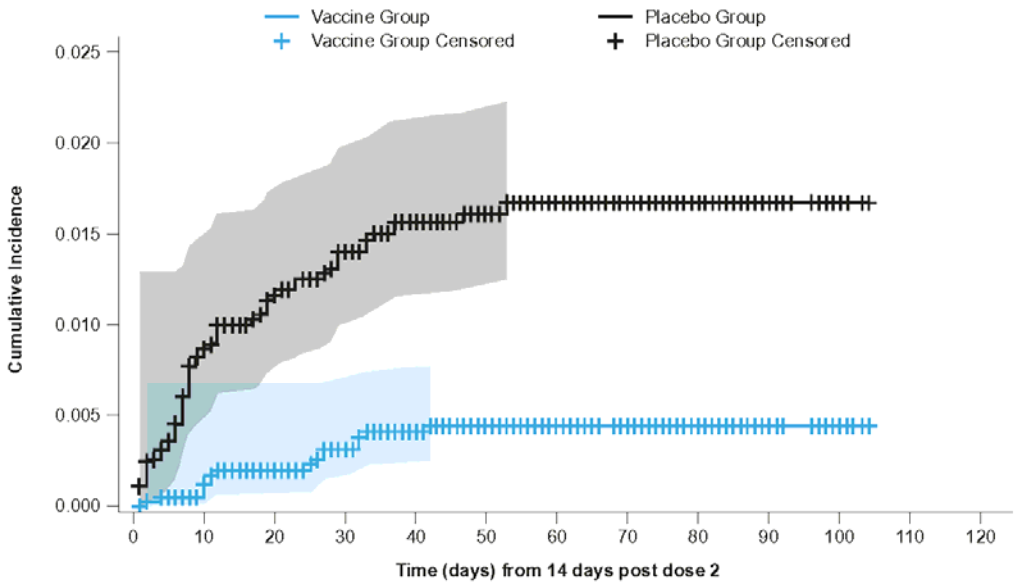
Number at Risk												
Vaccine Group	5311	4512	4142	3604	3295	2227	1017	559	220	30	16	0
Placebo Group	5287	4441	4071	3519	3232	2169	977	539	219	36	14	0
Cumulative Events												
Vaccine Group	0	9	14	22	27	31	31	32	32	32	32	32
Placebo Group	0	42	60	75	84	86	89	89	89	89	89	89

B. Naïve at second injection (PD2)



Number at Risk											
Vaccine Group	315	301	284	260	240	214	161	106	42	2	1
Placebo Group	333	313	290	268	244	218	160	87	36	2	0
Cumulative Events											
Vaccine Group	0	4	5	9	11	14	14	15	15	15	15
Placebo Group	0	5	12	16	19	20	22	22	22	22	22

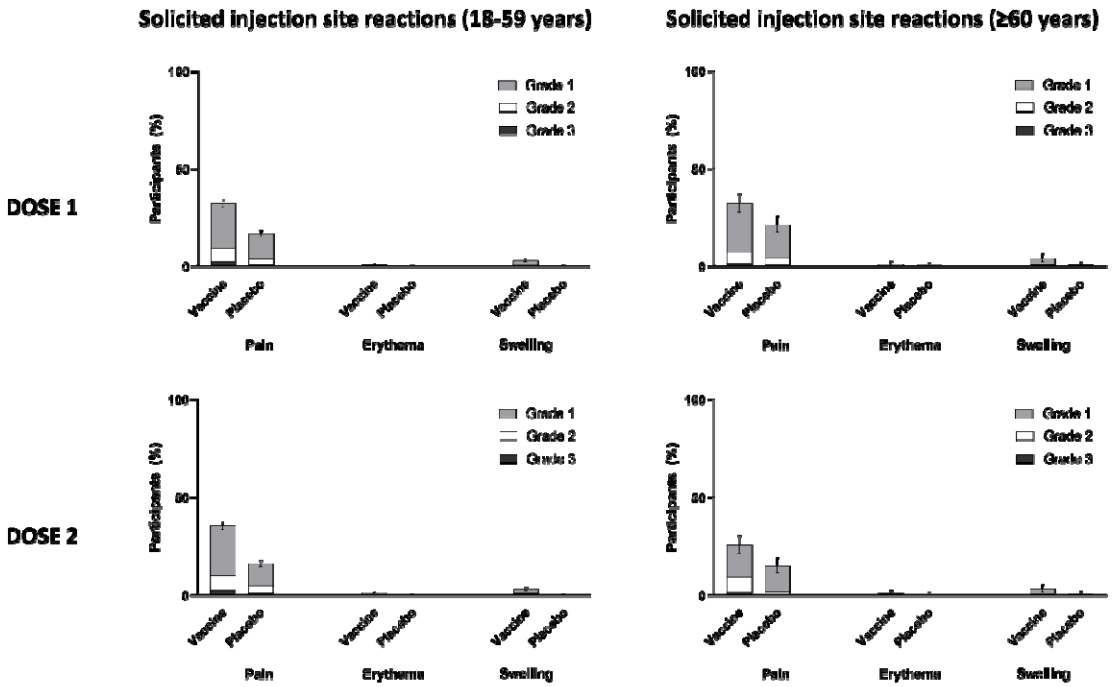
C. Non-naïve at second injection (PD2)



Number at Risk												
Vaccine Group	4519	3909	3674	3248	2972	1937	816	426	171	28	15	0
Placebo Group	4514	3846	3609	3164	2910	1896	786	426	179	34	14	0
Cumulative Events												
Vaccine Group	0	5	8	12	15	16	16	16	16	16	16	16
Placebo Group	0	37	48	56	61	62	63	63	63	63	63	63

Figure 5.

A.



B.