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Authors

Hardt, Karin
Vandebosch, An
Sadoff, Jerald
et al.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Efficacy, safety, and immunogenicity of a booster regimen of Ad26.COV2.S vaccine against COVID-19 (ENSEMBLE2): results of a randomised, double-blind, placebo-controlled, phase 3 trial

*Karin Hardt, An Vandebosch, Jerald Sadoff, Mathieu Le Gars, Carla Truyers, David Lowson, Ilse Van Dromme, Johan Vingerhoets, Tobias Kamphuis, Gert Scheper, Javier Ruiz-Guiñazú, Saul N Faust, Christoph D Spinner, Hanneke Schuitemaker, Johan Van Hoof , Macaya Douoguih, Frank Struyf, for the ENSEMBLE2 study group**

Summary

Background Despite the availability of effective vaccines against COVID-19, booster vaccinations are needed to maintain vaccine-induced protection against variant strains and breakthrough infections. This study aimed to investigate the efficacy, safety, and immunogenicity of the Ad26.COV2.S vaccine (Janssen) as primary vaccination plus a booster dose.

Methods ENSEMBLE2 is a randomised, double-blind, placebo-controlled, phase 3 trial including crossover vaccination after emergency authorisation of COVID-19 vaccines. Adults aged at least 18 years without previous COVID-19 vaccination at public and private medical practices and hospitals in Belgium, Brazil, Colombia, France, Germany, the Philippines, South Africa, Spain, the UK, and the USA were randomly assigned 1:1 via a computer algorithm to receive intramuscularly administered Ad26.COV2.S as a primary dose plus a booster dose at 2 months or two placebo injections 2 months apart. The primary endpoint was vaccine efficacy against the first occurrence of molecularly confirmed moderate to severe–critical COVID-19 with onset at least 14 days after booster vaccination, which was assessed in participants who received two doses of vaccine or placebo, were negative for SARS-CoV-2 by PCR at baseline and on serology at baseline and day 71, had no major protocol deviations, and were at risk of COVID-19 (ie, had no PCR-positive result or discontinued the study before day 71). Safety was assessed in all participants; reactogenicity, in terms of solicited local and systemic adverse events, was assessed as a secondary endpoint in a safety subset (approximately 6000 randomly selected participants). The trial is registered with ClinicalTrials.gov, NCT04614948, and is ongoing.

Findings Enrolment began on Nov 16, 2020, and the primary analysis data cutoff was June 25, 2021. From 34 571 participants screened, the double-blind phase enrolled 31 300 participants, 14 492 of whom received two doses (7484 in the Ad26.COV2.S group and 7008 in the placebo group) and 11 639 of whom were eligible for inclusion in the assessment of the primary endpoint (6024 in the Ad26.COV2.S group and 5615 in the placebo group). The median (IQR) follow-up post-booster vaccination was 36·0 (15·0–62·0) days. Vaccine efficacy was 75·2% (adjusted 95% CI 54·6–87·3) against moderate to severe–critical COVID-19 (14 cases in the Ad26.COV2.S group and 52 cases in the placebo group). Most cases were due to the variants alpha (B.1.1.7) and mu (B.1.621); endpoints for the primary analysis accrued from Nov 16, 2020, to June 25, 2021, before the global dominance of delta (B.1.617.2) or omicron (B.1.1.529). The booster vaccine exhibited an acceptable safety profile. The overall frequencies of solicited local and systemic adverse events (evaluated in the safety subset, n=6067) were higher among vaccine recipients than placebo recipients after the primary and booster doses. The frequency of solicited adverse events in the Ad26.COV2.S group were similar following the primary and booster vaccinations (local adverse events, 1676 [55·6%] of 3015 *vs* 896 [57·5%] of 1559, respectively; systemic adverse events, 1764 [58·5%] of 3015 *vs* 821 [52·7%] of 1559, respectively). Solicited adverse events were transient and mostly grade 1–2 in severity.

Interpretation A homologous Ad26.COV2.S booster administered 2 months after primary single-dose vaccination in adults had an acceptable safety profile and was efficacious against moderate to severe–critical COVID-19. Studies assessing efficacy against newer variants and with longer follow-up are needed.

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Janssen Research & Development, Beerse, Belgium (K Hardt PhD, A Vandebosch PhD, C Truyers PhD, I Van Dromme PhD, J Vingerhoets PhD, J Ruiz-Guiñazú MD, F Struyf MD); **Janssen Vaccines & Prevention, Leiden, Netherlands** (J Sadoff MD, M Le Gars PhD, T Kamphuis PhD, G Scheper PhD, H Schuitemaker PhD, J Van Hoof MD, M Douoguih MD); **Janssen Research & Development, High Wycombe, UK** (D Lowson MSc); **NIHR Southampton Clinical Research Facility and Biomedical Research Centre, Southampton, UK** (Prof S N Faust FRCPCH); **Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK** (Prof S N Faust); **Technical University of Munich, Munich, Germany** (Prof C D Spinner MD)

Correspondence to: Dr Frank Struyf, Janssen Research & Development, B-2340 Beerse, Belgium **fstruyf@its.jnj.com**

Introduction

The emergence of variant strains and occurrence of breakthrough infections[1] require the improvement and prolongation of vaccine-induced protection against SARS-CoV-2 infection and COVID-19. The initial WHO target profile recommended that COVID-19

Research in context

Evidence before this study

We previously reported the final analysis of the phase 3 single-dose Ad26.COV2.S vaccine (Janssen) efficacy trial, which showed 56·3% (95% CI 51·3–60·8) efficacy against moderate to severe–critical COVID-19 and 74·6% (64·7–82·1) efficacy against severe–critical COVID-19. Although several authorised vaccines are efficacious in preventing COVID-19 illness, waning efficacy over time for mRNA vaccines in particular and the continued emergence of variants highlight the need to consider booster vaccination. In a PubMed search up to June 1, 2022, with no language or date restrictions, using the terms "COVID", "vaccine", and "booster OR third dose" and filtering for randomised controlled trials (RCTs), we retrieved 30 results. No phase 3 RCTs evaluating the clinical efficacy of boosters were identified. The publications generally described acceptable safety profiles for booster vaccinations and showed increased neutralising antibody responses after boosting. Several publications compared the effect of boosting regimens among different COVID-19 vaccines. Although some reports have shown effectiveness and immunogenicity of a third (booster) dose of mRNA vaccines and inactivated whole-virion vaccines, to date no available publications describe large phase 3 clinical efficacy trials of booster regimens for Ad26.COV2.S.

Added value of this study

We evaluated the efficacy of a homologous booster dose of Ad26.COV2.S given 2 months after a single primary dose in a large, multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Observed vaccine efficacy varied by severity: a booster dose provided 75·2% (adjusted 95% CI 54·6–87·3) efficacy against moderate to severe–critical COVID-19 and 100% (33–100) efficacy against severe–critical COVID-19 by 14 days after boosting. We observed an increase in antibody titres post-boost, which coincided with increased efficacy, and reduced severity of illness in breakthrough cases. The variants alpha (B.1.1.7) and mu (B.1.621) were responsible for most of the COVID-19 cases that contributed to the primary endpoint analysis (17 and 14 cases at least 14 days after booster vaccination, respectively). Data collection for the primary analysis (Nov 16, 2020, until June 25, 2021) took place before the global dominance of delta (B.1.617.2) or omicron (B.1.1.529). Median (IQR) follow-up post-booster was 36·0 days (15·0–62·0), and events accrued without any substantial gaps. Although it was not possible to draw conclusions for all cases caused by specific variants, in part owing to low case numbers, variant-dependent efficacy after primary immunisation and boosting was observed for alpha and mu variants. Because this global study was done while the variant landscape was rapidly evolving, these results provide valuable information on the use of Ad26.COV2.S as a booster vaccine in the context of the ongoing pandemic.

Implications of all the available evidence

Despite the wide availability of vaccines, at least in most high-income countries, strategies are needed to manage COVID-19 surges, prevent the rise of new variants, and limit the effect of breakthrough infections. Available evidence suggests that homologous boosters are safe and effective, and Ad26.COV2.S represents a sound booster option. Additional studies and data are needed to evaluate Ad26.COV2.S vaccine efficacy against the current variants and over a longer period.

vaccines be highly efficacious as a single dose, with booster doses administered for long-term protection.[2] The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a prefusion conformation-stabilised, full-length, membrane-bound, wildtype SARS-CoV-2 spike protein.[3] In the phase 3 ENSEMBLE trial, vaccine efficacy against moderate to severe–critical COVID-19 at least 14 days after a single dose of Ad26.COV2.S was 56·3% (95% CI 51·3–60·8).[4] Results of an earlier phase 1/2a trial showed that reactogenicity following a second dose of Ad26.COV2.S was lower than after one dose.[5] Ad26.COV2.S was first granted emergency use authorisation (EUA) in the USA on Feb 27, 2021, and in Europe on March 11, 2021, as a single-dose primary regimen, and has since been granted authorisation in numerous countries globally. Additional doses of COVID-19 vaccines have become necessary to maximise protection against emerging variants. The purpose of the ENSEMBLE2 study was to evaluate the protection that an Ad26.COV2.S booster might provide against COVID-19. We report here the results of the placebo-controlled, double-blind portion of the phase 3 ENSEMBLE2 trial investigating the efficacy, safety, and immunogenicity of Ad26.COV2.S administered as primary vaccination plus a booster dose after a 56-day (2-month) interval.

See Online for appendix

Methods

Study design and participants

ENSEMBLE2 is an ongoing, randomised, double-blind, placebo-controlled, phase 3 trial (including crossover vaccination for the placebo group after EUA of COVID-19 vaccines) to assess vaccine efficacy against molecularly-confirmed moderate to severe–critical COVID-19 with onset at least 14 days after booster vaccination. The study was done at public and private medical practices and hospitals in ten countries: Belgium, Brazil, Colombia, France, Germany, the Philippines, South Africa, Spain, the UK, and the USA.

Participants were adults aged at least 18 years, healthy or with stable and well-controlled comorbidities, and without receipt of a COVID-19 vaccine at any time before study vaccination or during the study (appendix p 11). Participants with abnormal function of the immune

system (except for well-controlled HIV infection) were excluded.

The protocol and amendments were approved by ethics committees and institutional review boards per local regulations. All participants provided written informed consent. This trial adheres to the International Council for Harmonisation guidelines on Good Clinical Practice and Declaration of Helsinki principles.

Randomisation and masking

Participants were randomly assigned 1:1 via computer-generated randomly permuted blocks of size 4 to receive either two vaccine doses (referred to as a primary dose plus a homologous booster dose of Ad26.COV2.S) as part of the vaccine group or two doses of saline placebo (placebo group) 56 days apart. Central randomisation was implemented in this study. Participants were randomly assigned to one of two vaccination groups: active vaccine versus placebo. This was based on a computer-generated randomisation schedule prepared before the study by, or under the supervision of, the sponsor. The randomisation was balanced by using randomly permuted blocks and was stratified by vaccination unit, age group, and absence or presence of comorbidities that were, or might have been, associated with an increased risk of progression to severe COVID-19. Investigators, study site personnel, sponsor personnel, and laboratory personnel who did assays were masked to assignment until the unmasking visit, which was implemented with protocol amendment 4 after EUA of some COVID-19 vaccines (appendix p 13–14). Participants could be unmasked to enable vaccination of placebo recipients outside the study; once Ad26.COV2.S received EUA, placebo recipients without COVID-19 vaccination outside the study were offered open-label Ad26.COV2.S vaccination. The unmasking visit could occur at a scheduled (preferable) or unscheduled visit, as feasible for the participant.

Procedures

Participants in the vaccine group received two doses of Ad26.COV2.S (each containing 5×10^{10} viral particles in 0·5 mL of buffered vaccine-specific solution), and participants in the placebo group received two doses of saline (0·5 mL), intramuscularly into the deltoid muscle 56 days apart.

Participants were assessed for suspected symptomatic COVID-19 if they had a positive RT-PCR result for SARS-CoV-2 through a private or public laboratory independent of the study or prespecified clinical manifestations, including chest congestion, cough, runny nose, shortness of breath, sore throat, chills, fever, gastrointestinal symptoms, neurological symptoms, red or bruised looking toes, taste loss or new or changing sense of smell, or any symptoms suggestive of COVID-19 (see appendix p 16 for a full list). Asymptomatic COVID-19 was identified by a positive RT-PCR result in the absence of symptoms through a private or public laboratory independent of the study or testing of blood samples collected at fixed visits (baseline, day 71, and unmasking visit) by means of an ELISA assay against the SARS-CoV-2 nucleocapsid protein (appendix p 15). For efficacy assessments, COVID-19 cases were confirmed centrally using molecular diagnostic tests based on real-time RT-PCR-based or isothermic amplification technologies. Disease severity was assessed independently by a Clinical Severity Adjudication Committee (appendix p 15). Participants reported COVID-19 symptoms by means of the electronic Symptoms of Infection with Coronavirus-19 questionnaire.[6]

Immunogenicity was evaluated by measurement with ELISA (ELISA Unit [EU]/mL; Nexelis, Laval, Canada; see appendix p 15) of spike protein-specific binding antibodies against the Wuhan-Hu-1 isolate (NC_045512) in sera collected at days 1, 29, 57, and 71 in a subset of participants.

After each vaccination, a subset of participants recorded solicited local and systemic adverse events in an electronic diary for 7 days and unsolicited adverse events for 28 days or until unmasking. Symptom grading for local and systemic events ranged from grade 1 (mild) to grade 4 (potentially life-threatening; appendix p 17). We followed up all participants for medically attended adverse events for 6 months after each vaccination; serious adverse events, adverse events leading to study or vaccine discontinuation, and thrombosis with thrombocytopenia syndrome (an adverse event of special interest [as of protocol amendment 5]) were recorded throughout the study. Adverse events of clinical interest (not prespecified) were selected on the basis of lists proposed by expert groups and regulatory authorities (appendix p 17). A fatality was deemed to be COVID-19-related if it was COVID-19-related according to the adjudication committee or it resulted from a fatal adverse event that was COVID-19-related after the onset of a PCR-confirmed COVID-19 episode.

Outcomes

The primary objective was to show the efficacy of Ad26.COV2.S versus placebo in the prevention of molecularly confirmed moderate to severe–critical COVID-19 in SARS-CoV-2-seronegative adults. The primary endpoint was vaccine efficacy against the first occurrence of molecularly confirmed moderate to severe–critical COVID-19 with onset at least 14 days after the booster vaccination. Secondary endpoints were solicited local and systemic adverse events for 7 days after vaccination, unsolicited adverse events within 28 days after vaccination, serious adverse events and adverse events of special interest throughout the study, as well as the first occurrence at least 14 days after booster vaccination of severe–critical COVID-19, asymptomatic SARS-CoV-2 infection, COVID-19 requiring medical intervention, molecularly confirmed mild COVID-19,

COVID-19 according to the US Food and Drug Administration (FDA) harmonised case definition, molecularly confirmed symptomatic COVID-19 (mild, moderate, or severe–critical, defined as a burden-of-disease endpoint that combined all severities, as well as mild alone), and any SARS-CoV-2 infection (serologically or molecularly confirmed). The full list of prespecified objectives and endpoints, and whether they are reported in this manuscript or might be reported elsewhere, are given in the appendix (p 48). Evaluation of vaccine efficacy including non-centrally confirmed cases was a planned supplementary analysis.

Statistical analysis

Unless stated otherwise, efficacy assessments are presented for the first occurrence of molecularly confirmed COVID-19 with onset at least 14 days after booster vaccination in the risk set of the per-protocol (PP) population. The PP population included participants who received two doses of vaccine or placebo in the double-blind phase. Participants were excluded from the PP population if they had a baseline PCR-positive result, a SARS-CoV-2-positive result by serology at baseline or day 71, or major protocol deviations before unmasking that might affect efficacy. Participants who became unmasked were thereafter excluded from the PP population. The risk set of the PP population excluded participants from the PP population who had a positive PCR result (regardless of central confirmation) or discontinued the study before day 71.

Efficacy assessments post-dose 1 are presented for the risk set of the PP first-dose (PPFD) population. The PPFD population included participants in the full analysis set (FAS; all randomly assigned participants who received at least one dose of trial vaccine or placebo in the double-blind phase) with no major protocol deviations affecting efficacy; participants with positive results at baseline by PCR or serology were excluded. The risk set of the PPFD population excluded participants from the PPFD population who had a positive PCR result (regardless of central confirmation) or discontinued the study before day 15.

Immunogenicity analyses were done in the immunogenicity subset, which included approximately 400 participants (200 each in the Ad26.COV2.S and placebo groups) from the UK and the USA at selected sites. Participants were randomly selected from sites in North America, the Asia Pacific region, South Africa and Europe to ensure global representation. Serious adverse events and adverse events of special interest were summarised descriptively in the FAS. Solicited and unsolicited adverse events were summarised descriptively in the safety subset, which included approximately 6000 randomly selected participants from the FAS (accounting for participant availability and site capacity; appendix p 19). The selection and tracking of enrolment of the safety and immunogenicity subsets was done through the interactive web response system.

The sample size was based on an assumption of 65% vaccine efficacy against molecularly confirmed moderate to severe–critical COVID-19, a type 1 error rate of 0·025, and a 1:1 randomisation ratio. In total, we predicted that 104 events would provide approximately 90% power to reject the primary endpoint null hypothesis (vaccine efficacy for Ad26.COV2.S ≤30%, tested at a 0·025 one-sided significance level). The primary analysis was triggered when at least 90% of participants were unmasked. If the null hypothesis was rejected, confirmatory secondary endpoints (symptomatic infection of any severity, all SARS-CoV-2 infections, severe–critical COVID-19, asymptomatic SARS-CoV-2 infection, and COVID-19 requiring medical intervention, all evaluated with onset at least 14 days post-booster dose) were tested against a null hypothesis using a lower limit of efficacy of 0% or less, with a prespecified multiple testing strategy preserving the 0·025 family-wise error rate (and indicated with adjusted 95% CI; appendix pp 20, 56). All other endpoints or subgroup analyses were summarised descriptively with 95% CIs.

Efficacy and associated CI calculations were done by means of exact Poisson regression.[7] Estimated cumulative incidence rates to evaluate time to first occurrence of COVID-19 and vaccine efficacy over time were assessed by Kaplan-Meier methods. For any given endpoint, vaccine efficacy was derived from the ratio of the incidence of the endpoint (number of cases per person-years) in the vaccinated group relative to the incidence of the endpoint in the placebo group on the basis of Poisson regression (appendix p 21). Subgroup analyses were done according to various demographics, baseline risk factors, and by variant; these were prespecified, except for presence or absence of each of the specific comorbidities.

To assess immunogenicity, we calculated spike-specific binding antibody geometric mean concentrations (GMCs) and responder rates. A responder was identified by at least one of the following: a baseline sample value less than or equal to the lower limit of quantification (LLOQ) of the ELISA, with a post-baseline sample greater than the LLOQ, or a baseline sample value greater than the LLOQ and a post-baseline sample with at least a 4-times increase from the baseline sample value. Statistical analyses were done using SAS (version 9.4) and R 4.1.0 and later versions. An independent data monitoring committee was used. The trial is registered with ClinicalTrials.gov, NCT04614948.

Role of the funding source

The funder of the study was responsible for study design, study conduct, data collection, data analysis, and data interpretation, and authors employed by the sponsor contributed to the writing of the report and to the decision to submit for publication.

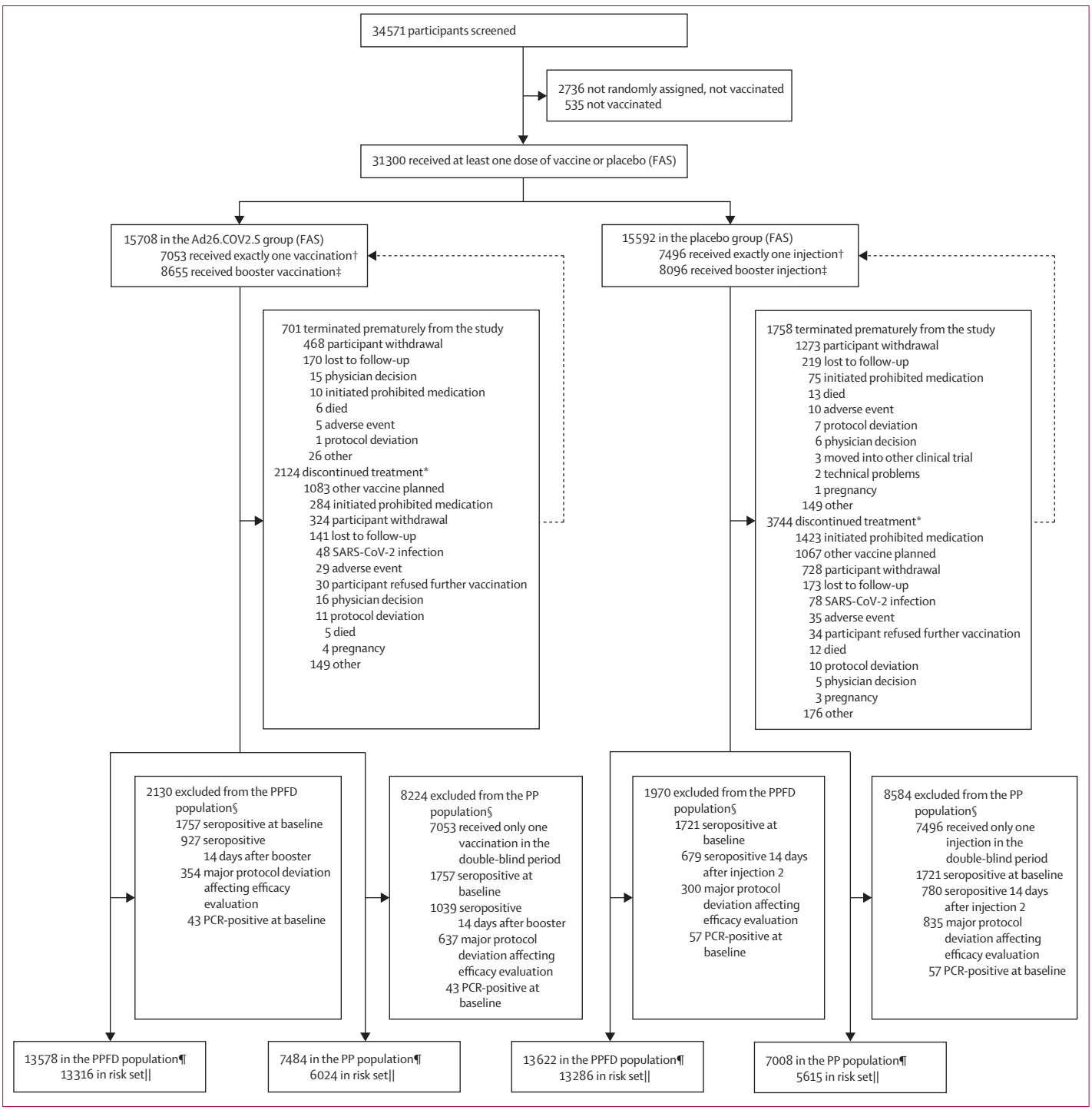


Figure 1: **Participant disposition**
FAS=full analysis set. PPFD=per-protocol first-dose. PP=per-protocol. *These individuals were still being followed up for safety as of the data cutoff date (June 25, 2021). †Of those receiving one vaccination, 1548 in the Ad26.COV2.S group and 2052 in the placebo group were unmasked before the unmasking visit and 148 in the Ad26.COV2.S group and 262 in the placebo group received a COVID-19 vaccine outside the study before unmasking. ‡Of those receiving a booster dose, 2719 in the Ad26.COV2.S group and 2628 in the placebo group were unmasked before the unmasking visit and 46 in the Ad26.COV2.S group and 168 in the placebo group received a COVID-19 vaccine outside the study before unmasking. §Participants could have more than one reason for exclusion. ¶The PPFD and PP sets are partially overlapping subsets of the FAS and do not sum to a total that equals the FAS. ||Risk sets excluded participants who had a positive PCR result between the first vaccination and day 15 (PPFD set) or day 71 (PP set), or who discontinued before 14 days after the first vaccination (PPFD set) or booster (PP set).

	Ad26.COV2.S (n=15 708)	Placebo (n=15 592)
Age, years†		
18–59	10 089 (64·2%)	9978 (64·0%)
≥60	5618 (35·8%)	5614 (36·0%)
Median (IQR)	53 (42·0–62·0)	53 (42·0–62·0)
Sex†		
Female	7391 (47·1%)	7429 (47·6%)
Male	8314 (52·9%)	8160 (52·3%)
Undifferentiated	2 (<0·1)	3 (<0·1)
Race‡		
American Indian or Alaskan Native§	393 (2·5%)	396 (2·5%)
Asian	1379 (8·8%)	1353 (8·7%)
Black or African American	1309 (8·3%)	1245 (8·0%)
Native Hawaiian or Other Pacific Islander	33 (0·2%)	43 (0·3%)
White	11 974 (76·2%)	11 933 (76·5%)
Multiracial	225 (1·4%)	219 (1·4%)
Not reported, unknown, or missing	395 (2·5%)	403 (2·6%)
Ethnicity‡		
Hispanic or Latinx	2827 (18·0%)	2806 (18·0%)
Not Hispanic or Latinx	12 430 (79·1%)	12 344 (79·2%)
Not reported, unknown, or missing	451 (2·9%)	442 (2·8%)
Country or region†		
Europe	6416 (40·8%)	6416 (41·1%)
Belgium	1489 (9·5%)	1492 (9·6%)
France	356 (2·3%)	358 (2·3%)
Germany	51 (0·3%)	49 (0·3%)
Spain	1563 (10·0%)	1569 (10·1%)
UK	2957 (18·8%)	2948 (18·9%)
Latin America	1325 (8·4%)	1324 (8·5%)
Brazil	251 (1·6%)	249 (1·6%)
Colombia	1074 (6·8%)	1075 (6·9%)
Philippines	784 (5·0%)	788 (5·1%)
South Africa	1037 (6·6%)	1035 (6·6%)
USA	6145 (39·1%)	6029 (38·7%)
SARS-CoV-2 serostatus		
Positive	1757 (11·2%)	1721 (11·0%)
Negative	13 803 (87·9%)	13 759 (88·2%)
Missing	148 (0·9%)	112 (0·7%)
Body-mass index, kg/m²¶		
Median (IQR)	26·5 (23·5–30·2)	26·6 (23·6–30·1)
≥30	4142 (26·4%)	4068 (26·1%)
One or more comorbidity at baseline	6519 (41·5%)	6434 (41·3%)

Data are n (%) or median (IQR). *The full analysis set included all participants who were randomly assigned and received at least one documented dose of Ad26.COV2.S vaccine or placebo, regardless of protocol deviations and serostatus at enrolment. †For one participant in the vaccine group, screening occurred but partial demographic data were missing; this participant was thus not included in the denominator for characteristics with missing data. ‡Race and ethnicity were self-reported by participants. §Participants responding "yes" to American Indian or Alaska Native in the Ad26.COV2.S group were from Colombia (n=326), the USA (n=38), Spain (n=24), Brazil (n=2), the UK (n=2), and the Philippines (n=1); in the placebo group, participants were from Colombia (n=321), the USA (n=39), Spain (n=28), the UK (n=4), and Belgium, Brazil, France, and South Africa (n=1 each). ¶Height and weight were recorded for only 15691 (Ad26.COV2.S) and for 15584 (placebo) participants at baseline.

Table 1: **Baseline characteristics (full analysis set*)**

Results

Enrolment began Nov 16, 2020, and the primary analysis data cutoff was June 25, 2021 (before delta became globally dominant and before the emergence of omicron). 34 571 participants were screened, 31 835 were randomly assigned, and 31 300 received at least one dose of vaccine or placebo (FAS). Of the FAS, 16 751 (53·5%) received both doses (Ad26.COV2.S, n=8655; placebo, n=8096), with 14 492 included in the PP population (Ad26.COV2.S, n=7484; placebo, n=7008; figure 1). Most (28 836 [92·1%] of 31 300) participants in the FAS were still in the study up to the data cutoff date (see appendix p 53 for the disposition of the PP population); reasons for not being in the study on June 25, 2021, were premature termination (n=2459; reasons for premature termination shown in figure 1), completed follow-up (n=4), and missing demographic or study disposition data, meaning the participant could not be assigned as completed, discontinued, or ongoing (n=1). At the time of the cutoff date, 5868 (18·7%) of 31 300 discontinued treatment but remained in the study for further safety follow-up (figure 1). Unsolicited adverse events leading to study or vaccine discontinuation in the safety subset are summarised in the appendix (p 55). After unmasking, more placebo recipients (3653 [23·9%] of 15 298) discontinued vaccination and received another vaccine outside the study than Ad26.COV2.S recipients (417 [2·7%] of 15 472). The median (IQR) follow-up post-primary vaccination in the FAS was 70·0 (52·0–99·0) days. In the PP population, median (IQR) follow-up was 36·0 (15·0–62·0) days post-booster; 4245 (29·3%) of 14 492 participants had at least 2 months follow-up post-booster. Despite discontinuations, follow-up times in the double-blind phase between groups in the PP population and FAS were similar (appendix p 23). Demographic and baseline characteristics are described for the FAS and PP sets in table 1 and the appendix (p 51), respectively.

The risk set of the PP population (Ad26.COV2.S, n=6024; placebo, n=5615) excluded 2853 participants (Ad26.COV2.S, n=1460; placebo, n=1393) for either having a positive PCR test result or discontinuing participation before day 71. At the primary analysis of the double-blind phase, 14 molecularly confirmed moderate to severe–critical COVID-19 cases with onset at least 14 days after booster vaccination were reported in the Ad26.COV2.S group and 52 in the placebo group, indicating a vaccine efficacy of 75·2% (adjusted 95% CI 54·6–87·3; table 2). Efficacy (from the pre-planned analysis) including non-centrally confirmed cases was similar (appendix p 56). The cumulative incidence curves of molecularly confirmed moderate to severe–critical COVID-19 cases with onset at least 1 day after vaccination began to separate 14 days post-primary vaccination (appendix p 25) and separated more widely shortly after booster vaccination (figure 2).

At the time of the study, the alpha variant was dominant in most countries, except for Colombia, Brazil, and South Africa, where dominant variants were mu, gamma (P.1), and beta, respectively. At the time of the analysis, sequencing data were available for 319 (68·0%)

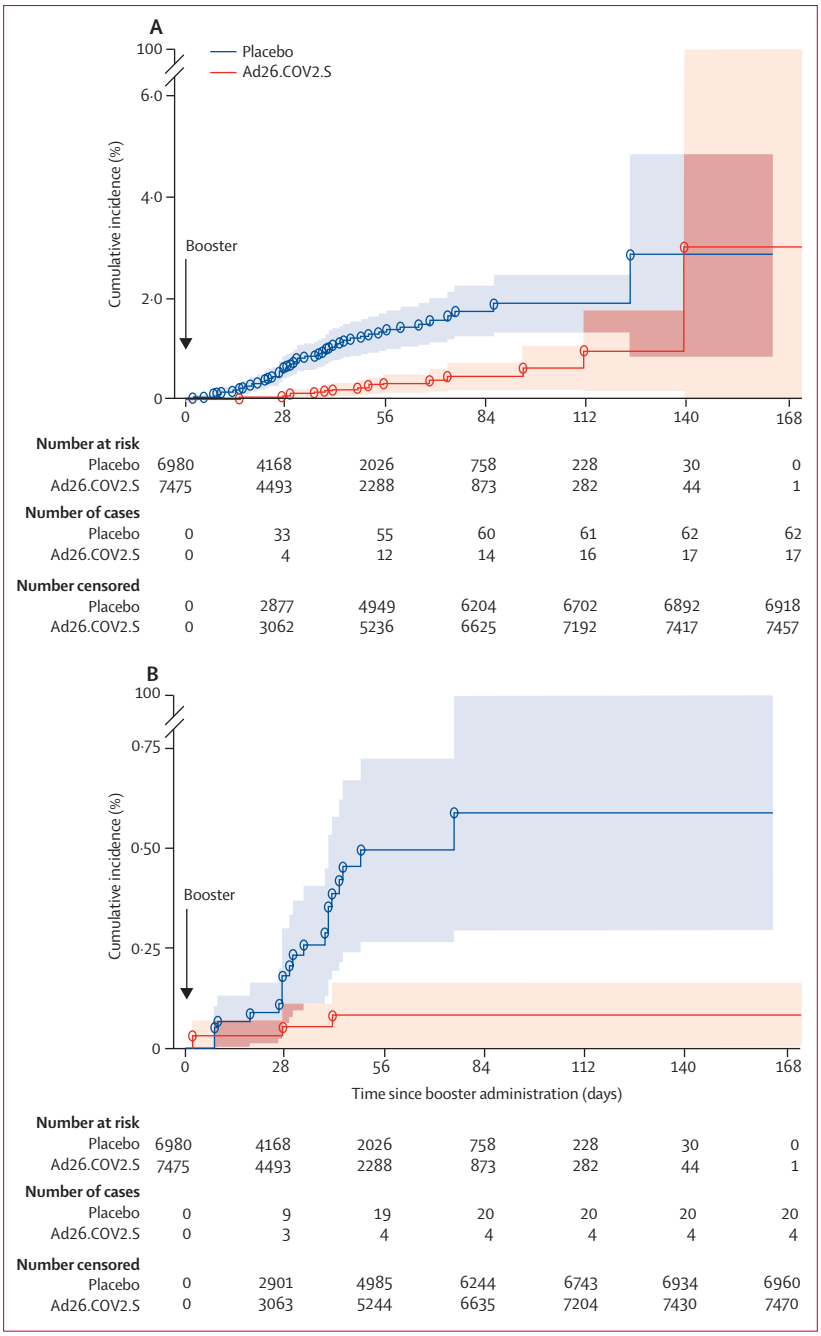
	Ad26.COV2.S (n=6024)		Placebo (n=5615)		Vaccine efficacy (95% CI)*
	Number of cases	Person-years†	Number of cases	Person-years†	
Moderate to severe–critical COVID-19 (primary endpoint)	14	1730·0	52	1595·0	75·2% (54·6 to 87·3)‡
18–59 years	10	1386·9	41	1276·4	77·6% (54·4 to 90·0)
≥60 years	4	343·1	11	318·6	66·2% (–14·0 to 92·2)
Symptomatic COVID-19 of any severity§	14	1730·0	53	1594·9	75·6% (55·5 to 87·5)
Mild¶	0	1730·0	1	1594·9	..
Moderate¶	14	1730·0	44	1595·0	70·7% (45·5 to 85·2)
Severe–critical§||	0	1730·7	8	1598·9	100·0% (32·6 to 100·0)‡
All SARS-CoV-2 infections§	60	1729·4	113	1593·4	51·1% (29·5 to 66·5)‡
Serologically confirmed and locally molecularly confirmed	1	1729·9	2	1594·8	..
Serologically confirmed and not molecularly confirmed	5	1729·5	2	1594·9	–130·5% (–2321·0 to 62·3)
Asymptomatic SARS-CoV-2 infections§	40	1729·9	56	1593·5	34·2% (–6·4 to 59·8)‡
COVID-19 requiring medical intervention or hospitalisation§	0	1730·7	5	1599·1	..
All-cause mortality**	1	1730·7	1	1599·4	..
COVID-19-related deaths**	0	1730·7	1	1599·4	..
COVID-19, according to FDA harmonised definition¶	12	1730·1	52	1595·1	78·7% (59·6 to 89·7)
Moderate to severe–critical COVID-19 by region or country**					
Europe	5	833·3	15	779·2	68·8% (9·8 to 91·1)
Latin America	6	85·0	16	78·8	65·2% (6·4 to 88·9)
Philippines	0	38·3	2	36·1	..
South Africa	2	141·0	5	141·1	60·0% (–144·5 to 96·2)
USA	1	632·4	14	559·7	93·7% (58·5 to 99·9)
Moderate to severe–critical COVID-19 by variant**					
Reference strain††	0	1730·0	0	1595·0	..
Variant substitution‡‡	7	1730·0	35	1595·0	81·6% (57·9 to 93·1)
Alpha	1	1730·0	16	1595·0	94·2% (62·9 to 99·9)
Mu	4	1730·0	10	1595·0	63·1% (–27·9 to 91·6)
Other§§	0	1730·0	3	1595·0	..

FDA=US Food and Drug Administration. *If fewer than six cases were observed for an endpoint, vaccine efficacy was not determined. †Follow-up time was defined as the time between primary vaccination (Ad26.COV2.S or placebo) and the time of onset of the case (for participants with molecularly confirmed COVID-19), the last available measurement, or the end of the double-blind phase or study discontinuation, whichever came first. ‡Adjusted 95% CI, which was calculated using type I error control for multiple testing and is presented on meeting the prespecified testing conditions. The hypothesis for asymptomatic infections was not significant at the alpha level 1·25% (obtained from all SARS-CoV-2 infections). No hypothesis testing was done for medical intervention, for which fewer than six cases were reported; therefore, no alpha was recycled for the hypothesis of asymptomatic infections. §Confirmatory secondary endpoint, included in the hypothesis testing, preserving the family-wise error rate. ¶Supportive secondary endpoint, not included in hypothesis testing. ||Sequencing of severe–critical COVID-19 cases with onset at least 14 days after a booster dose identified one case caused by alpha, two caused by mu, and one caused by lambda (C.37); variants were not identified for the other four cases. **Exploratory endpoint. ††The reference strain was the Wuhan-Hu1 variant including the D614G mutation (B.1 lineage). ‡‡Variant substitution refers to all variants combined, except for Other and reference strain categories. §§Includes strains not considered variants based on their mutations.

Table 2: **Vaccine efficacy against molecularly confirmed COVID-19 with onset at least 14 days after the administration of a booster dose or placebo (risk set of the per-protocol population)**

of 469 molecularly confirmed infections in the FAS during the double-blind phase (appendix p 30). The reference sequence (Wuhan-Hu1 plus D614G) was present in 19 (6·0%) of 319 sequenced strains (122 alpha, 45 mu, and 13 delta variants). No moderate to severe–critical cases involving the reference strain were reported after booster vaccination. Overall efficacy against moderate to severe–critical COVID-19 for pooled variants differing from the reference strain (including variants of concern and variants of interest and excluding strains not considered variants based on their mutations) was 81·6% (95% CI 57·9 to 93·1; table 2; appendix pp 31–32), with 94·2% (62·9 to 99·9) reported for alpha and 63·1% (–27·9 to 91·6) for mu variants during the follow-up period of case accrual for each of the respective variants (the last placebo event occurred at 56 days after booster vaccination for alpha and within 84 days for mu; figure 2B, C). Insufficient cases (fewer than six) were available to analyse other variants, including delta.

Eight severe–critical COVID-19 cases were reported, all in the placebo group, giving a vaccine efficacy of 100% (adjusted 95% CI 32·6–100·0; table 2). No cases of COVID-19 requiring medical intervention occurred in the Ad26.COV2.S group versus five cases in the placebo group. COVID-19-related death was reported for no Ad26.COV2.S recipients and for one placebo recipient.



(Figure 2 continues on next page)

Consistent efficacy was observed for subgroups with sufficient numbers of cases (six or more cases); for example, participants aged 18–59 years and 60 years and older or participants with and without comorbidities (appendix p 33). Low numbers of participants in some subgroups resulted in wide CIs, possibly confounded by differential distribution of variants across regions. In the USA, with the largest representation across all countries in the PP population (5290 [36·5%] of 14492), efficacy against moderate to severe–critical COVID-19 was 93·7% (95% CI 58·5–99·9); in Colombia, which contributed 620 participants (4·3%) to the PP population, efficacy was 65·2% (6·4–88·9).

Vaccine efficacy against all infections, including asymptomatic, was 51·1% (adjusted 95% CI 29·5 to 66·5), overall efficacy against asymptomatic infection was 34·2% (adjusted 95% CI −6·4 to 59·8), and efficacy against symptomatic infection of any severity was 75·6% (95% CI 55·5 to 87·5; table 2). Ad26.COV2.S recipients with breakthrough infections had fewer symptoms, lower symptom severity, and fewer cases lasting more than 28 days versus placebo recipients (appendix pp 36–38]).

The risk set of the PPFD population (Ad26.COV2.S, n=13 316; placebo, n=13 286) excluded 598 participants from the PPFD population (Ad26.COV2.S, n=262; placebo, n=336) because they either had a positive PCR test result or discontinued before day 15. Efficacy in the at-risk PPFD set against moderate to severe–critical COVID-19 with onset from day 15 to 56 (representing those who received only one dose) was 67·0% (95% CI 53·6–76·9) and efficacy against severe–critical COVID-19 was 86·6% (55·3–97·4; appendix pp 26–29, 57). Efficacy against moderate to severe–critical COVID-19 caused by variants with onset from day 15 to 56 was 71·6% (43·2–86·9) for alpha and 43·9% (−43·4 to 79·6) for mu (appendix pp 28–29).

In the immunogenicity subset, GMCs of spike-specific binding antibodies increased 7·2 and 40·5-times from baseline to day 29 and day 71, respectively, in the vaccine group (appendix p 39). Following a single vaccination, response rates were 113 (91·9%) of 123 by day 29; after boosting, response rates reached 68 (100%) of 68 by day 71. In the placebo group, GMCs of spike-binding antibody were below the LLOQ at all timepoints.

The Ad26.COV2.S booster had an acceptable safety and reactogenicity profile. More solicited adverse events were reported in the vaccine group than in the placebo group (appendix p 58). The overall frequencies of local and systemic solicited adverse events were similar between first and booster vaccinations within the Ad26.COV2.S group and within the placebo group (figure 3; appendix p 58). There was no increase in reactogenicity in older adults versus younger adults, and the frequency of solicited local and systemic adverse events was lower in older than in younger adults (appendix p 40).

The most frequently reported solicited local adverse event after both vaccinations in the Ad26.COV2.S and placebo groups was injection-site pain (figure 3; appendix p 58). Most solicited local adverse events were grade 1–2 in severity (appendix p 58). Grade 3 solicited local adverse events were reported in nine (0·3%) of 3015 Ad26.COV2.S recipients after dose one and ten (0·6%) of 1559 recipients after boosting (figure 3; appendix p 58). No grade 4 local adverse events were reported. Local reactogenicity was transient, with median

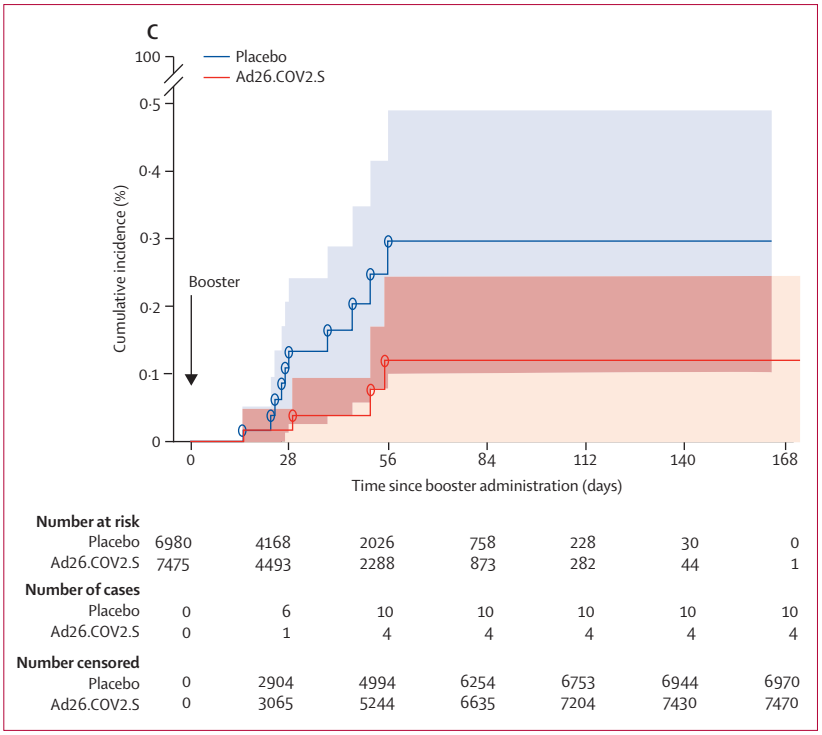
duration for any solicited local adverse event of 1–3 days after any vaccination.

The most frequently reported solicited systemic adverse events were fatigue, headache, and myalgia (figure 3, appendix p 58). Fatigue was the most common systemic adverse event in the Ad26.COV2.S and placebo groups after both vaccinations. Grade 3 solicited systemic adverse events were reported in 55 (1·8%) of 3015 Ad26.COV2.S recipients following dose one and 25 (1·6%) of 1559 post-booster. No grade 4 systemic adverse events were reported. Systemic reactogenicity was transient, with median duration for any solicited systemic adverse event of 1 to 2 days post-vaccination.

Most unsolicited adverse events were grade 1 or 2 in severity. After the first dose, 37 participants (Ad26.COV2.S, n=21; placebo, n=16) reported unsolicited events of grade 3 or higher severity; the most frequently reported was headache (Ad26.COV2.S, n=8; placebo, n=3). After the booster, 12 participants in the vaccine group and seven in the placebo group reported unsolicited events of grade 3 or higher severity; nausea was the only event reported by more than one participant (n=2 in the vaccine group; appendix pp 60–61). The most frequent unsolicited events considered related to vaccination included fatigue, vaccination site pain, headache, muscle aches, and nausea, which occurred more frequently after the first dose than after the booster (appendix pp 62–63).

11 participants had 13 serious adverse events considered related to the study vaccine (eight [0·1%] of 15 705 participants in the Ad26.COV2.S group and three [<0·1%] of 15 588 participants in the placebo group; appendix p 65). Adverse events of clinical interest are summarised in the appendix (p 66). No participant in the vaccine group reported an event that met the pre-established criteria for thrombosis with thrombocytopenia syndrome[8] during the double-blind phase. One placebo recipient had deep vein thrombosis on day 27, followed by pulmonary embolism in combination with thrombocytopenia on day 29. No cases of Guillain-Barré syndrome, immune thrombocytopenia, or encephalitis were reported during the double-blind phase. Numerical differences were observed during the entire double-blind phase for arthritis (38 [0·2%] of 15 705 participants in the Ad26.COV2.S group *vs* 22 [0·1%] of 15 588 in the placebo group) and tinnitus (nine [0·1%] of 15 705 *vs* five [<0·1%] of 15 588; appendix p 66). For adverse events occurring within 28 days after each vaccination, imbalances were seen for haemorrhagic disorders after each vaccination (24 [0·2%] of 15 705 in the Ad26.COV2.S group *vs* 14 [<0·1%] of 15 588 in the placebo group after dose one, and 17 [0·2%] of 8646 *vs* seven [<0·1%] of 8043 post-booster), mostly due to local injection-site adverse events (appendix p 66). Of these, eight were considered serious adverse events. No numerical differences were observed for convulsions or seizures, Bell's palsy, deep vein thrombosis, pulmonary embolism, myocarditis, or pericarditis. Furthermore, aside from events related to trauma, injury, or injection-site adverse events, no numerical differences between the Ad26.COV2.S group and placebo group were seen for any system organ class level within 28 days after any vaccination (appendix p 66).

As of June 25, 2021, five participants in the vaccine group discontinued the study owing to an adverse event (cerebral haemorrhage, bipolar disorder–suicidal ideation, urticaria [non-serious and the only adverse event considered vaccine-related], benign prostatic hyperplasia, cervical vertebral fracture). As of the data cutoff date, 17 deaths were reported in the entire double-blind phase (four in the vaccine group [two post-dose 1 and two post-booster] and 13 in the placebo group; appendix p 65). More deaths were related to COVID-19 in the placebo group than in the vaccine group (seven versus none; appendix p 65). None of these deaths were considered related to study vaccine.



Number at risk							
Placebo	6980	4168	2026	758	228	30	0
Ad26.COV2.S	7475	4493	2288	873	282	44	1
Number of cases							
Placebo	0	6	10	10	10	10	10
Ad26.COV2.S	0	1	4	4	4	4	4
Number censored							
Placebo	0	2904	4994	6254	6753	6944	6970
Ad26.COV2.S	0	3065	5244	6635	7204	7430	7470

Figure 2*: Cumulative incidence of first occurrence of molecularly confirmed moderate to severe–critical COVID-19 with onset at least 1 day after booster vaccination (PP population)
(A) Cumulative incidence of molecularly confirmed moderate to severe–critical COVID-19 with onset at least 1 day after booster vaccination in the PP population. (B) Cumulative incidence of molecularly confirmed moderate to severe–critical COVID-19 due to the alpha (B.1.1.7) variant with onset at least 1 day after booster vaccination in the PP population. (C) Cumulative incidence of molecularly confirmed moderate to severe–critical COVID-19 due to the mu (B.1.621) variant in the PP population. *Number in the PP group minus participants who had an event or were censored (because of outside vaccination) before the booster dose. PP=per protocol.

Discussion

In this analysis of ENSEMBLE2 (COV3009), a primary dose plus a booster dose of Ad26.COV2.S administered at a 2-month interval elicited an efficacy of 75·2% (adjusted 95% CI 54·6–87·3) against moderate to severe–critical COVID-19 and of 100% (32·6–100·0%) against

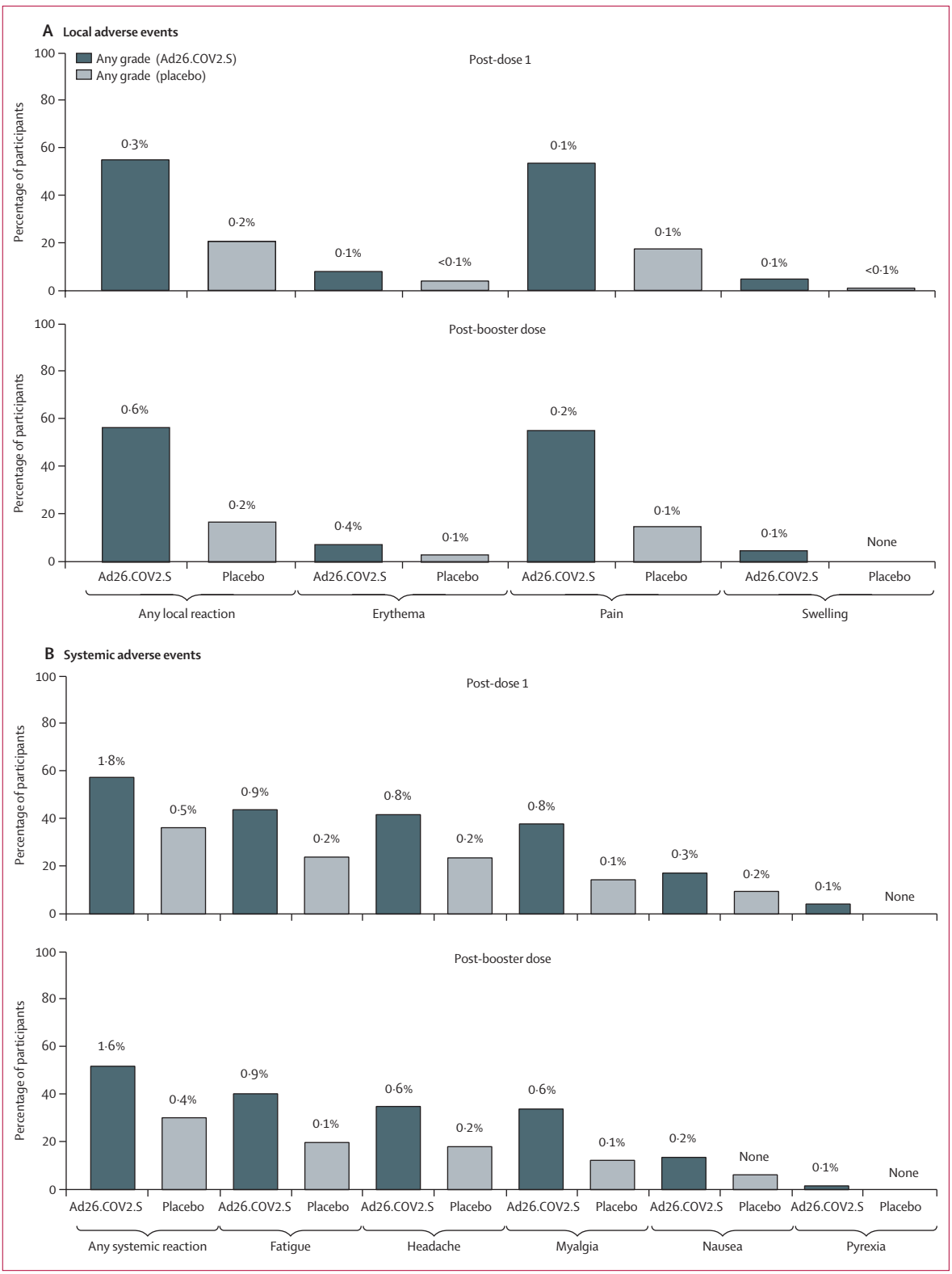


Figure 3: **Solicited local (A) and systemic (B) adverse events following a prime–boost vaccination regimen in adults (safety set)**
Percentages of participants specifically reporting grade 3 adverse events are shown above each column for the vaccine and placebo groups.

severe–critical COVID-19 by at least 14 days after boosting. No cases of COVID-19 requiring medical intervention and no COVID-19-related deaths were observed in the active group of the study. Additionally, vaccination reduced the duration, number, and severity of symptoms in breakthrough cases, suggesting a shift from more severe to milder COVID-19. An anamnestic response was shown, as antibody titres increased from baseline approximately 40-times by 2 weeks after the Ad26.COV2.S booster, as compared with 7·2-times 4 weeks post-primary vaccination, coinciding with increased efficacy and suggesting that increased immunogenicity corresponds to increased protection.

The Ad26.COV2.S booster appeared to improve efficacy against SARS-CoV-2 variants in ENSEMBLE2. Efficacy estimates against moderate to severe–critical COVID-19 caused by alpha and mu variants after primary single-dose Ad26.COV2.S vaccination (days 15–56) were 71·6% (95% CI 43·2 to 86·9) and 43·9% (–43·4 to 79·6), respectively. These estimates are consistent with those of the phase 3 ENSEMBLE (COV3001) trial (70·1% [35·1 to 87·6] for alpha and 35·8% [1·5 to 58·6] for mu),[4] which assessed efficacy outcomes after a single dose of Ad26.COV2.S and was the basis for licensure or conditional approval of the vaccine in many countries.[9] After the booster dose in ENSEMBLE2, observed efficacy estimates against moderate to severe–critical COVID-19 caused by alpha and mu were higher (94·2% [62·9 to 99·9] and 63·1% [–27·9 to 91·6], respectively), suggesting the benefit of boosting. In the USA, where alpha became dominant during both studies,[10] efficacy against moderate to severe–critical COVID-19 in the boosted population was 93·7% (58·5 to 99·9) in ENSEMBLE2 compared with 72·9% (65·7 to 78·7) in ENSEMBLE. In Colombia, where mu was predominant, efficacy in the boosted population in ENSEMBLE2 was 65·2% (6·4–88·9), compared with 51·6% (38·5 to 62·1) in ENSEMBLE.

When the delta variant surged in the USA from May to August, 2021, Ad26.COV2.S single-dose effectiveness against COVID-19 declined, but effectiveness against hospitalisation remained at least 80%.[11] During emergence of omicron, an Ad26.COV2.S booster dose 6–9 months after primary vaccination in South Africans elicited 72–74% vaccine effectiveness against hospitalisation.[12] These data support overall efficacy against these variants after the Ad26.COV2.S booster, although conclusions for specific variants are limited by low case numbers. Attenuated protection in some countries or regions might be attributable to reduced vaccine efficacy against specific SARS-CoV-2 variants and low case numbers.[13–15] The vaccine was also efficacious in participants with comorbidities in the current study.

Vaccine efficacy against moderate to severe–critical COVID-19 with onset at least 14 days after primary vaccination in ENSEMBLE2 (67·0% [95% CI 53·6–76·9]) was consistent with efficacy at the same timepoint in the final analysis of the double-blind phase of ENSEMBLE (56·3% [51·3–61·8]).[4] Between-study differences in efficacy might be attributed to differences in time, location, and epidemiological pressure. Importantly, efficacy against severe–critical disease was high and consistent between the studies. Real-world data suggest these efficacies translate into clinical settings.[12,16–19] Furthermore, Ad26.COV2.S elicited sustained $CD8^+$ and $CD4^+$ T-cell immune responses with cross-reactivity against omicron,[20,21] suggesting a potential mechanism for the protection observed against variants in real-world studies.[12,16–18]

Previous studies have shown that Ad26.COV2.S administered as either a homologous or heterologous booster can induce neutralising antibody titres against the reference strain and the delta and omicron variants of concern.[22–26] In these studies, both homologous and heterologous Ad26.COV2.S boosters had less effect on neutralising antibody titres than boosters of mRNA vaccines; both Ad26.COV2.S and mRNA boosters generally yielded lower titres against delta and omicron variants relative to the wild-type or reference strains.[22,24,25] Direct comparison of immune responses elicited at a single, early point in time limits the interpretation of results reported in previous booster studies in the context of actual protection over time. For example, mRNA immune responses typically decline over time, whereas immune responses elicited by Ad26.COV2.S generally remain more stable over time. This principle has been shown in the 3-month analysis of the COV-BOOST trial in which the protection decay rate of the Ad26.COV2.S booster dose was lower than that of the BNT162b2 booster by 3 months post-boost.[27] Considering the difference in kinetics among vaccine types, real-world evidence over time might be a suitable indicator of booster performance. Both primary and booster vaccinations with Ad26.COV2.S have shown real-world effectiveness against COVID-19-related hospital admissions, including those that require intensive care, during periods of delta and omicron predominance.[12,18]

The Ad26.COV2.S booster showed an acceptable safety profile in adults aged 18 years and older. Local and systemic reactogenicity was similar to that seen after the first dose, with no increase in adverse reactions post-booster. In the primary analysis of ENSEMBLE, more venous thromboembolic events and convulsions or seizure events were seen after Ad26.COV2.S versus placebo.[9] Conversely, in ENSEMBLE2, more thromboembolic events occurred after placebo compared with vaccine, and no imbalances were observed for convulsions or seizure. Although more non-infectious arthritis events occurred after Ad26.COV2.S than after placebo in ENSEMBLE2, the converse was seen in ENSEMBLE (more after placebo), and no signal has been identified in post-marketing data. The difference in numbers of haemorrhagic disorders between the vaccine and placebo groups in this study was mostly driven by

events related to vaccine administration. These inconsistencies in adverse event occurrence between studies suggest differences might be attributable to chance.

There are limitations to this study. As ENSEMBLE2 was done at the peak of the COVID-19 wave in early 2021, when COVID-19 vaccines were first made available by EUA, it was no longer ethical to maintain the placebo control, leading to early unmasking. All participants could request unmasking to establish whether they qualified for COVID-19 vaccination outside the study, and placebo recipients could receive the open-label crossover vaccination (timing varied by country depending on the date of Ad26.COV2.S authorisation). Unmasking and crossover reduced participant numbers receiving both doses and planned follow-up time in the double-blind phase, and led to low numbers of COVID-19 cases being available for evaluation of the booster dose compared with placebo; data within subgroups, including by variant, should thus be interpreted with caution. More participants in the placebo group than the Ad26.COV2.S group terminated prematurely, possibly because of non-study antibody testing before unmasking that could reveal a lack of antibody to the spike protein, and partly because after unmasking, placebo recipients terminated participation to receive another COVID-19 vaccine outside the study. Most participants nevertheless completed the double-blind phase; with 66 cases of molecularly confirmed moderate to severe–critical COVID-19 under the protocol assumptions, the study had 58% power to reject the primary endpoint null hypothesis. The person-years of follow-up in the PP population and FAS were generally similar, indicating that masking was properly maintained and bias minimised. Moreover, vaccine efficacy estimation methods accounted for differences in follow-up between the vaccine and placebo groups. Additionally, the primary analysis cutoff occurred before the global dominance of delta and omicron, and insufficient cases accrued to evaluate efficacy against these variants. Finally, the sample size of the immunogenicity subset was smaller than planned (157 participants *vs* 400 planned) owing to delays in timely reconciliation of serum samples collected. However, this sample size is sufficient to understand the magnitude of the binding antibody responses elicited by Ad26.COV2.S as a booster dose given 2 months after the first dose.

A single dose of Ad26.COV2.S is efficacious against symptomatic COVID-19, and a booster administered 2 months later substantially increased vaccine efficacy, including against symptomatic and severe–critical COVID-19. A booster dose of Ad26.COV2.S has received authorisation in several countries, including from the FDA and the European Medicines Agency in October and December, 2021, respectively. Additional studies and data are needed to characterise the incremental booster effect over a longer follow-up period, within subgroups, and for emerging variants.

The ENSEMBLE2 (COV3009) study group
Luis Humberto Anaya Velarde, Daniel Backenroth, Jisha Bhushanan, Börries Brandenburg, Vicky Cárdenas, Bohang Chen, Fei Chen, Polan Chetty, Pei-Ling Chu, Kimberly Cooper, Jerome Custers, Hilde Delanghe, Anna Duca, Tracy Henrick, Jarek Juraszek, Catherine Nalpas, Monika Peeters, Jose Pinheiro, Sanne Roels, Martin F Ryser, Jose Salas, Samantha Santoro Matias, Ilse Scheys, Pallavi Shetty, Georgi Shukarev, Jeffrey Stoddard, Willem Talloen, NamPhuong Tran, Nathalie Vaissiere, Elisabeth van Son-Palmen, Jiajun Xu, Erin A Goecker; Alexander L Greninger, Keith R Jerome, Pavitra Roychoudhury, and Simbarashe G Takuva.

Contributors
SNFand CDS collected data and contributed to interpretation. All data were available to the authors, who vouch for data accuracy, completeness, and adherence to the study protocol. KH, JS, GS, SNF, CDS, HS, JVH, MD, and FS contributed to the study conceptualisation. KH, AV, CT, DL, and IVD contributed to data curation. AV, MLG, CT, DL, IVD, JV, TK, JR-G, and HS contributed to formal analysis. SNF and CDS collected data as study investigators. KH, AV, JS, HS, MD, and FS contributed to methodology. KH facilitated project administration. KH and JVH provided supervision. KH, AV, JS, MD, and FS contributed to writing the original draft. AV, CT, DL, IVD, and CDS accessed and verified the data. All authors contributed to writing (review and editing) and approved the final manuscript for submission.

Declaration of interests
KH, AV, JS, MLG, JV, TK, GS, HS, JVH, MD, and FS are employees of Johnson & Johnson and hold Johnson & Johnson stock or stock options. FS is a former employee of GlaxoSmithKline and holds shares from the GlaxoSmithKline group of companies as part of past employee remuneration. CT and IVD are employees of Johnson & Johnson. DL is an employee of Johnson & Johnson and Cytel. JR-G is an employee of Johnson & Johnson and holds Johnson & Johnson stock or stock options; he is a former employee of GlaxoSmithKline, holds GlaxoSmithKline stock or stock options, and has received funding grants from GlaxoSmithKline Vaccines. CDS has received funding grants for research from Janssen-Cilag, AbbVie, Apeiron, B.Braun, Cepheid, Eli Lilly, GlaxoSmithKline, Corat Therapeutics, Gilead, Merck Sharpe & Dohme, Roche, and ViiV Healthcare; and consulting fees, honoraria, and travel support from AbbVie, Cepheid, Formycon, Gilead, GlaxoSmithKline, Molecular Partners, Merck Sharpe & Dohme, Swedish Orphan Biovitrium, Roche, and ViiV Healthcare. SNF has received research grants to his institution from Janssen–Johnson & Johnson, Pfizer, Sanofi, GlaxoSmithKline, Merck, AstraZeneca, and Valneva (no personal fees); has received consulting fees from Janssen–Johnson & Johnson, GlaxoSmithKline, and CureVac; has received fees to his institution for participation on data safety monitoring boards or advisory boards from AstraZeneca, Medimmune, Sanofi, Pfizer, Seqirus, Sandoz, Merck, and Janssen–Johnson & Johnson; and was chair of two UK National Institute for Health and Care Excellence (NICE) sessions (expenses paid per NICE financial regulations).

Data sharing
The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted at this website, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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