ORIGINAL ARTICLE

Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S

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ABSTRACT

BACKGROUND

The Ad26.COV2.S vaccine was highly effective against severe–critical coronavirus disease 2019 (Covid-19), hospitalization, and death in the primary phase 3 efficacy analysis.

METHODS

We conducted the final analysis in the double-blind phase of our multinational, randomized, placebo-controlled trial, in which adults were assigned in a 1:1 ratio to receive single-dose Ad26.COV2.S (5×10^{10} viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration in the per-protocol population. Safety and key secondary and exploratory end points were also assessed.

RESULTS

Median follow-up in this analysis was 4 months; 8940 participants had at least 6 months of follow-up. In the per-protocol population (39,185 participants), vaccine efficacy against moderate to severe–critical Covid-19 at least 14 days after administration was 56.3% (95% confidence interval [CI], 51.3 to 60.8; 484 cases in the vaccine group vs. 1067 in the placebo group); at least 28 days after administration, vaccine efficacy was 52.9% (95% CI, 47.1 to 58.1; 433 cases in the vaccine group vs. 883 in the placebo group). Efficacy in the United States, primarily against the reference strain (B.1.D614G) and the B.1.1.7 (alpha) variant, was 69.7% (95% CI, 60.7 to 76.9); efficacy was reduced elsewhere against the P.1 (gamma), C.37 (lambda), and B.1.621 (mu) variants. Efficacy was 74.6% (95% CI, 64.7 to 82.1) against severe–critical Covid-19 (with only 4 severe–critical cases caused by the B.1.617.2 [delta] variant), 75.6% (95% CI, 54.3 to 88.0) against Covid-19 leading to medical intervention (including hospitalization), and 82.8% (95% CI, 40.5 to 96.8) against Covid-19–related death, with protection lasting 6 months or longer. Efficacy against any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was 41.7% (95% CI, 36.3 to 46.7). Ad26.COV2.S was associated with mainly mild-to-moderate adverse events, and no new safety concerns were identified.

CONCLUSIONS

A single dose of Ad26.COV2.S provided 52.9% protection against moderate to severe–critical Covid-19. Protection varied according to variant; higher protection was observed against severe Covid-19, medical intervention, and death than against other end points and lasted for 6 months or longer. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.)

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The Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) is a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a full-length, membrane-bound severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion stabilized conformation.[1,2] Primary analysis of the phase 3 ENSEMBLE trial, performed when preset criteria had been met and conducted during the early emergence of variants and for a median follow-up of 58 days, showed 66.9% efficacy against moderate to severe–critical (i.e., severe or critical) coronavirus disease 2019 (Covid-19) and greater than 85% efficacy against severe–critical disease.[3] Here, we report the final analysis of the double-blind phase of ENSEMBLE, which was conducted in accordance with the protocol when data for more than 90% of the participants had been unblinded.

Methods

Trial Design and Oversight

We have reached the stage in this ongoing multinational, randomized, double-blind, placebo-controlled, phase 3 trial at which crossover vaccination of the participants in the control group has occurred. The trial was designed and conducted and the data were analyzed and interpreted by the sponsor (Janssen Research and Development) and collaborators (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial-site investigators collected and contributed to the interpretation of the data. All the data were available to the authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. Medical writers funded by the sponsor assisted in drafting the manuscript.

Trial Participants

Participants were adults who were 18 years of age or older and were in good or stable health, without coexisting conditions or with stable and well-controlled coexisting conditions. Key exclusion criteria were previous receipt of a Covid-19 vaccine or abnormal immune system function (see the Supplementary Methods section). After emergency use authorization, participants who received placebo during the double-blind phase became eligible for vaccination with Ad26.COV2.S (crossover vaccination), provided they had not received another Covid-19 vaccine outside the trial. This crossover shortened the follow-up time in the projected double-blind phase of the trial.

Procedures

Trial procedures are described in the Supplementary Methods section. Participants were randomly assigned in a 1:1 ratio with the use of randomly permuted blocks in an interactive Web-response system to receive Ad26.COV2.S (5×10^{10} viral particles) or saline placebo as an intramuscular injection (0.5 ml). The investigators at the trial sites and the participants remained unaware of the group assignments until the unblinding or crossover visit.

Primary and key secondary efficacy evaluations were based on centrally confirmed Covid-19 cases (confirmed molecularly with the use of m-2000 SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction [RT-PCR], Abbott); cases were clinically assessed independently by a clinical severity adjudication committee. Participants responded to a twice-weekly questionnaire assessing whether they had Covid-19 symptoms, which were reported with the use of the electronic Symptoms of Infection with Coronavirus-19 questionnaire. Additional details are provided in the Supplementary Methods section.

Efficacy Assessments

The two primary end points were vaccine efficacy against the first occurrence of centrally RT-PCR–confirmed moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration in the per-protocol population (Table S1 in the Supplementary Appendix). Covid-19 case definitions and protocol-defined secondary and exploratory end points (e.g., efficacy according to SARS-CoV-2 lineage) are provided in the Supplementary Methods.

Safety Assessments

Serious adverse events and suspected adverse events of special interest are recorded throughout the trial. During the double-blind phase of the trial, a safety subpopulation that included approximately 6000 participants recorded solicited local and systemic adverse events in an electronic diary for 7 days after administration and unso-

licited adverse events for 28 days after administration.

STATISTICAL ANALYSIS

The full analysis population included all the participants who underwent randomization and received a dose of trial vaccine or placebo. The at-risk population excluded participants who had a Covid-19 case with an onset before day 15 or before day 29 for the vaccine efficacy evaluations at least 14 days after administration or at least 28 days after administration, respectively. Efficacy analyses were conducted in the per-protocol population, which included participants who received vaccine or placebo in the double-blind phase; participants who were seropositive or RT-PCR–positive at baseline were excluded from the per-protocol population. Safety analyses were conducted with the full analysis population. Participant data were censored on unblinding or receipt of a Covid-19 vaccine outside the trial.

Statistical hypothesis testing was conducted in accordance with the prespecified scheme for the control of familywise type I error as indicated with adjusted 95% confidence intervals. End points that had already been inferentially evaluated in the primary analysis were summarized descriptively with 95% confidence intervals. Other prespecified end points not included in the prespecified scheme for familywise type I error control (such as exploratory end points) are summarized with descriptive 95% confidence intervals. Nonprespecified end points are designated as post hoc. Exact Poisson regression was used for analyses of efficacy and associated calculations of confidence intervals.[4] Cumulative incidence was estimated with Kaplan–Meier methods to evaluate time to the first occurrence of Covid-19 and vaccine efficacy over time.

The frequency of serious adverse events was tabulated for the full analysis population; the frequency and severity of solicited and unsolicited adverse events were tabulated in the safety subpopulation.

RESULTS

PARTICIPANTS

Trial enrollment began on September 21, 2020, and the data cutoff for the final analysis was July 9, 2021, with the end of the double-blind period varying among countries. Table S2 shows case numbers in each country according to viral lineage, and Figure 1 shows the detection of viral lineages over time according to country. Emergency use authorization for Ad26.COV2.S occurred on February 27, 2021; crossover began after approval of protocol amendment 4, with the first participant in the placebo group vaccinated on March 10, 2021. The characteristics of the participants at baseline were balanced between trial groups (Table S3) and were generally representative of the population at risk for Covid-19 in the United States (Table S4). Worldwide, 19.5% of the participants in the trial were 65 years of age or older, and 42.0% had coexisting conditions.

In total, 43,788 participants underwent randomization and received vaccine or placebo, and 39,185 participants who were seronegative for SARS-CoV-2 at baseline were included in the per-protocol analysis population for the double-blind phase (Fig. S1). At the time of the final analysis, 97% of the participants had completed the double-blind phase or had withdrawn prematurely. Median follow-up was 121 days (range, 1 to 284), and 35,788 (91.3%) and 8940 (22.8%) of the participants in the per-protocol population had follow-up of at least 2 months and at least 6 months, respectively, in the double-blind phase. Follow-up was nearly identical in the full analysis population (median, 123 days [range, 0 to 284]; 40,260 [91.9%] and 11,290 [25.8%] of the participants had follow-up of ≥2 months and ≥6 months, respectively).

EFFICACY AGAINST MODERATE TO SEVERE–CRITICAL COVID-19

In the per-protocol at-risk population, 484 moderate to severe–critical Covid-19 cases with onset at least 14 days after administration were noted in the vaccine group, as compared with 1067 in the placebo group (vaccine efficacy, 56.3%; 95% confidence interval [CI], 51.3 to 60.8) (Table 1). Vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 28 days after administration was 52.9% (95% CI, 47.1 to 58.1). The primary end point captured most symptomatic disease with onset at least 28 days after administration, with only 10 cases of mild Covid-19 occurring in the vaccine group and 12 in the placebo group, resulting in efficacy of 52.4% (95% CI, 46.6 to 57.6) against any symptomatic infection.

The Kaplan–Meier cumulative incidence curves

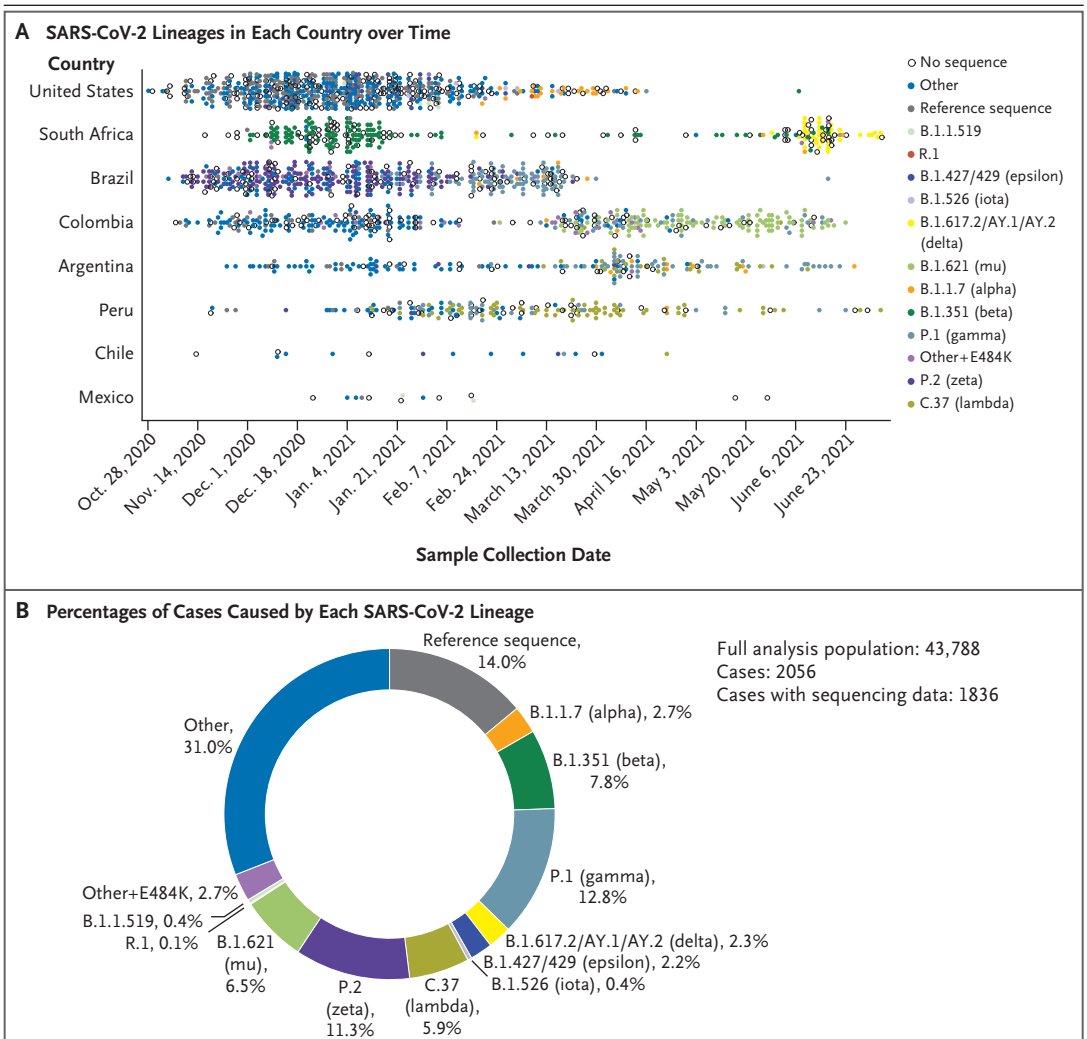


Figure 1. Cases of Covid-19 According to SARS-CoV-2 Lineage (Full Analysis Population).

The distribution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineages among cases of coronavirus disease 2019 (Covid-19) is shown for each country in the trial over time during the double-blind phase of the trial. The reference sequence is defined as the SARS-CoV-2 Wuhan-Hu-1 sequence but with the D614G amino acid variation. At the time of the trial, sequences categorized as "other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Next-generation sequencing was performed with the use of the Swift Biosciences SNAP Assay, version 2. Amino acid variants are defined as changes from the reference sequence. The last available visit date across countries was July 1 through 9, 2021, and the last available date of onset for a primary end-point case was June 26 (Argentina), March 24 (Brazil), April 22 (Chile), June 23 (Colombia), May 27 (Mexico), July 1 (Peru), July 5 (South Africa), and April 16 (United States). None of the cases were caused by the eta, kappa, theta, or C.36.3 variant. The alpha, beta, gamma, and delta variants were variants of concern according to World Health Organization definitions at the time of the analysis.

for moderate to severe–critical Covid-19 separated after 14 days (Fig. 2A); vaccine efficacy persisted through approximately 6 to 7 months after administration with a modest decline, after which wide confidence intervals and low numbers of at-risk participants preclude interpretation (Fig. 2B). This apparent reduction in efficacy may be related to the emergence of more neutralization-resistant variants toward the end of the trial (Fig. 1), as evidenced by the absence of a decline in efficacy against minor, "other" viral sequences (i.e., SARS-CoV-2 with substitu-

tions not considered to result in another lineage or variant) (Fig. S2). Because efficacy results for the primary end point were similar at 14 or more days and at 28 or more days after administration, only the latter results are shown for secondary and exploratory end points.

EFFICACY ACCORDING TO VIRAL LINEAGE

New viral lineages emerged and became dominant in most countries in the trial during the analysis period, with some variants occurring predominately in one country (e.g., B.1.351 [beta] in South Africa, C.37 [lambda] in Peru, and B.1.621 [mu] in Colombia) (Fig. 1). Vaccine efficacy was 70.2% (95% CI, 35.3 to 87.6) against moderate to severe–critical Covid-19 caused by the B.1.1.7 (alpha) variant; 69.0% (95% CI, 59.1 to 76.8) against moderate to severe–critical Covid-19 caused by SARS-CoV-2 classified as "other," with efficacy remaining stable through 195 days of follow-up; and 58.2% (95% CI, 35.0 to 73.7) against moderate to severe–critical Covid-19 caused by the reference strain (B.1.D614G). Overall efficacy was 44.4% (95% CI, 34.6 to 52.8) against SARS-CoV-2 lineages other than the reference strain (Fig. 3), including 51.9% (95% CI, 19.1 to 72.2) against the beta variant and 36.5% (95% CI, 14.1 to 53.3) against the P.1 (gamma) variant; at the end of the double-blind period, there was no observed difference between vaccine and placebo with respect to the 21 cases caused by the B.1.617.2 (delta) variant in South Africa (vaccine efficacy, –5.7%; 95% CI, –177.7 to 59.2). The Kaplan–Meier curves suggest that efficacy against the circulating reference strain and beta variant began 14 days and 25 days after immunization, respectively, and began immediately on exposure to the alpha variant, which emerged at least 2 months after vaccination of the participants in the vaccine group was completed (Fig. 1). Kaplan–Meier curves were plotted to the end of the double-blind phase, independent of whether cases were occurring in both groups. An additional variant analysis was conducted for cases that occurred during the double-blind period but were sequenced after database lock; results were consistent with those of the initial analysis (Fig. S3).

EFFICACY AGAINST SEVERE–CRITICAL COVID-19

For severe–critical Covid-19, overall vaccine efficacy was 74.6% (95% CI, 64.7 to 82.1) (Table 1). The cumulative incidence curves, which began to separate approximately 7 days after administration (Fig. 4), with no evidence of waning for approximately 6 to 7 months after administration.

Vaccine efficacy against severe–critical Covid-19 was 93.1% (95% CI, 54.4 to 99.8) for the reference strain; 71.8% (95% CI, 56.3 to 82.3) for non–reference strain SARS-CoV-2 lineages, including "other" sequences with the E484K mutation; 78.4% (95% CI, 34.5 to 94.7) for the beta variant; 63.6% (95% CI, 18.8 to 85.1) for the gamma variant; 67.6% (95% CI, –29.8 to 94.4) for the lambda variant; and 79.5% (95% CI, 38.5 to 94.9) for the mu variant. Only six cases of severe–critical Covid-19 caused by the alpha variant and four caused by the delta variant were reported (Fig. S4).

ADDITIONAL SECONDARY AND EXPLORATORY EFFICACY END POINTS

Vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 28 days after administration in all participants regardless of serostatus at baseline, excluding participants in whom Covid-19 developed before day 29 (at-risk population), was 53.2% (95% CI, 47.5 to 58.4). Vaccine efficacy against moderate to severe–critical Covid-19 with onset 1 day after administration was 52.6% (95% CI, 47.6 to 57.2).

Vaccine efficacy against Covid-19 with onset at least 28 days after administration that led to medical intervention (including hospitalization) was 75.6% (adjusted 95% CI, 54.3 to 88.0) (Table 1) and lasted 6 to 7 months (Fig. S5). Efficacy against severe–critical Covid-19 leading to medical intervention (including hospitalization) was approximately 90% initially and tapered to 70% by approximately 6 weeks, remaining at that level for 5 to 6 months. On the basis of available sequences, 3 such cases were caused by the reference strain (all in the placebo group) and 44 were caused by variants (11 in the vaccine group and 33 in the placebo group; vaccine efficacy, 67.5%; 95% CI, 34.1 to 85.2) (Fig. S6). The severity and duration of symptoms, the effect on Covid-19 lasting longer than 28 days, and vaccine efficacy against any infection, including asymptomatic infection, are described in the Supplementary Results (Figs. S7 through S10).

Among the 2131 participants in the vaccine group who were seropositive for SARS-CoV-2 nucleocapsid (N) protein at baseline as compared with the 18,924 participants in the placebo group

Table 1. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

End Point	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S (N=19,400)		Placebo (N=19,398)		Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,113)		Placebo (N=18,924)		Vaccine Efficacy (95% CI)
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	%	*no. of cases*	*person-yr*	*no. of cases*	*person-yr*	%
Moderate to severe–critical Covid-19§	484	6685.6	1067	6440.2	56.3 (51.3 to 60.8)	433	6658.4	883	6400.4	52.9 (47.1 to 58.1)
18–59 yr	381	4682.1	847	4514.2	56.6 (51.0 to 61.7)	340	4663.8	716	4486.7	54.3 (48.0 to 60.0)
≥60 yr	103	2003.5	220	1926.0	55.0 (42.9 to 64.7)	93	1994.6	167	1913.7	46.6 (30.7 to 59.0)
Symptomatic Covid-19 of any severity¶	495	6683.8	1082	6437.4	55.9 (51.0 to 60.5)	443	6656.8	895	6398.3	52.4 (46.6 to 57.6)
Mild‖	11	6683.8	15	6437.4	29.4 (–64.6 to 70.7)	10	6656.8	12	6398.3	19.9 (–102.3 to 69.0)
Moderate‖	429	6685.6	862	6440.2	52.1 (46.1 to 57.4)	388	6658.4	707	6400.4	47.2 (40.2 to 53.5)
Severe–critical¶	56	6774.6	205	6625.2	73.3 (63.9 to 80.5)	46	6733.8	176	6542.1	74.6 (64.7 to 82.1)
Any SARS-CoV-2 infection¶**††	—	—	—	—	—	1038	6560.8	1699	6257.5	41.7 (36.3 to 46.7)‡‡
Asymptomatic SARS-CoV-2 infection¶††	—	—	—	—	—	498	6581.0	669	6289.3	28.9 (20.0 to 36.8)‡‡
Covid-19 leading to medical intervention¶§§	18	6783.9	74	6656.7	76.1 (56.9 to 87.7)¶	16	6739.8	64	6567.1	75.6 (54.3 to 88.0)‡‡
Death from any cause¶¶	19	6787.0	45	6669.3	58.5 (27.6 to 77.1)	19	6742.4	37	6577.3	49.9 (10.6 to 72.8)
Covid-19–related death¶¶	3	6786.9	19	6668.4	84.5 (47.3 to 97.1)	3	6742.2	17	6576.4	82.8 (40.5 to 96.8)
Covid-19 according to FDA harmonized definition‖‖	492	6684.7	1067	6440.5	55.6 (50.5 to 60.2)	441	6657.3	884	6399.6	52.0 (46.2 to 57.3)

* All coronavirus disease 2019 (Covid-19) cases were centrally confirmed unless stated otherwise and occurred in participants who had been seronegative at baseline, had negative results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing before 14 or 28 days after administration of vaccine or placebo, and were considered to be at risk for Covid-19. The follow-up time for each participant was defined as the time from administration until onset of a Covid-19 episode or the end of the double-blind period (July 9, 2021). Mild Covid-19 cases were defined by a positive RT-PCR test result and at least one of the following signs or symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, loss of taste or smell, red or bruised-looking feet or toes, and shaking chills or rigors. Moderate Covid-19 cases were defined by a positive RT-PCR test result and two or more of the following symptoms: fever (body temperature, ≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, and red or bruised-looking feet or toes; or one or more of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while breathing room air at sea level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, and shortness of breath or difficulty breathing. Severe–critical Covid-19 cases were defined by a positive RT-PCR test result and one or more of the following features: signs of severe systemic illness (respiratory rate, ≥30 breaths per minute; heart rate, ≥125 beats per minute; oxygen saturation, ≤93% while breathing room air at sea level; or ratio of partial pressure of oxygen [in mm Hg] to fraction of inspired oxygen, <300); respiratory failure (leading to receipt of high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]); shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death.

who were seronegative at baseline, observed vaccine efficacy against moderate to severe–critical Covid-19 was 97.7% (post hoc 95% CI, 93.3 to 99.5) (Table S5); the small number of cases (3) in the vaccine group precludes analysis of this end point according to viral lineage. Previous infection alone, in an analysis involving seropositive and seronegative placebo recipients, was found to provide 90.4% (95% CI, 83.2 to 95.1) protection against moderate to severe–critical Covid-19.

Vaccine efficacy against Covid-19–related death was 82.8% (95% CI, 40.5 to 96.8) (Table 1), with protection sustained through at least 6 months after administration. At least 28 days after administration, 3 Covid-19–related deaths occurred in the vaccine group (all in participants who were ≥60 years of age), as compared with 17 in the placebo group.

EFFICACY IN SUBGROUPS

In subgroup analyses, vaccine efficacy against moderate to severe–critical Covid-19 in participants with human immunodeficiency virus (HIV) infection was found to be 23.5% (95% CI, –78.3 to 68.2). Vaccine efficacy against moderate to severe–critical disease varied according to country: 33.1 (95% CI, 6.3 to 52.5) in Peru, 45.3 (95% CI, 29.1 to 58.0) in Brazil, 49.3 (95% CI, 26.9 to 65.3) in South Africa, and 69.7 (95% CI, 60.7 to 76.9) in the United States. Data on additional subgroup analyses are provided in the Supplementary Results (Figs. S11 and S12 and Table S6).

SAFETY

The safety subpopulation included 3356 participants in the vaccine group and 3380 in the placebo group. Overall, more solicited adverse events occurred in the vaccine group than in the placebo group during the 7-day period after administration. Grade 3 local and systemic solicited adverse events during the 7-day period were similar to those reported in the primary analysis (Fig. S13). In general, lower reactogenicity was observed among older adults than among younger adults. Among the 155 participants in the vaccine group who were seropositive for SARS-CoV-2 at baseline (safety subpopulation), 60.0% and 52.9% reported a solicited local or systemic adverse event, respectively, similar to the percentages among the 3201 baseline-seronegative participants (54.5% and 60.6%, respectively). Grade

† The at-risk population excluded participants who were RT-PCR–positive between day 1 and day 14.
‡ The at-risk population excluded participants who were RT-PCR–positive between day 1 and day 28.
§ The primary end points were the first occurrence of centrally RT-PCR–confirmed moderate to severe–critical Covid-19 with onset at least 14 days after administration and at least 28 days after administration. One participant had a moderate case of Covid-19 and later had a severe case; the adjudication committee considered these to be two separate infections.
¶ This end point was a confirmatory secondary end point.
‖ This end point was a supportive secondary end point.
** This category includes undetected cases that were subsequently detected through a positive serologic result (according to the clinical severity adjudication committee), which did not count as either symptomatic cases (because they were RT-PCR–negative) or asymptomatic cases.
†† Data on this end point were not obtained for cases in which onset occurred after 14 days after administration.
‡‡ The 95% confidence intervals for vaccine efficacy against any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, asymptomatic infections, and Covid-19 leading to medical intervention were adjusted for multiplicity on the basis of prespecified procedures for familywise type I error control. All other confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance.
§§ Medical intervention included hospitalization as adjudicated by the clinical severity adjudication committee, admission to an intensive care unit, mechanical ventilation, and ECMO, linked to objective measures such as decreased oxygenation and findings on radiography or computed tomography.
¶¶ This end point was an exploratory end point.
‖‖ At the time the protocol was written, the Food and Drug Administration (FDA) harmonized Covid-19 definition was a positive RT-PCR test result plus any of the following symptoms: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.

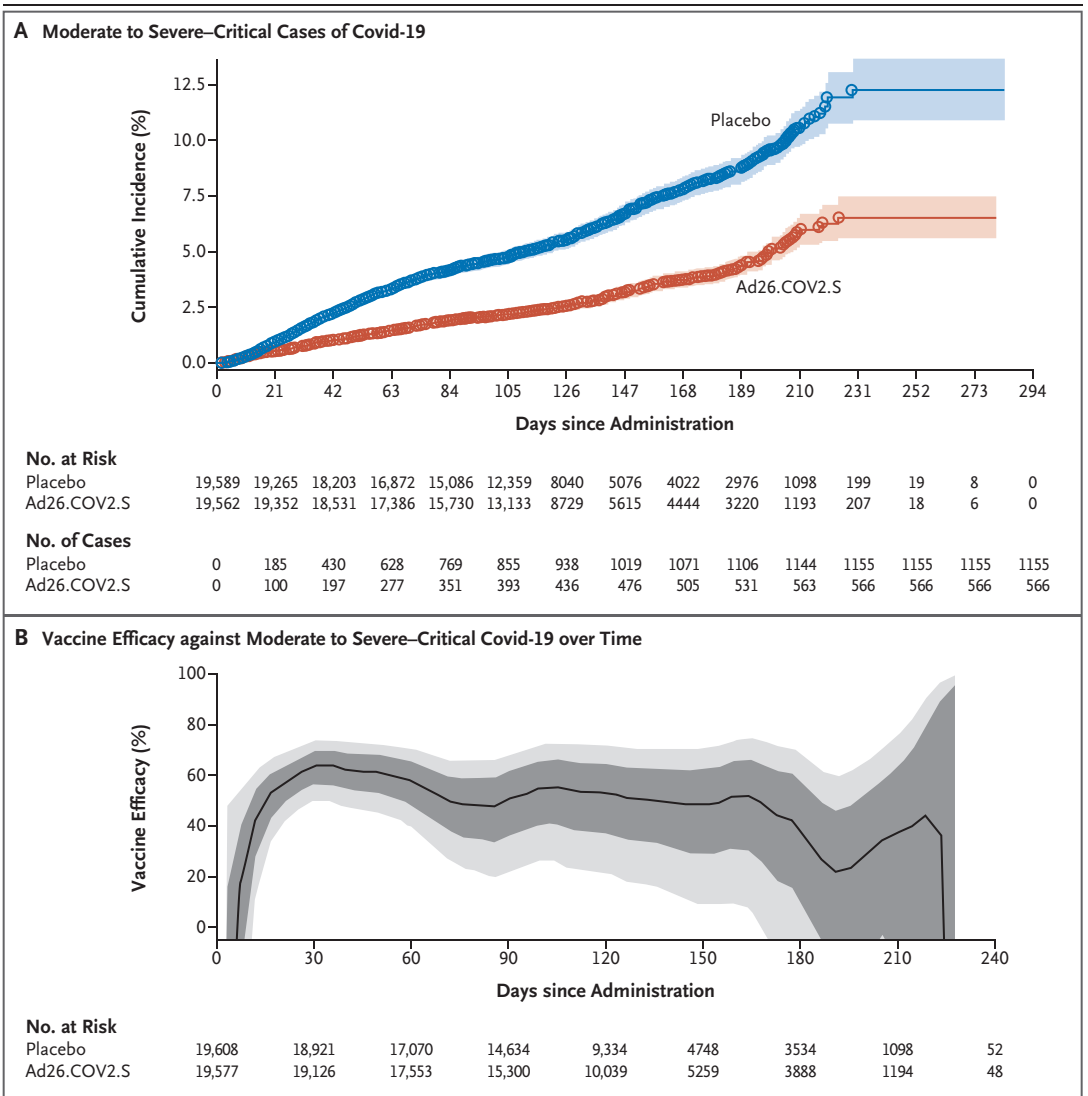


Figure 2. Cumulative Incidence of Moderate to Severe–Critical Covid-19 and Vaccine Efficacy over Time (Per-Protocol Population).

Panel A shows the Kaplan–Meier cumulative incidence of molecularly confirmed moderate to severe–critical Covid-19 with onset at least 1 day after administration of vaccine or placebo. Shading indicates the 95% confidence interval. Panel B shows vaccine efficacy against moderate to severe–critical Covid-19 over time; dark gray shading indicates the 95% pointwise confidence interval, and light gray shading the 95% simultaneous confidence interval. The graph includes 95% of the events that occurred before day 189, with the hazard smoothed over 21 days. Participants were seronegative at baseline, as determined by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) and serologic tests.

3 or higher solicited local adverse events were rare among vaccine recipients, regardless of their serostatus at baseline (occurring among 1.3% of those who were seropositive and 0.6% of those who were seronegative). Grade 3 or higher systemic adverse events occurred in 1.3% of seropositive vaccine recipients and 2.3% of seronegative vaccine recipients.

Unsolicited events of grade 3 or higher severity (safety subpopulation) and unsolicited events of grade 3 or higher that were considered by the investigators to be related to vaccine or placebo (full analysis population and safety subpopulation) are summarized in Tables S7 and S8. Serious adverse events that were not related to Covid-19 (full analysis population) occurred in 223 par-

ticipants (1.0%) in the vaccine group and in 265 participants (1.2%) in the placebo group. Additional information on serious adverse events is provided in Table S9.

Imbalances in adverse events that occurred during a 28-day risk window after administration are described in the Supplementary Results (Table S10). At the time of the final analysis with prolonged follow-up, imbalances were seen for tinnitus (15 cases in the vaccine group vs. 4 in the placebo group), urticaria (13 vs. 6), convulsion (9 vs. 4), pulmonary embolism (10 vs. 5), and deep-vein thrombosis (11 vs. 3); no imbalances were observed for the Guillain–Barré syndrome (1 case per group) or Bell's palsy (2 cases in the vaccine group and 1 in the placebo group) (Table S10). No cases of capillary leak syndrome, myocarditis, or encephalitis were reported. Thrombosis with thrombocytopenia was defined as an adverse event of special interest (Supplementary Methods). One event, which occurred in a 25-year-old man within 28 days after administration of Ad26.COV2.S, occurred in association with positivity for anti-PF4 antibodies and met the Centers for Disease Control and Prevention (CDC) tier 1–2 and Brighton Collaboration level 1 criteria for vaccine-induced immune thrombotic thrombocytopenia (VITT, also known as thrombosis with thrombocytopenia syndrome).

At the time of the final analysis, 83 deaths had been reported in the double-blind phase (28 in the vaccine group and 55 in the placebo group, with 5 and 22, respectively, related to Covid-19 in the full analysis population). All deaths were considered by the investigators to be unrelated to the vaccine or placebo.

DISCUSSION

In the final analysis of the double-blind portion of our phase 3 trial, median follow-up was 4 months, with 8940 participants having at least 6 months of follow-up. A single dose of the Ad26.COV2.S vaccine remained effective (52.9%) in preventing moderate to severe–critical Covid-19 and all symptomatic Covid-19 (52.4%), despite the emergence of variants during the trial. Efficacy against severe–critical disease remained higher (74.6%) than efficacy against moderate to severe–critical disease, with a lower point estimate for variants (93.1% efficacy against the reference strain and 71.8% efficacy against non–reference strain lineages, including "other" sequences with the E484K mutation), indicating that Ad26.COV2.S induces higher levels of protection in proportion to the severity of the disease and the nature of the viral mutation.

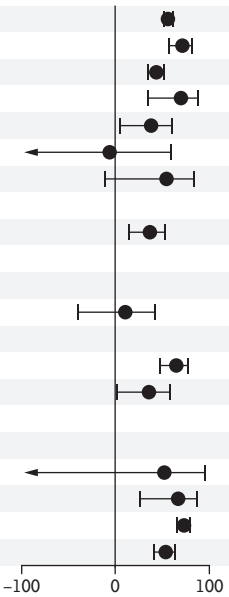
During the placebo-controlled period, which differed between countries on the basis of when the participants became aware of the trial-group assignments, the incidence of SARS-CoV-2 infection was highly variable geographically and over time as new viral variants emerged. The reduction in overall efficacy in the final analysis as compared with the primary analysis[3] (vaccine efficacy for the primary end point at least 28 days after administration, 66.1% in the primary analysis and 52.9% in the final analysis) was most likely due to lower vaccine efficacy against variants that appeared outside the United States (Latin America) in this multinational trial after the primary analysis — for example, 10.1% against the lambda variant and 36.5% against the gamma variant. Regional emergence of variants such as lambda and gamma contributed to the lower vaccine efficacy that was observed for some subgroups (e.g., Asian, Hispanic, and American Indian or Alaskan Native populations). In the United States, where the alpha variant emerged after the reference strain, vaccine efficacy against moderate to severe–critical Covid-19 was 69.7%.

The efficacy findings in this trial are consistent with durable immune responses being elicited by Ad26.COV2.S[5] and with immediate efficacy against the alpha variant occurring at least 60 days after vaccination. Furthermore, the onset of protection differed between the original strain (14 days) and the more neutralization-resistant beta variant (25 days). The higher vaccine efficacy observed against the more resistant beta variant[6] as compared with the lower efficacy against the less resistant lambda variant suggests that other factors also played a role in protection.

Conclusions about vaccine efficacy against symptomatic Covid-19 caused by the delta variant, including severe–critical Covid-19 (with only 4 cases among the participants), were not possible in this trial because of the wide confidence intervals. Real-world data from several studies[7-10] — some of which analyzed more severe symptomatic disease, against which this vaccine has higher efficacy — have shown varying degrees of efficacy of Ad26.COV2.S against symptomatic delta-variant infection. Effectiveness ranged from

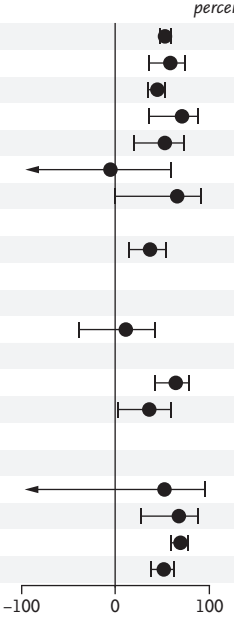
A Vaccine Efficacy against Moderate to Severe–Critical Covid-19 with Onset at least 14 Days after Administration

	Ad26.COV2.S (N=19,577)		Placebo (N=19,608)		Vaccine Efficacy (95% CI)
	no. of events/ no. of participants	*no. of person-yr*	*no. of events/ no. of participants*	*no. of person-yr*	*percent*
Any SARS-CoV-2	484/19,400	6685.60	1067/19,398	6440.18	56.3 (51.3 to 60.8)
Reference strain	32/19,400	6685.60	108/19,398	6440.18	71.5 (57.3 to 81.4)
Lineages other than reference strain	265/19,400	6685.60	454/19,398	6440.18	43.8 (34.4 to 51.9)
B.1.1.7 (alpha)	9/19,400	6685.60	29/19,398	6440.18	70.1 (35.1 to 87.6)
B.1.351 (beta)	36/19,400	6685.60	56/19,398	6440.18	38.1 (4.2 to 60.4)
B.1.617.2/AY.1/AY.2 (delta)	11/19,400	6685.60	10/19,398	6440.18	−6.0 (−178.3 to 59.2)
B.1.427/429 (epsilon)	8/19,400	6685.60	17/19,398	6440.18	54.7 (−10.8 to 83.1)
B.1.525 (eta)	0/19,400	6685.60	0/19,398	6440.18	
P.1 (gamma)	74/19,400	6685.60	112/19,398	6440.18	36.4 (13.9 to 53.2)
B.1.526 (iota)	0/19,400	6685.60	4/19,398	6440.18	
B.1.617.1 (kappa)	0/19,400	6685.60	0/19,398	6440.18	
C.37 (lambda)	43/19,400	6685.60	46/19,398	6440.18	10.0 (−39.5 to 42.0)
P.3 (theta)	0/19,400	6685.60	0/19,398	6440.18	
P.2 (zeta)	34/19,400	6685.60	93/19,398	6440.18	64.8 (47.3 to 77.0)
B.1.621 (mu)	38/19,400	6685.60	57/19,398	6440.18	35.8 (1.5 to 58.6)
C.36.3	0/19,400	6685.60	0/19,398	6440.18	
R.1	1/19,400	6685.60	0/19,398	6440.18	
B.1.1.519	2/19,400	6685.60	4/19,398	6440.18	51.8 (−236.1 to 95.6)
Other+E484K	9/19,400	6685.60	26/19,398	6440.18	66.7 (26.6 to 86.3)
Other	78/19,400	6685.60	280/19,398	6440.18	73.2 (65.4 to 79.4)
No sequencing data available	109/19,400	6685.60	225/19,398	6440.18	53.3 (41.1 to 63.2)



B Vaccine Efficacy against Moderate to Severe–Critical Covid-19 with Onset at least 28 Days after Administration

	Ad26.COV2.S (N=19,577)		Placebo (N=19,608)		Vaccine Efficacy (95% CI)
	no. of events/ no. of participants	*no. of person-yr*	*no. of events/ no. of participants*	*no. of person-yr*	*percent*
Any SARS-CoV-2	433/19,113	6658.36	883/18,924	6400.36	52.9 (47.1 to 58.1)
Reference strain	30/19,113	6658.36	69/18,924	6400.36	58.2 (35.0 to 73.7)
Lineages other than reference strain	239/19,113	6658.36	413/18,924	6400.36	44.4 (34.6 to 52.8)
B.1.1.7 (alpha)	9/19,113	6658.36	29/18,924	6400.36	70.2 (35.3 to 87.6)
B.1.351 (beta)	23/19,113	6658.36	46/18,924	6400.36	51.9 (19.1 to 72.2)
B.1.617.2/AY.1/AY.2 (delta)	11/19,113	6658.36	10/18,924	6400.36	−5.7 (−177.7 to 59.2)
B.1.427/429 (epsilon)	5/19,113	6658.36	14/18,924	6400.36	65.7 (−0.9 to 90.3)
B.1.525 (eta)	0/19,113	6658.36	0/18,924	6400.36	
P.1 (gamma)	74/19,113	6658.36	112/18,924	6400.36	36.5 (14.1 to 53.3)
B.1.526 (iota)	0/19,113	6658.36	4/18,924	6400.36	
B.1.617.1 (kappa)	0/19,113	6658.36	0/18,924	6400.36	
C.37 (lambda)	43/19,113	6658.36	46/18,924	6400.36	10.1 (−39.2 to 42.1)
P.3 (theta)	0/19,113	6658.36	0/18,924	6400.36	
P.2 (zeta)	25/19,113	6658.36	67/18,924	6400.36	64.1 (42.5 to 78.3)
B.1.621 (mu)	38/19,113	6658.36	57/18,924	6400.36	35.9 (1.7 to 58.7)
C.36.3	0/19,113	6658.36	0/18,924	6400.36	
R.1	1/19,113	6658.36	0/18,924	6400.36	
B.1.1.519	2/19,113	6658.36	4/18,924	6400.36	51.9 (−235.4 to 95.7)
Other+E484K	8/19,113	6658.36	24/18,924	6400.36	68.0 (26.3 to 87.6)
Other	68/19,113	6658.36	211/18,924	6400.36	69.0 (59.1 to 76.8)
No sequencing data available	96/19,113	6658.36	190/18,924	6400.36	51.4 (37.6 to 62.4)



60% to 94% against hospitalization,[7,8,10-12] 13% to 78% against SARS-CoV-2 infection,[8,9,12-14] and 52% to 82% against death after SARS-CoV-2 infection[9,10] during periods and in regions in which the delta variant was prominent.

Vaccine efficacy against symptomatic Covid-19

Figure 3 (facing page). Vaccine Efficacy against Moderate to Severe–Critical Covid-19 According to SARS-CoV-2 Lineage (Per-Protocol Population).

Shown is vaccine efficacy against moderate to severe–critical Covid-19 with onset at least 14 days after administration (Panel A) and at least 28 days after administration (Panel B). SARS-CoV-2 in the category of "Lineages other than the reference strain" were all variants of concern or interest, with "other" sequences excluded. At the time of the trial, sequences categorized as "other" were those with substitutions not resulting in another SARS-CoV-2 lineage or variant. "Other+E484K" refers to sequences with E484K but no other substitutions resulting in another SARS-CoV-2 lineage or variant. Vaccine efficacy was not calculated if fewer than 6 cases were observed for an end point. Confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance.

in participants with HIV infection in our trial was low, at 23.5%, with wide confidence intervals. However, in a large phase 3B study involving 477,234 participants, vaccine effectiveness was 73% against hospitalization and 65% against death among the approximately 37,000 participants living with HIV infection.[10]

We observed that participants with previous asymptomatic infection (defined by serologic positivity for SARS-CoV-2 N protein and an absence of history of symptomatic Covid-19) can benefit from immunization with a Covid-19 vaccine. In a post hoc analysis, previous infection alone provided 90.4% protection against symptomatic infection, and after administration of Ad26.COV2.S in seropositive participants, 97.7% protection was observed in a comparison with seronegative placebo recipients; these findings extended observations from previous immunologic studies.[15-17]

When Covid-19 developed in participants who had received Ad26.COV2.S, they had lower severity of illness, shorter duration of illness, and lower viral loads than placebo recipients. In addition, vaccination with Ad26.COV2.S led to fewer medical interventions (including hospitalization) than placebo (vaccine efficacy against medical intervention ≥28 days after administration, 75.6%). Vaccine efficacy against Covid-19–related death was 82.8% with onset at least 28 days after administration, and the three Covid-19–related deaths among vaccine recipients occurred in participants 60 years of age or older who were seronegative at baseline and had coexisting conditions associated with an increased risk of severe Covid-19.

Serious adverse events were rare: serious adverse events not associated with Covid-19 occurred in approximately 1% of the participants in each group during the double-blind period. Tinnitus was observed in postauthorization surveillance and is classified as "very rare" in the fact sheet associated with the label.[18] Of the very rare events occurring after vaccination that were identified after marketing began,[18,19] no cases of anaphylaxis or capillary leak syndrome occurred, and one case of VITT[20-22] meeting the CDC and Brighton Collaboration criteria occurred in this trial. With 3 to 4 cases per million vaccinations being reported in the postmarketing period, we would not expect to see more than 1 case of VITT in a clinical trial involving more than 43,000 participants (21,898 of whom received Ad26.COV2.S).

Strengths of the current analysis included a longer follow-up period than in our primary analysis that extends our primary findings, as well as the analysis of vaccine efficacy across geographic regions, across diverse populations, and against infection with variants. A limitation of the trial was the premature discontinuation of follow-up in the placebo-controlled phase and variable follow-up times among countries, depending on when approval of the post–emergency use authorization amendment occurred (which permitted group assignments to be revealed to participants and those in the placebo group to be vaccinated). Therefore, for the delta and omicron variants, limited or no data were obtained in the double-blind phase of the study. Going forward, vaccine effectiveness for new variants will need to come from studies involving real-world evidence.

On the basis of the reported results at the end of the double-blind phase, the efficacy of Ad26.COV2.S against moderate to severe–critical disease and against severe–critical disease was lower than that observed in clinical trials assessing messenger RNA vaccines.[23,24] The recently noted incidence of breakthrough infections with the omicron variant in vaccine-primed persons,[25] regardless of the primary vaccine regimen, suggests that a booster may be required for all primary vaccine regimens. Recent data from a study involving South African health care workers conducted during the omicron wave indicate 85% efficacy

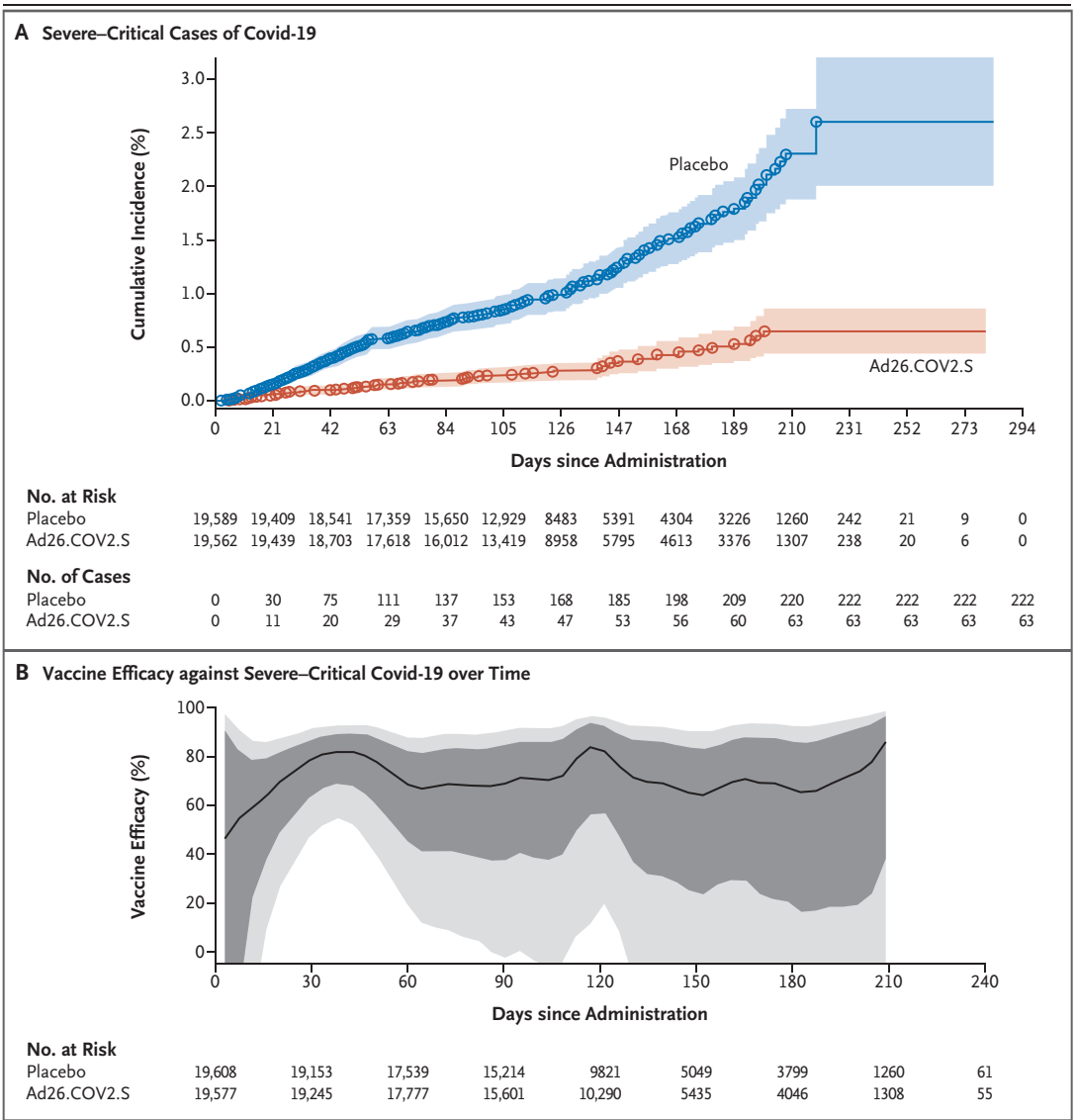


Figure 4. Cumulative Incidence of Severe–Critical Covid-19 and Vaccine Efficacy over Time (Per-Protocol Population).

Panel A shows the Kaplan–Meier cumulative incidence of molecularly confirmed severe–critical Covid-19 with onset at least 1 day after administration of vaccine or placebo. Shading indicates the 95% confidence interval. Panel B shows vaccine efficacy against severe–critical Covid-19 over time; dark gray shading indicates the 95% pointwise confidence interval, and light gray shading the 95% simultaneous confidence interval. The graph includes 95% of the events that occurred before day 189, with the hazard smoothed over 21 days. Participants were seronegative at baseline, as determined by RT-PCR and serologic tests.

of Ad26.COV2.S against hospitalization when given as a single priming dose followed by a booster 6 to 9 months later.[26]

Overall, our findings indicate that a single dose of Ad26.COV2.S provided protection against severe disease and hospitalization, which could be important in regions requiring mass vaccination or in populations with poor adherence to two-dose prime regimens, and support the use of Ad26.COV2.S in the ongoing effort against the global Covid-19 pandemic.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines 2020;5:91.
2. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med 2021;384:1824-35.
3. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 2021;384:2187-201.
4. Nauta J. Statistics in clinical vaccine trials. New York: Springer-Verlag, 2011.
5. Barouch DH, Stephenson KE, Sadoff J, et al. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. N Engl J Med 2021;385:951-3.
6. Alter G, Yu J, Liu J, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature 2021;596:268-72.
7. Grannis SJ, Rowley EA, Ong TC, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19–associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (Delta) variant predominance — nine states, June–August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1291-3.
8. Polinski JM, Weckstein AR, Batech M, et al. Effectiveness of the single-dose Ad26.COV2.S COVID vaccine. September 16, 2021 (https://www.medrxiv.org/content/10.1101/2021.09.10.21263385v2). preprint.
9. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. Science 2022;375:331-6.
10. Bekker L-G, Garrett N, Goga A, et al. Effectiveness of the Ad26.Cov2.S vaccine in health care workers in South Africa. SSRN. November 17, 2021 (https://ssrn.com/abstract=3979291).
11. de Gier B, Kooijman M, Kemmeren J, et al. COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the Netherlands, April-August 2021. September 17, 2021 (https://www.medrxiv.org/content/10.1101/2021.09.15.21263613v1). preprint.
12. Rosenberg ES, Dorabawila V, Easton D, et al. Covid-19 vaccine effectiveness in New York State. N Engl J Med 2022;386:116-27.
13. Institute Infectious Disease Epidemiology and Surveillance, AGES, Austrian Agency for Health and Food Safety. Estimates of COVID-19 vaccine effectiveness against SARS-CoV-2 infection following a nationwide vaccination campaign: a population-based cohort study. 2021 (https://wissenaktuell.ages.at/impfeffektivitaet-in-bezug-auf-sars-cov-2-infektion-der-in-oesterreich-eingesetzten-covid19-impfstoffe/).
14. Corchado-Garcia J, Zemmour D, Hughes T, et al. Analysis of the effectiveness of the Ad26.COV2.S adenoviral vector vaccine for preventing COVID-19. JAMA Netw Open 2021;4(11):e2132540.
15. Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect

of prior SARS-CoV-2 infection on repeat infection. Eval Health Prof 2021;44:327-32.
16. Crotty S. Hybrid immunity. Science 2021;372:1392-3 (https://www.science.org/doi/10.1126/science.abj2258).
17. Keeton R, Richardson SI, Moyo-Gwete T, et al. Prior infection with SARS-CoV-2 boosts and broadens Ad26.COV2.S immunogenicity in a variant-dependent manner. Cell Host Microbe 2021;29:1611-1619.e5.
18. Fact sheet for recipients and caregivers: emergency use authorization (EUA) of the Janssen COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19) in individuals 18 years of age and older. Horsham, PA: Janssen Biotech, 2021 (https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-Recipient-fact-sheet.pdf).
19. Shay DK, Gee J, Su JR, et al. Safety monitoring of the Janssen (Johnson & Johnson) COVID-19 vaccine — United States, March–April 2021. MMWR Morb Mortal Wkly Rep 2021;70:680-4.
20. See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. JAMA 2021;325:2448-56.
21. Rizk JG, Gupta A, Sardar P, et al. Clinical characteristics and pharmacological management of COVID-19 vaccine-induced immune thrombotic thrombocytopenia with cerebral venous sinus thrombosis: a review. JAMA Cardiol 2021;6:1451-60.
22. Rosenblum HG, Hadler SC, Moulia D, et al. Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna): update from the Advisory Committee on Immunization Practices — United States, July 2021. MMWR Morb Mortal Wkly Rep 2021;70:1094-9.
23. Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med 2021;385:1761-73.
24. El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385:1774-85.
25. Centers for Disease Control and Prevention. Omicron variant: what you need to know. 2021 (https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html).
26. Gray GE, Collie S, Garrett N, et al. Vaccine effectiveness against hospital admission in South African health care workers who received a homologous booster of Ad26.COV2 during an Omicron COVID19 wave: preliminary results of the Sisonke 2 study. December 29, 2021 (https://www.medrxiv.org/content/10.1101/2021.12.28.21268436v1). preprint.