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Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate in ten countries in Europe and Latin America (HERALD): a randomised, observer-blinded, placebo-controlled, phase 2b/3 trial

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Summary

Background Additional safe and efficacious vaccines are needed to control the COVID-19 pandemic. We aimed to analyse the efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate.

Methods HERALD is a randomised, observer-blinded, placebo-controlled, phase 2b/3 clinical trial conducted in 47 centres in ten countries in Europe and Latin America. By use of an interactive web response system and stratification by country and age group (18–60 years and ≥61 years), adults with no history of virologically confirmed COVID-19 were randomly assigned (1:1) to receive intramuscularly either two 0·6 mL doses of CVnCoV containing 12 µg of mRNA or two 0·6 mL doses of 0·9% NaCl (placebo) on days 1 and 29. The primary efficacy endpoint was the occurrence of a first episode of virologically confirmed symptomatic COVID-19 of any severity and caused by any strain from 15 days after the second dose. For the primary endpoint, the trial was considered successful if the lower limit of the CI was greater than 30%. Key secondary endpoints were the occurrence of a first episode of virologically confirmed moderate-to-severe COVID-19, severe COVID-19, and COVID-19 of any severity by age group. Primary safety outcomes were solicited local and systemic adverse events within 7 days after each dose and unsolicited adverse events within 28 days after each dose in phase 2b participants, and serious adverse events and adverse events of special interest up to 1 year after the second dose in phase 2b and phase 3 participants. Here, we report data up to June 18, 2021. The study is registered at ClinicalTrials.gov, NCT04652102, and EudraCT, 2020–003998–22, and is ongoing.

Findings Between Dec 11, 2020, and April 12, 2021, 39 680 participants were enrolled and randomly assigned to receive either CVnCoV (n=19 846) or placebo (n=19 834), of whom 19 783 received at least one dose of CVnCoV and 19 746 received at least one dose of placebo. After a mean observation period of 48·2 days (SE 0·2), 83 cases of COVID-19 occurred in the CVnCoV group (n=12 851) in 1735·29 person-years and 145 cases occurred in the placebo group (n=12 211) in 1569·87 person-years, resulting in an overall vaccine efficacy against symptomatic COVID-19 of 48·2% (95·826% CI 31·0–61·4; p=0·016). Vaccine efficacy against moderate-to-severe COVID-19 was 70·7% (95% CI 42·5–86·1; CVnCoV 12 cases in 1735·29 person-years, placebo 37 cases in 1569·87 person-years). In participants aged 18–60 years, vaccine efficacy against symptomatic disease was 52·5% (95% CI 36·2–64·8; CVnCoV 71 cases in 1591·47 person-years, placebo, 136 cases in 1449·23 person-years). Too few cases occurred in participants aged 61 years or older (CVnCoV 12, placebo nine) to allow meaningful assessment of vaccine efficacy. Solicited adverse events, which were mostly systemic, were more common in CVnCoV recipients (1933 [96·5%] of 2003) than in placebo recipients (1344 [67·9%] of 1978), with 542 (27·1%) CVnCoV recipients and 61 (3·1%) placebo recipients reporting grade 3 solicited adverse events. The most frequently reported local reaction after any dose in the CVnCoV group was injection-site pain (1678 [83·6%] of 2007), with 22 grade 3 reactions, and the most frequently reported systematic reactions were fatigue (1603 [80·0%] of 2003) and headache (1541 [76·9%] of 2003). 82 (0·4%) of 19 783 CVnCoV recipients reported 100 serious adverse events and 66 (0·3%) of 19 746 placebo recipients reported 76 serious adverse events. Eight serious adverse events in five CVnCoV recipients and two serious adverse events in two placebo recipients were considered vaccination-related. None of the fatal serious adverse events reported (eight in the CVnCoV group and six in the placebo group) were considered to be related to study vaccination. Adverse events of special interest were reported for 38 (0·2%) participants in the CVnCoV group and 31 (0·2%) participants in the placebo group. These events were considered to be related to the trial vaccine for 14 (<0·1%) participants in the CVnCoV group and for five (<0·1%) participants in the placebo group.

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Interpretation CVnCoV was efficacious in the prevention of COVID-19 of any severity and had an acceptable safety profile. Taking into account the changing environment, including the emergence of SARS-CoV-2 variants, and timelines for further development, the decision has been made to cease activities on the CVnCoV candidate and to focus efforts on the development of next-generation vaccine candidates.

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Introduction

SARS-CoV-2, which emerged in China's Wuhan province in December, 2019, has led to more than 225 million cases of COVID-19 and more than 4·5 million deaths globally as of September, 2021.[1] Through unprecedented effort from governments, national and international research funders, regulatory bodies, and research organisations, vaccine development has been, and continues to be, expedited. The first conditionally approved vaccine in Europe was administered in December, 2020, within 9 months of WHO characterising COVID-19 as a pandemic on March 11, 2020.[2]

More than 100 COVID-19 vaccines are currently in clinical development, and as of September, 2021, 21 are being offered to the general population.[3] These vaccines have been developed by use of different platforms, all with specific advantages and disadvantages.[4] mRNA is a promising platform that allows the rapid development of immunogens and vaccine production.[5,6] The BNT162b2 (Pfizer-BioNtech) and mRNA-1273 (Moderna) SARS-CoV-2 vaccines were the first mRNA preventive vaccines to be approved for emergency use in humans in Europe and the USA on the basis of data from phase 3 efficacy trials.[7,8]

CVnCoV is a chemically unmodified mRNA vaccine candidate based on the RNActive mRNA vaccine platform encoding the stabilised, full-length, native SARS-CoV-2 spike protein of the SARS-CoV-2 wild-type strain. The mRNA is protected by lipid nanoparticles used for delivery. Preclinical studies have shown that CVnCoV induces a robust immune response and protects against SARS-CoV-2 in hamster and primate virus challenge models.[9,10] In a phase 1 dose-escalation study, two doses of CVnCoV administered 28 days apart were safe and immunogenic, with dose-dependent increases in anti-spike protein IgG antibodies and SARS-CoV-2-neutralising antibodies.[11] Median antibody titres against spike protein and its receptor binding domain after two 12 µg doses of CVnCoV were similar to those observed in convalescent serum samples from patients with COVID-19, with seroconversion observed 2 weeks after the second dose in all participants receiving this dosage. On the basis of these findings, the 12 µg dose was selected for further phase 2/3 testing. We aimed to analyse the efficacy and safety of the

Research in context

Evidence before this study

We searched PubMed for clinical trials published between Jan 1, 2019, and Sept 19, 2021, without language restrictions, using the terms 'SARS-CoV-2' OR 'COVID-19' AND 'Vaccine' AND 'Efficacy'. At the time of the search, we identified 12 peer-reviewed publications of phase 2/3 and phase 3 clinical trials reporting the efficacy of COVID-19 vaccines in different populations. We did not consider press releases or preprints as sources of information. Eight primary publications reported vaccine efficacies ranging from 62% to 95%. The mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNtech) mRNA vaccines have shown 94% and 95% efficacy, respectively, in preventing COVID-19, with cases accrued at a time when no circulating variants had been identified. Variant-dependent differences in vaccine efficacy have been reported, with reductions in efficacy of up to 60 percentage points against newly emerged SARS-CoV-2 variants of concern.

Added value of this study

We report the primary efficacy analysis of the CVnCoV mRNA vaccine candidate from the phase 2b/3 HERALD trial that comprised 39 680 participants from ten countries in Europe and Latin America. CVnCoV had an acceptable safety profile. Solicited adverse events were common, and more frequently reported in the CVnCoV group than in the placebo group, but the median duration of grade 3 solicited adverse events was 1 day. CVnCoV was 48·2% efficacious in the prevention of COVID-19 of any severity in a variant-dominated setting. Indeed, only seven (3%) of all 204 sequenced COVID-19 cases were of B.1 lineage, with the others caused by 14 different variants. In Europe, 45 (92%) of 49 cases were caused by the alpha variant of concern (B.1.1.7), compared with Latin America where 20 (13%) of 155 cases were caused by the alpha variant and 35 (23%) cases were caused by the gamma variant of concern (P.1).

Implications of all the available evidence

In view of the changing environment, including the emergence of SARS-CoV-2 variants, and taking into account timelines for further development, the decision has been made to cease activities on the CVnCoV candidate and to focus efforts on the promising and rapidly progressing development of next-generation vaccine candidates. In addition, it might be necessary to consider alternative designs for future global efficacy trials given the number of rapidly emerging SARS-CoV-2 variants and the high uptake of COVID-19 vaccines under emergency use authorisation.

CVnCoV SARS-CoV-2 mRNA vaccine candidate in a phase 2b/3 trial.

Methods

Study design and participants

HERALD is an ongoing, randomised, observer-blinded, placebo-controlled, phase 2b/3, clinical trial in 47 public and private hospitals and clinics across four countries in Europe (ie, Belgium, Germany, the Netherlands, and Spain) and six countries in Latin America (ie, Argentina, Colombia, Dominican Republic, Mexico, Panama, and Peru). Participants were recruited by study sites through their databases and advertisements. Adults aged 18 years or older with no history of virologically confirmed COVID-19 were eligible for inclusion, unless they had received (within 28 days before first administration of CVnCoV), or planned to receive, any investigational or non-registered vaccine or drug; had received any live (within 28 days) or inactivated (within 14 days) vaccine; or had received, or planned to receive, any investigational SARS-CoV-2 vaccine or other coronavirus vaccine before trial initiation or during the trial. A list of all inclusion and exclusion criteria is provided in the appendix (p 4). Eligibility could be assessed and recording of baseline data could be done up to 21 days before administration of the trial vaccine, but had to be reviewed before administration on day 1.

The initial phase 2b part of the trial was designed to characterise the safety, reactogenicity, and immunogenicity of the CVnCoV vaccine candidate, and the phase 3 part of the trial was designed to evaluate its efficacy and safety. The two parts of the trial were designed to allow participants with COVID-19 accrued in the phase 2b part of the trial to be pooled with those in the phase 3 part of the trial for the primary analysis of vaccine efficacy. An independent data and safety monitoring board (DSMB) conducted interim safety reviews of the phase 2b part of the trial before enrolment for the phase 3 part of the trial was initiated and will continue to monitor safety until study end. An enrolment target was that 20–25% of the population would be aged 61 years or older. We planned to enrol the first 4000 participants in the phase 2b part of the trial and to include the first 600 participants in each age group in the assessment of immunogenicity endpoints. The DSMB reviewed the safety data when approximately 1800 participants (900 in both treatment groups) had been enrolled in the phase 2b part of the trial and had at least 1 week of safety follow-up after the first dose. Enrolment of participants into the phase 3 part of the trial would begin without interruption from the phase 2b part of the trial if the safety profile was considered acceptable. The DSMB also reviewed all safety data after all participants in each group in the phase 2b trial had received their second trial vaccination and had at least 1 week of safety follow-up.

The trial protocol and its amendments received ethics approval from the appropriate independent ethics committees or institutional review boards at each study centre. The trial is being conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All participants provided written informed consent before initiation of any trial procedures.

Randomisation and masking

Trial participants were randomly assigned (1:1) to receive either CVnCoV or placebo. Randomisation, stratified by country and age group (18–60 years and ≥61 years), was done centrally by use of an interactive web response system. The randomisation scheme was generated and managed by an independent statistics group at the contract research organisation, PRA. Due to the difference in appearance and presentation between the CVnCoV vaccine candidate and placebo, site personnel involved in preparing the vaccine masked the content of the syringe with a label and were not involved in further conduct of the trial. Investigators, site personnel, and others directly involved in the conduct of the trial were masked to participant allocation for the duration of the trial. The statisticians analysing the data were masked to group assignment until the final analyses. Unmasking of participants was allowed in emergency situations for reasons of participant safety or for participants who became eligible to receive an authorised SARS-CoV-2 vaccine and requested unmasking.

Procedures

Participants in both the phase 2b and the phase 3 parts of the trial received either two 0·6 mL doses of CVnCoV containing 12 µg of mRNA, formulated with the RNActive mRNA vaccine platform, or two 0·6 mL doses of 0·9% NaCl (placebo) on days 1 and 29. Each 0·6 mL dose was administered by intramuscular injection in the deltoid area. Blood samples (6 mL) were taken from all participants on day 1 and day 43 (14 days after the second dose) and will be taken on day 211 and day 393 (study end) to measure SARS-CoV-2 nucleocapsid protein serostatus. The samples were sent to one of two central laboratories in the USA or the Netherlands and tested with the Elecsys assay on the COBAS system (Roche Diagnostics; Mannheim, Germany). The results on day 1 and day 43 identified whether participants were naive to SARS-CoV-2 infection at trial entry and 15 days after the second vaccination, and were therefore eligible for inclusion in the efficacy analysis subset.

Participants were requested to contact site investigators if they had symptoms potentially indicating COVID-19 (eg, 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, or diarrhoea),[12] and participants were contacted twice per week by site staff via a mobile application to respond yes or no to having potential

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See Online for appendix

COVID-19 symptoms. Site personnel then contacted participants who replied yes to ascertain whether their symptoms were indicative of COVID-19 by following a scripted interview. Upon suspicion of COVID-19, participants underwent a rapid antigen test (Abbott Panbio COVID-19 Ag Rapid Test; Jena, Germany) to allow them to comply with local quarantine rules if the results were positive. In addition, samples were sent to central laboratories for SARS-CoV-2-specific RT-PCR testing (In-house test, with probes and primers from Eurofins [Louisville KY, USA]; Latin America testing done in Lancaster [PA, USA]; European testing done in Breda [Netherlands]) for virological confirmation of COVID-19. In case of discrepancies between tests, the RT-PCR test result was considered definitive. All primary efficacy cases were confirmed by an independent adjudication committee. Sequencing of the complete viral single stranded RNA genome was carried out using Illumina Next Generation Sequencing (Viracor-Eurofins, Lee's Summit, MO, USA).

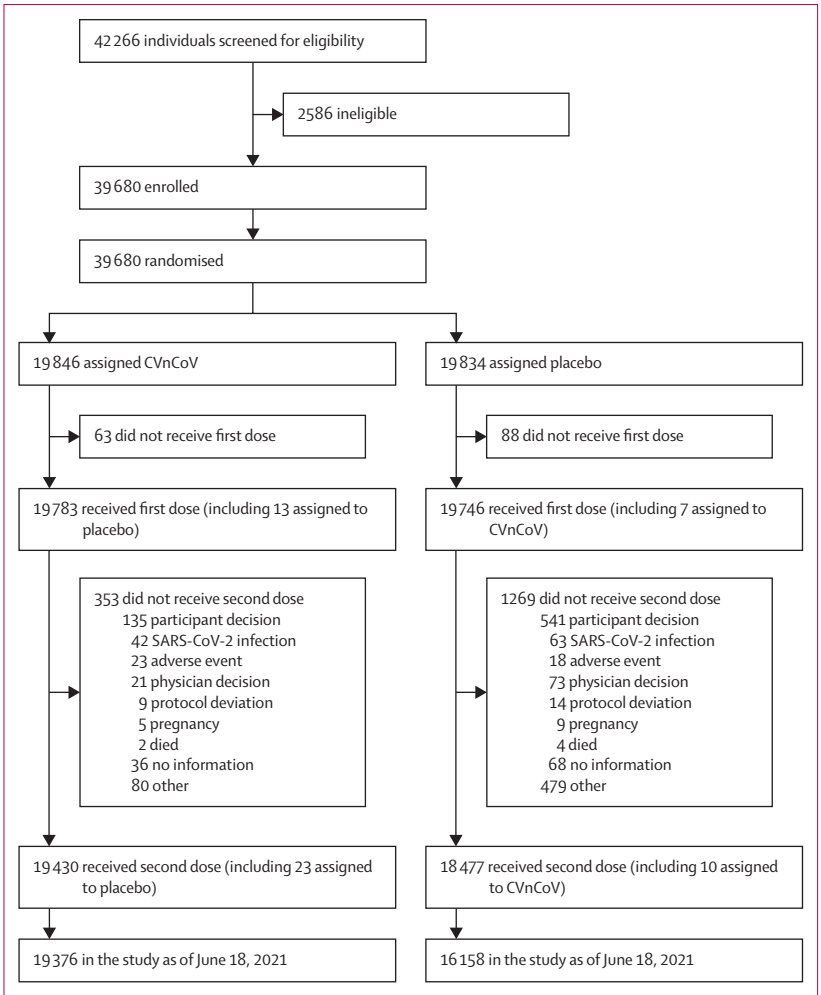

Figure 1: **Trial profile for the HERALD phase 2b–3 study**
25 participants who were randomly assigned to placebo received at least one dose of CVnCoV, and six participants who were randomly assigned to CVnCoV received two doses of placebo; they were analysed according to the treatment received. The reasons for discontinuing treatment or the study are summarised in the appendix (p 7).

Mild COVID-19 was defined as disease without shortness of breath or difficulty breathing, and an altitude-adjusted oxygen saturation (SpO_2) of at least 95%. Moderate disease was defined by the presence of symptoms and shortness of breath, difficulty breathing, a respiratory rate of 20–29 breaths per min, abnormal SpO_2 (but still >93% when adjusted for altitude), clinical or radiographic evidence of lower respiratory tract disease, or radiological evidence of deep vein thrombosis. Severe COVID-19 was defined by clinical signs at rest that are indicative of severe systemic illness (respiratory rate ≥30 breaths per min, heart rate ≥125 beats per min, altitude-adjusted SpO_2 ≤93%, or PaO_2/FiO_2 ratio <300 mm Hg), respiratory failure, evidence of shock, considerable renal, hepatic, or neurological dysfunction, admission to an intensive care unit, or death.[13]

The phase 2b participants used a diary to record solicited local adverse events (ie, injection-site pain, redness, swelling, and itching) and solicited systemic adverse events (ie, fever, headache, fatigue, chills, myalgia, arthralgia, nausea or vomiting, and diarrhoea) for 7 days after each dose. Solicited adverse events were graded by intensity from 0 (absent) to 3 (severe) according to predefined criteria provided in the appendix (p 5). Unsolicited adverse events were recorded in the diaries for 28 days after each dose, and investigators assessed their severity.

Medically attended adverse events will be collected for all participants from day 1 until 6 months after the second dose. Adverse events of special interest and serious adverse events will be collected until 1 year after the second dose. A list of adverse events of special interest is provided in the appendix (pp 6–7). The intensity of unsolicited adverse events, adverse events of special interest, and serious adverse events, and their relationship to study vaccination, were assessed by the study investigators.

Outcomes

The primary efficacy outcome was the occurrence of a first episode of virologically confirmed symptomatic COVID-19 of any severity and caused by any strain from 15 days after the second dose up to 1 year. The primary outcome was assessed by a blinded, central adjudication committee. Key secondary efficacy outcomes included the occurrence of a first episode of virologically confirmed moderate-to-severe COVID-19, and the occurrence of a first episode of virologically confirmed severe COVID-19, overall and by age group (18–60 years *vs* ≥61 years). An exploratory efficacy endpoint, which was added in the protocol amendment on March 29, 2021, was the occurrence of a first episode of virologically confirmed COVID-19 caused by an individual variant of concern or interest.

Primary safety outcomes were the monitoring of solicited local and systemic adverse events for 7 days after each dose and unsolicited adverse events for 28 days after

each dose in phase 2b participants, medically attended adverse events (which will be reported in the final analysis at study end) up to 6 months after the second dose, serious adverse events and adverse events of special interest up to 1 year after the second dose, fatal serious adverse events up to 1 year after the second dose, and adverse events leading to vaccine withdrawal or trial discontinuation for 1 year after the second dose (which will be reported in the final analysis at study end). A full list of study endpoints, including endpoints not reported on in this study, with reasons for omission, is included in the appendix (p 8).

Statistical analysis

HERALD is an event-driven trial, and sample size and power considerations were based on the primary objective of showing the efficacy of CVnCoV in preventing virologically confirmed cases of COVID-19 of any severity meeting the primary case definition. Assuming a vaccine efficacy of 60%, with an overall two-sided α of 5%, we estimated that 160 participants with COVID-19 of any severity, with a third of cases being moderate to severe, were needed for the final analysis to have a power of 90% to show a vaccine efficacy of more than 30% based on the lower bound of the CI for efficacy. Assuming a COVID-19 incidence of 0·15% per month in participants in the placebo group, an overall non-evaluable proportion of 20% (corresponding to participants excluded from the efficacy analysis set and those who dropped out), and a vaccine efficacy of 60%, we estimated that 36 500 participants (18 250 per group) enrolled over approximately 3 months would accrue 160 COVID-19 cases of any severity at approximately 9 months after the first vaccination.

During case accrual, before the second interim analysis was done, we observed that the actual proportion of participants with moderate-to-severe COVID-19 was approximately 20%, which was lower than the expected 30%. The protocol was amended to allow accrual of more cases to obtain the planned sample size (about 53 participants with moderate-to-severe COVID-19) needed for the key secondary endpoint of measuring vaccine efficacy against moderate-to-severe COVID-19.

Vaccine efficacy against symptomatic disease was analysed in the primary efficacy analysis set, which comprised all participants in the phase 2b and phase 3 parts of the trial who received both doses of either CVnCoV or placebo according to their treatment allocation, had not developed virologically confirmed COVID-19 before day 43 (15 days after the second dose), and were SARS-CoV-2-naive at baseline and day 43. Vaccine efficacy was defined as 1 minus the ratio of the attack rate in participants receiving CVnCoV to participants receiving placebo, multiplied by 100. In each group, the attack rate was defined as the number of participants presenting with virologically confirmed COVID-19 divided by the total follow-up time. For the primary analysis, the hypothesis was tested with the exact test for binomial proportions. The trial was considered successful if the lower limit of the exact two-sided Clopper-Pearson 95% CI (subject to adjustment for multiple testing according to the cumulative O'Brien-Fleming type error spending function, giving an actual CI of 95·826%) of the primary efficacy endpoint

	CVnCoV (n=19 783)	Placebo (n=19 746)
Characteristic		
Sex		
Female	8923 (45·1%)	8934 (45·2%)
Male	10 860 (54·9%)	10 812 (54·8%)
Age, years	43·0 (31·0–54·0)	43·0 (31·0–54·0)
18–60 years	17 277 (87·3%)	17 248 (87·3%)
≥61 years	2506 (12·7%)	2498 (12·7%)
BMI, kg/m²	25·7 (23·0–29·0)	25·7 (23·0–29·0)
Comorbidities		
Hypertension	1173 (5·9%)	1160 (5·9%)
Obesity (BMI >30 kg/m²)	881 (4·5%)	890 (4·5%)
Diabetes	301 (1·5%)	312 (1·6%)
Chronic pulmonary disease	103 (0·5%)	103 (0·5%)
Region or country*		
Europe	5026/19 846 (25·3%)	5017/19 834 (25·3%)
Belgium	1078/19 846 (5·4%)	1077/19 834 (5·4%)
Germany	1405/19 846 (7·1%)	1406/19 834 (7·1%)
Netherlands	1082/19 846 (5·5%)	1078/19 834 (5·4%)
Spain	1461/19 846 (7·4%)	1456/19 834 (7·3%)
Latin America	14 820/19 846 (74·7%)	14 817/19 834 (74·7%)
Argentina	3382/19 846 (17·0%)	3382/19 834 (17·1%)
Colombia	2178/19 846 (11·0%)	2178/19 834 (11·0%)
Dominican Republic	883/19 846 (4·4%)	884/19 834 (4·5%)
Mexico	3148/19 846 (15·9%)	3145/19 834 (15·9%)
Panama	1504/19 846 (7·6%)	1502/19 834 (7·6%)
Peru	3725/19 846 (18·8%)	3726/19 834 (18·8%)
Serology status at baseline†		
Seronegative	17 093 (86·4%)	16 974 (86·0%)
Seropositive	2311 (11·7%)	2404 (12·2%)
Unknown	379 (1·9%)	368 (1·9%)
Serology status at day 43†‡		
Seronegative	14 345 (72·5%)	12 951 (65·6%)
Seropositive	2220 (11·2%)	2257 (11·4%)
Unknown	3218 (16·3%)	4538 (23·0%)

Data are n (%), median (IQR), or n/N (%). The phase 2b–3 safety analysis set comprises all participants who received at least one dose of CVnCoV or placebo, who are analysed in the group of the treatment dose received. BMI=body-mass index. *Region and country data were evaluated in the population who were randomly assigned. †Serology status was based on retrospective assessment using anti-SARS-CoV-2 nucleocapsid protein antibody concentrations. ‡Day 43 was the first day of COVID-19 case collection, 14 days after the second dose; serology status was not available for all participants at the time of database lock.

Table 1: **Baseline and day 43 characteristics in the phase 2b–3 safety analysis set**

	CVnCoV		Placebo		Vaccine efficacy (95% CI)
	n/N	Person-years	n/N	Person-years	
COVID-19 of any severity					
Overall	83/12 851	1735·29	145/12 211	1569·87	48·2% (31·0–61·4)*
18–60 years	71/11 532	1591·47	136/11 031	1449·23	52·5% (36·2–64·8)
≥61 years	12/1319	143·82	9/1180	120·64	··†
COVID-19 of any severity by region‡					
Europe	21/4091	684·22	33/3919	604·83	43·7% (–0·2 to 69·1)
Latin America	62/8760	1051·07	112/8292	965·03	49·2% (30·1–63·3)
COVID-19 of any severity by strain§					
Alpha variant (B.1.1.7/501Y.V2)	20/11 532	1591·47	42/11 031	1449·23	55·1% (23·5–73·6)
Gamma variant (P.1/501Y.V3)	9/11 532	1591·47	26/11 031	1449·23	67·1% (29·8–84·6)
Lambda variant (C.37)	13/11 532	1591·47	26/11 031	1449·23	52·8% (8·2–75·8)
Mu variant (B.1.621)	11/11 532	1591·47	17/11 031	1449·23	··†
Other	7/11 532	1591·47	13/11 031	1449·23	··†
Moderate-to-severe COVID-19					
Overall	12/12 851	1735·29	37/12 211	1569·87	70·7% (42·5–86·1)
18–60 years	9/11 532	1591·47	36/11 031	1449·23	77·2% (51·8–90·4)
≥61 years	3/1319	143·82	1/1180	120·64	··†
Severe COVID-19					
Overall	4/12 851	1735·29	10/12 211	1569·87	··†
18–60 years	2/11 532	1591·47	9/11 031	1449·23	··†
≥61 years	2/1319	143·82	1/1180	120·64	··†

*For COVID-19 of any severity, the 95·826% CI is provided (due to adjustment for multiplicity across interim analyses). †Not reported; the number of cases was too low to be statistically meaningful. ‡Vaccine efficacy by region was evaluated post-hoc. §Efficacy against strains was evaluated in adjudicated and sequenced cases in participants aged 18–60 years; other strains includes B.1 lineage SARS-CoV-2.

Table 2: **Efficacy of CVnCoV against virologically confirmed COVID-19 occurring 15 days or more after the second dose in the primary efficacy analysis set**

(COVID-19 cases of any severity) was more than 30%. Success for key secondary endpoints was defined as the lower limit of the exact two-sided 95% CI being more than 20% for moderate-to-severe disease, and more than 10% for severe disease. Kaplan-Meier curves and associated log-rank tests were done in a key prespecified sensitivity analysis to evaluate time to first occurrence of virologically confirmed COVID-19. Post-hoc, we evaluated vaccine efficacy by region.

Solicited adverse events were evaluated in the phase 2b reactogenicity analysis set, which comprised all participants in the phase 2b part of the trial who received at least one dose of CVnCoV or placebo according to treatment received and for whom at least one diary entry reporting the presence or absence of a solicited adverse event was available. Unsolicited adverse events were evaluated in the phase 2b safety analysis set, which comprised all participants in the phase 2b part of the trial who received at least one dose of CVnCoV or placebo according to treatment received. Serious adverse events and adverse events of special interest were assessed in the phase 2b/3 safety analysis set, which comprised all participants in the phase 2b and phase 3 parts of the trial who received at least one dose of CVnCoV or placebo, according to the actual dose received. All analyses were done by use of SAS, version 9.4. For the primary outcome, a p value of less than 0·02087 was considered significant. This trial is registered at ClinicalTrials.gov, NCT04652102, and EudraCT, 2020–003998–22.

Role of the funding source

CureVac was responsible for trial design and conduct, data analysis, data interpretation, and writing of the report. The German Federal Ministry of Education and Research had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

HERALD is an ongoing clinical trial and the cutoff date for this analysis was June 18, 2021. Between Dec 11, 2020, and April 12, 2021, 3999 participants were enrolled and randomly assigned in the phase 2b trial (appendix p 11), of whom 3994 were vaccinated with at least one dose (2007 received CVnCoV; 1987 received placebo). Altogether, 39 680 participants were enrolled and randomly assigned in the phase 2b and phase 3 parts of the trial, of whom 39 529 (99·6%) received at least one dose of CVnCoV (n=19 783) or placebo (n=19 746; figure 1). 25 participants who were randomly assigned to placebo received at least one dose of CVnCoV, and six participants who were randomly assigned to CVnCoV received two doses of placebo. Any participant who received at least one dose of CVnCoV was considered as being in the CVnCoV group for the safety analyses. Both groups had similar demographic characteristics (table 1). Before the final efficacy analysis, 14 410 (36·5%) of 39 529 vaccinated participants requested to be unmasked (6715 [33·9%] of 19 783 in the CVnCoV group; 7695 [39·0%] of 19 746 in the placebo group), as allowed per protocol when a SARS-CoV-2 vaccine became available. 3494 (69·8%) of 5004 participants aged 61 years or older were unmasked, compared with 10 913 (31·6%) of 34 525 participants aged 18–60 years. These unmasked participants were censored in the efficacy analysis at the time of unmasking. Reasons for exclusion from the primary efficacy analysis set have not yet been analysed per treatment group, but the most frequent reasons were positive or missing serostatus result at baseline or day 43, unmasked within 15 days after the second dose, did not receive two doses of randomised treatment, or developed COVID-19 disease, discontinued the trial, or received a licenced COVID-19 vaccine within 15 days after the second dose.

The primary efficacy analysis included 12 851 participants in the CVnCoV group and 12 211 in the placebo group. The mean observation period, starting 15 days after administration of the second dose, was 48·2 days (SE 0·2). Of the 228 adjudicated COVID-19 cases of any

severity caused by any strain, 83 occurred in the CVnCoV group after a total follow-up of 1735·29 person-years and 145 occurred in the placebo group after a total follow-up of 1569·87 person-years, resulting in a vaccine efficacy against symptomatic disease of 48·2% (95·826% CI 31·0–61·4; p=0·016) in the overall study population (table 2). 179 (79%) of the 228 COVID-19 cases were mild. In participants aged 18–60 years, 71 adjudicated cases of COVID-19 occurred in the CVnCoV group after 1591·47 person-years of follow-up and 136 occurred in the placebo group after 1449·23 person-years of follow-up (vaccine efficacy 52·5%, 95% CI 36·2–64·8). There were too few participants aged 61 years or older with virologically confirmed COVID-19 to evaluate vaccine efficacy in this age group (table 2). We show the cumulative incidence of symptomatic COVID-19 starting on day 43 in the primary efficacy analysis set for all participants (figure 2A) and those aged 18–60 years (figure 2B).

Overall, 49 participants (12 in the CVnCoV group and 37 in the placebo group) developed moderate-to-severe COVID-19, against which vaccine efficacy was 70·7% (table 2). Of these, 45 participants were aged 18–60 years (nine in the CVnCoV group and 36 in the placebo group), for whom vaccine efficacy was 77·2% (table 2). The number of cases of moderate-to-severe COVID-19 in participants aged 61 years or older and the number of participants with severe COVID-19 overall were insufficient to meaningfully evaluate vaccine efficacy (table 2).

Vaccine efficacy was similar between Europe and Latin America in post-hoc analyses (table 2). Sequence data were available for 184 of 207 adjudicated cases in people aged 18–60 years. Seven (3%; two in the CVnCoV group and five in the placebo group) of these cases in the overall population were wild-type, defined as WT/D614G lineages A.1/B.1 without the B.1.1.7 (alpha), B.1.351 (beta), and B. 1.429 (epsilon) variants of concern. A full list of sequenced variants is presented in the appendix (p 9). 102 (50%) of 204 cases of COVID-19 were caused by variants of concern, and 23 (35%) were caused by variants of interest. The remaining cases were caused by wild type (seven [3%]) and various variants listed in the appendix, p 8 (23 [11%]).[14] In Europe, 45 (92%) of 49 cases were caused by the alpha variant (the remaining four cases were caused by the gamma variant [P.1; two], by the delta variant [B.1.617.2; one], and by an unidentified variant at the time [one]). In Latin America, 20 (13%) of 155 cases were caused by the alpha variant, 34 (22%) were caused by the gamma variant, 43 (28%) were caused by the lambda variant of interest (C.37), and 29 (19%) were caused by the Mu variant of interest (B.1.621). The remaining cases were caused by alpha (20 [13%]), B.1.526 (iota; one [1%]), wild-type (seven [5%]), P.2 (zeta; one [1%]), and other (20 [13%]). Vaccine efficacies against the alpha, gamma, and lambda variants in people aged 18–60 years were similar to the overall efficacy (table 2).

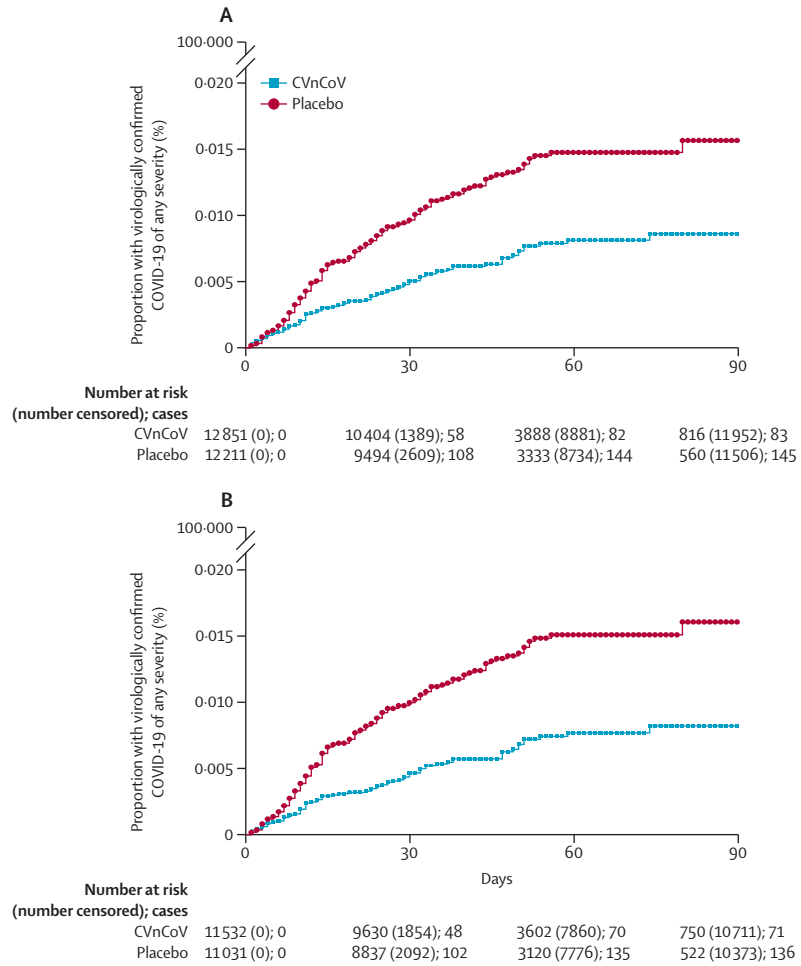

Figure 2: **Kaplan-Meier cumulative incidence of virologically confirmed COVID-19 of any severity in the primary efficacy analysis set**

(A) Overall study population. (B) Participants aged 18–60 years. On the graphs, day 0 corresponds to day 43 of the study, which is 15 days after administration of the second dose. Data are not shown for participants aged 61 years or older as there were too few events to be statistically meaningful. Participants were censored if they were unmasked, received an authorised COVID-19 vaccine, or discontinued participation in the trial for any other reason; censoring started on the day the event occurred. Log-rank tests evaluating group differences were significant (p<0·0001) in the overall study population and the 18–60 years age group.

At least one solicited local or systemic adverse event was reported by 1933 (96·5%) of 2003 participants in the CVnCoV group, with 542 (27·1%) reporting grade 3 events, and by 1344 (67·9%) of 1978 participants in the placebo group, with 61 (3·1%) reporting grade 3 events (table 3). Local reactions were more common in participants receiving CVnCoV than in those receiving placebo (table 3; figure 3A, B). The most frequently reported local reaction after any dose in the CVnCoV group was injection-site pain (83·6%, 1678 of 2007), with 22 grade 3 reactions. Local reactions were transient, with a median duration of 2 days for pain and 1 day for redness, swelling, and itching in participants receiving CVnCoV (appendix p 10). The median duration of all grade 3 local reactions was 1 day for all reactions (appendix p 8).

	CVnCoV	Placebo
Any solicited adverse event*		
Overall	1933/2003 (96·5%)	1344/1978 (67·9%)
Grade 3	542/2003 (27·1%)	61/1978 (3·1%)
Local	1699/2003 (84·8%)	477/1978 (24·1%)
Grade 3	25/2003 (1·2%)	1/1978 (<0·1%)
Systemic	1881/2003 (93·9%)	1255/1978 (63·4%)
Grade 3	536/2003 (26·8%)	60/1978 (3·0%)
Any unsolicited adverse event*		
Overall	1010/2007 (50·3%)	898/1987 (45·2%)
Grade 3	45/2007 (2·2%)	38/1987 (1·9%)
Considered vaccination-related	510/2007 (25·4%)	268/1987 (13·5%)
Any serious adverse event†		
Overall	82/19783 (0·4%); 100	66/19746 (0·3%); 76
Considered vaccination-related	5/19783 (<0·1%); 8	2/19746 (<0·1%); 2
Any adverse event of special interest†		
Overall	38/19783 (0·2%); 44	31/19746 (0·2%); 35
Considered vaccination-related	14/19783 (0·1%); 18	5/19746 (<0·1%); 6
Any adverse event with fatal outcome†		
Overall	8/19783 (<0·1%)	6/19746 (<0·1%)
Considered vaccination-related	0	0

Data are n/N (%) or n/N (%); number of events. Serious adverse events are reported from immediately after the second dose to the date of data cutoff (June 18, 2021). *Solicited and unsolicited adverse events were analysed in the reactogenicity analysis set, which comprised participants in the phase 2b trial who received at least one dose of CVnCoV or placebo and and for whom at least one diary entry reporting the presence or absence of a solicited adverse event was available (phase 2b reactogenicity) and all participants who had received at least one dose of CVnCoV or placebo (phase 2b safety). In the phase 2b part of the study, solicited local and systemic adverse events were reported in participant diaries for 7 days following any dose and unsolicited adverse events were reported in participant diaries for 28 days following any dose. †Serious adverse events and adverse events of special interest or with a fatal outcome were analysed in the phase 2b–3 safety analysis set, which comprised all participants who received at least one dose of CVnCoV or placebo; participants were analysed in the group corresponding to the dose they actually received.

Table 3: **Adverse events**

Solicited systemic reactions, and grade 3 solicited systemic reactions, were also more common in participants in the CVnCoV group than in those in the placebo group (table 3; figure 3C, D). The most frequently reported solicited systemic reactions after any dose in participants receiving CVnCoV were fatigue (1603 [80·0%] of 2003) and headache (1541 [76·9%]). The median duration of systemic reactions was 2 days for headache, fatigue, and myalgia, and 1 day for fever, chills, arthralgia, nausea or vomiting, and diarrhoea in CVnCoV recipients (appendix p 10). The median duration of grade 3 systemic reactions was 1 day for all reactions (appendix p 10). No increase in solicited reactions was seen between the first and second CVnCoV doses (figure 3).

The proportions of participants reporting unsolicited adverse events and grade 3 unsolicited adverse events occurring during the 28 days following any vaccination were slightly higher in the CVnCoV group than in the placebo group (table 3). The most frequently reported unsolicited adverse events in the CVnCoV group were headache (210 [10·4%] of 2007; 42 [2·1%] considered vaccine-related) and nasal congestion (127 [6·3%]; 28 [1·4%] considered vaccine-related).

176 serious adverse events were reported by 148 (0·4%) of 39529 participants in the phase 2b–3 safety analysis set (table 3). 100 serious adverse events occurred in 82 (0·4%) of 19783 participants in the CVnCoV group and 76 serious adverse events occurred in 66 (0·3%) of 19746 participants in the placebo group. Eight serious adverse events in five CVnCoV recipients (acute myocardial infarction, atrial fibrillation, and cardiac arrest [n=1]; supraventricular extrasystoles and ventricular tachycardia [n=1], appendicitis [n=1], cellulitis [n=1], and seizure [n=1]) and two serious adverse events in two placebo recipients (hypersensitivity [n=1] and deep vein thrombosis [n=1]) were considered vaccination-related by study investigators. Fatal adverse events were reported for eight participants in the CVnCoV group and for six participants in the placebo group, none of which were considered related to vaccination (table 3). Adverse events of special interest were reported for 38 participants (0·2%) in the CVnCoV group and 31 participants (0·2%) in the placebo group. Adverse events of special interest considered to be related to the trial vaccine were reported for 14 participants (<0·1%) in the CVnCoV group and for five participants (<0·1%) in the placebo group. The primary safety outcomes for 1 year after the second dose are not provided to preserve study blinding. Data for these outcomes up to 1 year will be reported in a future publication.

Discussion

The phase 2b/3 HERALD trial evaluating the CVnCoV vaccine candidate met the prespecified success criteria for efficacy against symptomatic COVID-19 of any severity (lower limit of the 95% CI >30%) and for efficacy against moderate-to-severe COVID-19 (lower limit of the 95% CI >20%), as defined in the protocol. WHO guidelines recommend a lower bound of at least 30% and a vaccine efficacy of at least 50%.[15] Vaccine efficacy against COVID-19 of any severity was 48·2% (95·826% CI 31·0–61·4) in the overall primary efficacy analysis set of SARS-CoV-2-naive participants, and 52·5% (95% CI 36·2–64·8) in those aged 18–60 years. Vaccine efficacy against moderate-to-severe COVID-19 was 70·7% (42·5–86·1) overall and 77·2% (51·8–90·4) in participants aged 18–60 years. There were too few participants aged 61 years or older who developed COVID-19 to allow a meaningful estimate of efficacy in this age group.

Although the prevalence of solicited and unsolicited adverse events was higher in CVnCoV recipients than in placebo recipients, these events were transient and mostly mild-to-moderate (grade 1–2). The proportion of CVnCoV recipients reporting solicited local and systemic adverse events in the 7 days following any dose was similar to that

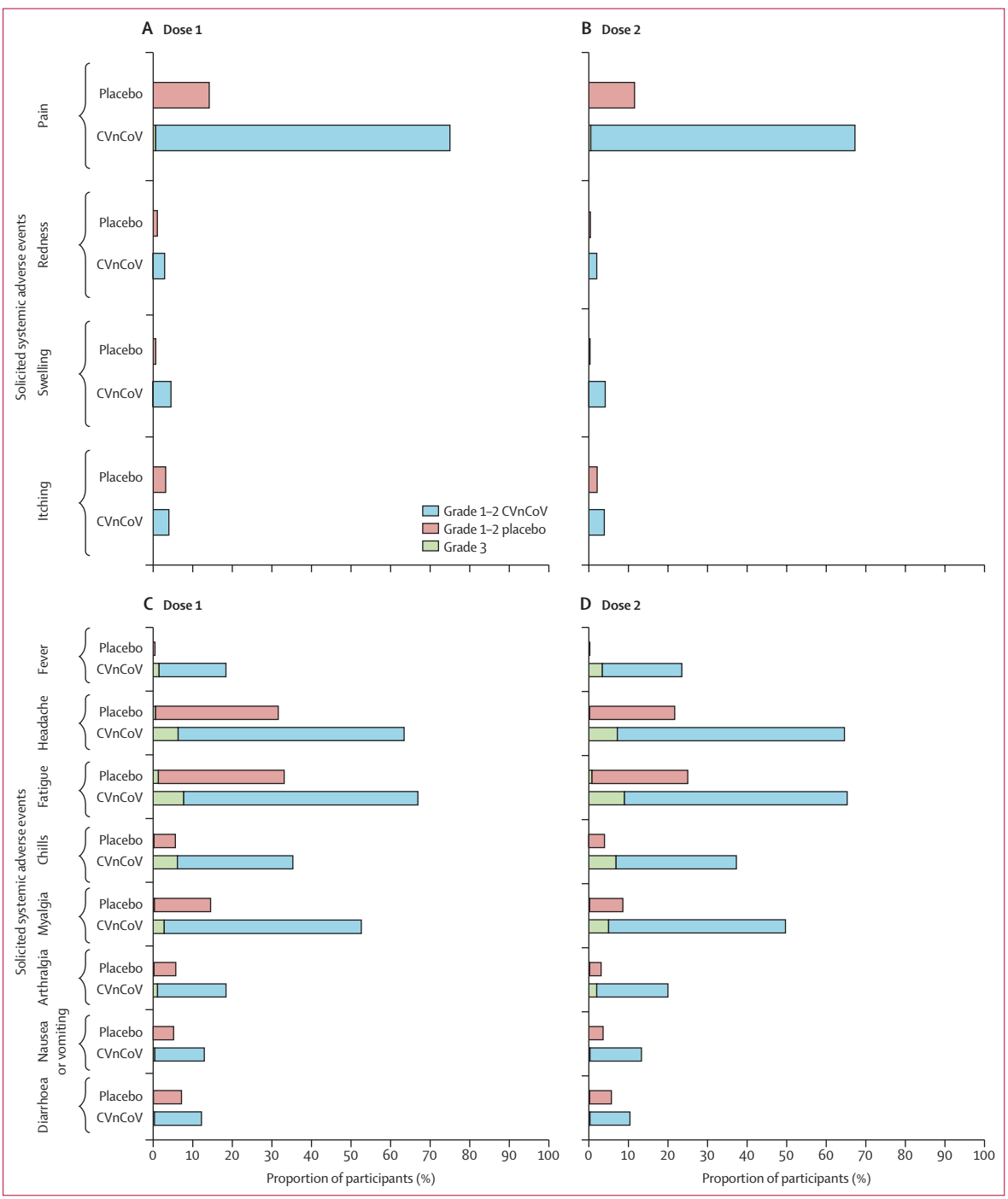

Figure 3: **Solicited local and systemic adverse events in the phase 2b reactogenicity analysis set**
Solicited local adverse events occurring within 7 days of the first dose (A) and the second dose (B), and solicited systemic adverse events occurring within 7 days of the first dose (C) and the second dose (D).

seen in other mRNA vaccine phase 3 trials.[7,8] No increase in solicited reactions was seen between the first and second CVnCoV doses. Serious adverse events and adverse events of special interest were uncommon and similar in frequency between the CVnCoV and placebo groups, although the short follow-up duration needs to be considered when interpreting these findings. The safety of the CVnCoV vaccine candidate will continue to be monitored for the duration of the trial, and findings will be presented in a future publication. Taken together with

the safety data from phase 1 trials with CVnCoV and with the CV7202 rabies mRNA vaccine,[11,16] the findings observed in this trial provide further support for the safety of the RNActive mRNA vaccine platform.[17]

HERALD was conducted in an unprecedented evolving landscape that reflects the changing reality of the global COVID-19 pandemic, with an increasing number of SARS-CoV-2 variants adding additional challenges to the assessment of COVID-19 vaccine candidates. The mRNA component of the CVnCoV vaccine candidate encodes the SARS-CoV-2 spike protein, like the two mRNA vaccines (BNT162b2 and mRNA-1273) that have been approved as of August, 2021. However, only 3% of adjudicated and sequenced cases of COVID-19 in HERALD were identified as resulting from B.1 lineage SARS-CoV-2. About 50% of cases of COVID-19 in our trial were caused by variants of concern, 35% were caused by variants of interest, as classified by WHO in September, 2021, and about 3% were caused by wild-type, with the remaining 11% caused by other variants.[14] Although we were only able to evaluate vaccine efficacy against these variants in participants aged 18–60 years, the results indicate that the vaccine had similar efficacies against alpha, gamma, and lambda variants. Many newly emerged strains have shown increased transmissibility,[18] and differences in neutralising antibody activity against these strains might alter vaccine efficacy.[19] These concerns are supported by results from other phase 3 efficacy trials, with SARS-CoV-2 variant-dependent differences in efficacy reported for the ChAdOx1 nCoV-19 (Oxford-AstraZeneca),[20–22] NVX-CoV2373 (Novavax),[23,24] and Ad26.COV2.S (Janssen) SARS-CoV-2 vaccines.[25] The point estimates for real-world mRNA vaccine effectiveness, in settings with increasing diversity of variants, are lower than the point estimates for efficacy as reported in clinical trials.[26–28] In this context, the comparison of vaccine efficacy against different SARS-CoV-2 variants and between Europe and Latin America, although not prespecified in the protocol, is important from a public health perspective. Broad geographical representation should therefore be considered when designing future studies evaluating the efficacy of SARS-CoV-2 vaccines and vaccine efficacy against emerging variants.

HERALD was initiated when the first SARS-CoV-2 vaccines were authorised for emergency use. As national COVID-19 vaccination programmes prioritised the vaccination of older adults, recruiting non-vaccinated participants aged 61 years or older was difficult, and this limitation might have contributed to the proportion of the study population aged 61 years or older being less than the non-binding target enrolment of 20–25%. In addition, per protocol, participants eligible for an authorised vaccine could request unmasking and subsequent vaccination with an available vaccine, and this allowance resulted in further censoring of participants in the efficacy analyses. Only 12·7% (5004 of 39 529) of the participants in the phase 2b–3 safety analysis set and 10·0% (2499 of 25 062) of participants in the primary efficacy analysis set were aged 61 years or older. In addition, 69·8% of participants aged 61 years or older in the primary efficacy analysis set were unmasked compared with 31·6% of those aged 18–60 years. This unblinding resulted in markedly fewer analysable participants aged 61 years or older in our study than in most other phase 3 efficacy trials assessing COVID-19 vaccines.[7,8,20,23,25] The low recruitment, combined with the large number of older participants who were unmasked and therefore contributed less follow-up time to the efficacy analyses, limited the interpretability of our findings in this age group and affected the overall study results.

The broad case definition and the twice weekly reminders to participants to report any potential COVID-19 symptoms in HERALD meant that symptoms that probably would not have triggered RT-PCR confirmation in other trials of SARS-CoV-2 vaccines might have resulted in confirmation of mild COVID-19 in HERALD, as evidenced by the fact that almost 80% of cases were mild. Most vaccines, including CVnCoV, have shown increased efficacy against COVID-19 with increasing disease severity.[7,8,23,25] The clinical implications of CVnCoV's 70·7% efficacy against moderate-to-severe COVID-19, nearly all cases of which were caused by variants of concern or variants of interest, suggest a high potential for a positive impact on public health. Access to vaccines protecting against moderate-to-severe disease, and thus preventing disruption to the normal functioning of hospitals and intensive care units, is essential to prevent non-COVID-19-associated morbidity and mortality.[29–31]

CVnCoV contains 12 µg of mRNA, considerably less than BNT162b2 (30 µg) and mRNA-1273 (100 µg) contain. We cannot dismiss the possibility that this dose was insufficient to elicit a protective immune response. However, in a phase 1 dose-escalation study of participants aged 18–60 years, two 12 µg doses of CVnCoV induced antibodies against the SARS-CoV-2 spike protein and its receptor binding domain and anti-SARS-CoV-2 neutralising titres that were similar to those seen in convalescent serum samples from patients who had had COVID-19.[11] However, in view of the changing environment, including the emergence of SARS-CoV-2 variants, and taking into account timelines for further development, the decision had been made to cease activities on the CVnCoV candidate, and to focus efforts on the promising and rapidly progressing development of the next generation vaccine candidates. One of these, the CV2CoV candidate, has already been shown to induce high humoral and cellular immune responses in non-human primate studies.[32]

In conclusion, the two-dose regimen of CVnCoV had an acceptable safety profile and was efficacious in the prevention of symptomatic COVID-19 in adults. In addition, we observed vaccine efficacy against newly emerged variants, including variants of concern.

Contributors

PGK, AK, IL-R, PM, OS-K, TV, and LO conceived the HERALD trial; PGK is the coordinating investigator and LO is study lead. HJ is the qualified physician and co-chair of the DSMB. PGK, RC, EJLDB, MAGG, AK, IL-R, PM, MFM-R, OS-K, TV, and LO contributed to the trial design and protocol. PGK, HJ, PM, and TV participated in the data curation and had full access to and verified all study data. PGK, AK, PM, OS-K, TV, and LO did the statistical analyses. PGK, RAAG, EA-A, GJAM, MB, RC, RC GC, EJLDB, LE, JJG, CAGL, LG, MAGG, NG, MPG, ADH, CFL, CL, IL-R, MFM-R, TJO, CAP, MJRF, LMRM, VVRH, XS-L, MS, ASG, IV, and MV are study site principal investigators. PGK, PM, OS-K, and LO were in the core writing group responsible for preparation of the manuscript and received support from a medical writer. Manuscript drafts were reviewed by all authors, and the content of the submitted version was approved by all authors before submission. All authors had final responsibility for the decision to submit for publication. Because the study is ongoing, authors could not be given access to the whole dataset analysed in this Article, but they will be given full access when the study is terminated.

Declaration of interests

MB declares institutional funding from CureVac during the conduct of this study, institutional funding from Janssen Vaccines, Molecular Partners, and Merck outside the submitted work, and consulting fees from Janssen Vaccines outside the submitted work. EJLDB, MFM-R, TJO, and XS-L declare institutional funding from CureVac during the conduct of this study. LE and LG declare institutional funding from CureVac during the conduct of this study and outside the submitted work. CFL declares institutional funding from CureVac during the conduct of this study and outside the submitted work and is a member of the WHO Covid-19 Vaccine Effectiveness Working Group and the WHO Product Development for Vaccines Advisory Committee. CL declares institutional funding from CureVac during the conduct of this study and is a member of the German Society of Infection board. IL-R declares institutional funding from CureVac during the conduct of this study and institutional funding from Johnson & Johnson and OSE Immunotherapeutics outside the submitted work. PGK declares institutional funding from CureVac during the conduct of this study and is a member of the scientific advisory board for the HERALD clinical trial. VVRH declares institutional funding from CureVac during the conduct of this study and speakers fees from Gilead outside the submitted work. HJ declares consultant fees from CureVac, is the qualified physician for the HERALD clinical trial, and is co-chair of the DSMB for the HERALD clinical trial. AK and PM are employed by CureVac and hold stock options. OS-K declares consultant fees from CureVac during the conduct of this study and is a member of the DSMB for a CVnCoV phase 1 trial. TV declares consultant fees from CureVac during the conduct of this study, and consultant fees from CureVac, AstraZeneca, Pfizer, Johnson & Johnson, and Moderna outside the submitted work. LO is employed by CureVac and holds stock options and is the holder of a pending patent. All other authors declare no competing interests.

Data sharing

Anonymised participant data will be made available when the trial is complete, on requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can only be shared through a secure online platform after a data access agreement is signed. All data will be made available for a minimum of 5 years from the end of the trial.

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