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Safety and immunogenicity of an inactivated whole virion SARS-CoV-2 vaccine, TURKOVAC, in healthy adults: Interim results from randomised, double-blind, placebo-controlled phase 1 and 2 trials

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ABSTRACT

Background: Development of safe and effective vaccine options is crucial to the success of fight against COVID-19 pandemic. Herein, we report interim safety and immunogenicity findings of the phase 1&2 trials of ERUCoV-VAC, an inactivated whole virion SARS-CoV-2 vaccine.

Methods: Double-blind, randomised, single centre, phase 1 and 2 trials included SARS-CoV-2 seronegative healthy adults aged 18–55 years (18–64 in phase 2). All participants, except the first 4 in phase 1 who received ERUCoV-VAC 3 μg or 6 μg unblinded and monitored for 7 days for safety purposes, were assigned to receive two intramuscular doses of ERUCoV-VAC 3 μg or 6 μg (an inactivated vaccine containing alhydrogel as adjuvant) or placebo 21 days apart (28 days in phase 2) according to computer-generated randomisation schemes. Both trials are registered at ClinicalTrials.gov (phase 1, NCT04691947 and phase 2, NCT04824391).

Results: Forty-four participants (3 μg [n:17], 6 μg [n:17], placebo [n:10]) in phase 1 and 250 (3 μg [n:100], 6 μg [n:100], placebo [n:50]) in phase 2 received ≥1 dose. In phase 1 trial, 25 adverse events AEs (80 % mild) occured in 15 participants (34.1 %) until day 43. There was no dose-response relationship noted in safety events in ERUCoV-VAC recipients (p = 0.4905). Pain at injection site was the most common AE (9/44;20.5 %). Both doses of ERUCoV-VAC 3 μg and 6 μg groups were comparable in inducing SARS-CoV-2 wild-type neutralising antibody (MNT50): GMTs (95 %CI) were 8.3 (6.4–10.3) vs. 8.6 (7.0–10.2) at day 43 (p = 0.7357) and 9.7 (6.0–13.4) vs. 10.8 (8.8–12.8) at day 60 (p = 0.8644), respectively. FRNT50 confirmed MNT50 results: SARS-CoV-2 wild-type neutralising antibody GMTs (95 %CI) were 8.4 (6.3–10.5) vs. 9.0 (7.2–10.8) at day 43 (p = 0.5393) and 11.0 (7.0–14.9) vs. 12.3 (10.3–14.5) at day 60 (p = 0.8578). Neutralising antibody seroconversion rates (95 %CI) were 86.7 % (59.5–98.3) vs 94.1 % (71.3–99.8) at day 43 (p = 0.8727) and 92.8 % (66.1–99.8) vs. 100 % (79.4–100.0) at day 60 (p = 0.8873), in ERUCoV-VAC 3 μg and 6 μg groups, respectively. In phase 2 trial, 268 AEs, (67.2 % moderate in severity) occured in 153 (61.2 %) participants. The most common local and systemic AEs were pain at injection site (23 events in 21 [8.4 %] subjects) and headache (56 events in 47 [18.8 %] subjects), respectively. Pain at

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injection site was the only AE with a significantly higher frequency in the ERUCoV-VAC groups than in the placebo arm in the phase 2 study (p = 0.0322). ERUCoV-VAC groups were comparable in frequency of AEs (p = 0.4587). ERUCoV-VAC 3 μg and 6 μg groups were comparable neutralising antibody (MNT_{50}): GMTs (95 %CI) were 30.0 (37.9–22.0) vs. 34.9 (47.6–22.1) at day 43 (p = 0.0666) and 34.2 (23.8–44.5) and 39.6 (22.7–58.0) at day 60, (p = 0.2166), respectively. FRNT50 confirmed MNT50 results: SARS-CoV-2 wildtype neutralising antibody GMTs were 28.9 (20.0–37.7) and 30.1 (18.5–41.6) at day 43 (p = 0.3366) and 34.2 (23.8–44.5) and 39.6 (22.7–58.0) at day 60 (p = 0.8777). Neutralising antibody seroconversion rates (95 % CI) were 95.7 % (91.4–99.8) vs. 98.9 % (96.9–100.0) at day 43 (p = 0.8710) and 96.6 % (92.8–100.0) vs 98.9 % (96.7–100.0) at day 60 (p = 0.9129) in ERUCoV-VAC 3 μg and 6 μg groups, respectively.

Conclusions: Two-dose regimens of ERUCoV-VAC 3 μg and 6 μg 28 days both had an acceptable safety and tolerability profile and elicited comparable neutralising antibody responses and seroconversion rates exceeding 95 % at day 43 and 60 after the first vaccination.

1. Introduction

COVID-19 outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in China [1] in December 2019 and described as a pandemic by the World Health Organization (WHO) in March 2020. [2] As of the end of February 2022, there have been over 434 million confirmed COVID-19 cases worldwide, including approximately 6 million deaths [3].

Vaccination is a well-established, cost-effective public health measure to prevent and control infectious diseases. [4–6] Therefore, development of safe, effective, and accessible vaccines has been prioritized to control the COVID-19 disease and mitigate the devastating effects of the pandemic. [6,7] Conventional approaches such as inactivated or live attenuated virus and protein-based vaccines as well as newer platforms like viral vectors, DNA and messenger RNA (mRNA), nanoparticle-based and virus-like particles have been investigated. [8].

Turkiye initiated a vaccine development programme shortly after the first COVID-19 case was seen in the country, in March 2020. ERUCoV-VAC which is a whole-virion β-propiolactone-inacti vated SARS-CoV-2 vaccine adjuvanted with Alhydrogel, is one of the vaccines in this program, now known as TURKOVAC. Its preclinical safety and efficacy were demonstrated by its high immunogenicity in BALB/c mice, complete protection against a lethal SARS-CoV-2 challenge in transgenic mice (K18-hACE2), and positive safety profile in ferret models. [9] The clinical development programme, including the phase 1 and phase 2 trials as well as the phase 3 comparative efficacy and safety trial (NCT04942405) versus CoronaVac (Sinovac Life Sciences, Beijing, China), is ongoing. TURKOVAC received emergency use authorisation (EUA) by the Turkish Medicines and Medical Devices Agency in December 2021.

Herein, we report the interim safety and immunogenicity results of the phase 1 and phase 2 trials of two different strengths (3 μg and 6 μg) of TURKOVAC up to day 60 (month 2).

2. Methods

2.1. Study design and participants

The double-blind, randomised, parallel, placebo-controlled phase 1 and 2 clinical trials of ERUCoV-VAC (named as TURKOVAC as of phase 3) were designed by Erciyes University Hakan Çetinsaya Good Clinical Practice and Research Centre and Erciyes University Vaccine Research, Development and Application Centre (ERAGEM) and were conducted at a single centre (IKUM) in Turkiye. In both trials, the participants were allocated to receive two intramuscular injections (0.5 mL) of 3 μg or 6 μg doses of the vaccine, or placebo (0.9 % saline) into deltoid muscle with 21- and 28- days intervals in the phase 1 and 2 trials, respectively.

SARS-CoV-2-seronegative (IgG and/or IgM) healthy volunteers aged 18 to 55 years and 18 to 64 years were included in the phase 1 and phase 2 trials, respectively. History of COVID-19 or COVID-19 associated symptoms, contact with people with known COVID-19 in the last 14 days and positive COVID-19 real time polymerase chain reaction (RT-PCR) test were the key exclusion criteria for both trials. The list of eligibility criteria is provided in the Supplementary Appendix A.

Studies were approved by the Ethics Committee for Clinical Trials of Erciyes University and Turkish Ministry of Health (2020/548, October 28, 2020 for phase 1 and 2021/74, February 01, 2021 for phase 2). Both trials are registered at ClinicalTrials.gov (phase 1, NCT04691947 and phase 2, NCT04824391).

2.2. Randomisation and masking

The phase 1 trial was the first-in-human study of ERUCoV-VAC. The first two participants received ERUCoV-VAC 3 μg and monitored for 7 days. As there were no significant safety issues in these patients, the next two participants received ERUCoV-VAC 6 μg and were also followed up for 7 days. Since the Data Monitoring Committee (DMC) confirmed no significant safety issues with both doses, 40 subsequent subjects were double-blindly randomized to one of the trial arms (placebo, ERUCoV-VAC 3 μg and 6 μg). In the phase 2 trial, all participants were blinded and randomly assigned to receive 3 μg or 6 μg doses of ERUCoV-VAC or placebo (2:1:1). Placebo recipients were unmasked after day 43 and released from the trials as per the study protocols, to allow them to receive a vaccine accessible via EUA, but the analytical facility remained unblinded for these participants until the end of the studies.

2.3. Procedures

ERUCoV-VAC was manufactured using the SARS-CoV-2 strain (hCoV-19/Turkiye/ERAGEM-001/2020 strain, GenBank accession number, MT327745.1 and GISAID; EPI_ISL_424366) isolated from a patient's nasopharyngeal sample in the Kayseri City Training and Research Hospital, Kayseri, Turkiye. [10] The virus was cultivated in a Vero cell line for 72–96 h at multiplicities of infection of 0.05. The infected cell supernatant was harvested and inactivated with β-propiolactone (1:4000 volume/volume at 2–8 °C for 6 h). Following clarification and ultrafiltration, the second β-propiolactone inactivation was performed (1:2000 volume/volume at 2-8 °C for 6 h). After purification, the vaccine was adsorbed onto aluminium hydroxide adjuvant (alhydrogel). The vaccine was manufactured as a liquid formulation containing 3 μg or 6 μg total protein with aluminium hydroxide adjuvant (0.5 mg/dose) in 0.5 mL

sterile saline solution (0.9 % NaCl) without preservative. A rocking motion bioreactor (Biostat® RM 20, Sartorius Stedim Biotech, Melsungen, Germany) was used in the phase 2 trial to increase vaccine production capacity. Placebo consisted of 0.5 mL sterile saline (0.9 % NaCl) in prefilled syringes in the phase 1 trial; vials were used instead of prefilled syringes in the phase 2 trial and stored at refrigerator between 2 and 8 °C.

The clinical and laboratory evaluations for the phase 1 and 2 trials are given in Supplementary Appendix B. In the phase 1 trial, all subjects fulfilling the eligibility criteria were isolated in the Training Hotel of Erciyes University Faculty of Tourism, five days before vaccination to minimise the risk of infection The day before receiving the vaccine, participants were transferred to IKUM and discharged 24 h after vaccination. The same procedures were repeated before the second injection, on day 21. The study procedures evaluated in the interim analysis included adverse event (AE) questioning and vital sign follow up (before dosing and 2 h, 4 h, 8 h, 12 h, and 24 h after administration; on day 3 to 7 and 14 after each dose, day 43 and month 2), laboratory safety data on days 2, 7, 14, 21, 22, 27, 35, 43, and month 2; immunogenicity analysis (anti-SARS-CoV-2 S1 RBD [Spike S1 Receptor Binding Domain] IgG and anti-SARS-CoV-2 IgG antibodies); neutralising antibodies against wild-type SARS-CoV-2 before each dose on vaccination day, on days 7, 14, 21, 27, 35, 43, and at month 2. Neutralising antibodies to wild-type SARS-CoV-2 (hCoV-19/Turkiye/ERAGEM-001/2020 strain, GenBank accession number; MT327745.1 and GISAID; EPI_ISL_424366) in serum samples were determined by a microneutralisation test (MNT_{50}) and confirmed with a focus-reduction neutralisation test ($FRNT_{50}$). The Euroimmune anti-SARS CoV-2 (IgG) enzyme linked immunoassay (ELISA) kit was used for measuring anti-SARS-CoV-2 S1 RBD IgG levels and an in-house IgG ELISA (based on purified whole- SARS-CoV-2) was used for detecting anti-SARS-CoV-2 IgG levels. Methods of the immunogenicity assessments are detailed in Supplementary Appendix C.

The phase 2 trial was initiated after the pre-scheduled interim safety and immunogenicity analyses at day 43 of phase 1 trial. In the phase 2 study, the immunisation schedule was changed to a two-dose regimen on day 0 and 28 considering the findings of the phase 1 trial and the results of a previous inactivated COVID-2 vaccine trial. [11] Participants were randomised to receive 3 μg or 6 μg doses of the vaccine or placebo. AEs and vital signs up to month 2; laboratory safety data (haematology, blood chemistry) on day 7, 14, 21, 28, 35, 43, and at month 2 and the immunogenicity tests (same as phase 1) before the dose on vaccination day, on day 7, 14, 21, 28, 35, 43, and at month 2 were evaluated. We also analysed vaccine stimulated *T*-cell response at day 43, by interferon (IFN)-γ ELISPOT assay using a commercial kit (Human IFN-γ ELISpotPRO [3420-2APT-2]; Mabtech, Sweden). The results were expressed as the number of spot-forming cells (SFCs) per 100000 cells and compared versus baseline.

2.4. Outcomes

Here, we describe the outcomes evaluated in the scope of the 2-month interim analyses of the phase 1 and 2 trials of ERUCoV-VAC.

In the phase 1 trial, the primary outcome was AEs observed within 43 days after the first vaccination, reported as the number and proportion of participants. Solicited and unsolicited AEs were collected. AE questioning was made at the time-points specified in the trial protocols for local reactions (pain, redness or swelling) and general health state (fever, headache, myalgia, malaise, gastrointestinal and cardiovascular symptoms) for the 7 consecutive days after each vaccination and in each visit. All AEs were evaluated based on the joint decision of the researchers in this single centre study. AEs related to vaccine administration (including placebo) were defined as adverse drug reactions (ADR). AEs were graded as mild (grade 1; no intervention required; no impact on daily activities), moderate (grade 2; local/minimal/non-invasive intervention required, moderate impact on daily activities) and severe (grade 3; requirement for invasive interventions, major impact on daily life; subject seeks medical attention, needs major assistance with ADL).

The distribution of AEs between the study groups were compared. Abnormal laboratory test results, on injection dates (before vaccination) and on the seventh day, requiring repeat testing, were also reported as the number of events. The key immunogenicity outcomes were SARS-CoV-2 neutralising and anti-SARS-CoV-2 S1 RBD and anti-SARS CoV-2 total titres on day 43, expressed as geometric means and 95 % confidence interval (GMT[95 %CI]). Antibody titres on day 60 were also evaluated. Seroconversion was defined as at least fourfold increase in antibody titre versus baseline (before vaccination) and the proportion of participants achieving seroconversion at day 43 and 60 were presented.

In the phase 2 trial, the primary outcomes were the antibody titres against SARS-COV-2 S1 RBD and whole SARS-CoV-2, and SARS-CoV-2 neutralising antibody titres on day 43. Antibody titres and seroconversion rates were evaluated at day 43 and 60 and expressed as described for phase 1 trial. The key safety outcome was AEs within the 43 days of first vaccination, reported as described for the phase 1 study.

In addition, ELISPOT assay was performed to evaluate the extent of *T*-cell response at day 43 (14 days after the second vaccination) and the results were expressed as the number of spot-forming cells (SFCs) per 100 000 cells. Details about ELISPOT testing are provided in Supplementary Appendix C.

2.5. Statistical analysis

As the phase 1 trial was the first-in-human study of ERUCoV-VAC, no formal sample size calculation was made. Instead, we included 17 participants in each vaccine arm and 10 participants in the placebo arm, considering the minimum sample size requirement to allow for a reasonable statistical evaluation. Safety outcomes were assessed in the safety population which comprised all participants who received at least one dose of the vaccine (placebo recipients were excluded from assessments after the first 43 days as described in the randomisation and masking section). Immunogenicity outcomes were assessed for antibody measurement on day 43 and 60.

The phase 2 trial included 100 participants in each vaccine arm and 50 participants in the placebo arm. The size of the resulting safety database was considered large enough to estimate the frequency of uncommon AEs.

Immunogenicity analyses were performed in the per-protocol set that included all subjects with no major protocol deviations who met all inclusion/exclusion criteria and vaccinated according to the vaccination time schedule described in the study protocol. All patients who received at least one dose of the vaccine or the placebo constituted the safety set.

We used Graph Pad Prism 9.0.1 program and Phoenix WinNonlin V8.2.0.4383 for the analyses. Fisher's exact test and chi-square test were used for categorical data analysis during safety assessment. Statistical analyses and graphical representations of immunological data were conducted using Graph Pad Prism 9.0.1. A chi-square test was used to compare seroconversion rates among the groups. Likewise, an unpaired *t*-test was utilized to compare 3 μg, and 6 μg vaccinated groups in ELISA, neutralising antibody assay, and ELISPOT assay. Similarly, one-way ANOVA was used to compare vaccinated and unvaccinated groups. Spearman's correlation curve was used to measure the relationship between MNT and FRNT results in each trial. The r-value indicates

the degree of correlation. For all analyses, a p value < 0.05 denotes statistical significance.

3. Results

Between October 31 and November 18, 2020, 69 volunteers were screened of whom 44 were enrolled in the phase 1 trial. The phase 2 trial enrolled 250 of 376 volunteers who were screened between February 10 and March 12, 2021. The study profiles are displayed in Fig. 1A and Fig. 1B. Two-dose vaccination rates were 94.1 %, 100 % and 100 %, and 93 %, 97 %, and 96 % in the ERUCoV-VAC 3 μg, ERUCoV-VAC 6 μg and placebo groups, in the phase 1 and phase 2 trials, respectively. Baseline key demographics of participants enrolled in both trials are summarised in Table 1.

3.1. Safety

In the phase 1 trial, 25 AEs were reported in 15 (34.1 %) of 44 participants until day 43. The frequencies of AEs were significantly different between the study groups (p = 0.0002); while there were no AEs in placebo recipients, the frequency of AEs was similar among the ERUCoV-VAC groups (p = 0.4905) (Table 2). Most AEs (80 %) were mild in severity and resolved within a few days; no severe or serious AEs were seen in any of the participants (Table S1, Supplementary Appendix D).The majority of ADRs occurred within the first week of vaccination. Pain at injection site was the most common AE (10 events in 9 (20.5 %) subjects) followed by headache (6 events in 4 (9.1 %) subjects) (Table S2, Supplementary Appendix D). Pain at injection site occurred in 16 % (7/44) and 4.5 % (2/44) of study participants after the first and second vaccination, respectively. Fifteen days after the first vaccination, COVID-19 RT-PCR test was positive in one subject in the ERUCoV-VAC 3 μg arm and was confirmed with repeat testing. A clinically relevant low white blood cell count occurred in one participant on day 14 and resolved after 3 days. The code was broken on day 17 and revealed that the participant was an ERUCoV-VAC 3 μg recipient. The causal relationship between the event and the investigational product was judged as "unlikely" by the investigators and the DMC. A total of 62 laboratory test results (grade 3) requiring repeat testing were detected on the days of vaccination (before injection) and seven days later (1st injection: ERUCoV-VAC 3 μg: 11, ERUCoV-VAC 6 μg: 28, placebo: 3; 2nd injection: ERUCoV-VAC 3 μg: 10, ERUCoV-VAC 6 μg: 7, placebo: 3) (Table S3, Supplementary Appendix E).

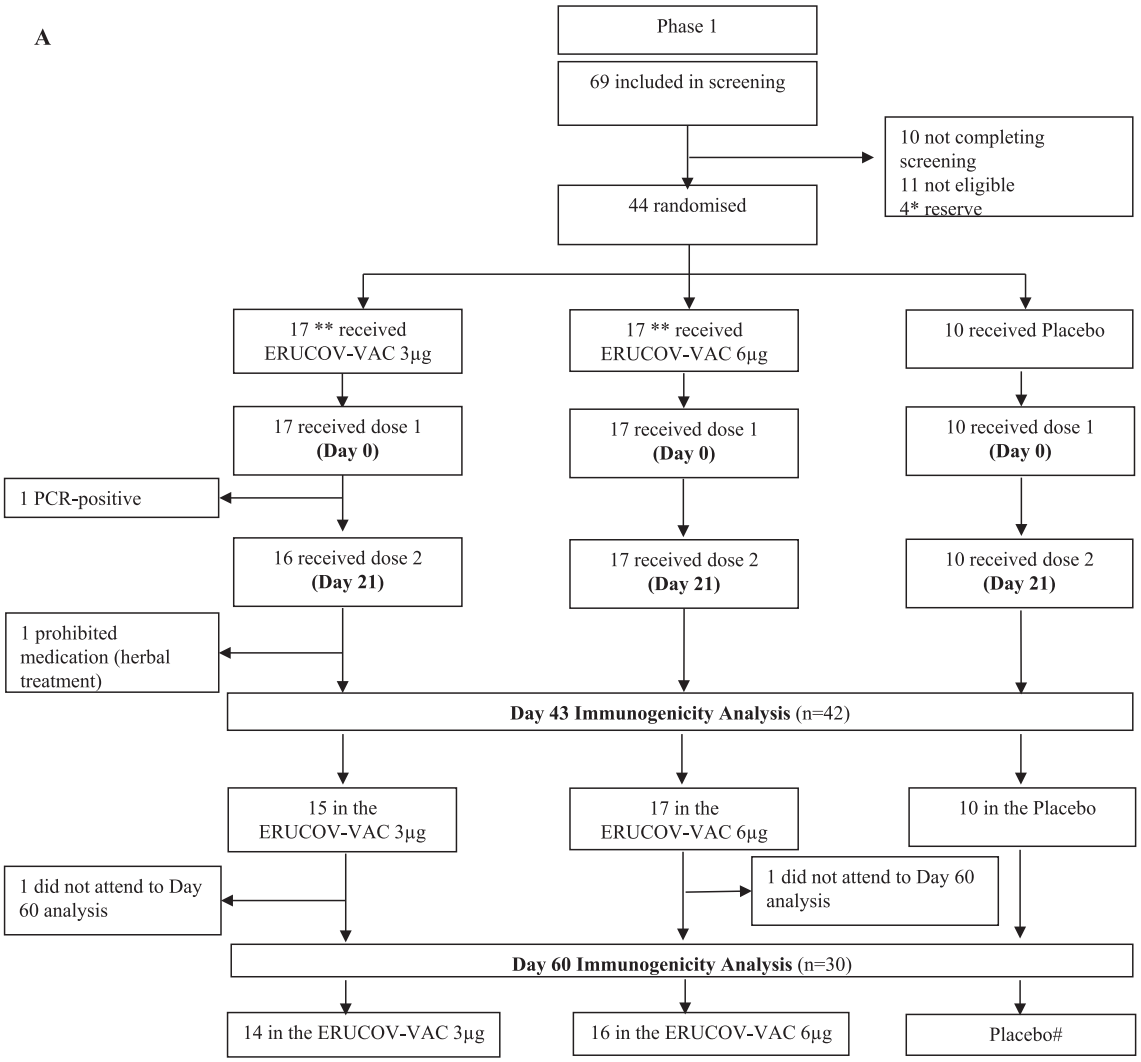

Fig. 1. Study profiles for **(A)** phase 1 and **(B)** phase 2 trials. n = number of participants.*not included as the targeted number of randomised patients was achieved. **The first four patients enrolled in the study (two in each vaccine arm) unblindly received ERUCoV-VAC and were monitored for a week for safety purposes (see randomisation and masking). #Placebo recipients were released from the trials to allow them to receive one of the vaccines that became available for emergency use.

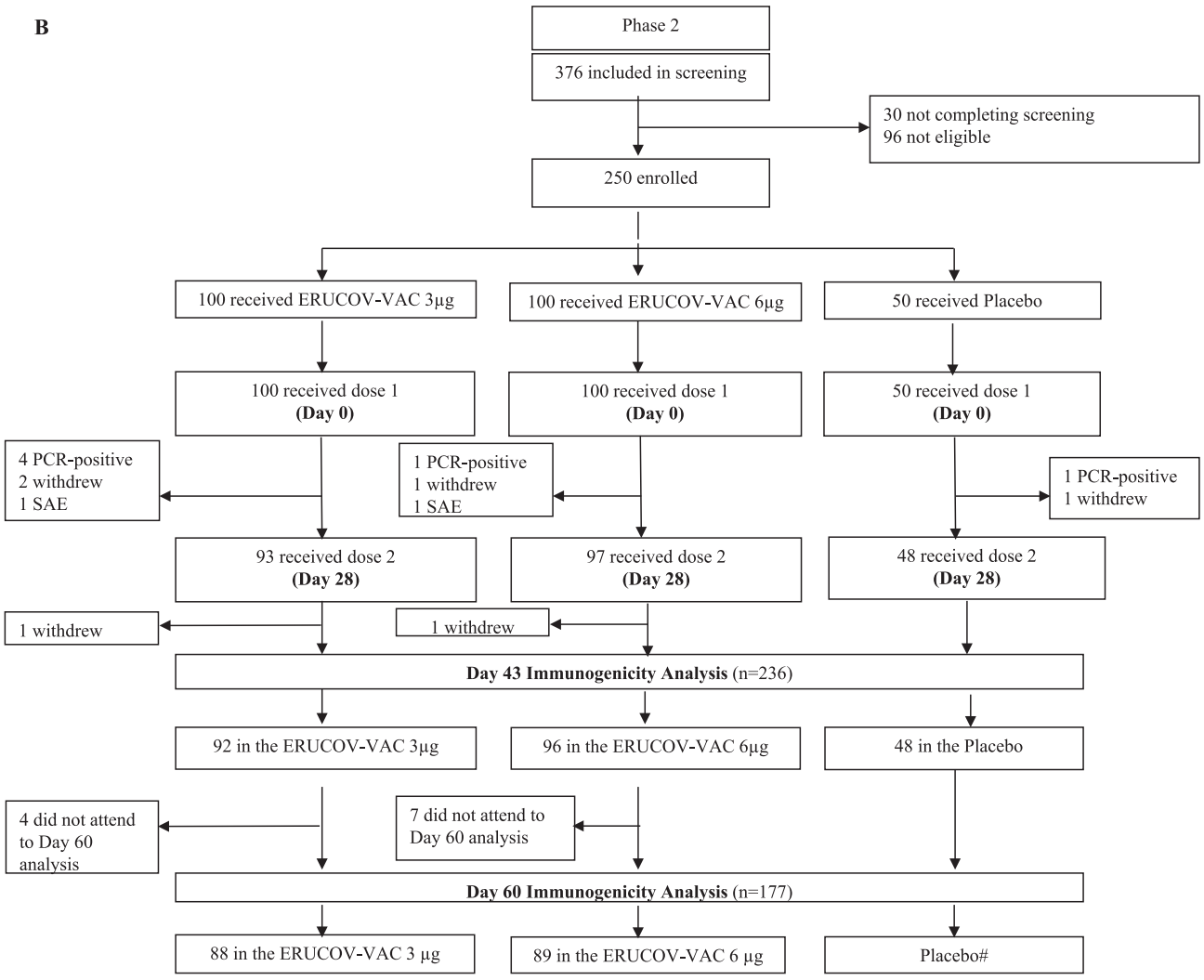

Fig. 1 (*continued*)

Table 1
Baseline demographic characteristics of participants in the phase 1 and phase 2 trials.

	ERUCoV-VAC 3 µg	ERUCoV-VAC 6 µg	Placebo	Overall
Phase 1				
Participants	n = 17	n = 17	n = 10	n = 44
Age (years)	31.9 ± 8.7	32.5 ± 8.9	34.6 ± 11.0	32.8 ± 9.2
Sex				
Male	13 (76.5)	12 (70.6)	10 (100.0)	35 (79.5)
Female	4 (23.5)	5 (29.4)	0 (0.0)	9 (20.5)
BMI (kg/m^2)	25.2 ± 3.3	24.0 ± 3.4	26.6 ± 3.8	25.0 (3.5)
Phase 2				
Participants	n = 100	n = 100	n = 50	n = 250
Age (years)	37.0 ± 10.2	37.9 ± 9.6	37.5 ± 9.5	37.5 ± 9.8
Sex				
Male	80 (80.0)	78 (78.0)	33 (66.0)	191 (76.4)
Female	20 (20.0)	22 (22.0)	17 (34.0)	59 (23.6)
BMI (kg/m^2)	26.2 ± 3.8	27.1 ± 3.4	26.4 ± 3.6	26.6 ± 3.6

Data are mean ± SD or n (%). BMI = body mass index.

In the phase 2 trial, 268 AEs, two-thirds of which (n = 176; 67.2 %) were moderate in severity, occurred in 153 (61.2 %) of 250 participants within 43 days of first vaccination (Table S4, S5, Supplementary Appendix F). The AEs were less frequent in the placebo arm than in ERUCoV-VAC arms (p = 0.0327), but the frequencies of AEs were comparable in the ERUCoV-VAC groups (p = 0.4587) (Table 2). Headache was the most common AE (56 events in 47 (18.8 %) participants), followed by weakness (37 events in 33 (13.2 %) participants), and pain at injection site (23 events in 21 (8.4 %) participants). Pain at injection site was the only AE with a significantly higher frequency in the ERUCoV-VAC groups than in the placebo arm (p = 0.0322). PCR test for

Table 2
Grading of adverse events until day 60, phase 1 and 2 trials (Safety set).

	ERUCoV-VAC* 3 µg	ERUCoV-VAC* 6 µg	Placebo*	Overall	p1**	p2***
Phase 1 trial	n = 17	n = 17	n = 10	n = 44		
Until day 43*						
Any grade	13 (9; 52.9 %)	12 (6; 35.3 %)	0 (0; 0 %)	25 (15; 34.1 %)	0.0002**	0.4905
Grade 1 (mild)	11 (7; 41.1 %)	9 (6; 35.3 %)	0 (0; 0 %)	20 (13; 29.5 %)	0.0036**	>0.9999
Grade 2 (moderate)	2 (2; 11.8 %)	3 (1; 5.9 %)	0 (0; 0 %)	5 (3; 6.8 %)	0.3770**	>0.9999
Grade 3 (severe)	0 (0; 0 %)	0 (0; 0 %)	0 (0; 0 %)	0 (0; 0 %)	–	–
Day 43 to 60*				n = 34		
Any grade	0 (0; 0 %)	0 (0; 0 %)	NA	0 (0; 0 %)	–	–
	ERUCoV-VAC 3 µg	**ERUCoV-VAC 6 µg**	**Placebo***	**Overall**	p1**	p2***
Phase 2 trial	n = 100	n = 100	n = 50	n = 250		
Until day 43*						
Any grade	106 (68; 68 %)	122 (62; 62 %)	40 (23; 46 %)	268 (153; 61.2 %)	0.0327	0.4587
Grade 1 (mild)	34 (22; 22 %)	41 (21; 21 %)	16 (9; 18 %)	91 (52; 20.8 %)	0.8488	>0.9999
Grade 2 (moderate)	72 (46; 46 %)	80 (40; 40 %)	24 (14; 28 %)	176 (100; 40 %)	0.1054	0.4752
Grade 3 (severe)	0 (0; 0 %)	1 (1; 1 %)	0 (0; 0 %)	1 (1; 0.4 %)	0.4709	>0.9999
Day 43 to 60****				n = 200	p***	
Any grade	3 (2; 2 %)	5 (3; 3 %)	NA	8 (5; 2.5 %)	–	0.7209
Grade 1 (mild)	1 (1; 1 %)	5(3; 3 %)	NA	6 (4; 2 %)	–	0.2116
Grade2 (moderate)	2 (2; 2 %)	0 (0; 0 %)	NA	2 (2; 1 %)	–	0.4975
Grade 3 (severe)	0 (0; 0 %)	0 (0; 0 %)	NA	0 (0; 0 %)	–	–

Safety set consists of patients who received at least one dose of ERUCoV-VAC or placebo. Data are total number of AEs (number and percentage of patients). AEs = adverse events; NA = not applicable (placebo recipients were released from the trial after day 43 as per protocol to allow them to receive the vaccine approved for emergency use. *Reported as number of events (number and % of participants who experienced events). **Chi-square test comparing placebo vs ERUCoV-VAC 3 µg vs ERUCoV-VAC 6 µg; *** Fisher's exact test comparing ERUCoV-VAC 3 µg vs ERUCoV-VAC 6 µg. **** Calculated out of 200 participants since placebo recipients had been released after day 43 evaluation to allow them being vaccinated with one of the vaccines approved for emergency use.

Table 3
Incidence of adverse events (≥3%) until day 43 in the phase 2 trial.

Type of AEs	ERUCoV-VAC 3 µg (n = 100)	ERUCoV-VAC 6 µg (n = 100)	Placebo (n = 50)	Overall* (number and % of 250 participants)	p value*
Until day 43					
Headache	20 (17; 17 %)	20 (18; 18 %)	16 (12; 24 %)	56 (47; 18.8 %)	0.1907
Weakness	16 (14; 14 %)	16 (16; 16 %)	5 (5; 10 %)	37 (33; 13.2 %)	0.5650
Pain at injection site	13 (12; 12 %)	10 (9; 9 %)	0 (0; 0 %)	23 (21; 8.4 %)	0.0322
Positive PCR COVID-19 test	6 (6; 6 %)	3 (3; 3 %)	3 (3; 6 %)	12 (12; 4.8 %)	0.5539
Nausea	3 (3; 3 %)	7 (6; 6 %)	0 (0;0%)	10 (9; 3.6 %)	0.0960
Sore throat	3 (3;3%)	4 (4; 4 %)	2 (2; 4 %)	9 (9; 3.6 %)	0.9172
Fatigue	5 (5; 5 %)	4 (4; 4 %)	0 (0; 0 %)	9 (9; 3.6 %)	0.2897
Arthralgia	3 (3; 3 %)	4 (4; 4 %)	2 (2; 4 %)	9 (9; 3.6 %)	0.9172

Data are number or total number of AEs and (n and % of 250 participants). *Chi-square test for intergroup comparison of events.

COVID-19 was positive in 12 participants (three in placebo, six in ERUCoV-VAC 3 µg and three in ERUCoV-VAC 6 µg groups) (Table 3; Table S5, S6, Supplementary Appendix F). None of them required hospitalisation. Eight AEs, mostly mild (75 %), were detected in five participants (three in ERUCoV-VAC 3 µg and five in ERUCoV-VAC 6 µg groups) between days 43 and 60 (Table S4, Supplementary Appendix F). Three serious AEs (SAEs) were reported during the initial 43 days, which were all judged as unlikely to be related by the investigators and the DMC. First, a rib fracture occurred in a participant who fell while skiing one day after the first vaccination. The patient stayed in hospital for four days and followed up for eight months without any complication. Unblinding revealed that the subject received ERUCoV-VAC 3 µg. Second, a 53-year-old participant with a BMI of 29.4 kg/m^2 and no known cardiovascular disease, died of myocardial infarction while exercising, 20 days after the first injection. The code was broken, and the patient was in the ERUCoV-VAC 6 µg arm. The third SAE was hospitalisation due to COVID-19 symptoms and PCR test positivity against SARS-CoV-2 12 days after the second vaccination. The participant was hospitalized for six days with mild disease. Unblinding revealed that the subject was in the placebo arm. Additionally, a total of 85 laboratory test abnormalities requiring repeat testing were detected on the 1st and 7th days of both vaccinations, (for the first and second injection: ERUCoV-VAC 3 µg: 11 and 31, ERUCoV-VAC 6 µg: 10 and 23, placebo: 6 and 4, respectively) (Table S7, Supplementary Appendix G).

3.2. Immunogenicity

3.2.1. SARS-CoV-2 wild-type neutralising antibody (MNT_{50}, $FRNT_{50}$)

In the phase 1 trial, SARS-CoV-2 wild-type neutralising antibody (MNT_{50}) GMTs (95 %CI) were comparable across the trial groups at baseline: 2.0 (1.5–2.5) in ERUCoV-VAC 3 µg, 1.8 (1.6–2.0) in ERUCoV-VAC 6 µg, and 1.6 (1.3–2.0) in placebo groups (p = 0.3988), and increased to 8.3 (6.4–10.3) and 8.6 (7.0–10.2) at day 43, and to 9.7 (6.0–13.4) and 10.8 (8.8–12.8) at day 60, in ERUCoV-VAC 3 µg and 6 µg groups, respectively (Fig. 2A; Table S8, Supplementary Appendix H). SARS-CoV-2 wild-type neutralising antibody (MNT_{50}) GMTs at day 43 (p = 0.7357) and day 60 (p = 0.8644) were similar in the vaccine arms (Fig. 2A; Table S8 Supplementary Appendix H).

Consistent with MNT_{50} results, SARS-CoV-2 wild-type neutralising antibody ($FRNT_{50}$) GMTs were comparable across the trial groups at baseline: 1.8 (1.6–1.8) in ERUCoV-VAC 3 µg, 1.7 (1.4–1.7) in ERUCoV-VAC 6 µg, and 1.4 (1.1–1.4) in placebo groups (p = 0.1688), and increased to 8.4 (6.3–10.5) and 9.0 (7.2–10.8) at

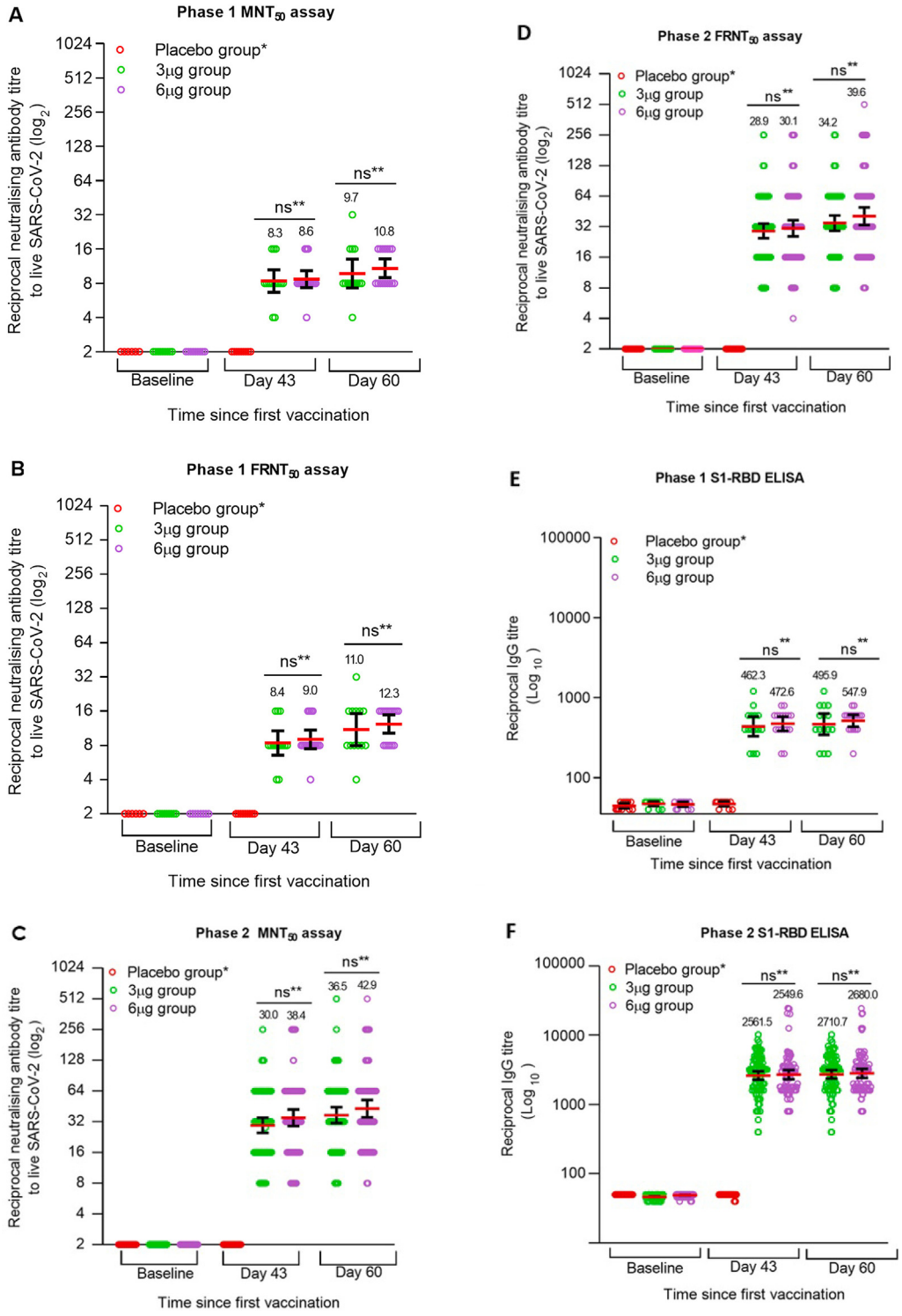

Fig. 2. Titres of SARS-CoV-2 wild-type neutralising antibodies **(A-D)** and anti-S1-RBD IgG **(E-F)** and anti- SARS-CoV-2 total IgG **(G-H)** antibodies at baseline, day 43 and day 60 in the ERUCoV-VAC (3 µg and 6 µg) and placebo groups in the phase 1 and phase 2 trials. Dose schedule: two doses 21 days apart in the phase 1 trial; two doses 28 days apart in the phase 2 trial. *placebo recipients were released from the trial after day 43, therefore not included in day 60 analyses. **ns = not significant. The numbers above the spots are the GMT estimates, the error bars represent the 95 %CI of the GMT and the spots indicate the individual antibody titres. ELISA = enzyme-linked immunosorbent assay; FRNT = focus-reduction neutralisation test; GMT = geometric mean titre; IgG = immunoglobulin G. MNT = microneutralisation test. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; S1-RBD = spike 1-receptor binding domain.

day 43 and to 11.0 (7.0–14.9) and 12.3 (10.3–14.5) at day 60 in ERUCoV-VAC 3 µg and 6 µg groups, respectively (Fig. 2B; Table S8 Supplementary Appendix H). SARS-CoV-2 wild-type neutralising antibody ($FRNT_{50}$) GMTs at day 43 (p = 0.5393) and day 60 (p = 0.8578) were also similar in the vaccine arms (Fig. 2B; Table S8 Supplementary Appendix H). There was a strong positive correlation between the $FRNT_{50}$ and MNT_{50} results at day 43 (r = 0.7065; p = 0.0001) (Fig. S1A, Supplementary Appendix I). The seroconversion rates (95 % CI) of SARS-CoV-2 wild-type neutralising antibody (MNT_{50} and $FRNT_{50}$) were 86.7 % (59.5–98.3) and

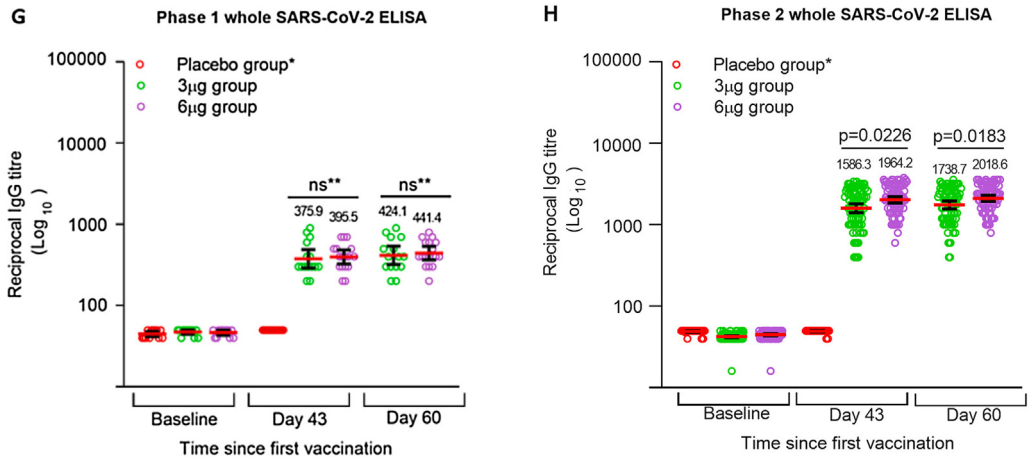

Fig. 2 (*continued*)

94.1 % (71.3–99.8) at day 43, and 92.8 % (66.1–99.8) and 100.0 % (79.4–100.0) at day 60, in the ERUCoV-VAC 3 µg and 6 µg groups, respectively (Table 4). No significant difference was found in the seroconversion rates of SARS-CoV-2 wild-type neutralising antibody titres at day 43 (p = 0.8727) and day 60 (p = 0.8873) between the vaccine groups (Table 4).

In the phase 2 trial, SARS-CoV-2 wild-type neutralising antibody (MNT_{50}) GMTs (95 %CI) were comparable across the groups at baseline: 2.0 (2.0–2.0) in the ERUCoV-VAC 3 µg, 2.0 (1.9–2.1) in the ERUCoV-VAC 6 µg, and 1.9 (1.8–2.0) in the placebo groups (p = 0.8692) and increased to 30.0 (22.0–37.9) and 34.9 (22.1–47.6) at day 43, and to 36.5 (23.0–49.9) and 42.9 (26.6–60.1) on day 60, in the ERUCoV-VAC 3 µg and 6 µg arms, respectively (Table S9, Supplementary Appendix J). SARS-CoV-2 wild-type neutralising antibody (MNT_{50}) GMTs at day 43 (p = 0.0666) and day 60 (p = 0.2166) was similar in the vaccine groups (Fig. 2C; Table S9, Supplementary Appendix J).

SARS-CoV-2 wild-type neutralising antibody ($FRNT_{50}$) GMTs (95 %CI) were comparable across the trial groups at baseline: 2.0 (2.0–2.0) in the ERUCoV-VAC 3 µg, 2.0 (1.9–2.1) in the ERUCoV-VAC 6 µg, and 2.0 (1.9–2.1) in the placebo groups (p = 0.8421), and increased to 28.9 (20.0–37.7) and 30.1 (18.5–41.6) at day 43, and to 34.2 (23.8–44.5) and 39.6 (22.7–58.0) at day 60 in the ERUCoV-VAC 3 µg and 6 µg groups, respectively. (Fig. 2D, Table S9, Supplementary Appendix J). SARS-CoV-2 wild-type neutralising antibody GMTs at day 43 (p = 0.3366) and day 60 (p = 0.8777) were similar in the ERUCoV-VAC groups (Fig. 2D; Table S9, Supplementary Appendix J). There was a strong positive correlation between the $FRNT_{50}$ and MNT_{50} results regarding SARS-CoV-2 wild-type neutralising antibody responses at day 43 (r = 0.9156; p = 0.0001) (Fig. S1B, Supplementary Appendix I). Seroconversion rates (95 % CI) of SARS-CoV-2 wild-type neutralising antibody titres (MNT_{50} and $FRNT_{50}$) were 95.7 % (91.4–99.8) and 98.9 % (96.9–100.0) at day 43, and 96.6 % (92.8–100.0) and 98.9 % (96.7–100.0) at day 60 in ERUCoV-VAC 3 µg and 6 µg groups, respectively (Table 4). There were no significant differences between the seroconversion rates of SARS-CoV-2 wild-type neutralising antibodies in the ERUCoV-VAC 3 µg and 6 µg groups at day 43 (p = 0.8710) and day 60 (p = 0.9129) (Table 4).

Table 4
Seroconversion rates of SARS-CoV-2 wild-type neutralising antibodies, anti-S1-RBD IgG and anti-SARS-CoV-2 total IgG antibody (per-protocol population).

		SARS-CoV-2 wild-type neutralising antibody* (MNT_{50})				SARS-CoV-2 wild-type neutralising antibody* ($FRNT_{50}$)			
		3 µg group	6 µg group	Placebo	p**	3 µg group	6 µg group	Placebo	p**
Phase 1	Day 43	86.7 % (13/15) [59.5–98.3]	94.1 % (16/17) [71.3–99.8]	0.0 % (0/10) [0.0–30.0]	0.8727	86.7 % (13/15) [59.5–98.3]	94.1 % (16/17) [71.3–99.8]	0.0 % (0/10) [0.0–30.0]	0.8727
	Day 60	92.8 % (13/14) [66.1–99.8]	100.0 % (16/16) [79.4–100.0]	NA***	0.8873	92.8 % (13/14) [66.1–99.8]	100.0 % (16/16) [79.4–100.0]	NA***	0.8873
Phase 2	Day 43	95.7 % (88/92) [91.4–99.8]	98.9 % (95/96) [96.9–100.0]	0.0 % (0/48) [0.0–7.4]	0.8710	95.7 % (88/92) [91.4–99.8]	98.9 % (95/96) [96.9–100.0]	0.0 % (0/48) [0.0–7.4]	0.8710
	Day 60	96.6 % (85/88) [92.8–100.0]	98.9 % (88/89) [96.7–100.0]	NA***	0.9129	96.6 % (85/88) [92.8–100.0]	98.9 % (88/89) [96.7–100.0]	NA***	0.9129
		Anti-S1-RBD IgG* (ELISA)				**Anti-SARS-CoV-2 total IgG antibody* (ELISA)**			
		3 µg group	6 µg group	Placebo	p**	3 µg group	6 µg group	Placebo	p**
Phase 1	Day 43	100.0 % (15/15) [78.2–100.0]	100.0 % (17/17) [80.4–100.0]	0.0 % (0/10) [0.0–30.0]	1.0000	100.0 % (15/15) [78.2–100.0]	100.0 % (17/17) [80.4–100.0]	0.0 % (0/10) [0.0–30.0]	1.0000
	Day 60	100.0 % (14/14) [76.8–100.0]	100.0 % (16/16) [79.4–100.0]	NA***	1.0000	100.0 % (14/14) [76.8–100.0]	100.0 % (16/16) [79.4–100.0]	NA***	1.0000
Phase 2	Day 43	100.0 % (92/92) [96.0–100.0]	100.0 % (96/96) [96.2–100.0]	0.0 % (0/48) [0.0–7.4]	1.0000	100.0 % (92/92) [96.0–100.0]	100.0 % (96/96) [96.2–100.0]	0.0 % (0/48) [0.0–7.4]	1.0000
	Day 60	100.0 % (88/88) [95.9–100.0]	100.0 % (89/89) [95.9–100.0]	NA***	1.0000	100.0 % (88/88) [95.9–100.0]	100.0 % (89/89) [95.9–100.0]	NA***	1.0000

*Data are % (n/N) [95 %CI]. Seroconversion was defined as fourfold rise over baseline. Dose schedule: two doses 21 days apart in the phase 1 trial; two doses 28 days apart in the phase 2 trial. Timepoints show the time elapsed since the administration of the first dose. **p value, for comparison of ERUCoV-VAC 3 µg and 6 µg groups. ***NA = not applicable (placebo recipients were released from the trial after day 43). ELISA = enzyme-linked immunosorbent assay; FRNT = focus-reduction neutralisation test; IgG = immunoglobulin G; n = number of participants who achieved seroconversion. N = number of participants included in the immunogenicity analysis; CI = confidence interval.

3.2.2. Anti-S1-RBD IgG antibody

In the phase 1 trial, at baseline, anti-S1-RBD IgG antibody GMTs (95 %CI) of trial groups were comparable: 47.2 (43.6–49.8) in ERUCoV-VAC 3 μg, 46.4 (43.6–49.2) in ERUCoV-VAC 6 μg, and 45.4 (42.6–48.4) in placebo groups (p = 0.4533) (Fig. 2E, Table S8, Supplementary Appendix H). Increases to 462.3 (327.8–596.9) and 472.6 (432.6–513.0) at day 43, and to 495.9 (352.4–639.2) and 547.9 (515.8–580.0) at day 60 occurred in ERUCoV-VAC 3 μg and 6 μg groups, respectively. Vaccine groups did not differ regarding the elicited anti-S1-RBD IgG antibody GMTs at day 43 (p = 0.9147) and day 60 (p = 0.8393) (Fig. 2E; Table S8, Supplementary Appendix H). Seroconversion of anti-S1-RBD IgG antibodies was achieved in all ERUCoV-VAC recipients at day 43 and maintained at day 60 (Table 4).

In the phase 2 trial, at baseline, the GMTs (95 %CI) of anti-S1-RBD IgG antibodies were comparable across the study groups: 46.3 (45.6–47.5) in ERUCoV-VAC 3 μg, 48.8 (47.9–49.4) in ERUCoV-VAC 6 μg, and 50.0 (49.5–50.8) in placebo groups (p = 0.5979) (Fig. 2F;Table S9, Supplementary Appendix J). anti-S1-RBD IgG GMTs (95 %CI) increased to 2561.5 (2153.1–2969.8) and 2549.6 (1749.7–3349.4) on day 43, and to 2710.7 (2277.8–3143.5) and 2680.0 (1851.3–3524.6) at day 60, in ERUCoV-VAC 3 μg and 6 μg groups, respectively (Fig. 2F; Table S9, Supplementary Appendix J). The elicited anti-S1-RBD IgG antibody GMTs at day 43 (p = 0.2301) and day 60 (p = 0.3157) were similar in the vaccine groups (Fig. 2F; Table S9, Supplementary Appendix J). Seroconversion was achieved for anti-S1-RBD IgG antibodies in all participants in ERUCoV-VAC 3 μg and 6 μg groups at day 43 and maintained at day 60 (Table 4).

3.2.3. Anti-SARS-CoV-2 total IgG antibody

In the phase 1 trial, the anti-SARS-CoV-2 total IgG antibody GMTs (95 %CI) across the trial groups were comparable at baseline: 47.2 (44.7–49.8) in ERUCoV-VAC 3 μg, 46.4 (43.6–49.2) in the ERUCoV-VAC 6 μg, and 44.7 (41.7–47.6) in the placebo groups (p = 0.7065), and increased to 375.9 (264.0–487.3) and 395.5 (319.4–471.0) at day 43, and to 424.1 (297.4–531.5) and 441.4 (364.2–519.7) at day 60, in the ERUCoV-VAC 3 μg and 6 μg groups, respectively (Table S8, Supplementary Appendix H). The elicited anti-SARS-CoV-2 total IgG antibody GMTs at day 43 (p = 0.7990) and day 60 (p = 0.9906) were similar in ERUCoV-VAC groups (Fig. 2G; Table S8, Supplementary Appendix H). Seroconversion rates of 100 % were achieved for anti-SARS-CoV-2 total IgG antibody in ERUCoV-VAC 3 μg and 6 μg groups at day 43 and maintained at day 60 (Table 4).

In the phase 2 trial, the anti-SARS-CoV-2 total IgG antibody GMTs (95 % CI) across the trial groups were comparable at baseline: 42.3 (41.4–43.2) in ERUCoV-VAC 3 μg, 44.8 (43.8–45.9) in ERUCoV-VAC 6 μg, and 49.1(48.6–50.1) in placebo groups (p = 0.6839), and increased to 1586.3 (1398.8–1773.73) and 1964.2 (1788.7–2139.6) on day 43, and to 1738.7 (1538.6–1954.3) and 2018.6 (1846.9–2266.0) on day 60, in ERUCoV-VAC 3 μg and 6 μg groups, respectively (Table S9, Supplementary Appendix J). ERUCoV-VAC 6 μg induced significantly higher anti-SARS-CoV-2 total IgG antibody GMTs than ERUCoV-VAC 3 μg at both day 43 (p = 0.0226) and day 60 (p = 0.0183) (Fig. 2G; Table S9, Supplementary Appendix J). Seroconversion rates were 100.0 % for anti-SARS-CoV-2 total IgG antibody in ERUCoV-VAC 3 μg and 6 μg groups at day 43 and maintained at day 60 (Table 4).

GMT ratios for SARS-CoV-2 wild-type neutralising antibody (MNT_{50}, $FRNT_{50}$), anti-S1-RBD IgG antibody and anti-SARS-CoV-2 total IgG antibody responses are presented for both doses of ERUCoV-VAC in Table S10 and Table S11 in the Supplementary Appendix K.

3.2.4. ELISPOT assay

In the ELISPOT assay, stimulated peripheral blood mononuclear cells (PBMCs) on day 14 after the second vaccination showed significantly higher spots compared to non-stimulated PBMCs collected at the same time point and stimulated PBMCs collected on day 0. The 3 μg vaccinated PBMCs resulted in numerically higher spot-forming units than those vaccinated with 6 μg (GMT [95 % CI]: 136.2 [177.9–154.4] vs 120.1 239 [101.9–138.2] (Table S12, Supplementary Appendix L; Fig. S2 Supplementary Appendix I).

4. Discussion

This report presents the 2-month interim findings from the phase 1 and 2 trials of ERUCoV-VAC, an inactivated whole virion vaccine against SARS-CoV-2, in healthy adults aged < 65 years. The 3 μg and 6 μg doses of the vaccine, scheduled 21 and 28 days apart in the phase 1 and 2 trials, respectively, had an acceptable safety and tolerability profile and induced robust humoral immune response against SARS-CoV-2.

ERUCoV-VAC 3 μg and 6 μg were comparable in short-term safety and tolerability. Although this report is confined to 2 months follow up data, we think that the current findings are valuable in terms of the overall safety of the vaccine, as adverse reactions in both previous SARS-CoV-2 inactivated vaccine studies [11–16] and in ours were mostly seen within the first week after vaccination. It is worth emphasizing that the two vaccine doses were comparable in AE frequency and did not pose a major safety concern. SAEs were very rare and were judged as unlikely to be related to ERUCoV-VAC. Consistent with the other inactivated vaccine studies, [11–16] pain at injection site was common in our study; it occurred more frequently in vaccine groups than in the placebo group. It might be associated with the reactogenicity of the adjuvant. The frequency of fever, a common symptom observed in subjects vaccinated with RNA-based COVID-19 vaccines, was relatively low (none in phase 1 and 2.8 % in phase 2) in our study, in line with most of the previously reported findings from several inactivated SARS-CoV-2 vaccine trials. [11–16] As a tentative observation, we would like to underline that nausea was only reported in ERUCoV-VAC recipients, although the difference versus placebo was not significant. The final results of the phase 2 trial and future studies will provide more insight on this point. Two-dose vaccination rates were over 90 % in both trials; however, the percentages of participants who were included in immunogenicity assessments on day 60 were lower compared to day 43. The main reason for this is the release of placebo recipients from the trials after day 43 to allow them to receive one of the vaccines approved for emergency use.

Two-dose regimens of both ERUCoV-VAC 3 μg and 6 μg elicited significant humoral immune responses at days 43 and 60 after the first dose. The magnitude of the responses was comparable between the two doses in both trials, except for anti-SARS CoV-2 total IgG antibody titres in the phase 2 trial where ERUCoV-VAC 6 μg led to significantly higher antibody titres compared to ERUCoV-VAC 3 μg. This may be at least partly explained by the higher abundance of the nucleocapsid protein.

Due to the differences in antibody measuring methods, reference samples, dosing and assessment schedules between the studies, it might not be appropriate to compare the results of various inactivated SARS-CoV-2 vaccine studies. However, we achieved high levels of neutralising and anti-spike antibody titres consistent with the findings from the other inactivated COVID-19 vaccine studies. [11–16] We comprehensively evaluated the immunogenicity of an inactivated COVID-19 vaccine in both studies and used live virus-based neutralising tests for immunogenicity assessments. We confirmed that the results of MNT findings were

consistent with FRNT findings. There was a high correlation between the results of the two well standardized neutralisation assays, in both phase 1 and 2 trials.

It is noteworthy to mention that the antibody GMTs measured on days 43 and 60 in phase 2 trial were at least 3-fold higher than those in phase 1 trial, for both ERUCoV-VAC doses. Although it is possible to comment on the potential reasons for the higher immune response rates in the phase 2 trial, we would like to point out that the findings of these two studies, which differ in terms of vaccine administration and immunogenicity evaluation schedule, were not statistically compared in this interim analysis. Previously reported results from several inactivated COVID-19 vaccines indicated that longer intervals (21 or 28 days versus 14 days) between doses resulted in better immunogenicity outcomes. [11,12,14] We therefore preferred a 28-day dosing interval in the phase 2 trial and achieved higher antibody levels and seroconversion rates than those in the phase 1 trial, where the dosing interval was 21 days. Another reason for better immunogenicity outcomes in phase 2 might be the use of bioreactors in the production of investigational products in this trial. It has been previously reported that the manufacturing process contributes to the maintenance of spike proteins, thereby enhancing immune responses. [12] The improved purification process in vaccine production for Phase 2 may also have played a role in achieving better immunogenicity results in that trial.

This interim report has several limitations. First, individuals younger than 18 years or older than 65 years and those with known health problems were not included. Therefore, it would not be appropriate to draw conclusions about the effects of the vaccine in children, the elderly or people with comorbidities. Second, we could not compare the antibody responses elicited by ERUCoV-VAC and natural SARS-CoV-2 infection, as we did not collect convalescent sera. Third, the times elapsed between the second vaccinations and post-dose immune response evaluation time-points were different in the phase 1 and 2 trials (one week longer in the phase 1 trial). This might have affected our immunogenicity findings. We would like to emphasize that we only evaluated the differences in the outcomes between the two dose strengths (3 and 6 μg) administered with a similar dose range in the same study and that we did not compare the findings from the two studies. Furthermore, we think that the different post-dose evaluation time-points have no effect on safety outcomes, as the ADRs mostly occurred within the first week of vaccinations in this study. The fact that all women were assigned to the placebo arm in the phase 1 trial is purely coincidental as the study was randomized and double-blinded. The number of women who applied for participation into that trial was low, therefore few women were included in that trial. Sex-specific vaccination behaviour differences may be an interesting area for future real-life studies.

Data on the long-term safety and cellular/humoral immunogenicity of ERUCoV-VAC (including durability of immune responses and its impact on memory cells), its activity against SARS-CoV-2 variants (alpha, delta and Omicron), and the effects of getting a third booster dose are not yet available. Twelve-month results of the phase 1 and 2 trials will be available later in 2022 and provide information on these topics. Furthermore, a randomized, double-blind, active-controlled phase 3 trial comparing TURKOVAC and CoronaVac for efficacy, safety, and immunogenicity is ongoing.

In conclusion, the preliminary findings from the phase 1 and 2 trials of ERUCoV-VAC indicated that 3 μg and 6 μg doses of the inactivated whole virion vaccine had comparable safety, tolerability, and immunogenicity profiles in healthy adults aged < 65 years. Higher antibody responses were achieved with two-dose schedule with 28 days interval versus 21 days. The larger phase 3 trial will provide further insight into how well the immunogenicity of ERUCoV-VAC is reflected in its clinical efficacy. ERUCoV-VAC 3 μg has been selected for further investigation for efficacy and safety in an ongoing active-controlled phase 3 trial and authorized for emergency use in Turkiye since December 2021 under the name of TURKOVAC.

Data sharing

Anonymous participant data that support the findings of this study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Aykut Ozdarendeli: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Zafer Sezer:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Shaikh Terkis Islam Pavel:** Data curation, Investigation, Methodology, Resources, Validation, Writing – review & editing. **Ahmet Inal:** Data curation, Investigation, Methodology, Resources, Validation, Writing – review & editing. **Hazel Yetiskin:** Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Busra Kaplan:** Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Muhammet Ali Uygut:** Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Adnan Bayram:** Investigation, Methodology, Writing – review & editing. **Mumtaz Mazicioglu:** Investigation, Methodology, Writing – review & editing. **Gamze Kalin Unuvar:** Investigation, Methodology, Writing – review & editing. **Zeynep Ture Yuce:** Investigation, Methodology, Writing – review & editing. **Gunsu Aydin:** Investigation, Methodology, Writing – review & editing. **Ahmet Furkan Aslan:** Investigation, Methodology, Writing – review & editing. **Refika Kamuran Kaya:** Methodology, Writing – review & editing. **Rabia Cakir Koc:** Funding acquisition, Writing – review & editing. **Ihsan Ates:** Writing – review & editing. **Ates Kara:** Conceptualization, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Aykut Ozdarendeli, Shaikh Terkis Islam Pavel, Hazel Yetiskin, Muhammet Ali Uygut and Gunsu Aydin are the named inventors on patent applications covering inactivated COVID-19 vaccine development.

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final manuscript, and the decision to submit for publication, but had no role in data collection, data analysis, data interpretation, or writing of the report. Ideal CRO (Ankara, Turkiye) acted as the contract research organization representing TUSEB and contributed to correspondence between investigators, the ethics committee, and the Ministry of Health; monitoring, site management, storage, and distribution of the consumables; developing electronic case report forms, and data management, statistical analyses, and overall project management. Kocak Pharma provided the investigational products.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.10.093.

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