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Safety and immunogenicity of a homologous booster dose of a SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with AS03: 12 months follow-up result of an open-label, nonrandomized extension of a phase 1/2 trial

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ABSTRACT

Objectives: This study evaluated the safety and immunogenicity of a homologous GBP510/AS03 booster given 6-12 months after a primary two-dose series.
Methods: In an open-label extension of a phase 1/2 trial in Korea, healthy adults aged 19-85 years who had completed two doses received a single GBP510/AS03 booster. The primary objective was to assess safety and reactogenicity. Secondary objectives included assessment of humoral and cellular immunogenicity against the ancestral D614G strain and Omicron variants.
Results: Between December 2021 and January 2022, 81 participants received the booster and 56 completed 12-month follow-up. No immediate systemic reactions were reported. The most common local

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adverse event was injection site pain, while systemic events such as myalgia, fatigue, and chills were mostly mild to moderate. No serious adverse events related to vaccination occurred. Neutralizing antibody titres and seroconversion rates against D614G following the booster were noninferior to those observed after the primary series. Cross-neutralization responses to Omicron variants improved after boosting, and neutralizing antibody titres to early Omicron variants and the ancestral strain were sustained for up to 12 months.

Conclusions: A homologous GBP510/AS03 booster was well tolerated and induced robust, durable neutralizing antibody responses against SARS-CoV-2, including Omicron variant.

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Introduction

Vaccination has played a crucial role in limiting the spread of SARS-CoV-2 and mitigating severe COVID-19 outcomes [1,2]. Although the pandemic phase has officially ended, COVID-19 remains widespread and continues to challenge global public health systems. As of December 2023, approximately 67% of the global population had completed a primary vaccination series [3]. However, the emergence of new SARS-CoV-2 variants continues to affect both transmission and vaccine effectiveness.

Declining vaccine-induced effectiveness [4] together with waning humoral responses [5–7], compounded by viral evolution, underscores the continuing need for booster immunization, particularly among high-risk populations [8,9]. Real-world evidence and multiple clinical trials have demonstrated that booster doses enhance the production of neutralizing antibodies against both ancestral SARS-CoV-2 and circulating variants [10–13], reinforcing their role in sustaining antibody-mediated protection.

GBP510 is a recombinant protein vaccine comprising self-assembling, two-component nanoparticles that display the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein [14]. It is formulated with AS03, an α-tocopherol and squalene-based adjuvant that enhances immune responses [15,16] and is hereafter referred to as GBP510/AS03. A randomized, observer-blinded phase 1/2 trial previously demonstrated that GBP510/AS03 was highly immunogenic and generally well tolerated in healthy adults aged 19-85 years [16]. Interim findings from a pivotal phase 3 trial involving 4,037 adults across six countries further indicated an acceptable safety profile and demonstrated both immunogenic superiority and noninferiority of GBP510/AS03 compared with the ChAdOx1-S vaccine [17].

Following its approval in South Korea in June 2022 for primary immunization (tradename: SKYCovione^{TM}), GBP510/AS03 has been further evaluated as a homologous booster in a phase 3 extension trial (NCT05007951), with no updated formulation incorporating circulating variants. In parallel, a phase 1/2 extension study offered participants who had received two 25 μg doses of GBP510/AS03 a homologous booster 6-12 months later, using the same dosage regimen as in the phase 3 study. Here, we report the safety and immunogenicity outcomes up to 12 months following the booster in the phase 1/2 extension.

Methods

Study design

A single booster dose of GBP510, adjuvanted with AS03 (a proprietary adjuvant developed by GSK), was administered in an open-label extension of a phase 1/2, randomized, placebo-controlled, observer-blinded trial conducted across 14 hospital sites in Korea. The overall study comprised three stages. The primary stage (Stages 1 and 2) evaluated the safety and immunogenicity of two doses of the GBP510 vaccine (with or without AS03) in healthy younger and older adults; full details have been reported previously [13]. Participants who received two 25 μg doses of GBP510/AS03 and had valid IgG binding antibody and/or neutralizing antibody results 1 month after the second dose were eligible for the booster extension phase (Stage 3). In this stage, participants received a single booster dose of 25 μg GBP510/AS03 at 6-12 months after the second vaccination, on a time convenient for each participant, and were followed for 12 months post-booster.

The trial was designed by SK bioscience with support from the Coalition for Epidemic Preparedness Innovations (CEPI) and GSK. The study reporting complies with the Consolidated Standards of Reporting Trials (CONSORT) 2025 Statement.

Participants

Participants who had received two 25 μg doses of GBP510/AS03 during the primary series were invited to enroll in the extension phase and receive a homologous booster. Exclusion criteria included: clinically significant respiratory symptoms, febrile or acute illness within 72 hours prior to enrolment; history of SARS-CoV-1, SARS-CoV-2, or MERS infection; prior receipt of COVID-19 medications or vaccines other than GBP510/AS03; positive screening for hepatitis B, hepatitis C, or HIV; immunocompromised status; history of autoimmune disease, malignancy within 5 years, bleeding disorders, or thrombocytopenia; receipt of immunoglobulins or blood products within 12 weeks prior to enrolment; receipt of any vaccine within 4 weeks before, or plans to receive one within 4 weeks after, the booster (2 weeks for influenza vaccine); and pregnancy or breastfeeding. Full inclusion and exclusion criteria are provided in the study protocol (Supplementary Appendix).

Randomization and masking

The primary stage of the study was randomized and observer-blinded between the GBP510 formulations and placebo groups. The extension phase was an open-label, nonrandomized study. Written reconsent was obtained prior to participation in the extension phase. Only those who were randomized to receive GBP510/AS03 in the primary phase were eligible for participation in the extension phase.

Procedures

During the extension phase, participant received a single intramuscular injection (0.5 mL) of GBP510/AS03 into the deltoid muscle.

Participants attended scheduled visits at baseline (prebooster), and at 2 weeks, 4 weeks, 6 months, and 12 months post-booster. They were monitored for 30 minutes following vaccination for immediate systemic reactions. Participants recorded solicited local and systemic adverse events (AEs) for 7 days, and unsolicited AEs for 28 days, via electronic diary or telephone contact. Serious AEs

(SAEs), medically attended AEs (MAAEs), and AEs of special interest (AESIs; Supplementary Tables S1 and S2) were documented throughout the study period.

Blood samples were collected at all time points. An immunoassay for qualitative detection of antibodies against the SARS-CoV-2 nucleocapsid (N) protein was performed prior to, and 2 weeks after, the booster dose to identify intercurrent infection. Immunogenicity assessments included IgG responses to SARS-CoV-2 RBD (measured by enzyme-linked immunosorbent assay; ELISA) and neutralizing antibody responses (via focus reduction neutralization test [FRNT] using wild-type virus), conducted prior to, and at 2 weeks, 4 weeks, 6 months, and 12 months after the booster.

Cell-mediated immune responses were evaluated by intracellular cytokine staining at baseline, and at 2 and 4 weeks post-booster. Following stimulation with SARS-CoV-2 RBD, CD4+ and CD8+ *T* cell cytokine expression was quantified by mean percentage, including interferon-γ (IFN-γ), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and IL-4.

Outcomes

Primary outcomes were safety measures, including the occurrence of immediate systemic reactions, solicited local/systemic AEs within 7 days, unsolicited AEs within 28 days, and SAEs, MAAEs, and AESIs over 12-months.

Secondary outcomes included geometric mean titres (GMTs), geometric mean fold rise (GMFR) from baseline, and seroconversion rate (SCR; defined as the percentage of participants with $a \geq$ 4-fold rise from baseline) for RBD-specific IgG and neutralizing antibodies against the SARS-CoV-2 ancestral D614G strain, assessed pre- and post-booster. Antibody titres against D614G were converted to binding antibody unit (BAU)/mL and international unit (IU)/mL using WHO international standard (NIBSC 20/136). Neutralizing responses to Omicron subvariants (BA.1, BA.5, XBB.1.5) were also evaluated pre- and post-booster, without standard unit conversion. CD4+ and CD8+ *T* cell cytokine expression (IFN-γ, IL-2, IL-4, IL-5, TNF-α) was also evaluated. During the primary stage, neutralization was measured using a pseudovirus-based neutralization assay (PBNA) and plaque reduction neutralization test (PRNT). In the extension phase, FRNT, the validated assay adopted in the phase 3 pivotal trial, was applied throughout.

Statistical analysis

In the primary phase, 104 participants received two 25 μg doses of GBP510/AS03. Assuming a 40% exclusion rate in the extension phase—due to reconsent refusal, screening failure, or dropout before the 2-week post-booster visit—it was estimated that 62 participants would be sufficient to test the noninferiority hypothesis. A sample of 27 participants was calculated to provide 90% power for comparing neutralizing antibody GMTs and SCRs between 2 weeks post-booster and 2 weeks post-second primary dose.

All participants who received the booster were included in the Safety Set for safety analysis. Those who received the booster and had both prebooster and at least one valid post-booster immunogenicity result were included in the Full Analysis Set (FAS). A per-protocol set was defined as participants in the FAS who remained COVID-19 uninfected during the analysis period and had no major protocol deviations.

Safety outcomes were summarized as frequencies (%) with 95% confidence intervals (CIs). GMTs and GMFRs for RBD-specific IgG and neutralizing antibodies were calculated after log-transformation and expressed with geometric standard deviations (GSDs) and 95% CIs. SCRs were also presented with 95% CIs. CD4+ *T* cell cytokine expression was reported as mean percentages with standard deviations and 95% CIs.

Noninferiority of the booster immunogenicity response (wild-type neutralizing antibody titres) was demonstrated if the lower bound of the two-sided 95% CI for the GMT ratio (2 weeks post-booster / 2 weeks post-second dose) exceeded 0.67, and if the lower bound of the 95% CI for the SCR difference (2 weeks post-booster minus post-second primary dose) exceeded −10%. The paired t-test was used for the ratio of post-vaccination GMTs (with 95% CIs calculated based on the t-distribution of log-transformed values, back transformed to the original scale). McNemar's test was used to assess differences in SCRs (with 95% CIs calculated using the Clopper-Pearson method and Miettinen and Nurminen method).

Subgroup analyses were conducted for immunogenicity (by age: 19-64 and ≥65 years) and safety (by age and sex). Missing data were not imputed and were handled using prespecified rules. All analyses were conducted using SAS version 9.4. A statistical analysis plan was finalized prior to data analysis.

Results

Between 1 February and 28 May 2021, a total of 358 participants were screened and enrolled in the primary series, receiving the assigned study vaccines with different dosages. Among the 103 who received two 25 μg doses of GBP510/AS03, 81 were re-screened and received a booster dose of the same formulation after providing reconsent (Figure 1).

Among the 81 participants enrolled for the booster, one discontinued (lost to follow-up), leaving 80 who completed the 12-month extension between 14 December 2021 (first participant, first visit) and 18 January 2023 (last participant, last visit). The safety set included all 81 participants who received the booster. All participants were also included in the per-protocol set for the primary immunogenicity analysis, based on data up to 2 weeks post-booster vaccination (with a 4-week period considered for the primary safety analysis; primary cut-off date: February 17, 2022). Long-term immunogenicity was evaluated at 12 months post-booster in 56 participants who met the criteria for the per-protocol criteria. COVID-19 infection status, an exclusion criterion for the per-protocol set, was assessed via passive and active surveillance following the primary analysis (Figure 1).

Demographic and baseline characteristics of the 81 participants are presented in Table 1. All were Korean; 54.3% were female.

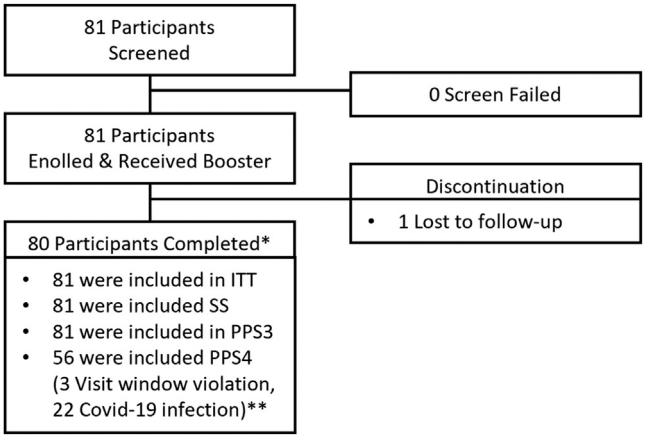


Figure 1. Disposition and analysis set of extension study participants. ITT: Intention-to-treat; SS: Safety Set; PPS3: Per-protocol Set up to 2 weeks post-booster, PPS4: Per-protocol Set up to 12 months post-booster
*Participants who completed 12-month follow-up are classified as "Completed."
**Excluded from PPS = 4 during the 12-month follow-up period, though included in PPS3. occurred from 4 weeks after the booster vaccination up to 12-month post-vaccination.

Table 1
Demographic and baseline characteristics.

	GBP510/AS03 (N = 81)
Age (years)	
Mean (SD)	45.04(13.98)
Median (min, max)	42.00 (19.00, 74.00)
Age, n (%)	
19-64 years	71 (87.65)
65-85 years	10 (12.35)
Sex, n (%)	
Male	37 (45.68)
Female	44 (54.32)
Race, n (%)	
Korean	81 (100.00)
Other Asian	0 (0.00)
Caucasian	0 (0.00)
Black	0 (0.00)
Hispanic	0 (0.00)
Other	0 (0.00)
Height (cm)	
Mean (SD)	164.86(9.00)
Median (min, max)	165.40 (149.30,184.00)
Weight (kg)	
Mean (SD)	65.77(11.82)
Median (min, max)	63.90 (43.90, 97.30)
BMI (kg/m^2)	
Mean (SD)	24.03(2.60)
Median (min, max)	23.80 (18.00, 29.60)

BMI = body mass index, max = maximum, min = minimum, SD = standard deviation.

Mean (SD) age was 45.0 (14.0) years, and 12.4% were elderly (≥65 years). Mean (SD) body mass index was 24.0 (2.6) kg/m^2.

The mean interval between the second primary dose and the booster was 7.5 months.

Safety outcomes

A summary of AE incidence up to 12 months after the primary series and booster dose is provided in Supplementary Figure S1. None of participants experienced an immediate systemic reaction following any of the vaccinations.

Within 7 days post-booster, 88.9% of participants (72/81) reported solicited local AEs, compared to 90.1% (73/81) after any primary dose and 84.0% (68/81) for each individual dose. Injection site pain was the most common solicited local AE across all doses, mostly mild or moderate (Figure 2A and Supplementary Table S4).

In the same period, solicited systemic AEs were reported by 88.9% of participants (72/81), 86.4% (70/81) after any primary dose, 70.4% (57/81) after the first dose, and 87.7% (67/81) after the second dose. The most frequently reported terms were myalgia, fatigue, and chills (Figure 2B and Supplementary Table S5) with most events being mild or moderate.

Unsolicited AEs within 28 days post-booster occurred in 8.6% of participants (7/81), which was lower than 21.0% (17/81) after any primary dose, with rates of 13.6% (11/81) and 12.4% (10/81) after the first and second doses, respectively. Vaccine-related unsolicited AEs (ADRs) were reported by 4.9% of (4/81) post-booster, compared to 7.4% (6/81) after any primary dose, with a rate of 4.9% (4/81) for each individual dose. Most unsolicited AEs/ADRs were mild or moderate (Supplementary Table S6).

No SAEs were reported within 28 days post-booster. By study completion, 2.5% of participants (2/81) reported SAEs (endometriosis, uterine polyp, and arthralgia). All SAEs were assessed as unrelated to the vaccine and had either fully resolved or were recovering in a stable condition (arthralgia).

MAAEs within 28 days post-booster occurred in 2.5% of participants (2/81), with 1.2% (1/81) assessed as vaccine-related (MAADRs). Additional MAAEs were reported by 27.2% (22/81) during follow-up, with none deemed vaccine related. No AESIs or deaths occurred throughout the study period. A total of 23 participants contracted COVID-19 during follow-up, with none of the cases occurring within 28 days post-booster. All cases were mild to moderate and nonserious (Supplementary Table S7).

Safety profiles were generally comparable between sexes, with minor differences in solicited local AE rates. Incidence appeared generally lower in the elderly (≥65 years; n = 10) than younger adults (19-64 years; n = 71). However, the small sample size limits its meaningful interpretation (Supplementary Table S8 and S9).

Immunogenicity outcomes

Immunogenicity analysis was conducted in 81 participants from baseline to 2 weeks post-booster (primary analysis) and in 56 participants from 4 weeks to 12 months post-booster (final analysis), in accordance with the predefined per-protocol set definition.

Neutralizing antibody GMT against the ancestral D614G strain (assessed by FRNT ND_{50}) increased from 8.08 IU/mL at baseline to 226.64 IU/mL at 2 weeks post-primary series, declined to 42.01 IU/mL prebooster (7.5-month interval), and increased to 1775.39 IU/mL at 2 weeks post-booster, indicating a GMFR of 7.83 from the 2-weeks post-primary GMT (Figure 3a and Supplementary Table S10). Post-booster GMT was noninferior to post-primary GMT, with the lower 95% CI (6.55) exceeding the margin of 0.67. The SCR increased from 97.53% (79/81 participants) post-primary series to 100.00% (81/81 participants) post-booster, with the lower CI for difference (−2.14%) exceeding the margin of −10%. (Table 2).

Long-term immunogenicity analysis was conducted up to 12 months. The neutralizing antibody GMT was 651.88 IU/mL at 6 months, and 715.74 IU/mL at 12 months post-booster. The fold-reduction of GMT from 2 weeks post-booster was 2.7-fold at 6 months and 2.5-fold at 12 months, remaining above the peak GMT recorded at 2 weeks post-primary series (226.64 IU/mL).

RBD-specific IgG antibody GMT (assessed by ELISA) increased from 14.30 BAU/mL at baseline to 2583.62 BAU/mL at 2 weeks post-primary series, declined to 236.86 BAU/mL prebooster, and increased to 2468.64 BAU/mL at 2 weeks post-booster, reaching a level comparable to that observed post-primary series (Supplementary Figure S2 and Table S12). GMFR from baseline was 180.72 post-primary series and 172.67 post-booster, with SCR of 100.0% (81/81 participants) at both time points. Long-term GMT were 940.42 BAU/mL at 6 months (2.6-fold reduction from the post-booster) and 866.28 BAU/mL at 12 months (2.8-fold reduction from the post-booster) (Supplementary Table S13).

Similar trends in neutralizing antibody results (in IU/mL) and RBD-specific IgG antibody responses against the ancestral strain were observed in the participants aged 19-64 years (n = 48) and ≥65 years (n = 8), though titres were generally lower in the elderly (Supplementary Table S10-11).

Neutralizing antibody responses to Omicron BA.1 (n = 81), BA.5 (n = 20) and XBB.1.5 (n = 20) variants were evaluated up to 2 weeks post-booster using FRNT ND_{50} (values not converted to IU/mL). At 2 weeks after the primary series, GMTs were 87.56, 49.30, and 13.09, respectively; declining to 30.32, 33.23 and 10.00 at prebooster; and rising to 2170.27,844.71, and 97.56 at 2 weeks post-booster. Corresponding GMFRs from prebooster to post-booster were 71.57, 25.42, and 9.76, respectively (Figure 3b and Supplementary Table S14-17).

Cell-mediated immune response showed increased CD4+ T cell expression of IFN-γ, IL-2, and TNFα post-booster, with no notable change in IL-4 expression. CD8+ T cells responses remained limited throughout (Supplementary Figure S3-10 and Table S18-19). Trends in participants aged 19-64 years (n = 15) were consistent

with the overall population, while the small sample size ($n = 2$) in those aged ≥65 years precluded meaningful evaluation.

Discussion

This report presents the first findings on the safety and immunogenicity of a homologous booster dose of GBP510/AS03. Administered to healthy adults approximately 7.5 months after the primary series, the booster exhibited a safety profile comparable to the initial doses and elicited strong neutralizing antibody responses. Consistent with primary series, a Th1-skewed cellular response was observed.

Among the 81 per-protocol participants, neutralizing antibody GMT against the ancestral D614G strain at 2 weeks post-

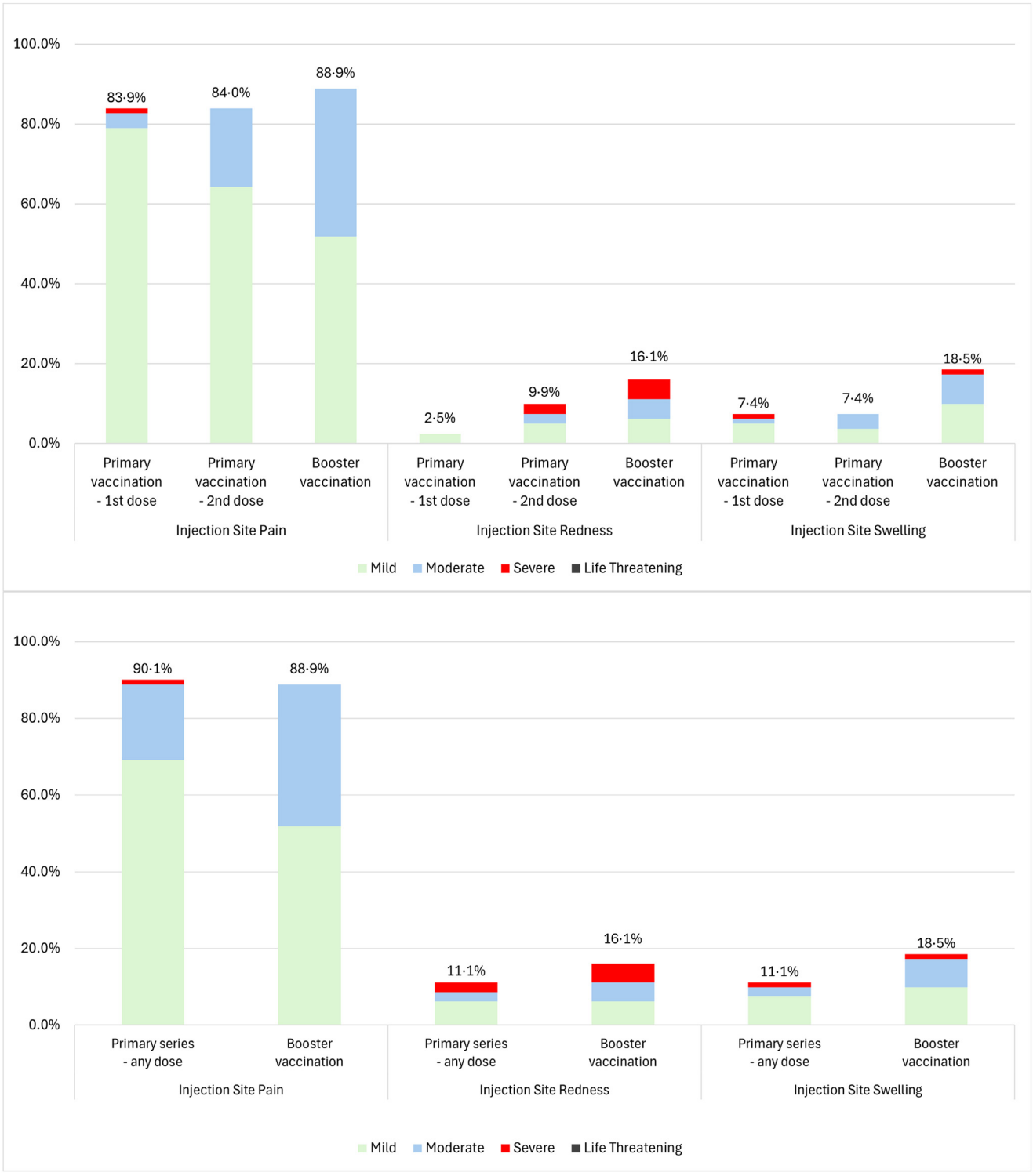


Figure 2. Solicited local (A) and systemic (B) adverse events within 7 days after primary (first/second) vaccination and after the booster vaccination within 7 days (safety set) (A) Solicited Local AEs by maximum severity after primary (1st and 2nd) and booster (3rd) vaccinations (Safety Set) %: n / (No. of subject in Safety Set) * 100 (B) Solicited Systemic AEs by maximum severity after primary (1st and 2nd) and booster (3rd) vaccinations (Safety Set) %: n / (No. of subject in Safety Set) * 100.

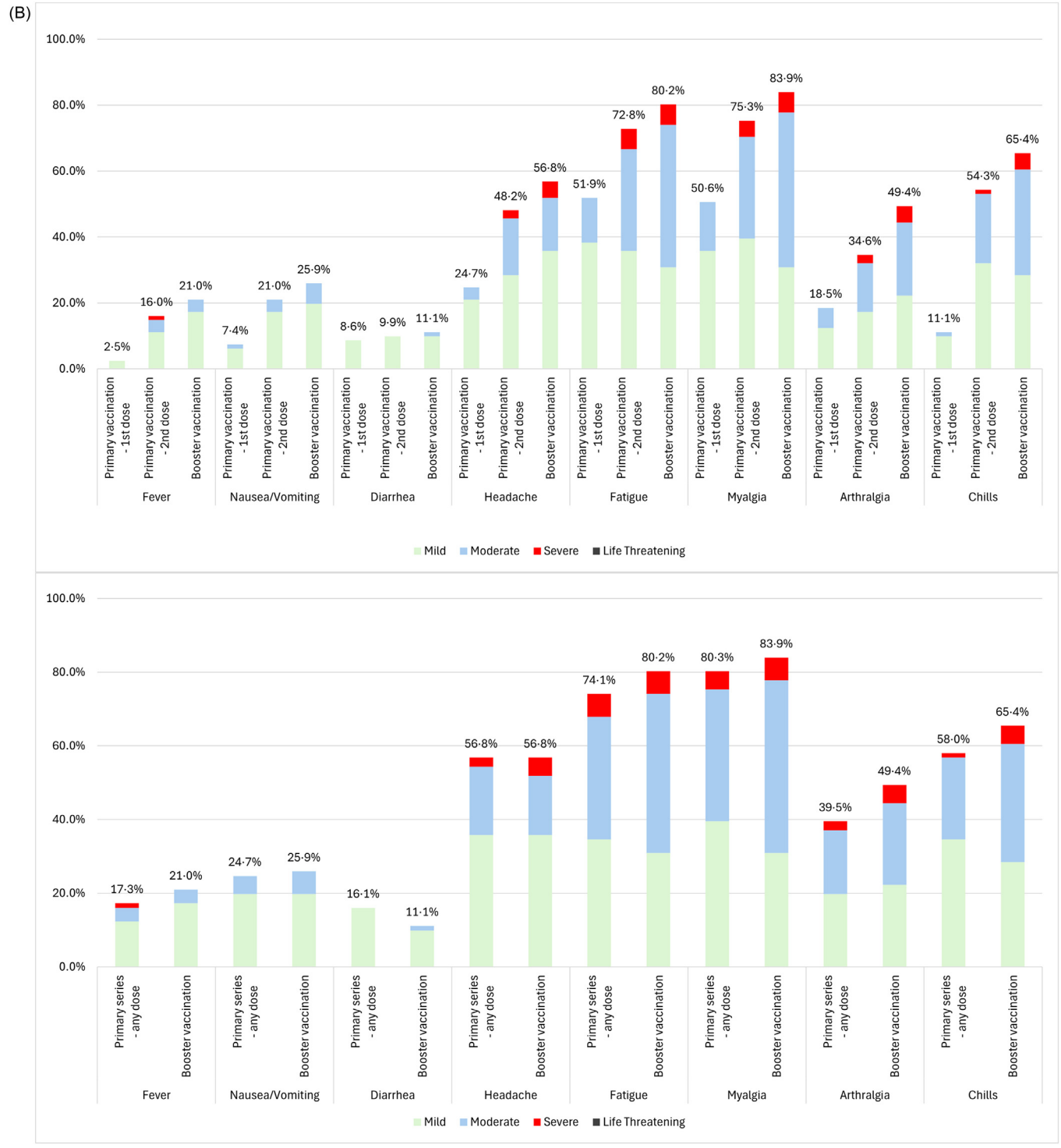


Figure 2. Continued

booster represented 42.3-fold rise from prebooster levels (42.01 to 1775.39 IU/mL) and 7.8-fold increase from GMT at 2 weeks post-primary series (226.64 to 1775.39 IU/mL). Both the post-booster GMT ratio and SCR exceeded the predefined noninferiority margins. Although a gradual reduction was noted from the post-booster peak, the neutralization antibody titres remained stable between 6 months and 12 months.

While direct comparisons with other studies are challenging due to differing neutralization assays, similar patterns of waning antibody titres post-primary series and subsequent boosting have been noted for other COVID-19 vaccines [6,7,13]. Neutralizing antibody titres following mRNA-based COVID-19 vaccination declined approximately 5.2-fold from post-primary peak and increased 44.6-fold post-booster and declined again by 5.5-fold at 16-20 weeks post-booster [18], consistent with trends observed for GBP510/AS03.

RBD-specific IgG titres also increased after the boosting, reaching levels comparable to post-primary responses. This pattern re-

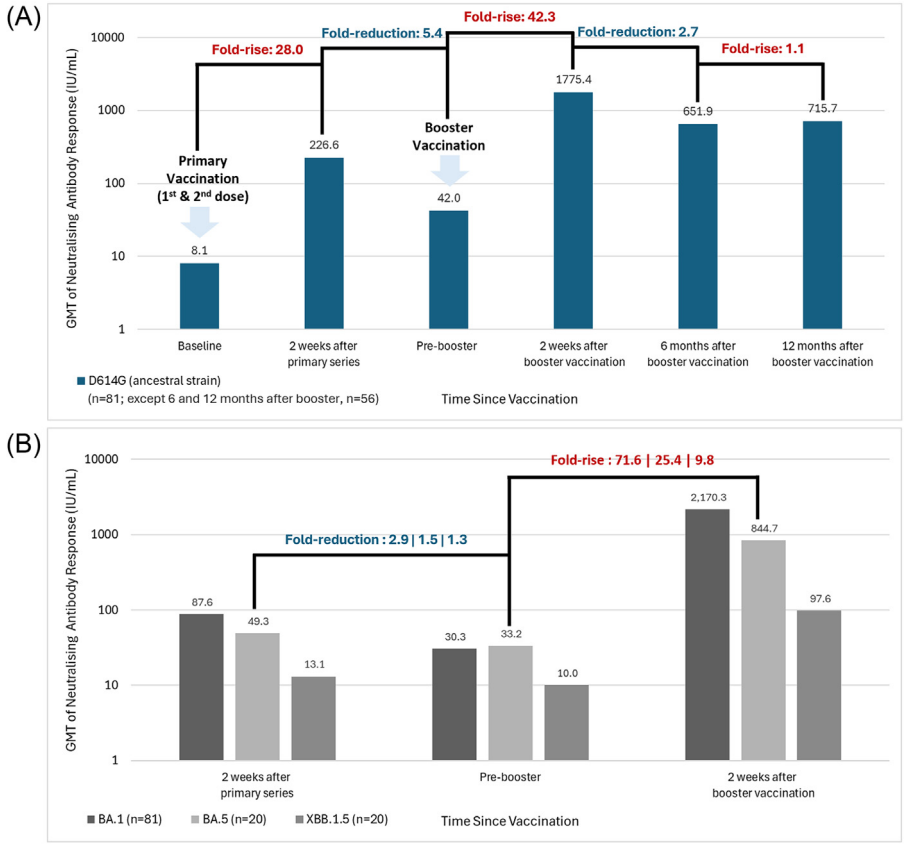


Figure 3. Neutralizing antibody responses following primary and booster vaccinations by FRNT (Per Protocol Set). (A) Geometric mean titres (GMTs, IU/mL) against the SARS-CoV-2 ancestral D614G strain. (B) Cross-neutralisation GMTs against BA.1, BA.5, and XBB.1.5 variants at selected timepoints. Fold-reduction and fold-rise values are annotated above the bars as numbers in order from left to right: BA.1, BA.5, XBB.1.5.

Table 2
Noninferiority of geometric mean titre and seroconversion rate of neutralizing antibody.

	2 weeks after primary series ($N = 81$)	2 weeks after booster vaccination ($N = 81$)	
GMT ± geometric standard deviation	226.64 ± 2.56	1,775.39 ± 1.97	
95% CI (lower, upper)	(184.05,279.09)	(1,528.94, 2,061.57)	
The ratio of post-vaccination GMTs at 2 weeks (Visit 3B / Visit 6) ± geometric standard deviation			7.8336 ± 2.24
95% CI (lower, upper)			(6.55, 9.36)
P-value[a]			<0.0001
Noninferiority (Lower limit of 95% CI > margin of 0.67)			Yes
SCR, n (%)	79 (97.53)	81 (100.00)	
95% CI (lower, upper)	(91.36, 99.70)	(95.55,100.00)	
The difference in SCR at 2 weeks (Visit 3B - Visit 6)			2.4691
95% CI (lower, upper)			(−2.14, 8.59)
P-value[b]			0.1573
Noninferiority (lower limit of 95% CI > margin of −10%)			Yes

GMT (Geometric Mean Titer), SCR (Seroconversion rate): Percentage of participants with ≥ 4-fold rise from Visit 2 (Baseline), CI (Confidence Interval)%: n / (No. of subject who information was collected at each visit) * 100
The 95% CI for GMT was calculated based on the t-distribution of the log-transformed values for geometric means, then back transformed to the original scale for presentation.
The 95% CI for SCR was calculated by Clopper-Pearson Methods.
The 95% CI for the difference of SCRs was calculated by Miettinen and Nurminen Methods.
[a] Paired t-test for the ratio of GMTs.
[b] McNemar's test for the difference in SCR.

flects the "immune plateau" phenomenon observed with mRNA- and adenovirus-based booster, where neutralizing antibody titres rise significantly without a corresponding increase in IgG binding responses [19,20].

Neutralizing GMTs against Omicron BA.1, BA.5, and XBB.1.5 increased markedly post-booster, indicating cross-reactive responses. Although cross-study comparisons remain limited, these findings align with trends observed following mRNA-1273 vaccination

against Omicron BA.1 [21]. A homologous GBP510/AS03 booster given more than 6 months after the primary series enhanced neutralizing antibody titres to both ancestral and Omicron strains, supporting the persistence of measurable humoral responses. Given the year-round circulation and frequent emergence of SARS-CoV-2 variants, this finding provides important evidence for the role of boosting in maintaining neutralizing antibody responses.

Safety outcomes following the GBP510/AS03 booster were favorable. The booster dose was well tolerated, with most AEs being mild to moderate and transient. No immediate systemic reactions were observed. Solicited local AEs occurred at slightly higher or comparable rates post-booster than after primary doses, while systemic AEs were marginally more frequent [22]. The most common solicited AEs—pain, myalgia, fatigue, and chills—were consistent with previous GBP510 phase 3 pivotal study,[22] and other COVID-19 vaccine studies [12,13,23]. Fewer unsolicited AEs were reported post-booster compared to the primary series, and all SAEs reported during the 12-month follow-up were unrelated to vaccination. No AESIs or deaths were reported throughout the study.

However, this study has several limitations. It was conducted in a single country with a modest sample size, restricting geographic diversity. While the booster elicited responses to Omicron subvariants, its effect on newer variants remains unexplored. Subgroup analysis in elderly participants was limited by small numbers, and only healthy participants were included, necessitating further research in populations with comorbidities. Additionally, undetected COVID-19 infections during follow-up may have influenced immunogenicity results, as natural infection was not systematically assessed. Broader studies with enhanced surveillance are warranted to validate and extend these findings.

Phase 3 trials evaluating both homologous and heterologous GBP510/AS03 boosters have been completed. Together with the phase 1/2 findings, combined analysis across studies will inform public health strategies regarding recombinant protein-based COVID-19 booster vaccination.

Conclusion

The GBP510/AS03 homologous booster was well tolerated in healthy adults aged 19-85 years and induced robust immune responses compared to those after the primary series. These findings support its potential role in COVID-19 booster strategies.

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Ethical approval

The study protocol (Supplementary Appendix) was approved by the Institutional Review Board (IRB) of each participating hospital and conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all participants before enrolment in the primary series, with written reconsent obtained prior to the booster phase. The trial is registered at ClinicalTrials.gov (NCT 04,750,343).

Data sharing statement

The datasets generated and analyzed during this study will not be made publicly available due to participant privacy and institutional restrictions requiring third-party approval.

Author contributions

HJC, YYL, HKP, SJL, YWP, HK, FS, MAC, and MK contributed to the conception and design of this study. SS and PT managed the project administration. WSC, JYH, JSL, DSJ, SWK, KHP, JSE, SJJ, JL, KTK, HJC, JWS, YKK, BWY, IJJ, EJK, and YRK were principal investigators at each study site and contributed to clinical and laboratory data acquisition. JYS, SJJ, YKK, BWY, IJJ, PW, FS, MAC, MK, TB, and HJC interpreted the data. JYS and HJC had full access to and verified all data, prepared the manuscript, and take responsibility for the decision to submit it for publication. All authors critically reviewed and approved the final version. Medical writing and editorial assistance were provided by Content Ed Net.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108108.

References

[1] Graña C, Ghosn L, Evrenoglou T, et al. Efficacy and safety of COVID-19 vaccines. *Cochrane Database Syst Rev* 2022;**12**(12):CD015477.
[2] Liu Y, Ye Q. Safety and efficacy of the common vaccines against COVID-19. *Vaccines (Basel)* 2022;**10**(4):513.
[3] World Health Organization. WHO coronavirus (COVID-19) dashboard. [accessed 31 January 2024]. Available from: https://covid19.who.int/
[4] Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022;**399**(10328):924–44.
[5] Hyun H, Choi MJ, Heo JY, et al. Immunogenicity and reactogenicity of Ad26.COV2.S in Korean adults: a prospective cohort study. *J Korean Med Sci* 2022;**37**(27):e210.
[6] Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med* 2021;**385**(24):e84.
[7] Lim S, Lee Y, Kim DW, et al. Anti-SARS-CoV-2 neutralizing antibody responses after two doses of ChAdOx1 nCoV-19 vaccine (AZD1222) in healthcare workers. *Infect Chemother* 2022;**54**(1):140–52.
[8] World Health Organization *WHO SAGE roadmap on uses of COVID-19 vaccines in the context of Omicron and substantial population immunity*; 2023. [accessed 31 May 2023]Available from *https://apps.who.int/iris/handle/10665/366671*.
[9] World Health Organization. Highlights from the meeting of the Strategic Advisory Group of Experts (SAGE) on immunization. 2023. [accessed 31 May 2023]. Available from https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination-guidance.
[10] Burckhardt RM, Dennehy JJ, Poon LLM, et al. Are COVID-19 vaccine boosters needed? The science behind boosters. *J Virol* 2022;**96**(3):e0197321.
[11] Cheng H, Peng Z, Si S, et al. Immunogenicity and safety of homologous and heterologous prime-boost immunization with COVID-19 vaccine: systematic review and meta-analysis. *Vaccines (Basel)* 2022;**10**(5):798.
[12] Chu L, Vrbicky K, Montefiori D, et al. Immune response to SARS-CoV-2 after a booster of mRNA-1273: an open-label phase 2 trial. *Nat Med* 2022;**28**(5):1042–9.
[13] Mallory RM, Formica N, Pfeiffer S, et al. Novavax 2019nCoV101 Study Group. Safety and immunogenicity following a homologous booster dose of a SARS–CoV-2 recombinant spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomized, placebo-controlled, phase 2 trial. *Lancet Infect Dis* 2022;**22**(11):1565–76.
[14] Walls AC, Fiala B, Schäfer A, et al. Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2. *Cell* 2020;**183**(5):1367–1382.e17.
[15] Morel S, Didierlaurent A, Bourguignon P, et al. Adjuvant system AS03 containing alpha-tocopherol modulates innate immune response and leads to improved adaptive immunity. *Vaccine* 2011;**29**(13):2461–73.
[16] Song JY, Choi WS, Heo JY, et al. Safety and immunogenicity of a SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with AS03: a randomized, placebo-controlled, observer-blinded phase 1/2 trial. *EClinicalMedicine* 2022;**51**:101569.
[17] *SK bioscience and GSK announce Biologics License Application approval of SKYCovione™ in Republic of Korea* [accessed 31 May 2023]Available from https://www.skbioscience.com/en/news/news_01_01?mode=view&id=132&page=3&category=subjectcience.

[18] Regev-Yochay G, Gonen T, Gilboa M, et al. Efficacy of a fourth dose of COVID-19 mRNA vaccine against Omicron. *N Engl J Med* 2022;**386**(14):1377–80.
[19] Van Gils MJ, Lavell A, van der Straten K, et al. Antibody responses against SARS-CoV-2 variants induced by four different SARS-CoV-2 vaccines in health care workers in the Netherlands: a prospective cohort study. *PLoS Med* 2022;**19**(5):e1003991.
[20] European Medicines Agency *Vaxzevria (previously COVID-19 vaccine AstraZeneca)*; 2021. [accessed 31 May 2023]Available from *https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria.*
[21] Pajon R, Doria-Rose NA, Shen X, et al. SARS-CoV-2 Omicron variant neutralization after mRNA-1273 booster vaccination. *N Engl J Med* 2022;**386**(11):1088–91.
[22] Song JY, Choi WS, Heo JY, et al. Immunogenicity and safety of SARS-CoV-2 recombinant protein nanoparticle vaccine GBP510 adjuvanted with AS03: interim results of a randomised, active-controlled, observer-blinded, phase 3 trial. *EClinicalMedicine* 2023;**64**:102140.
[23] Moreira ED Jr, Kitchin N, Xu X, et al. C4591031 Clinical Trial Group. Safety and efficacy of a third dose of BNT162b2 Covid-19 vaccine. *N Engl J Med* 2022;**386**(20):1910–21.