First-in-Human Phase 1 Trial of an Adjuvanted SARS-CoV-2 Spike Ferritin Nanoparticle Vaccine

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Background

Next-generation coronavirus (COV) vaccines must confer broader protection against a range of SARS-CoV-2 variants as well as novel species that may cross over from zoonotic reservoirs in the future. The SARS-CoV-2 recombinant spike ferritin nanoparticle (SpFN) vaccine co-formulated with Army Liposomal Formulation (ALFQ) adjuvant containing monophosphoryl lipid A and QS-21 (SpFN/ALFQ) was previously shown to be immunogenic and protective in challenge experiments in rodents and non-human primates against SARS-CoV-2 and variants of concern (VoC). This study reports the first-in-human randomized, double-blind, placebo-controlled clinical trial of SpFN/ALFQ.

Methods

Phase I Clinical Trial

Healthy, SARS-CoV-2 seronegative and unvaccinated adults aged 18-55 years were randomly assigned to receive either 25μg or 50μg of SpFN/ALFQ or saline placebo intramuscularly at days 1 and 29, with an optional open-label third vaccination at day 181. Local and systemic reactogenicity, adverse events and humoral immunity were quantified and analyzed by Clopper-Pearson. Binding and neutralizing antibody responses of volunteers against multiple COV were quantified.

In vivo Passive Transfer of Human IgG

To further test breadth of cross-protection, IgG antibodies from vaccinees were passively transferred into Syrian Golden hamsters (SGH) prior to SARS-CoV-1 Urbani challenge. Lung tissue was recovered at days 3 and 6 post challenge for virus detected by quantitative RT-PCR, as well as immunohistochemistry staining.

Results

All received two vaccine doses and a subset who did not receive EUA vaccines received three vaccine doses. Local and systemic reactogenicity was mild to moderate, and no participants experienced any adverse events of special interest. Binding and neutralizing antibody responses peaked at day 43. Neutralizing antibody titers against Omicron subvariants and clade 1 sarbecoviruses were detectable after two immunizations and peaked after the subset of volunteers who received a third immunization and were present at day 361. Passive IgG transferred from vaccinated volunteers into hamsters-controlled replication of SARS-CoV-1 post challenge.

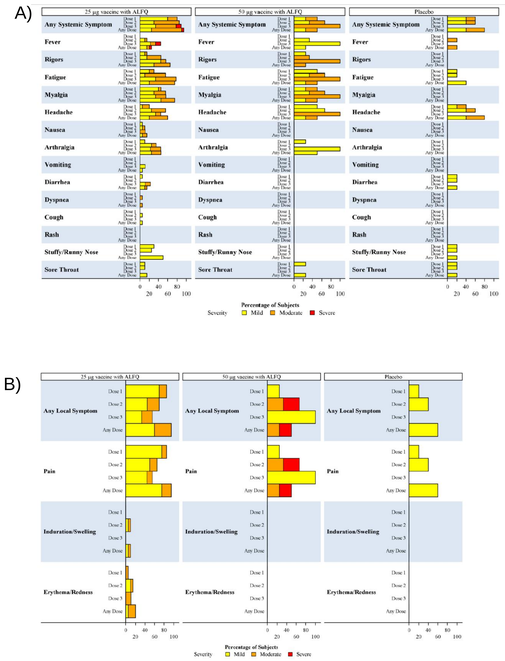

Figure 1A-B. Figure 2A-B. The percentages of participants reporting solicited adverse events, comprised of
566 (A) systemic and (B) local reactogenicity
symptoms, are summarized by maximum severity over
567 the 8 days post-each study vaccination and post-
any study vaccination.

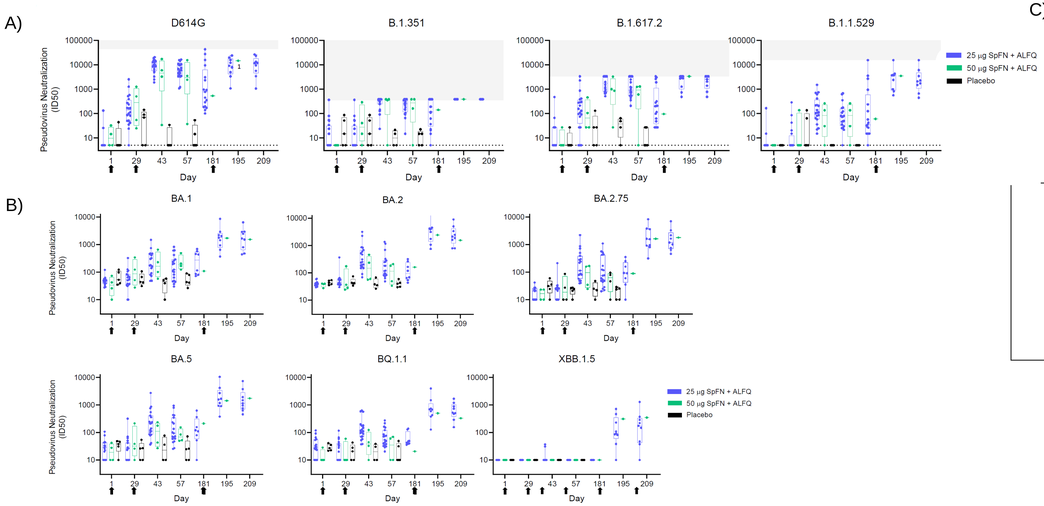

Figure 2A-C. Pseudovirus Neutralizing Antibody Geometric Mean IC50 Titer Against SARS-CoV-2, by Group and Variant. (A) and (B) Individual participant titers, with boxes and horizontal bars to denote interquartile range (IQR) and median, respectively. Whisker endpoints are equal to the maximum and minimum values. Grey boxes indicate upper limit of detection for these validated assays. Arrows at the base of the Figure indicate day of vaccination. (C) A heatmap of reciprocal neutralization titers (ID50) for the nine volunteers included in the 25μg group of the trial against variant of concern authentic viruses for study day 43 (two weeks post second vaccination), study day 181 (day of third vaccination), and study day 195 (two weeks post third vaccination).

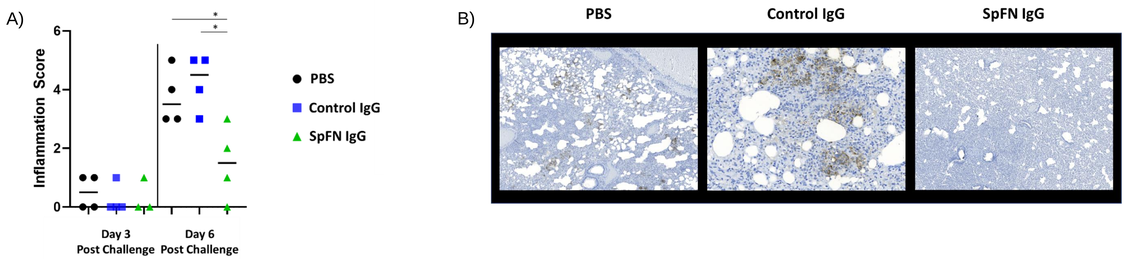

Figure 3A-B. Figure S3. Passive IgG Transfer from SpFN Vaccinees Protects Syrian Golden Hamsters from SARS-1 Urbani Challenge. (A) Inflammation score from lung tissue of Syrian golden hamsters challenged intranasally with SARS-CoV-1 Urbani 24 hours after intraperitoneal administration of PBS, Control IgG, or IgG purified from individuals vaccinated with SpFN+ALFQ. (B) Representative immunostaining of lung tissue 6 days post SARS-CoV-1 Urbani challenge.

Conclusion

Individuals vaccinated with SpFN/ALFQ mounted neutralizing antibody responses against multiple clade 1 sarbecoviruses, including generating neutralizing antibody responses to SARS CoV-2 XBB 1.5 after three vaccinations. Further, the breadth generated by this WA-1 based vaccine was supported by lack of detectable SARS-CoV-1 Urbani virus by IHC following passive transfer of purified IgG in SGH. The promising results of this first-in-human SpFN/ALFQ clinical trial represents a platform upon which to build future sarbecovirus vaccine development.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted under an IACUC-approved animal use protocol in an AAALAC International - accredited facility with a Public Health Services Animal Welfare Assurance and in compliance with the Animal Welfare Act and other federal statutes and regulations relating to laboratory animals. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.