The reactogenicity and immunogenicity of a booster dose after the second dose of a protein subunit vaccine MVC-COV1901.

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Abstract: In this extension of the phase 1 clinical study, we report the immunogenicity and reactogenicity of the booster dose of a COVID-19 vaccine, MVC-COV1901, administered six months after the completion of the primary two dose schedule. Antibody persistence was detected at 6 months after the second dose of MVC-COV1901, albeit at reduced levels. At 28 days after the booster dose, the neutralizing antibody titer was 1.7-fold higher compared to the previous peak at 2 weeks after the second dose. These data demonstrated the safety and immunogenicity of booster shot of MVC-COV1901 after the primary schedule of the vaccine.

Introduction: MVC-COV1901 is a protein subunit COVID-19 vaccine based on the stable prefusion spike protein S-2P adjuvanted with CpG 1018 and aluminum hydroxide. Interim results of phase 2 clinical trial demonstrated favorable reactogenicity and immunogenicity and the vaccine has been authorized for use in Taiwan since August 2021 [1]. However, the antibody persistence after the second dose and the effects of a booster dose remained unknown at the time. We describe the antibody durability until 180 days after the second dose. Also, we report reactogenicity and the immunogenicity of the booster shot of MVC-COV1901 administered to 45 healthy adults from 20 to 49 years of age on day 209 in an extended Phase 1 study.

Methods: Three different dose levels employed in the original Phase 1 trial were low dose (LD), middle dose (MD), and high dose (HD) (5 mcg, 15 mcg, and 25 mcg, respectively) of S-2P protein adjuvanted with CpG 1018 and aluminum hydroxide [2]. MD was used as the booster dose for the LD and MD group, while HD was used for the HD group. Antibody level was measured on day 209 by enzyme-linked immunosorbent assay (ELISA) against SARS-CoV-2 spike protein, and by live-virus SARS-CoV-2 neutralization assay [1], with NT₅₀ GMTs expressed as neutralization titer.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
To facilitate comparison, units of measurements for antibody titers are expressed in Binding Antibody Unit per mL (BAU/mL), and neutralization titers are expressed in WHO Standardized International Unit per mL (IU/mL, WHO Standardized).

**Results:** Anti-SARS-CoV-2 antibody levels persisted in all groups at day 209 (6 months after the second vaccination), with geometric mean titers (GMTs, in BAU/mL) of 40.1, 59.9, and 86.6 for LD, MD, and HD groups, respectively (Figure A and Appendix A). The corresponding neutralizing NT$_{50}$ GMTs (IU/mL) were 59.4, 79.4, and 113.2 for LD, MD, and HD groups, respectively (Figure B and Appendix B). At 28 days after the booster dose, the neutralizing GMTs (IU/mL) of the live-virus SARS-CoV-2 neutralizing assay were 1719.6, 818.3, and 1345.6 for LD, MD, and HD groups, respectively (Figure B and Appendix B). Reactogenicity after the third dose for all participants was comparable to that after the previous doses (Appendix C).

**Discussion:** Although the Correlates of Protection (CoP) is yet to be established for COVID-19 vaccines, neutralizing antibody titers have been reported to be highly correlated with vaccine efficacy [3]. Based on Khoury’s modelling, a level of neutralizing NT$_{50}$ 54 IU/mL could render 50% of vaccine efficacy against the prototype strain, which meets the WHO target product profile for COVID-19 vaccine approval. The trough, at 6 months after the primary two doses of MVC-COV1901, of neutralizing NT$_{50}$ for MD group was 79.4 IU/mL, which still exceed the above cut-off. The dynamics of antibody titer after the second dose is similar to that of other vaccines, namely increasing to peak at 2 weeks after the administration and decline afterwards but remain detectable on day 209 [4]. The GMT of neutralizing antibody titers of MD showed a 6.2 fold-reduction (495.9/79.4) at 180 days - which is comparable to other platforms [5, 6] - compared to the peak at 14 days after the second dose. At 28 days after the booster dose, a fold-increase of 1.7 (818.3/495.9) was noted compared to the previous peak. The results showed that antibody response against SARS-CoV-2 can be boosted by the third dose. The data supports the use of the vaccine in further clinical development that involves a 3$^{rd}$ dose boost. Ongoing monitoring is planned and will give insights to antibody persistence after the third dose.
Figure A) anti-SARS-CoV-2 IgG antibody titer expressed in binding antibody titers (BAU/mL) and B) neutralizing antibody titer expressed in WHO International Units (IU/mL) of LD, MD, and HD groups at various time points.

Conflict of Interest Disclosure:
H.-Y.C. and C.E.L. are employees of Medigen Vaccine Biologics Corporation and have received grants from the Taiwan Centers of Disease Control, Ministry of Health and Welfare. S.-M.H., S.-C.C., and S.-R.S. declared no conflict of interest.

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Author Contributions:

Concept and design: S.-M.H.
Acquisition and interpretation of data: S.-M.H. and S.-C.C.
Drafting of the manuscript: S.-M.H., H.-Y.C., C.E.L., and S.-C.C.
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Additional Contributions:

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Ethics Statement:

The trial protocol and informed consent form were approved by the Taiwan Food and Drug Administration and the Research Ethics Committee of National Taiwan University Hospital. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. An independent data and safety monitoring board (DSMB) was established to monitor safety data and the trial conduct. (ClinicalTrials.gov NCT04487210)

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