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Emergency Task Force

ETF statement on the use of the EMA approved bivalent original/Omicron BA.4-5 mRNA vaccines for primary series

Introduction

The development and use of mRNA vaccines against the original SARS-CoV-2 spike protein (Wuhan-Hu-1, hereafter abbreviated to Wuhan) have proven highly effective against symptomatic and severe COVID-19. Since the declaration of the COVID-19 public health emergency in early 2020, the SARS-CoV-2 virus has continuously evolved, resulting in a series of variants of concern. Currently, the viruses circulating worldwide are of the Omicron lineage, with several subvariants recognised[1]. In response, some marketing authorisation holders (MAHs) have adapted their approved vaccines. The EU-approved mRNA vaccines (Comirnaty and Spikevax) have been adapted to provide bivalent vaccines containing two mRNAs: one encoding the original Wuhan SARS-CoV-2 spike protein included in the monovalent vaccines (original vaccine) and another encoding the Omicron sublineage BA.1 or BA.4-5 spike protein.

The bivalent Wuhan/Omicron BA.4-5 Pfizer-BioNTech vaccine was recently approved by the EMA for booster doses in children and adults, while the bivalent Wuhan/Omicron BA.4-5 Moderna vaccine is currently approved for boosting adults and adolescents. These vaccines were authorised based on human trials of vaccines that incorporated mRNA encoding spike protein of an earlier Omicron variant (BA.1), data on boosting with mRNA encoding spike protein of BA.4/BA.5 in animals and limited Wuhan/Omicron BA.4-5 Pfizer-BioNTech vaccine clinical safety data.

The paucity of seronegative persons (i.e. with no serological evidence of prior natural infection and no history of vaccination) poses challenges to generating clinical data to support rapid updating of strains in vaccines indicated for use as a primary series. At this time, there are no clinical data to support use of the bivalent mRNA vaccines for a primary series. However, it may be necessary to consider using the bivalent Wuhan/Omicron mRNA vaccines for the primary series in previously unvaccinated adults and children.

[1] https://nextstrain.org/ncov/gisaid/global/6m

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Summary of data

Preclinical supportive data

Mouse vaccination-challenge models have been exploited by both MAHs to study the immune responses induced by bivalent COVID-19 vaccines as a primary series. Robust serum immunoglobulin binding was observed against Wuhan, BA.1 and BA.4-5 spike proteins at 2 weeks post priming with 2 doses of Moderna bivalent Omicron BA.1 or BA.4-5 vaccines. Bivalent vaccines induced a broader neutralising antibody response compared to administration of each of the mRNA constituents when given alone.[2] Immunisation of SARS-CoV-2 naïve mice with the Pfizer/BioNTech bivalent mRNA vaccine encoding both the Wuhan and the Omicron BA.4-5 spike proteins induced neutralising activity against Omicron subvariants (BA.1, BA.2, BA.2.12.1, and BA.4-5) as well as previous variants of concern (Wuhan, Alpha, Delta)[3]. These non-clinical data suggest that a primary series with bivalent vaccines could induce broad immune responses in SARS-CoV-2 naïve humans.

Clinical supportive data

There are no clinical studies available for primary vaccination with the bivalent mRNA vaccines.

The bivalent vaccines currently available contain half of original dose of the Wuhan formulation. Dose-finding clinical studies for the original Comirnaty (30 micrograms) showed only limited differences in immunogenicity when comparing 10, 20 and 30 microgram doses[4]. Also, for Spikevax (100 micrograms original dose), a dose finding study in humans showed that 50 and 100 microgram doses induce similar immune responses[5]. Therefore, it can be expected that primary vaccination with the bivalent vaccine will at least elicit immune responses to variants that are similar to those of the original Wuhan monovalent vaccines.

Preliminary data in humans suggest that SARS-COV-2 Omicron BA.4-5 infection in unvaccinated subjects in South Africa induces a broader serum neutralisation capacity (i.e. against D614G, Beta, Delta, BA.1, BA.2 and BA.4) compared to Omicron BA.1 infection as measured by a pseudovirus neutralisation assay[6]. These data suggest that vaccines that contain mRNA encoding Omicron BA.4-5 spike protein may provide some cross-protection to currently circulating variants. In contrast, preliminary clinical data with a monovalent Omicron BA.1 mRNA vaccine suggest that it elicited a very limited cross-neutralisation immune response[7].

Although the level of protection achieved by booster doses cannot be used to infer protection for the primary series, it is encouraging that the first real world evidence data on the use of bivalent mRNA vaccines for boosting indicates that they provide protection against symptomatic SARS-COV-2 infection[8]. More data with respect to protection against hospitalisation and severe COVID-19 are awaited.

[2] Bivalent SARS-CoV-2 mRNA vaccines increase breadth of neutralization and protect against the BA.5 Omicron variant in mice | Nature Medicine
[3] Exposure to BA.4/5 S protein drives neutralization of Omicron BA.1, BA.2, BA.2.12.1, and BA.4/5 in vaccine-experienced humans and mice | Science Immunology
[4] https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
[5] https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf
[6] SARS-CoV-2 BA.4 infection triggers more cross-reactive neutralizing antibodies than BA.1 | bioRxiv
[7] https://www.fda.gov/media/159496/download
[8] Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022 | MMWR (cdc.gov)

Clinical studies suggest that the reactogenicity profile is overall comparable for the variant-containing mRNA vaccines used for boosting and for the original mRNA vaccines used for the primary series or for boosting. Clinical studies conducted by the MAHs with other adapted vaccines indicated no new safety concern and acceptable reactogenicity profile[94]. This suggests that the safety profiles of variant-containing vaccines based on the approved mRNA platform can generally be expected to be comparable to the already licensed mRNA vaccines, for which the safety profile is established.

ETF conclusion

Although there are limitations to available data, it is reasonably expected that the bivalent original/Omicron BA4-5 mRNA vaccines can elicit priming against SARS-CoV-2 and that they would have a similar safety profile as the originally approved mRNA vaccines in previously unvaccinated persons.

The ETF considers it acceptable that the bivalent original/Omicron BA.4-5 mRNA vaccines currently authorised in the European Union/European Economic Area for boosting may also be used to deliver a primary series should this become necessary to support vaccination campaigns.

Further clinical research, including observational studies, is expected to provide additional information on use of the bivalent vaccines for the primary series, especially in children.

This ETF statement is intended to support decisions made at national level. It is not a change of the product information for the authorised vaccines.

[9] A Bivalent Omicron-Containing Booster Vaccine against Covid-19 - PubMed (nih.gov)