8 February 2023
EMA/67738/2023

Summary report of the Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants

Monoclonal antibody therapies are designed to bind to the spike protein of SARS-CoV-2 and thereby interfere with the ability of the virus to attach to and enter the host cells. Monoclonal antibodies (mAbs) have demonstrated the ability to decrease the risk of symptomatic SARS-CoV-2 infection in the context of pre-exposure or post-exposure prophylaxis, and to reduce the risk of progression to severe disease, hospitalisation and death in patients with early disease not requiring supplemental oxygen and who are at an increased risk for progressing to severe COVID-19 disease.

The SARS-CoV-2 virus has continuously evolved and several variants of concern that carry mutations in the spike protein that reduce the ability of the mAbs to bind, which may reduce their efficacy, have emerged since the initial outbreak due to the SARS-CoV-2 virus WUHAN strain (Wuhan-Hu-1). In view of the rapidly evolving SARS-CoV-2 variants, the observed loss of *in vitro* neutralising activity of monoclonal antibodies, and challenges concerning in conducting clinical trials to generate efficacy data in a timely fashion against variants in circulation, a Joint EMA-FDA workshop was held on the 15th December 2022. The objectives of the workshop were to bring together the expertise of academics, clinicians, industry, and regulatory bodies to address the acceptability and challenges of alternative strategies to support the development of novel monoclonal antibody therapies including those based on prototype products that have demonstrated safety and efficacy in clinical trials. Further, the workshop aimed to discuss the current evidence for the use of surrogates of clinical efficacy (e.g., neutralisation titers, PK/PD modelling, viral RNA shedding) to support the activity of already approved/authorised monoclonals and the development of novel monoclonal antibodies against variants of concern (VoC). In addition, the workshop aimed to foster potential way(s) forward to support the development of novel monoclonal antibody therapies.

Experts from academia, industry and regulatory bodies attended the meeting. During the workshop, different scientific topics were addressed by the speakers, including an overview of clinical trial data that led to the approval of mAbs in the European Union. The audience was informed about the available neutralisation activity data of mAbs against VoC and about the potential use of serum neutralisation data as a surrogate of clinical efficacy or correlate of protection in the prevention setting. The advantages and disadvantages of the PK/PD modelling approach and CMC considerations for products with an established platform were presented by the FDA. Data on the potential use of viral RNA shedding as surrogate marker of clinical efficacy were presented to the participants. The industry perspective was also presented at the workshop, highlighting that the use of neutralisation approaches is the preferred strategy of industry to foster the development of new monoclonal antibody products.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

At the end of the workshop there was an open discussion on the potential way forward. During this discussion a number of important topics were covered, including the strengths and weaknesses of the immunobridging approaches based on serum neutralisation titres (SNT), PK/PD modelling, pharmacodynamic markers and potential other approaches for the bridging of efficacy from a monoclonal antibody product that has already demonstrated safety and efficacy in clinical trials to a new monoclonal antibody product. Additionally, the advantages and disadvantages of comparing the activity of a new product against current circulating variants to the activity of a prior product against variants that were in circulation during the clinical trial that demonstrated efficacy of the prior product were discussed. The potential way(s) forward for development of new monoclonal antibody products that are not based on monoclonal antibody products/platforms that have already demonstrated safety and efficacy in clinical trials were addressed; it was determined that this situation would require additional scientific consideration to determine whether this pathway is possible. Also, different considerations for developing products for prophylaxis vs treatment were discussed at the meeting.

There was overall agreement on the need to expedite the development of new monoclonal antibody products against emerging variants of concern (especially in the context of pre-exposure prophylaxis for immunocompromised patients), with an understanding that demonstrating safety in humans for any new product remains essential. There was general support for the use of a biomarker approach based on immunobridging (GMT of neutralising antibodies at specific timepoints) preferably with a combination of PK modelling and confirmation of clinical efficacy post-approval/post-authorisation. Overall, participants did not believe that a cross-variant comparison would be significantly impacted by assay constraints, if it is ensured that assay performance criteria, i.e., linearity, range, precision, slope and response, are comparable. The need for post-marketing efficacy data, i.e., the investigation of breakthrough cases, monitoring of neutralising antibody and drug concentration to determine the timing of waning antibodies, and to support the surrogate markers of efficacy used for initial regulatory action was highlighted. Concerning the clinical trial designs for immunobridiging studies and the potential approach for collecting post-marketing efficacy data, it was agreed that further discussion with regulatory authorities is considered necessary. All participants agreed that the prevention of COVID-19 in immunocompromised patients should be a primary target of future monoclonal antibody development.