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Provisional title of the paper: Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron Variant of Concern

Project name and executive summary: Currently, 3 anti-SARS-CoV-2 monoclonal antibody products have received Emergency Use Authorizations from the Italian Medicines Agency (AIFA) for the treatment of mild to moderate COVID-19 in non hospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization (bamlanivimab plus etesevimab, sotrovimab, and casirivimab plus imdevimab). Differently from casirivimab/imdevimab and sotrovimab, the European Medicines Agency (EMA) has never recommended authorising the combination bamlanivimab/etesevimab for treating COVID-19. Moreover, the evidence on sotrovimab relies on the interim analysis results of an ongoing randomised placebo-controlled clinical trial, unlike the combinations bamlanivimab/etesevimab and casirivimab/imdevimab, whose results of the randomised placebo-controlled trials were published after having completed the enrolment. The study aims at assessing the non-inferiority of bamlanivimab plus etesevimab and sotrovimab vs. casirivimab plus imdevimab on COVID-19 progression in patients aged at least 50 years at an early stage of the disease. The progression of COVID-19 disease (hospitalization, need for supplementary oxygen therapy at home, death) within 14 days of randomisation is the composite outcome variable on which the calculation of the sample size is based. Based on available data regarding the reduction in the number of hospitalisations and medical visits with the use of casirivimab plus imdevimab at an early-stage of COVID-19, a disease progression of 5% has been estimated in the reference arm. 5% delta margin was considered clinically relevant, taking into account both the estimates of disease progression in the study population in absence of early treatment with monoclonal antibodies (20%, based on national data) and the efficacy of the reference standard. Therefore, 1260 participants will be randomly assigned in an equal ratio between the reference standard and each of the other two experimental arms (1:1:1). Randomization will be computer-generated in permuted blocks with a stratification based on site.

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Methods of data processing and analysis: Data were collected during the implementation of a randomised clinical trial (Clinical trial number NCT05205759). Study data were collected and managed using REDCap electronic data capture tool hosted at the Verona University Hospital. A web-based eCRF (electronic Case Report Form) was developed and patient's randomisation was centrally managed and monitored by the coordinating centre. Data monitoring was also carried out with STATA and the variables for the analysis were manipulated and created using the same software. The MANTICO trial is a non-inferiority randomised controlled trial comparing the clinical efficacy of bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab in outpatients aged 50 or older with early COVID-19. As the patient enrolment was interrupted for possible futility after the onset of the Omicron wave, the analysis was performed according to the SARS-CoV-2 VOC. The primary outcome was COVID-19 progression (hospitalisation, need of supplemental oxygen therapy, or death through day 14). Secondary outcomes included the time to symptom resolution, assessed using the product-limit method. Kaplan-Meier estimator and Cox proportional hazard model were used to assess the association with predictors. Log rank test was used to compare survival functions.

De-identification procedures for sensitive human subjects: Pseudonymization method was used in order to guaranty patients' anonymity. Patients were therefore linked to anonymous alphanumeric codes and the linking key, stored off-line, was available only to the clinician coordinating the data collection. In line with ethics board approval and informed consent signed by study participants, some variables, namely age, gender, height, weight, smoking habit, were removed from the original dataset used for the analysis. The anonymised dataset record order was randomised so the resulting dataset is now a file very similar in terms of length, fields and content to the original version, except for row order which is completely random, and the record id variable deleted.

Specialized software used for analyses was STATA v.17 and the dataset file type is a compressed data file with the extension DTA. A codebook with the variable’s description is provided as part of the documentation files.