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Study Design (Part 3 of Phase 3 study of Vaccine Candidate for COVID-19)

In 1 collection

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1 Works for me dx.doi.org/10.17504/protocols.io.bj5wkq7e

Coronavirus Method Development Community

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ABSTRACT

This is Part 3 of "Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of **Vaccine Candidate** against COVID-19 in adults > 18 years of age"

This generic Phase 3 protocol was developed by the PATH team with support of the Bill and Melinda Gates Foundation. The aim of the collection is to share recommended best practices in designing and implementing a Phase 3 study of a COVID-19 vaccine candidate. As Phase 3 trials of different Vaccine Candidates proceed around the world, following the same protocols will ensure consistency and comparability of the Phase 3 trial results.

Please note that this is an evolving document, to be versioned and updated, based on community feedback and new data.

ATTACHMENTS

Generic Phase 3 Protocol COVID-19 Vaccine - 25AUG2020-version 1.docx

DOI

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PROTOCOL CITATION

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COLLECTIONS

Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

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Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

GUIDELINES

The study will be a **(multinational)**, endpoint-driven, randomized, double-blind, placebo-controlled, adaptive, group-sequential trial in which participating adults will be randomized 1:1 to receive **XX** dose(s) of either **Vaccine Candidate** adjuvanted with **XX** or a **control (licensed vaccine or a placebo vaccine [e.g., normal saline plus aluminum hydroxide])** on Day(*s*) 1 (and) **XX**. Participants will be followed for efficacy, safety, and immunogenicity.

Each country **(site)** participating in the study will have a site-specific protocol addendum that will allow for site/country-specific guidelines and variance (such as IRB requirements and local case surveillance and clinical management guidelines). Endpoint definitions and data collection instruments will be common across sites. Participants will be randomized 1:1 to either **Vaccine Candidate** or placebo, stratified by site, age group (<60, ≥60), and sex. At least **XX** participants will be ≥60 years old.

The study is adaptive, in that the total sample size may be increased at an early time point depending upon the rate of confirmed primary efficacy endpoint events. An Adjudication Committee will be constituted to review and confirm each case determined to be an endpoint. In addition, a Data and Safety Monitoring Board (DSMB) will be established to provide independent continuous monitoring of vaccine safety and operational quality, as well as to evaluate an interim efficacy analysis. The DSMB will compare the actual number of events accrued under blind in a pre-defined analytical plan and will make recommendations regarding sample size adjustments according to predefined criteria, as well as recommendations for closing/opening sites to target enrollment in places where cases are accruing most rapidly. The DSMB will evaluate unblinded safety data periodically and additionally upon sponsor request.

The study will be group-sequential, to allow the DSMB to review interim unblinded efficacy data and determine whether there is overwhelming evidence of early efficacy or futility, and thus make recommendations in light of data accrued and predefined stopping criteria. Sample size adaptations are not planned following the unblinded efficacy analysis.

The DSMB risk/benefit evaluation will include additional vaccine-specific information from similar studies or other vaccines based on the same platform (inactivated vaccines), and potentially will link with the Safety Platform for Emergency Vaccines (SPEAC), the meta-DSMB established by the Coalition for Epidemic Preparedness Innovations (CEPI) to oversee COVID-19 vaccine safety from all the vaccine development activities they support.

3.1. Success criteria

The point estimate for vaccine efficacy (VE) should be at least 50 percent, in agreement with the minimum requirement given in the WHO Target Product Profile. Success will be defined by a sequential-monitoring-adjusted 95 percent lower bound of the confidence interval (CI) on vaccine efficacy that exceeds 30 percent for the primaryendpoint. The International Coalition of Medicines Regulatory Authorities noted that “a specific numeric value to be used for the lower bound and vaccine efficacy point estimate was not agreed upon at this stageIt was also reflected that efficacy estimates crossing a certain pre-specified lower bound for efficacy, due to factors such as epidemiological evolution of the pandemic, would not preclude the possibility of a positive benefit risk conclusion if there also were other data supportive of efficacy”[16].

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It is anticipated the 6-month COVID-19 attack rate in the placebo arm will be approximately **XX** percent. The trial is endpoint driven; the main analysis for each vaccine arm is triggered by accrual of primary endpoints across the two arms, at which point the results will be reported. In the event overwhelming efficacy is detected during the interim analysis, placebo participants may be provided with closeout vaccinations.

The study has a set target vaccine efficacy (VE) of 50 percent point estimate with 90 percent power to reject VE, less than or equal to 30 percent if true VE is 60 percent. Vaccine efficacy will be estimated using 1 – HR, where HR is the hazard ratio estimated from the Cox proportional hazards model. Should efficacy criteria be met at interim analysis (when approximately 40 percent of events have been confirmed), active endpoint surveillance will cease but safety monitoring will continue for one year following vaccination. Should **Vaccine Candidate** be found non-efficacious during the interim analysis, the DSMB may declare futility, in which case enrollment of additional volunteers will cease. In this case the DSMB may provide a recommendation for continuous safety monitoring of **Vaccine Candidate** recipients or all the participants in the cohort for an additional limited time. Should neither efficacy nor futility criteria be met at interim analysis with enrollment not yet complete, enrollment of the remaining participants will continue.

All sites will monitor the incidence of severe COVID-19 and death attributable to COVID-19. Although the study may lack power for formal statistical inference about vaccine efficacy against severe disease and death, this secondary endpoint will be calculated and reported.

LITERATURE CITED

16. Considerations for study design for Phase 3 clinical trial. International Coalition of Medicines Regulatory Authorities. http://www.icmra.info/drupal/news/22june2020/summary

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