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Commentary

Ethics and execution of developing a 2nd wave COVID vaccine – Our interim phase I/II VSV-SARS-CoV2 vaccine experience

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1. Balancing ethics and clinical study quality in light of a massive national vaccination campaign.

The Israel Institute of Biological Research (IIBR) is developing an rVSV-Sars-CoV2 vaccine, currently in Phase II. Following Pfizer's Emergency Use Authorization (EUA) in the US (December 10th, 2020) and Israel (shortly thereafter), the State of Israel has embarked on a major COVID-19 vaccination campaign (currently covering about 86% of people above 50). The massive vaccination campaign has posed significant ethical and executional challenges on us as vaccine developers, as well as on the respective principal investigators, safety review boards and regulators. Should we continue to maintain (and recruit) for the placebo arms (especially in elderly subjects whom are eligible and have access to an approved and effective vaccine), and if so, for how long should we maintain placebo monitoring? When to trigger unblinding, and which vaccine to offer such unblinded placebo subjects (the approved one, or to request re-consent for our investigational one)?

We conclude that placebo is critical for study quality and a follow-up prior to unblinding of 56 days maintains a reasonable balance between ethics and execution. The study offers subjects who are unblinded and found on Placebo, to either vaccinate with an approved vaccine outside the study, or to re-consent to the study (with a 1:3 chance of receiving the placebo assigned to that dosing group).

Following EUA of two mRNA vaccines in the US, Pfizer-BioNtech and Moderna's, on December 10th and 17th 2020, respectively, and their approval by the State of Israel immediately thereafter, Israel has launched perhaps the fastest COVID vaccination campaign (per population) globally. Israel has administered nearly 10 million vaccine doses and fully vaccinated nearly 51% of its population, followed by UK (~23%) and the US (~19.7%) [1].

As previously reported [2,3], the State of Israel, through its Israel Institute of Biological Research (IIBR), embarked on the development of a replication-competent recombinant VSV Sars-CoV-S2 vaccine, and initiated a randomized, placebo controlled, Phase I study on November 1st, 2020. Recruitment of elderly subjects and subjects with chronic diseases into Phase II began on December 14th, 2020.

Our Phase I (NCT04608305), first-in-human placebo-controlled, double-blinded clinical trial for evaluation of the IIBR-100 COVID vaccine candidate included 80 participants, aged 18–55, in four groups (3:1 active/placebo in each group) [4]. The recruitment was completed shortly before arrival of the EUA vaccines to Israel and the initiation of Israel's rapid vaccination campaign.[5] Initially, an approved vaccine was offered to front-line medical personnel and to people aged 60 and over. The campaign is gradually expanding and now includes anyone above 16.

To date, all Phase I subjects have been unblinded and the majority has received the EUA vaccine.

Although not unprecedented, as the EUA vaccination campaign picked up in Israel, the changing reality posed significant ethical and executional challenges for our development team, including our principal investigators, as well as to the program's, regulators and ethical committees, namely:

- Should we continue to maintain placebo arms, particularly in the elderly and in those with increased risk of severe COVID, while these cohorts have access to highly efficacious and safe vaccines?
- If the answer to the above is "yes", after what duration, and upon which trigger, should we unblind and vaccinate such placebo subjects?
- Finally, which vaccines should be offered to such unblinded placebo subjects – the investigational one they originally volunteered for, or a commercial/EUA vaccine that is (or will soon be) available to them?

Struggling with these questions and the balancing of subjects' wellbeing vs. the quality of the clinical study (as further elaborated in our own letter to Wendler et al in Science) [6,7], we have attempted to refer to leading regulators and vaccine programs,

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although this too was quite challenging. In particular, the FDA has not updated its guidance for placebo-controlled efficacy studies to date, and remains in the position that placebo subjects should be followed for "as long as feasible". This approach was recently put to test with the FDA approval of NovaVax's Phase III study, which included a placebo arm (albeit at 2:1 ratio). Pfizer, in its own EUA submission from December 10th, 2020, has requested to continue to follow-up subjects on placebo for 6 months prior to unblinding, setting a relatively long-duration bar compared to its close rival Moderna (which, in its own EUA, seven days later, recommended that all placebo subjects be immunized with the m1273 vaccine, effectively unblinding the study altogether immediately and prior to natural completion).

However, in reviewing the strategies proposed or executed by the leading developers of the "first wave" of COVID vaccines, we were also required to attend to our unique situation in which by the foreseen time of recruitment of the full Phase II study, all recruited subjects would be eligible, and have access to an EUA vaccine.

Importantly, IIBR's vaccine program is unique, in that it aims to bestow the State of Israel with the ability, capacity and infrastructure to develop and produce pandemic vaccines. Replicating viral vector vaccines such as rVSV may continue to be an important complimentary vaccine platform for COVID-19 and other future pandemic threats because of their seemingly benign safety profile, as well as potentially their breadth of protection. Thus, a strategic decision was taken to continue the development into Phase II despite Israel being supplied with a very efficacious mRNA vaccine. As a consequence, recruiting subjects under such circumstances has become significantly more challenging, although the dedicated team of investigators were able to continue recruitment in fair numbers, and to date, met the full recruitment allocation for young as well as the elderly cohorts.

Our plan proposes to maintain placebo subjects until their Day 56 visit (56 days post prime vaccination and 28 days post boost, for those who received a booster shot).

Once unblinded, subjects that were on placebo are presented with the choice of being referred to receive the approved vaccine with their HMO (while continuing follow-up as planned for 12 months), or, if they are reluctant to vaccinate with the approved vaccine, re-consent to the trial, to be re-randomized into any active dosage arm. Importantly, subjects are notified that they may be re-randomized into placebo arms again (with the same chance of 1:3 to receive the placebo) to ensure study blinding, alongside a commitment that if they are indeed re-randomized to receive placebo they will be unblinded again at Day 56 and referred to receive an approved vaccine. This approach was undertaken in order to maintain the study randomization scheme and blinding, while taking into account the prolonged risk for these double-placebo assignment subjects, and limiting subjects' anxiety for lack of protection.

Day 56 was selected because it was the first date at which all of the study's primary immunogenicity endpoint data (defined as seroconversion, GMT fold rise and GMTs relative to Day 0) for both the prime and prime-boost cohorts, are available. Second, Day 56 enables capture of most acute phase adverse events for any vaccine, probably including COVID vaccines. While this does not precisely meet FDA's recent request for EUA submissions' median 2 month follow-up from last vaccination (effectively about 3 months), we consider it sufficient for Phase I/II, and consistent with every vaccine AE report reviewed thus far (for example, peak AE's are typically at Day 2–3 post vaccination for both mRNA vaccines, as well as viral vector vaccines. Lastly, the study was not structured as a Phase III efficacy study for which long term placebo controls are indispensable for directly estimating Vaccine Efficacy (VE). In submitting our protocol amendment we tried to balance the additive risk of exposure to COVID-19 in both young and elderly subjects, relative to the known incidence in Israel at the time, with the benefit of such a control for both safety and immunogenicity. The calculated R0 around the date of protocol submission was 0.91 (data on file) and the incidence of positive COVID-19 PCR testing in the population was about 9.6%. However, Israel was undergoing a stringent lock-down, and the sponsor relied on its proficient investigators to provide effective social distancing guidance and education to all subjects – to mitigate said exposure risk. While debating such risks, we voted against limiting placebo to young healthy subjects only, as they are at lower risk for severe COVID-19, and because of the detrimental effect on the quality of the study for the elderly, whom are the primary population to benefit from this vaccine, if registered. An alternative of converting a part of the study to open-label was also considered, however if adopted, would have caused, we felt, irreparable harm to the study's quality.

So far, we have unblended ~80% Phase II subjects. In communicating our protocol amendment and the blinding procedures, the investigators have informed all subjects of the availability of an effective, EUA-approved, vaccine, and the potential risk of being immunized with the investigational yet-to-be-proven, vaccine product.

We also would like to report that despite these said challenges, our clinical sites have been able to enroll 100% of the target for all open cohorts into Phase II, suggesting that we have overcome this immense recruitment challenge.

Lately, Israel has issued a "Green Pass" for anyone fully vaccinated with an EUA vaccine, or with evidence of virologically-confirmed COVID-19 convalescence (regardless of titer). The sponsor and principal investigators worked with the Israeli MoH to grant all subjects recruited into IIBR's clinical study, the same "Green Pass". While this poses another layer of ethical and immunological considerations beyond the scope of this commentary, suffice it to say that we, and our regulators, had to carefully balance the benefits and rights of volunteering subjects, relative to the general immunized population, where there is still little evidence of high vaccine efficacy for IIBR's vaccine candidate.

2. Discussion

Vaccinology is changing at an unprecedented rate, and so does the reality of vaccine developers. In a previous letter to Science Magazine, we've argued that placebo-controlled vaccine efficacy studies will no longer be possible once efficacious vaccines become prevalent in the community [7], due to ethical as well as practical reasons. Further, other types of studies, such as classic non-inferiority studies, or cross-over studies are unlikely to be possible, due to the sheer size of the former, and the complexity of the latter. While regulators have not cast a final unanimous verdict on the use of placebo with the duration for exposure that is ethical and reasonable, vaccine developers need to react to the situation rapidly and decisively. Indeed, some developers have already reported major challenges in recruiting elderly subjects while EUA vaccination campaigns are ongoing [8,9].

In a recent viewpoint published in JAMA [10], Rid et al. argue that placebo subjects not otherwise eligible for EUA vaccines (in the US) should not be prioritized for access to such vaccines, until such time as would be scheduled according to their risk stratification. However – this is not the case in Israel, where all citizens above 16 years of age are now being offered the vaccines. Currently in the case of Israel, one could argue that equity means providing vaccine access for placebo subjects that volunteered to advance science, rather than preventing their prioritization.

To conclude, we wish to reiterate the position of Rid *et al.* on the importance of both equity for vaccine access [10], as well as the critical importance of maintaining placebo groups' blinding for as long as feasible, to ensure the quality of vaccine development trials.

We hereby present our approach to the challenge, which attempts to balance individual risk with the Common Good – without utterly compromising the quality of randomized clinical studies which are the foundation of best clinical practice.

Our approach is an interim measure, but it is our opinion that the challenges will persist beyond the 2nd wave of COVID vaccine development. Indeed, COVID-19 may evolve into new and more challenging variants, and humanity will require additional vaccines and vaccine trials, beyond the ones presently in the late-stage pipeline.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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