Concerns About Vaccine Candidate Used as Basis for Emergency Use Authorization

Team 5 Report
DRAFT 4-28-22

At least one Pfizer study left many safety concerns unanswered, concerns that one would expect to be investigated and resolved before any mRNA vaccine was authorized for emergency use.

Beginning in April 2020, Pfizer, along with study sponsor BioNTech, conducted a Phase 1/2 study to identify preferred vaccine candidates and dose levels (https://clinicaltrials.gov/ct2/show/NCT04368728). One vaccine candidate that Pfizer studied was BNT162b1, which was *not* chosen as the final version of the Pfizer mRNA vaccine but which was discussed in documents submitted to the Food and Drug Administration (FDA) in support of the Pfizer vaccine emergency use authorization.

One of those documents was a paper based on the Phase 1/2 trial of vaccine candidate BNT162b1 published by Mulligan et al. (2020) in the journal *Nature* (https://phmpt.org/wp-content/uploads/2022/04/125742_S1_M5_5351_c4591001-fa-interim-publications.pdf). The paper describes the results of administering BNT162b1 to adults over 18 at three different dosages and at one or two different times (10 or 30 micrograms on days 1 and 21; or 100 micrograms on day 1).

Mulligan et al. argue that in RNA-based vaccines, the RNA is not incorporated into the host genome (p. 3, https://phmpt.org/wp-content/uploads/2022/04/125742_S1_M5_5351_c4591001-fa-interim-publications.pdf). But this is contrary to findings by other researchers who demonstrate that RNA from the SARS-CoV-2 virus integrates into the host genome (Zhang et al., 2021, https://www.pnas.org/doi/10.1073/pnas.2105968118). It is also contrary to findings that the final version of the Pfizer mRNA vaccine, BNT162b2, is reverse-transcribed into host DNA beginning 6 hours after contact with the vaccine (Alden et al., 2022, https://mdpi-res.com/d_attachment/cimb/cimb-44-00073/article_deploy/cimb-44-00073.pdf). Alden et al. noted that whether the DNA that is reverse-transcribed from BNT162b2 is integrated into the cell genome is not known.[1]

The research paper by Mulligan et al. raises additional safety questions. They note that the vaccine candidate they studied (BNT162b1) incorporates N1-methyl-pseudouridine "which dampens innate immune sensing and increases mRNA translation *in vivo*" (p. 3, https://phmpt.org/wp-content/uploads/2022/04/125742_S1_M5_5351_c4591001-fa-interim-publications.pdf). They report that for the patients who showed changes in their blood after receiving the mRNA vaccine, the largest changes were decreased numbers

[1] mRNA is reverse transcribed into DNA in both studies cited in this paragraph. It is not known whether the DNA resulting incorporates into the host genome.

of lymphocytes (a type of white blood cell that plays a vital role in immune response). In fact, about 50% of the patients receiving their first 30 or 100 microgram dose showed decreased lymphocyte counts. Could the incorporation of N1-methyl-pseudouridine in the vaccine formulation be related to decreased lymphocyte counts? Could N1-methyl-pseudouridine be related to the unexpectedly long bioavailability of mRNA products?

Changes in blood cell counts were not the only side effects for patients in this study. In a Phase 1/2 study, "patients usually receive the highest dose of treatment that did not cause harmful side effects in the phase 1 part of the clinical trial" (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/phase-1-phase-2-clinical-trial). Mulligan et al. found that as the dosage increased from 10 to 100 micrograms, adverse events such as fever, fatigue, headache, chills, diarrhea, and muscle and joint pain also increased. Reactogenicity was dose-related, as shown by Daily Clout volunteer researchers in Team 5, at a statistically significant level (https://www.dropbox.com/home/Pfizer%20Research/Team%20Reports?preview=Team+5+Report+-++-+Phase+1_2+f.pdf).

These concerns and more arise from the research by Mulligan et al. on a variant of the mRNA vaccine that was ultimately approved by FDA for emergency use. And in spite of these concerns, the researchers state that "the clinical findings for the BNT162b1 RNA-based vaccine candidate are encouraging and strongly support accelerated clinical development . . . for the rapid production of a SARS-CoV-2 vaccine to prevent COVID-19" (p. 5, https://phmpt.org/wp-content/uploads/2022/04/125742_S1_M5_5351_c4591001-fa-interim-publications.pdf).

Instead of giving a green light to further development, perhaps Pfizer should have thoroughly investigated all safety questions and resolved these concerns before FDA approved any version of the vaccine?