COVID-19 Clinical Advisory Task Force

December 14, 2020

The Honorable Andrew M. Cuomo
Governor of New York State
NYS State Capitol Building
Albany, NY 12224

Commissioner Howard A. Zucker, M.D., J.D.
New York State Department of Health
Corning Tower
Empire State Plaza
Albany, NY 12237

Dear Governor Cuomo and Commissioner Zucker,

This letter serves as the formal recommendation of New York State's Clinical Advisory Task Force on COVID-19 Vaccines regarding use of Pfizer and BioNTech's BNT162b2 COVID-19 vaccine in New York State (NYS). As of this writing, over 740,000 New Yorkers have been diagnosed with COVID-19, with 10,178 new positives and a 7-day rolling average of 5.2% positive COVID-19 test results on December 9, 2020 alone. Following review of all current, publicly available safety and efficacy data from clinical trials of the BNT162b2 vaccine as well as the findings of the U.S. Food and Drug Administration (FDA)'s Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the current context of COVID-19 disease in New York, **the Clinical Advisory Task Force unanimously recommends that the New York State Department of Health (NYSDOH) distribute BNT162b2 to NYS healthcare providers for administration to individuals age 16 years and older in those populations studied in the Pfizer/BioNTech Phase 3 clinical trial in accordance with Advisory Committee on Immunization Practices (ACIP) recommendations and NYSDOH COVID-19 vaccine allocation plans**. The Task Force recognizes that some populations at higher risk of severe COVID-19 infection were not studied in the trial. These higher-risk patients and their healthcare providers deserve the flexibility to decide whether to vaccinate based on analyses of the risks and benefits for each patient. The Task Force encourages close follow-up as these populations are vaccinated to ensure that the vaccine is still efficacious and there are no unexpected adverse events. The Task Force reserves the right to modify this recommendation in the future should additional data warrant.

Findings of the Task Force

BNT162b2 is a messenger RNA (mRNA) vaccine developed in collaboration between Pfizer and BioNTech. It is administered as two intramuscular doses given at least 21 days apart. It delivers mRNA encoding the spike protein of the SARS-CoV-2 virus (the antigen) in order to provoke immune responses against the spike protein. The vaccine is a nucleoside-modified messenger RNA (modRNA) encapsulated in lipid nanoparticles (LNP). The modRNA encodes membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation by 2 proline mutations. The LNP deliver the modRNA inside host cells, where the modRNA is translated into membrane-anchored SARS-CoV-2 full-length spike protein displayed on the surface of the cell and also activates the immune system. Importantly, the vaccine only encodes a single component of the SARS-CoV-2 virus, and not the whole virus, so one cannot "get" COVID-19 from the vaccine. Also, since the vaccine RNA cannot be converted into DNA and integrated in the cellular chromosomes, *it does not genetically alter the host cells*. The combination of the adjuvanting properties and the presence of the SARS-CoV-2 antigen induces neutralizing and protective immune responses involving both B cell/antibody responses and T cell responses targeting the spike protein.

The LNP-modRNA approach represents cutting-edge molecular biology-based technology in vaccine development, which has allowed for unprecedented speed in developing a COVID-19 vaccine for human use. It is however important to note that while BNT162b2 and similar vaccines appear safe and effective in clinical trials, BNT162b2 would be the first mRNA vaccine to be used on a large scale. Because there is no prior large-scale population nor long term experience with mRNA vaccines, it is difficult to predict what the large scale vaccine performance characteristics and long term effects (protection against infection, late side effects) might be. These will need to be followed closely during the EUA use of BNT162b2, to make any necessary adjustments in real time if needed.

The protection of the vaccine against symptomatic COVID-19 infection is thought to be through the induction of neutralizing antibodies against the spike protein (humoral immune responses), with a possible contribution of spike-specific T cells that target COVID-19-infected cells (cell-mediated immune responses). Studies of a related COVID-19 RNA vaccine in a phase I clinical trial (BNT162b1, Mulligan *et al*, *Nature* Aug 2020 and Sahin *et al*, *Nature* Sept 2020) demonstrated that a 2 dose prime+boost vaccination induced neutralizing antibody levels (titers) in a dose-dependent fashion that were equivalent to or greater than those found in patients who had recovered from natural COVID-19 infection (convalescent serum drawn at least 14 days after PCR confirmation of infection, from moderate COVID-19 infections that did not require hospitalization). There was some decline in the vaccine-induced antibody titers by day 43 post vaccination (from the priming dose), which was the last timepoint studied. In addition, Sahin *et al* determined BNT162b1 vaccination elicited robust CD4 (with a Th1 cytokine profile) and CD8 T cell responses that would be predicted to have anti-viral activity. It is important to note that these 2 studies were in healthy adults (predominantly Caucasian) age 18-55 years, and how race, younger/older age, and/or other medical problems affect the magnitude of vaccine-induced immune responses cannot be determined from these studies. It is also important to note that no direct correlation has yet been established between a specific level of antibody response/titer (or any other immune parameter) and protection against COVID-19 disease, so immune measurements cannot be used as surrogates of vaccine protection at this moment. This will require additional study in a larger cohort of people getting the vaccine. Moreover, the ability of the vaccine to protect against asymptomatic infection and subsequent transmission of the SARS-CoV-2 has not yet been determined.

The Phase 1 study comparing the BNT162b1 vaccine to the BNT162b2 vaccine (Walsh and Frenck *et al*, *NEJM*, Oct 2020) was done in healthy adults age 18-55 and a separate cohort age 65-85. The side effects of vaccinating with BNT162b2 were milder than with BNT162b1 (especially in the older

cohort), while the induction of immune responses was comparable. Two dose prime+boost administration of BNT162b2 elicited dose-dependent neutralizing antibody responses that were equivalent to or greater than those seen in patients who had been infected with COVID-19 (same convalescent serum samples used in the previous Nature papers), with lower antibody titers in the older 65-85 year cohort (although still higher than natural infection) vs. the younger 18-55 year group. The antibody titers elicited by BNT162b2 showed a slight decline by day 35 after vaccination (priming dose), which was the last time point tested. T cell responses were not reported. Aside from the impact of age on immune responses, the same limitations exist for this study that were acknowledged in the previous studies of the BNT162b1 vaccine.

No serious adverse events were detected during Phase 1 studies. The most commonly reported adverse effects during the Phase 1 studies were pain at the injection site (75-92% following dose 1 and 67-83% following dose 2), fatigue (25-42% following dose 1 and 42-75% following dose 2), chills (0-33% following dose 1 and 17-58% following dose 2) and fever (0-17% following dose 1 and 8-17% following dose 2). Local reactions were greater following the first dose than the second dose, whereas systemic events were greater following the second dose, and more adverse events were reported by participants age 18-55 years than in those 65-85 years old.

The combined Phase 2/3 study of BNT162b2 began on July 27, 2020 for participants age 18 years or older. As of November 13, 2020, 43,661 study participants have been enrolled, and 41,135 have received a second dose of either vaccine or placebo. Half of enrolled participants have been assigned to receive 2 doses of the BNT162b2 vaccine and half have been assigned to receive 2 doses of a saline placebo. Thirty percent (30%) of U.S. participants and 42% of global participants have diverse racial and ethnic backgrounds, and 45% of U.S. participants and 41% of global participants are age 56-85 years.

In the Phase 2 portion of the BNT162b2 clinical trial, 360 patients were enrolled and randomized 1:1 to vaccine or placebo. Immunogenicity data were reported for pre-vaccination and 1-month post dose 2 (boost) timepoints. BNT162b2 vaccination induced significant neutralizing antibody titers against SARS-CoV-2 at this 1 month timepoint, greater in younger subjects (18-55 years of age) vs. older subjects (56-85 years), but both were equal to or greater than those seen following natural SARS-CoV-2 infection (using the same convalescent serum panel used in the phase I studies). Additional subset analyses (e.g., by sex, race, ethnicity, co-morbid conditions, etc.) and assessment of longer term responses after 1 month have not yet been reported.

For the Phase 3 trial, the Data and Safety Monitoring Board did not observe any serious safety concerns. The most common Grade 3 (severe) adverse events were fatigue (3.8%) and headache (2.0%). Older adults tended to report fewer and milder adverse events. Rates of local reactions and systemic events reported in the vaccine group during the Phase 3 trial were similar to those reported in the Phase 1 trial. Pain at the injection site (71% after dose 1 and 66% after dose 2), fatigue (47% after dose 1 and 59% after dose 2), headache (42% after dose 1 and 52% after dose 2), new/worsened muscle pain (21% after dose 1 and 37% after dose 2) and chills (14% after dose 1 and 35% after dose 2) were the most common adverse events reported in the vaccine group. For all age groups studied, the median onset of local reactions (e.g., pain at the injection site) occurred on the day of vaccination and lasted for 1 to 2 days. Systemic reactions, such as fatigue or chills, began 1-2 days after vaccination and lasted a median of 1 day.

The BNT162b2 Phase 3 clinical trial found a vaccine efficacy of 95% ($p < 0.0001$) in the prevention of COVID-19 at 7 days following the second dose. The vaccine efficacy was equal in persons with or without a prior history of COVID-19 infection at the time they enrolled in the trial, and across all age, gender, race and ethnicity groups. Importantly, the vaccine was also effective (vaccine efficacy >95%) in persons with other chronic health issues (comorbidities), including cardiovascular

disease, chronic lung disease, obesity, diabetes and hypertension. To date, researchers observed 10 severe cases of COVID-19 among study participants; 9 in the placebo group and 1 in the vaccine group.

Immune parameter data have not been reported yet for the Phase 3 portion of this trial. We encourage continued analysis of the immune response to define immune correlates of protection.

In October 2020, the study opened to adolescents age 12-17 years. At the data cutoff date for the EUA, 77 adolescents age 16 to < 18 years had received 2 doses of BNT162b2 and 76 had received 2 doses of placebo. Solicited reactogenicity events were not collected for adolescents age 16 to 17 years, but they were detected and reported as unsolicited adverse events. One case of COVID-19 occurred in the placebo arm of this age group, and none in the vaccine arm. No adverse events judged related to the vaccine were reported in this age group. Studies of the use of BNT162b2 in adolescents age 12-15 years and solicited reactogenicity events in adolescents age 16 to 17 years are still underway.

Female Phase 3 study participants of childbearing potential were screened for pregnancy prior to each vaccination; those with a positive pregnancy test were excluded or discontinued from the study. However, twenty-three pregnancies were reported among study participants after the last dose of vaccine or placebo (12 vaccine, 11 placebo). Analysis of pregnancy outcomes among study participants is underway.

This mRNA vaccine development program represents a major public health advance which has the potential to become a landmark in our fight against infectious diseases. Continued study of this vaccine going forward is warranted to provide as detailed a picture as possible of this vaccine in particular and to gain insight into the potential of the mRNA platform in general. The following questions remain unanswered or only partially answered to date and we encourage further studies to better understand the full potential of this vaccine:

1. What is the duration of the immune responses elicited by the vaccine, for both antibody and T cell responses? Are there differences in different subpopulations?
2. What are the levels of immune responses (e.g. antibody titers, T cell responses) that correlate with protection against:
    a. Asymptomatic SARS-CoV-2 infection,
    b. Symptomatic COVID-19 disease, and
    c. Severe COVID-19 disease?
3. How does the vaccine perform in immunocompromised patients, such as cancer patients, in terms of induction of immune responses as well as protection against infection?
4. Are there late side effects from the vaccine that were not seen in the initial 2-month (median) follow-up reported for the Phase 3 trial? If this is the case, are these associated with any particular subgroup, such as those with prior SARS-CoV-19 infection, before vaccination?
5. In vaccinated patients who subsequently develop COVID-19, is this due to new viral mutations in the spike protein that are not targeted by immune response elicited by the vaccine?
6. What is the safety and effectiveness in children and pregnant women?

As BNT162b2 is implemented on a large scale, infrequent, if not rare and unanticipated adverse events will likely occur (e.g., anaphylactoid reactions in two vaccine recipients in the first days of the rollout in the U.K.). Such adverse events need to be carefully investigated to determine whether there is true association with the vaccine or not.

The FDA convened a public meeting of the VRBPAC on December 10, 2020 to review Pfizer and BioNTech's request for an EUA for BNT162b2. Following review of the EUA package, the VRBPAC

concluded, in a vote of 17 in favor, 4 against and 1 abstention, that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 vaccine outweigh its risks for use in individuals16 years of age and older.

On December 11, 2020, the FDA issued an EUA for the use of BNT162b2 for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

The Task Force agrees with the FDA EUA assessment and looks forward to the recommendations of the ACIP on BNT162b2 vaccine administration.

In conclusion, New York State's Clinical Advisory Task Force on COVID-19 Vaccines finds that BNT162b2 has demonstrated impressive efficacy for the prevention of COVID-19 and an acceptable safety profile in the populations studied in the Phase 3 trial. Healthcare providers serving populations that were not studied in the clinical trial should make a case-by-case determination of the risks and benefits of BNT162b2 vaccine for each patient after considering the patient's specific medical circumstances and COVID-19 risk. The Clinical Advisory Task Force will continue to review data on BNT162b2 and other COVID-19 vaccines as they become available and reserves the right to modify this recommendation in the future should additional data become available necessitating such a change. After careful review of the available information, the Task Force enthusiastically supports FDA's issuance of the EUA. Access to this vaccine is important for the health and welfare of the citizens of the State of New York.

Respectfully,

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