COVID-19 Clinical Advisory Task Force

December 19, 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 Moderna's mRNA-1273 COVID-19 vaccine in New York State (NYS). As of this writing, over 815,000 New Yorkers have been diagnosed with COVID-19, with 10,914 new positives and a 7-day rolling average of 5.2% positive COVID-19 test results on December 16, 2020 alone. Following review of all current, publicly available safety and efficacy data from clinical trials of the mRNA-1273 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 mRNA-1273 to NYS healthcare providers for administration in individuals 18 years and older 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

mRNA-1273 is a messenger RNA (mRNA) vaccine encoding for a prefusion stabilized form of the spike protein of the SARS-CoV-2 virus encapsulated in lipid nanoparticles (LNP), which was co-developed by Moderna and investigators from the National Institute of Allergy and Infectious Diseases (NIAID)'s Vaccine Research Center. The LNP deliver the mRNA inside host cells, where the mRNA is

translated into membrane-anchored SARS-CoV-2 full-length spike protein displayed on the surface of the cell and induces neutralizing and protective immune responses involving both B cell/antibody responses and T cell responses targeting the spike protein. 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.

mRNA-1273 remains stable at -20° C (-4°F) for up to six months, at 2° to 8°C (36° to 46°F) for up to 30 days and at room temperature for up to 12 hours. It is administered as two intramuscular doses given at least 28 days apart. There is no evidence that mRNA-1273 can be used interchangeably with Pfizer-BioNTech's BNT162b2 COVID-19 vaccine, and the FDA has mandated that vaccine series begun with one vaccine should be completed with the same vaccine.

The LNP-mRNA approach represents cutting-edge molecular biology-based technology in vaccine development, which has allowed for unprecedented speed in developing COVID-19 vaccines for human use. It is however important to note that while mRNA-1273 and similar vaccines appear safe and effective in clinical trials, mRNA-1273 would be only the second 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 mRNA-1273, to make any necessary adjustments in real time if needed.

Phase 1 studies of mRNA-1273 included 45 healthy adults age 18 to 55 years (Jackson, Anderson *et al.*, *NEJM*, Jul 2020), 20 healthy adults age 56-70 years and 20 healthy adults age 71 years or older (Anderson, Rouphael, *et al., NEJM,* Sept 2020). Participants age 18 to 55 years were randomized to receive two doses of mRNA-1273 at doses of 25 µg, 100 µg or 250 µg; because of clinically significant systemic reactogenicity observed at the 250 µg dose, participants age 56 years and older were randomized to receive 2 doses at either 25 µg or 100 µg. Two dose prime+boost administration of mRNA-1273 elicited dose-dependent neutralizing antibody responses that were equivalent to or greater than those seen in patients who had been infected with COVID-19, which declined slightly over time but remained elevated through 90 days after the second vaccination (Widge, Rouphael *et al., NEJM,* Dec 2020). The decline in neutralizing antibody titers was more evident in the older subjects, and longer term follow-up regarding the durability of anti-SARS-CoV-2 titers will be important. These studies also found a dose-dependent induction of robust CD4/Th1 T cell responses against spike protein peptides that would be predicted to have anti-viral efficacy, with only low level CD8 T cell activation following vaccination.

No serious adverse events were detected during Phase 1 studies and no prespecified trial-halting criteria were met. Most local and systemic adverse events were classified as mild to moderate. The most commonly reported adverse effects during the Phase 1 studies were injection site pain (80-93% after dose 1 and 90-100% after dose 2), fatigue (27-50% after dose 1 and 70-80% after dose 2), headache (0-26% after dose 1 and 40-80% after dose 2), myalgia (7-20% after dose 1 and 53-80% after dose 2), chills (7-10% after dose 1 and 45-80% after dose 2) and fever (0% after dose 1 and 10-40% after dose 2). These events were dose-dependent, and more common after the second dose.

The Phase 3 study of mRNA-1273 began on July 27, 2020, for participants age 18 years or older. Moderna's EUA application included data on 30,350 study participants (15,184 vaccine,15,165 0.9% sodium chloride placebo). The study includes more than 7,500 participants over the age of 65 and more than 11,000 participants from communities of color. This includes more than 6,000 participants who identify as Hispanic or LatinX, and more than 3,000 participants who identify as Black or African American. Nearly 7,000 participants (22%) have at least one risk factor for severe COVID-19 disease,

including chronic lung disease (4.8%), significant cardiac disease (4.9%), severe obesity (6.5%), diabetes (9.4%), liver disease (0.6%) and HIV infection (0.6%).

The mRNA-1273 Phase 3 clinical trial found a vaccine efficacy of 94.1% in the prevention of symptomatic COVID-19 at 2 weeks following the second dose. Efficacy was consistent across age, race and ethnicity, gender, among persons with or without risk factors for severe COVID-19 and among persons with and without antibodies to SARS-CoV-2 at baseline. At the cutoff for EUA data analysis, researchers observed 30 severe cases of COVID-19 among study participants (30 in the placebo group and none in the vaccine group) and one COVID-19 related death, which occurred in the placebo group.

A preliminary analysis of asymptomatic COVID-19 infection among vaccine and placebo recipients examined the results of scheduled SARS-CoV-2 nasopharyngeal swabs prior to the first and second injections. Among participants with baseline negative swabs, two-thirds fewer vaccine recipients than placebo recipients had positive swabs without symptoms of COVID-19 at the time of the second dose (14 asymptomatic positives in the vaccine group versus 38 in the placebo group). This suggests that mRNA-1273 may have meaningful efficacy against asymptomatic infection after the first dose. The Task Force looks forward to the studies that will ensue to definitively answer this important question.

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.

The Data and Safety Monitoring Board did not observe any serious safety concerns for the mRNA-1273 Phase 3 trial, with the majority of adverse events being mild or moderate in severity. Overall, rates of adverse events were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2, and higher rates of systemic reactions after dose 2 than dose 1. Pain at the injection site (84% after dose 1 and 88% after dose 2), fatigue (39% after dose 1 and 68% after dose 2), headaches (35% after dose 1 and 63% after dose 2), new/worsened joint pain (17% after dose 1 and 45% after dose 2), axillary lymphadenopathy in the vaccination arm (10% after dose 1 and 14% after dose 2) and fever (1% after dose 1 and 17% after dose 2) were the most common adverse events reported in the vaccine group. The median onset of local reactions occurred on Day 1 and lasted for 2 to 3 days. Systemic reactions, such as fatigue or chills, began on Day 1 or 2 and lasted a median of 2 days.

In December 2020, Moderna launched a Phase 2/3 study of mRNA-1273 in adolescents age 12-17 years. The first doses of mRNA-1273 were administered in adolescents following submission of Moderna's first EUA package to the FDA, and therefore data on its use in this age group has not been considered by the FDA, VRBPAC nor the Task Force as of this writing. This study is still underway, and the Task Force will revisit use of mRNA-1273 in this age group after data becomes available.

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, thirteen pregnancies were reported among study participants through December 2, 2020 (6 vaccine, 7 placebo). Analysis of pregnancy outcomes among study participants is underway.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

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 mRNA-1273 is implemented on a large scale, infrequent, if not rare and unanticipated adverse events will likely occur. 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 17, 2020 to review Moderna's request for an EUA for mRNA-1273. Following review of the EUA package, the VRBPAC concluded, in a vote of 20 in favor, 0 against and 1 abstention, that based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older.

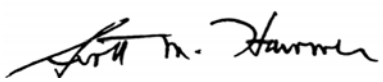
On December 18, 2020, the FDA issued an EUA for the use of mRNA-1273 in individuals 18 years of age and older.

The Task Force agrees with the FDA EUA assessment and looks forward to the recommendations of the ACIP on mRNA-1273 vaccine administration.

In conclusion, New York State's Clinical Advisory Task Force on COVID-19 Vaccines finds that mRNA-1273 has demonstrated impressive efficacy, comparable to Pfizer-BioNTech's BNT162b2 vaccine, for the prevention of COVID-19 and an acceptable safety profile in the populations studied in the Phase 3 trial. It is important to emphasize that two independent large phase 3 trials of 2 different mRNA vaccines against SARS-CoV-2 have yielded very similar results in terms of safety and vaccine efficacy – giving additional confidence that this new mRNA vaccine technology is safe and effective. 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 mRNA-1273 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 mRNA-1273 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. Having multiple COVID-19 vaccine options available, including mRNA-1273's temperature stability at standard freezer and refrigerated temperatures, will improve vaccine accessibility for the citizens of the State of New York.

Respectfully,



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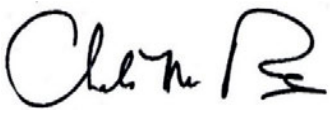

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