

**National Institute of Allergy and Infectious Diseases (NIAID)
COVID-19 VACCINE DATA AND SAFETY MONITORING BOARD**

August 28, 2020

MEETING SUMMARY

The NIAID COVID-19 Vaccine Data and Safety Monitoring Board (DSMB) met via teleconference on August 28, 2020 to perform a safety review mRNA-1273 (P301/MODERNA). NIAID DSMB Executive Secretary Sally Hunsberger, Ph.D., Division of Clinical Research, welcomed Board members in attendance: Richard J. Whitley, M.D., (Chair); Abdel Babiker, Ph.D.; Lisa Angeline Cooper, M.D., M.P.H., FACP; Susan Smith Ellenberg, Ph.D.; Alan Fix, M.D., M.S.; Marie R. Griffin, M.D., M.P.H.; Steven Joffe, M.D., M.P.H.; Jorge Kalil, M.D.; Myron Levine, M.D.; Malegapuru William Makgoba, MB., ChB; DPhil., FRCP and Anastasios A. Tsialis, Ph.D. Also, in attendance was Martha A. Nason, Ph.D., back up NIAID Executive Secretary (open session only).

**Closed Session was attended by DSMB Members, NIAID DSMB Executive Secretary and unblinded statistician. Executive closed session was attended by DSMB Members and NIAID DSMB Executive Secretary. Both session attendance was in accordance with the Vaccine COVID DSMB Charter. All other participants attended the open session discussions only.*

(mRNA-1273-P301/ MODERNA)
A PHASE 3, RANDOMIZED, STRATIFIED, OBSERVER-BLIND, PLACEBO
CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND
IMMUNOGENICITY OF mRNA-1273 SARS CoV-2 VACCINE IN ADULTS AGED 18
YEARS AND OLDER

Protocol Team Participants:

(b) (6) BARDA ^(O)
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 (b) (6) BARDA ^(O)
 (b) (6) BARDA ^(O)

Brett Leav, M.D., Medical Lead, Moderna ^(O)
 Conor Knightly, M.P.H., Senior Director/ Clinical Operations Lead, Moderna ^(O)
 Honghong Zhou, Ph.D., Senior. Director/ Biostatistics Lead, Moderna ^(O)
 Melissa Rossi, M.S., Senior Director/ Pharmacovigilance Lead, Moderna ^(O)
 Jacqueline M. Miller, M.D., F.A.A.P., Senior Vice President/ Therapeutic Area Head, Moderna ^(O)
 Melanie Ivarsson, Ph.D., Chief Development Officer, Moderna ^(O)
 Shu Han, Ph.D., Head of Biostatistics, Moderna ^(O)
 Hamilton Bennett, M.S., Program Lead, Moderna ^(O)
 Tal Zaks, Ph.D., M.D., CMO, Moderna ^(O)
 Lisa A. Jackson, M.D., M.P.H., Protocol Chair, DMID 20-003 (Phase 1 Moderna mRNA1273 trial) and PI, Vaccine Treatment and Evaluation Unit, Kaiser Permanente ^(O)
 Lindsey Baden, MMSc., M.D., Co-Coordinating Investigator, CoVPN ^(O)
 Hana El Sahly, M.D., Co-Coordinating Investigator, CoVPN ^(O)
 Brandon Essink, M.D., Co-Coordinating Investigator, Meridian Research Network ^(O)
 Larry Corey, M.D., HVTN Network Leadership, CoVPN ^(O)
 Peter Gilbert, Ph.D., Statistician, CoVPN ^(O)
 Holly E. Janes, Ph.D., Statistician, CoVPN ^(O)
 Kathy Nuezil, M.D., Director, Center for Vaccine Development, University of Maryland School of Medicine, CoVPN ^(O)
 (b) (6) PPD ^(O)
 (b) (6) PPD ^(O)
 Weiping Deng, Ph.D., Director/ Biostatistics Lead for P301, Moderna ^(O)
 (b) (6) PPD ^(O)
 (b) (6) PPD ^(O)
 Julie Ledgerwood, D.O., Investigator, Vaccine Research Center, NIAID ^(O)
 Tatiana Beresnev, M.D., MSHS, Medical Monitor, OCRA, DMID ^(O)
 Laura Polokowski, M.D., M.S.P.H., HIV Vaccine Research Program, NIAID ^(O)
 Julia Hutter, M.D., M.P.H., DAIDS Medical Officer ^(O)
 Mamodikoe Makhene, M.D., Medical Officer, Division of Microbiology and Infectious Diseases, NIAID ^(O)
 Mary Marovich, M.D., Director, Vaccine Research Program, DAIDS, NIAID ^(O)
 Emily J. Erbeling, M.D., M.P.H., Director, Division of Microbiology and Infectious Diseases, NIAID ^(O)
 Dean A. Follmann, Ph.D., Chief, Biostatistics Research Branch, DCR, NIAID ^(O)
 H. Clifford Lane, M.D., Director, Division of Clinical Research, NIAID ^(O)

Others Attending:

Sally Hunsberger, Ph.D., NIAID Executive Secretary ^(C)

Martha Nason, Ph.D., Back Up NIAID Executive Secretary ^(C)

Conflicts of Interest:

All DSMB members confirmed in writing that they had no financial or professional conflicts with this study.

Date of This Review: August 28, 2020

Purpose of This Review: This was a safety review of mRNA-1273 (P301/MODERNA)

^(C) Participated in Open Session only

^(C) Unblinded Participant/Statistician (Closed Session)

Primary Objectives:

1. To demonstrate the efficacy of mRNA-1273 to prevent COVID-19.
2. To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.

Secondary Objectives:

1. To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.
2. To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.
3. To evaluate VE against a secondary definition of COVID-19.
4. To evaluate VE to prevent death caused by COVID-19.
5. To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP.
6. To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.
7. To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.

Observations:

1. The DSMB recognizes the huge amount of work that has gone into all aspects of this study and congratulates the team on the rapid accrual to the study. The board recognizes that the DSMB reports, reviews and discussions will evolve and improve over time as the board and study team work together to develop processes that will be used for this study and other OWS vaccine studies.
2. The DSMB is pleased with the accrual of older participants and younger participants with COVID-19 risk factors that have been accrued to the study. Currently, the proportion of study participants in these two groups exceeds the protocol specified maximum proportion of 40%.
3. All participants are symptom free and swabbed (with results yet to be determined) before receiving vaccination. Due to the delay in obtaining RT-PCR results some participants may be vaccinated who were RT-PCR positive at baseline. It is not clear if these participants should count toward harm monitoring if they become symptomatic days after receiving the vaccination.

4. The study team noted that accrual has slowed somewhat as study sites are beginning to focus on both accrual and providing second vaccinations to the first participants who were entered into the study.
5. The proportion of study participants from underrepresented minority groups is much lower than the US population proportions. The study team reports that the accrual of minority groups has increased in recent weeks.

Recommendations:

1. The DSMB would recommend performing harm analysis by both including and excluding pre-vaccinated asymptomatic RT-PCR positive cases who then become symptomatic.
2. The DSMB is concerned that accrual will slow as other vaccine studies are opened for accrual. In the next report please provide accrual rates for sites that do not have competing studies versus those that are also performing competing studies.
3. The DSMB recognizes the effort the study team has made to accrue populations with health disparities and the difficulty in enrolling these populations. But the board remains very concerned that the study proportions are much lower than those of the US census. The study team must continue to adapt and implement new strategies to improve enrollment of populations with health disparities. The board recommends the OWS team enlist the assistance of several health disparity experts to help with this issue across all vaccine studies. The study team should consider slowing or pausing recruitment at sites that are enrolling mainly white participants.
4. Demonstrating safety in populations with health disparities will be critical to public acceptance of any vaccine reported to be efficacious, especially among these communities. This may be among the most important reasons to have robust minority enrollment. Given the smaller sample size in minority subgroups there will be less power to identify any safety signals that exist in these populations. Please provide power calculations for showing between arm differences in grade 3 or 4 AE's using the expected sample size of the racial subgroups.
5. Currently the PSRT includes reviews of SAE's, AE's and COVID-19 cases. The PSRT group includes site PI's. The board has concerns with several aspects of the PSRT reviews.
 - a. The board is concerned that if PSRT members see linked data of a participant that is a COVID-19 case and their reactogenicity the PSRT may be able to determine which vaccine group they are in. The board recommends that reactogenicity data and COVID-19 case data information be unlinked.
 - b. The board recommends only the PSRT have access to the cumulative number of all cases. It is imperative to maintain confidentiality of all information on COVID-19 cases due to the worldwide interest in the results of this study.
6. The board notes that the statisticians involved in the study demonstrated clear fluency and understanding of the data. However, the closed and open data reports were not presented in a format that allowed the DSMB to interpret the data or identify safety problems. Therefore, the board recommends that the study team engage a consultant to help develop a template for reports that will allow the DSMB to interpret large amounts of data and identify potential safety concerns. Of note, templates for such reports are available on the University of Wisconsin website at (https://biostat.wiscweb.wisc.edu/wpcontent/uploads/sites/1008/2019/05/Sample_Report_Closed_20160920.pdf).

7. The board noted that there did not appear to be good communication between PSRT safety concerns and the unblinded statistician. Please ensure that safety concerns that the PSRT identifies are explored in the closed session report.

Conclusion: Continue as planned.

Next Planned Review: The DSMB will work with the statistician to determine when the next safety review should occur.

Recommendations:

1. The DSMB would recommend performing harm analysis by both including and excluding pre-vaccinated asymptomatic RT-PCR positive cases who then become symptomatic.

Sponsor response: We are updating the harm monitoring analyses by both including and excluding subjects who were pre-vaccinated asymptomatic RT-PCR positive cases and expect to have the updated analysis by week of 8/14.

2. The DSMB is concerned that accrual will slow as other vaccine studies are opened for accrual. In the next report please provide accrual rates for sites that do not have competing studies versus those that are also performing competing studies.

Sponsor response: Based on publicly available information posted on clinicaltrials.gov, we have performed a high-level assessment of enrollment rates for sites presumed to also overlap with each the Pfizer, AstraZeneca and Janssen Phase 3 studies. Some Moderna sites are participating across multiple coronavirus Phase 3 programs. The majority of participating sites [n = 57 (58%)] do not have concurrent Phase 3 trial with another sponsor. Twenty-five sites [n=25 (25%)] have one other concurrent Phase 3 trial; however, these sites have the highest enrollment rates. A smaller proportion of sites have two and three concurrent Phase studies [n= 15 (15%) and n= 1 (1%), respectively]. These sites have marginally lower rates of enrollment. Please see table below for an overview.

It is also important to note that rates of enrollment may be confounded by operational steps taken by Moderna over the past month to limit non-minority enrollment at certain sites.

Number of overlapping Phase 3 Coronavirus Vaccine Studies	Number of Moderna Clinical Sites	Average enrollment rates (participants per day)
0 studies	57	6.1
1 study	25	7.1
2 studies	15	5.9
3 studies	1	5.5

3. The DSMB recognizes the effort the study team has made to accrue populations with health disparities and the difficulty in enrolling these populations. But the board remains very concerned that the study proportions are much lower than those of the US census. The study team must continue to adapt and implement new strategies to improve enrollment of populations with health disparities. The board recommends the OWS team enlist the assistance of several health disparity experts to help with this issue across all vaccine studies. The study team should consider slowing or pausing recruitment at sites that are enrolling mainly white participants.

Sponsor response: Moderna understands and acknowledges the DSMB's concern, as this is one of our top priorities. We are currently collaborating with OWS, NIAID, and BARDA on an ongoing basis to monitor diversity trends in our enrollment and are working with our sites closely to increase enrollment diversity. A number of new initiatives have been implemented recently, which include the following:

- *Over the past 4 weeks, we've Directed approximately 25 study sites who have enrolled primarily Caucasian subjects to divert their enrollment efforts and concentrate on enrolling subjects of ethnic minorities.*

- *Most recently, as of 11-Sep-20, we communicated to all sites that newly scheduled enrollments through 25-Sep-20 must come from efforts to engage minority communities.*
- *All sites receive a dashboard twice a week specific to their site's enrollment performance, which outlines where they need to further prioritize their enrollment efforts based on their local census data*
- *All network directors receive an enrollment report twice a week on their collective sites for additional oversight and management Each week Moderna hosts a PI Q&A hour long session, with different areas of focus. The study team kicks off these meetings by reviewing enrollment numbers by percentage of each ethnic/racial group. Many of the meetings are focused on minority enrollment, with examples below:*
 - *On 18-Aug-20, Michele Andrasik, PhD, Director, Social & Behavioral Sciences and Community Engagement, HIV Vaccine Trials Network spoke to the PIs regarding the impact of implicit bias and health disparities*
 - *On 01-Sep-20, Dr. Anthony Fauci and Dr. Jerome Adams joined this meeting to discuss the importance of diversity to the success of the study and potential strategies to recruit minority subjects. The sites found this extremely engaging, and we have had a lot of positive feedback about the helpfulness of that session.*
 - *On 08-Sep-20, we introduced the Community Engagement Alliance (CEAL) initiative to the sites, with a follow up meeting on 10-Sep-20 of those sites that would benefit from this support the most*
- *In an effort to further help support this focused enrollment effort, we've developed new recruitment materials including a poster and brochure that are more reflective of a diverse audience to use in your recruitment efforts of these populations.*
- *Our weekly site newsletter includes recommendations and considerations for communicating with minority populations regarding study enrollment.*
- *We have also partnered with TrialScope for recruitment of African American, and Hispanic, and American Indian participants, prescreening interested subjects and sending those that pre-qualify to the study sites.*
- *We have also added 10 study sites with a strong history of minority enrollment to the study, and all study sites have access to CoVPN resources for diversity recruitment.*
- *All sites are continually being pushed to utilize the CoVPN Registry where potential participants have opted to be contacted about the study.*
- *Moderna has also made a strong commitment to transparency in our recruitment efforts, and now posts our weekly enrollment numbers and diversity percentages on the COVE Study page of the Moderna website.*
- *All efforts have been discussed with and endorsed by our Diversity and Inclusion Advisory Board, a group of health disparity experts who are helping Moderna by reviewing our weekly demographics and outreach, recruitment, and retention strategies in communities disproportionately impacted by COVID-19.*
- *In addition, based on the DSMB's feedback, Moderna plans to engage the services of a consultant with expertise in addressing racial and socioeconomic health care disparities in a large metropolitan hospital network, to advise on the COVE study.*

4. Demonstrating safety in populations with health disparities will be critical to public acceptance of any vaccine reported to be efficacious, especially among these communities. This may be among the most important reasons to have robust minority enrollment. Given the smaller sample size in minority subgroups there will be less power to identify any safety signals that exist in these populations. Please provide power calculations for showing between arm differences in grade 3 or 4 AE's using the expected sample size of the racial subgroups.

Sponsor response: Moderna thanks the DSMB for pointing out the importance of having robust minority enrollment. Moderna agrees with the DSMB that there will be less power to identify any safety signals that exist in subgroups with relatively small sample size, and results in subgroups need to be interpreted with caution.

We have performed power calculations of detecting difference in rates of grade 3 or 4 AEs in subgroups between arms under various scenarios including sample sizes of the subgroups and rates of AE, please see the attached [table](#) in the Appendix. The study is not designed or powered to detect difference in rate of AEs in subgroups between the arms. When the subgroups have relatively small sample size, there is not sufficient power to detect difference in AE parameters with low incidence, results need to be interpreted with caution.

5. Currently the PSRT includes reviews of SAE's, AE's and COVID-19 cases. The PSRT group includes site PI's. The board has concerns with several aspects of the PSRT reviews.

a. The board is concerned that if PSRT members see linked data of a participant that is a COVID-19 case and their reactogenicity the PSRT may be able to determine which vaccine group they are in. The board recommends that reactogenicity data and COVID-19 case data information be unlinked.

b. The board recommends only the PSRT have access to the cumulative number of all cases. It is imperative to maintain confidentiality of all information on COVID-19 cases due to the worldwide interest in the results of this study.

Sponsor response: Moderna plans to remove line listings of solicited adverse reactions and aggregate counts of COVID-19 and severe COVID-19 cases from the PSRT review going forward. The PSRT will, however, continue to review interval symptom logs of all COVID-19 cases to assess for safety. Moderna has discussed this with the PSRT and there was no disagreement with this proposal.

6. The board notes that the statisticians involved in the study demonstrated clear fluency and understanding of the data. However, the closed and open data reports were not presented in a format that allowed the DSMB to interpret the data or identify safety problems. Therefore, the board recommends that the study team engage a consultant to help develop a template for reports that will allow the DSMB to interpret large amounts of data and identify potential safety concerns. Of note, templates for such reports are available on the University of Wisconsin website at (https://biostat.wiscweb.wisc.edu/wpcontent/uploads/sites/1008/2019/05/Sample_Report_Closed_20160920.pdf).

Sponsor response: Moderna proposes to provide a set of slides for the closed session that follow the same format of the open session presented on 28-Aug as the summary for future DSMB data review meetings.

The slides along with an executive summary, a table of content (TOC) of the DSMB data review package will be provided to the DSMB in addition to the DSMB data review package that includes tables and listings. The data review package will include separate files for tables and listings in PDF format. The number of tables and listings will be reduced to provide relevant information for the DSMB.

7. The board noted that there did not appear to be good communication between PSRT safety concerns and the unblinded statistician. Please ensure that safety concerns that the PSRT identifies are explored in the closed session report.

Sponsor response: Moderna has invited the unblinded study statistician to participate in PSRT meetings for awareness of ongoing safety concerns so that these can be coordinate the unblinded analysis provided to the DSMB.

Appendix Table. Power to test difference in rates of grade 3 or 4 AEs in subgroups between arms with various sample sizes (study planned total sample size N=30,000, ratio of 1:1 in Arm 1 vs Arm 2)

True rate of Grade 3 or 4 AEs			Power to test arm difference				
Arm 1	Arm 2	Diff (Arm 1 vs. Arm 2)	n=900 (3% of N) 450:450	n=1200 (4% of N) 600:600	n=1500 (5% of N) 750:750	n=3000 (10% of N) 1500:1500	n=4500 (15% of N) 2250:2250
0.1%	0.5%	- 0.4%	19.4%	24.4%	29.4%	51.8%	69.0%
0.1%	0.8%	- 0.7%	34.9%	44.2%	52.7%	81.8%	94.0%
0.2%	0.8%	- 0.6%	24.7%	31.4%	37.8%	64.5%	81.5%
0.4%	0.8%	- 0.4%	11.8%	14.4%	16.9%	29.4%	41.2%
0.1%	1.0%	- 0.9%	44.8%	56.0%	65.6%	91.6%	98.3%
0.2%	1.0%	- 0.8%	34.3%	43.5%	51.9%	81.1%	93.6%
0.4%	1.0%	- 0.6%	18.9%	23.8%	28.6%	50.5%	67.6%
0.2%	1.5%	- 1.3%	56.7%	69.1%	78.5%	97.3%	99.7%
0.4%	1.5%	- 1.1%	39.9%	50.3%	59.5%	87.5%	96.8%
0.6%	1.5%	- 0.9%	26.3%	33.4%	40.2%	67.7%	84.2%
0.8%	1.5%	- 0.7%	16.5%	20.5%	24.6%	43.6%	59.6%
0.6%	2.0%	- 1.4%	45.9%	57.3%	66.9%	92.4%	98.6%
0.8%	2.0%	- 1.2%	33.5%	42.5%	50.8%	80%	92.9%
1.0%	2.0%	- 1.0%	23.4%	29.7%	35.7%	61.6%	78.9%
1.0%	3.0%	- 2.0%	57.7%	69.9%	79.2%	97.5%	99.8%
1.5%	3.0%	- 1.5%	33.0%	41.8%	50.0%	79.2%	92.5%
2.0%	3.0%	- 1.0%	15.9%	19.8%	23.6%	41.9%	57.5%

Note: Using asymptotic method in EAST.