

**RESPONSE TO CBER COMMUNICATION REGARDING CLINICAL TOPICS RECEIVED ON  
DECEMBER 08, 2020**

The Sponsor acknowledges CBER's communication regarding Clinical topics.

This document provides the Sponsor's responses to CBER's requests (in **Bold**).

**ITEM 1:**

**A teleconference between CBER and Moderna was held on December 8<sup>th</sup> 2020 to discuss mRNA-P301 BIMO Inspection findings. CBER expressed concerns that 2 sites out of the 9 inspected sites (US393 and US387) were issued a form FDA 483 (483), 20% of the inspected sites. CBER wanted to understand how generalizable these findings are.**

**In an email sent by Carla Vinals on December 8<sup>th</sup> 2020, Moderna committed to provide by December 9<sup>th</sup> 2020 the following information:**

**1. Overall study monitoring and oversight plan**

- **Overview of site monitoring activities**
- **Data management monitoring metrics**
- **Quality plan**

**2. 483 issues identified – focus on safety calls, eDiary data entry, out of visit windows dosing**

- **Study level monitoring for each activity**
- **Site level information, looking at how issue was identified and what remediation steps in place**

**Sponsor Response:**

- 1. Executive summary**
- 2. Initial sponsor response to the issues identified in the 483s**
- 3. Moderna monitoring and oversight processes**

## **1. Executive Summary**

Moderna takes the findings identified in the 483s for Sites US387 (Dr Levin) and US 393 (Dr Sheth) very seriously and appreciates the opportunity given to us for an initial discussion with CBER on 08 Dec 2020. As discussed during our call, we have prepared an initial sponsor response to the findings. It is our assessment that the findings occurred in sites that have been proactively identified by Moderna's ongoing monitoring activities to be in the lowest 6 performing sites across the 99 sites. Of note, site US393 was 70% compliant with attempting safety follow up calls, compared to a median of 99.4% compliance across all sites. At Site US387, 19.2% of subjects had an out of visit window dose 2 event compared to approximately 5% for the study overall. As a result of the issues identified by monitoring at site US387, enrollment was discontinued by Moderna on 10 Sep 2020.

Moderna has a comprehensive monitoring and oversight framework in place as described in Section 3. The ongoing monitoring of overall quality and compliance supports our assessment that the 483 findings are outliers rather than being representative of all sites.

## **2. Issues identified in the 483s**

Nine Clinical Investigator Site inspections were conducted as part of FDA's BIMO program at sites participating in the mRNA-1273-P301 study. Seven (7) of the 9 sites were found to be compliant and 2 of the 9 sites (Site US393 – Dr Sheth; Site US387 – Dr Levin) were issued a Form FDA 483 (483) noting 2 inspectional observations each. FDA 483 observations for both sites were cited as 1) An investigation was not conducted in accordance with the signed statement of investigator and investigational plan, and 2) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifics related to the issues relevant to the observations were included. Further information regarding each issue, how it was monitored throughout the study (where applicable) and the specific site remediation plans are included below. It should be noted that while Moderna is working with the sites on the completion of their 483 responses, these will be submitted directly by the sites to the FDA according to their due dates.

Site US393: Dr Sheth. Enrollment commenced on 24 Aug 2020 and last subject first visit occurred on 23 Oct 2020. A total of 282 participants were enrolled and as of 08 Dec 2020 one participant from this site had been identified as having Covid-19 infection.

Site US387: Dr Levin. Enrollment commenced on 31 Jul 2020 and was put on hold on 10 Sep 2020 by Moderna due to performance issues. A total of 492 subjects were enrolled and as of 08 Dec 2020 no participants from this site had been identified as having Covid-19 infection contributing to the primary endpoint.

As requested by CBER (EUA IR#0001), a sensitivity analysis of the efficacy endpoints has been performed excluding the data from sites US393 and US387. This was provided to CBER on December 6<sup>th</sup> 2020 (EUA SN0004).

### ***Safety Follow Up calls***

The protocol requires for safety follow up calls to be conducted weekly during the Vaccination Phase (through Day 57) and monthly thereafter during the Surveillance Phase until the end of the study.

The intent of weekly calls during the first 57 days of participation is to foster direct contact with participants as part of an active and robust safety collection process driven by frequent participant interaction around study vaccine dosing. All safety calls are conducted according to an IRB-approved script meant to consistently elicit the participant's ongoing safety experience. Between scheduled clinic visits and the weekly safety calls each participant has 9 scheduled contacts with the clinic site to assess safety within the first 2 months of participation. If contact is not established for a safety call for a given week, the site is expected to collect the cumulative safety experience reported since the last contact at the next weekly safety call or clinic visit the following week.

Sites are requested to enter into the EDC when an attempt to contact a participant is made. As of 07 Dec 2020, a median of 99.4% of safety calls were attempted by the site personnel as per protocol. Sixty-one (61) of 99 sites are compliant with attempting safety follow up calls 99% of the time. Sites US393 (70%) and US387 (92%) are 2 of only 6 sites that have an overall compliance rate of less than 95% with this requirement. The other sites are 309 (72.4%), 305 (84%), 311 (91.8% and 392 (94%).

Site US393 – Dr Sheth: The observation cited in the FDA 483 noted that 28 of the 31 subject records reviewed had missed visits or diary reviews. Twenty-seven (27) of the 28 subjects had missed safety calls. Twenty-two of the 27 subjects with missed safety calls were limited to 1 or 2 missed calls (13 subjects had one missed call and 9 subjects had 2 missed calls). Of the 47 missed safety calls cited in the 483 at this site, the majority of missed safety calls was limited to 1. The PPD CRA identified that the site was not attempting to make all safety follow up calls as per protocol during a routine monitoring visit of the site (06-08 Oct 2020). Site staff were retrained on the requirement to make these calls and staffing levels at the site were increased. Overall, this site has a compliance rate of 70% for attempting to make safety calls as per protocol, making this the lowest performing site in this study for this metric, and a clear outlier.

Site 387 – Dr Levin: The observations cited in the FDA 483 noted that 47 of 102 subjects reviewed had safety calls that were not completed as per protocol. Of the 47 missed safety calls, the majority of missed calls was limited to 1 (1 safety call was missed for 27 subjects, 2 calls were missed for

8 subjects, 3 calls were missed for 9 subjects, 4 calls were missed for 2 subjects, and 6 calls were missed for 1 subject). Overall, this site has a compliance rate of 92% for attempting to make safety calls as per protocol. Enrollment was initiated on 31-Jul-2020. The CRA began to identify deviations related to failure to make safety calls at an on-site monitoring visit (24 –25 Aug 2020). At the subsequent monitoring visit (08 – 09 Sep 2020) the CRA noted a significant backlog of data entry into the eCRF, including lack of documentation of expected Day 8 and Day 15 safety calls filed in the source. The outcome of these monitoring visits, coupled with recent feedback from the Remote Site Monitor (RSM) regarding the site's failure to keep up with data entry, query resolution and laboratory discrepancy resolution led to an escalation from the PPD Clinical Trial Manager to the Moderna Lead CRA and Clinical Operations Lead, where the decision was made to halt enrollment on 10-Sep-2020. Enrollment was never resumed at the site and the focus shifted to remediating performance gaps related to data entry, laboratory discrepancies and safety calls. Over the monitoring visits (06-07 Oct; 19-20 Oct 2020) gradual improvement was noted as the site allocated additional resources.

Moderna is working with the sites on appropriate remediation to the observations noted and continued oversight to ensure the sites are brought into compliance.

***Diary entry at the 30 min post dose 2 timepoint (site US393)***

The protocol requires participants to make an eDiary entry 30 mins after being dosed and while on site. The purpose of this activity is to observe the participant following dosing as well as to ensure that the participant is able use their device appropriately. eDiary completion for the study overall is monitored daily by PPD and the site level information sent to sites. Moderna monitors these metrics weekly at a meeting with PPD and during a cross-functional team meetings.

The compliance with the eDiary 30-minute post-dosing timepoint at site US393 is 94% and 85% for Dose 1 and Dose 2, respectively. Comparatively, compliance with the 30-minute post-dosing timepoint for all study sites stands at 97% for Dose 1 and 96% for Dose 2. The eDiary completion for the study overall at all timepoints (Dose 1 and Dose 2) is currently 94.9%. This metric has been identified as a 'Key Risk Indicator' with the expectation that eDiary completion should be above 90%. The eDiary completion rate for site US393 overall is 91.2%, indicating that this site has a data completion rate above the expected rate for this study. Since eDiary completion has been high for the study overall, it is not believed that the observation noted at site US393 is indicative of a systemic issue across the study.

***Dose 2 administration occurring outside of a visit window (site US387)***

The protocol requires participants to attend 2 dosing visits 28 days apart. For Dose 2 there is an allowable dosing window of -3 to +7 days. Out of visit window dosing information was collected throughout the study and monitored regularly by the study team. On average, for all sites, ~5% of dosing occurred outside the dosing window, as per protocol. The window for receiving Dose 2 is narrow for a study of this size. There was no expected safety impact to participants to receive a dose of vaccine out of window. In consideration of the ongoing pandemic and commitment made by our study participants, out of window was permitted to ensure a 2<sup>nd</sup> dose of vaccines for those who may have been randomized to mRNA-1273, in situations where this could not be avoided.

Site US387 – Dr Levin: At this site Dose 2 occurred outside of the visit window for 82 participants (19.2%). PPD and Moderna became aware of this issue through monitoring of the site starting in September. The disproportionate number of Dose 2 administered out of window at Site US387 relative to other study sites was multi-factorial, but largely driven by:

- 1) Delays in the release of Day 1 nasopharyngeal swab COVID-19 result needed to determine continuing eligibility for receipt of Dose 2 due to timeliness of lab discrepancy resolution.
- 2) Lack of required Day 29 laboratory kits resultant from inventory management gaps by site staff, coupled with high overall re-supply demand for the study.

Moderna are working with the site on appropriate remediation to the observation noted.

***Data entry of concomitant medicine & adverse event information (site US387)***

Data entry metrics are monitored regularly by the study team to ensure timely completion of the EDC. Metrics are generated at the end of each week and shared with the clinical project team within PPD and Moderna. The overall data entry metrics for the study have generally maintained a benchmark between 80 – 90% for the life of the study. Challenges with the backlog of data entry were noted in the monitoring of site US387 in early September, and the site brought on additional staff to assist in catching up with data entry. A considerable improvement with data entry has been observed each month with the rate of 60% in September to a current rate of 86%. Moderna will continue to work with the site to progress resolution of the remaining backlog of data entry.

***Monitoring of the temperature of a laboratory freezer (site US387)***

All sites are required to have continuous temperature monitoring for equipment storing clinical study specimens (serum and nasal/saliva specimens). This requirement was evaluated as part of the site selection/activation process beginning with initial clinical site feasibility and confirmed at

both the Pre-Study and Site Initiation Visits for each site. Additionally, the study Monitoring Plan includes the requirement for CRAs to ensure adequate storage conditions are maintained for laboratory specimens at each interim monitoring visit and captured as part of the monitoring visit report.

At site US387, it was identified during the BIMO inspection, that staff had not been properly monitoring laboratory freezer temperatures. The site utilizes an alarmed freezer that produces a readout. However, the readout is only available for the previous week. The site records a single current temperature daily and monitors the alarm. Since the readout produced by the freezer is not cumulative beyond the current week, there is no documented record other than the daily temperature recorded rendering the temperature monitoring log incomplete as noted by the FDA Investigators. This issue is a documentation issue caused by the limitations of the freezer recording device and at no time was an alarm triggered indicating a fluctuation in temperature outside required storage parameters. The site utilizes a second freezer also used for sample storage for which a cumulative record is available to document minimum and maximum temperatures. Moderna will work with the site to provide an appropriate response to the FDA 483 and to ensure that adequate freezer temperature monitoring is implemented and maintained. At this time, we do not believe that this finding is indicative of a systemic issue across sites.

### **3. Moderna monitoring and oversight processes**

Moderna conducts a review of site and data monitoring metrics on an ongoing basis. These data provide Moderna with an overall assessment of site health to ensure the appropriate management of site activities.

#### ***Site Monitoring Activities***

As the Sponsor, Moderna is responsible for ensuring monitoring of investigational sites is conducted. Moderna has delegated this responsibility to a preferred partner CRO, PPD Development, as defined in the Transfer of Regulatory Obligations (TORO) under 21 CFR 312.52. The oversight of monitoring activities is managed by the Clinical Study Team at PPD, led by the Study Clinical Project Manager and a team of Clinical Team Managers. As Sponsor, the Moderna Clinical Trial Team, led by the Clinical Operations Lead and team of Lead CRAs, has oversight of all activities conducted by PPD.

Site monitoring is conducted during Blinded and Unblinded Monitoring Visits by appropriately qualified and trained CRAs, augmented by Remote Study Monitors who manage routine operational issues and site follow up. As per the Blinded Monitoring Plan, both on-site and remote Interim Monitoring Visits (IMV) are utilized by the CRO (PPD). To date, 73% of IMVs have

been on-site and 27% remote, with an average of number of IMVs per site 7.75 (approximately every 2.5 weeks not considering staggered site start-up), with an average duration of 3 days.

As part of Moderna's oversight of PPD monitoring activities, a minimum of 3 meetings per week are conducted to ensure appropriate oversight of site and monitoring activities. Consolidated site metrics are reviewed including: FSFV, #IMVs, #IMVs on site, #IMVs remote, av. Days between IMVs, enrollment, e-diary compliance, GCL missing samples, GCL open queries, CTMS open issues, PDs, dosing errors, CRA assignments and visit restrictions. These metrics are reviewed to identify site issues indicative of a lack of adequate staffing, repetitive errors by site staff, e-diary compliance issues, high numbers of protocol deviations, or data entry or query backlogs. Comprehensive follow up actions are discussed to include mitigation activities such as phone calls with sites, to follow up on issues and establish appropriate mitigations or provide additional support as needed.

Centralized Monitoring (CM) is part of the overall risk-based monitoring strategy and activities conducted by PPD. CM combines statistical and analytical tools to analyze and monitor the clinical trial data. CM is a cross-functional, holistic and ongoing remote review of operational indicators and subject data at the study, site and subject levels that identifies emerging risks. These activities complement onsite monitoring.

The CM team conducts analysis on a bi-weekly basis to identify signals which support a proactive approach to risk detection. The outputs of these analyses are provided to Moderna for review. The PPD study team uses these outputs to focus their oversight of study and site performance. Internal Moderna review of the CM analyses, periodically result in additional follow-up with PPD based on identified signals. Follow-up typically occurs through targeted meetings to align on actions, either ongoing or planned by PPD, to address site or study level risk indicators highlighted by the bi-weekly report.

### ***Centralized Data Management Monitoring Metrics***

The mRNA-1273-301 study team holds cross-functional data review meetings on a weekly basis. These meetings are led by PPD. Moderna participants include Clinical Operations, Clinical Research, Biostats, Statistical Programming, Risk Management, Safety & Pharmacovigilance, Data Management, Biomarker and Sample Management; PPD participants include Study Management, Clinical Monitoring, Data Management, Data Analytics and Global Clinical Lab (GCL). Each week the collective team reviews study metrics which include, but are not limited to, the status of subject enrollment, CRF metrics, query metrics, eDiary compliance, SAEs, laboratory samples and protocol deviations.

Significant study and site level data trends are also identified for other data categories not specifically defined in the above, through review of open and outstanding queries, missing pages and protocol deviations. The review identifies risks or gaps in clinical data. These outlier data were shared with the cross functional team for follow-up or action with the site(s) as appropriate.

### ***Quality Plan***

Moderna Research & Development Quality (Moderna R&D Quality) Study Audit Plans are generated at the onset of a study and are periodically reviewed and updated as necessary. An Initial Study Audit Plan for m-RNA-1273-P301 was finalized on 14Aug2020 and subsequently updated on 08Dec2020 to include detail for Investigator Site and Study Oversight Audits. The current approved version of the Study Audit Plan is provided as [Appendix A](#). To date, four (4) sites have been audited and reports have been issued. No Critical observations were noted. Responses to the audit observations are in progress and Corrective and Preventative Action Plans (CAPAs) are being developed. CAPAs will be tracked and followed to completion and verified for effective remediation. An additional 11 site audits are planned to be conducted between Q1 and Q3 2021. Interim and Final Study Oversight Audits are planned for Q1 2021 and Q4 2021, respectively. In addition to planned audits, directed/for cause audits may be conducted when warranted.

Moderna R&D Quality also conducts System/Process audits as part of a comprehensive audit program. These audits are conducted to assess the level of compliance to applicable regulations, guidelines and internal standards of Moderna's systems and processes used in the conduct, oversight and reporting of clinical trials.



## **Appendix A**

### **Study Audit Plan**