

RESPONSE ADDENDUM 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:

Addendum to "1.11.3 Response to Comments regarding Clinical Topics – Inspection Findings" submitted 09Dec20 to EUA27073 (SN 0010).

Sponsor Response:

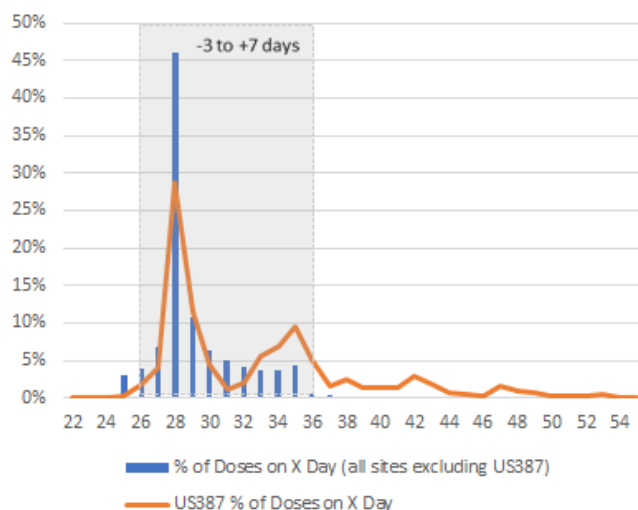
Addendum

Please find below additional information regarding Dose 2 administration occurring outside of a visit window and data entry for site US387. For ease of reading we have included the full response for these topics (submitted to EUA27073 SN0010) and highlighted new text in green.

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 (**Day 26-Day 36**). Out of visit window dosing information was collected throughout the study and monitored regularly by the study team. **Overall, 94.9% of participants were dosed within the appropriate dosing window in the study as shown in Figure 1 below (indicated by the gray shaded area). Of the 5.1% of dosing that occurred outside the dosing window, 56.5% of the events were due to participants being dosed 1 day early, on Day 25 following the first dose (2.91% of dosing). Seventy-three percent of out of window dosing for the study occurred within 3 days of the allowable dosing window. For 81 out of 99 sites, out of visit window dosing occurred in less than 10% of participants, including 5 sites where there were no out of visit window events.**

Figure 1: Distribution of Dose 2 by Study Day



Site US387 was among the five sites with the highest percentage of out of window dosing events. At site US387, dosing occurred out of the visit window for 19.2% participants (a total of 82 participants), as shown in Figure 1 above. The other sites having the highest percentage of out of window dosing events were US339 (22.8%), US310 (21%), US302 (19.3%) and US328 (19.3%).

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 2nd 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: As described above, 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. Average monthly data entry metrics (%) are shown for the study overall and for Site US387 in the table below.

Month	Average Data Entry for Study (%)	Average Data Entry for Site US387 (%)
August	75	63
September	77	60
October	84	81
November	87	85
December	89	86

Overall data entry has shown improvement each month for the life of the study. However, site US387 has consistently had data entry metrics below the average for the study. Challenges with the backlog of data entry were noted in the monitoring of site US387 in early September, and the site was put on enrollment hold on 10 Sep 2020. The site brought on additional staff to assist in catching up with data entry and a considerable improvement with data entry was observed between September and October and has continued to improve consistently. Moderna will continue to work with the site to progress resolution of the remaining backlog of data entry.

In summary, US387 was one of the 5 lowest performing sites for safety follow up calls (92% per protocol) and for Dose 2 administration in window (80.8% within window). In addition, the site has been consistently one of the lowest performing sites for data entry (currently 86% complete). Proactive monitoring by the Sponsor and PPD identified these issues. Given a lack of sufficient remediation by early September, enrollment at US387 was put on hold by the Sponsor and PPD on 10 Sep 2020 and was never restarted. The Sponsor and PPD have worked closely with US387 since that time to remediate the identified issues.