

125741/0 Data validation Report Summary and Subsequent follow-up with Merck

Our Reference: STN 125741/0

Sponsor: Merck

Product: Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) (V114) is a pneumococcal conjugate vaccine that contains 15 distinct pneumococcal capsular polysaccharides individually conjugated to the CRM197 carrier protein originating from *Corynebacterium diphtheriae* C7.

Proposed Indication: active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older. V114 is a 0.5-mL suspension for injection (intramuscular administration only), administered as a single dose in adults.

On October 21, 2020, the sponsor submitted the original biologics license application

On December 15, 2020, the the eDATA team discussed the validation results with the review committee for STN 125741/0. Based on the validation results of the datasets P007, P016, P017, P018, P019, P020 and P021 (beginning page 6 below) and a deeper dive into the datasets, the following comments were written and sent to Merck on Feb 12, 2021.

1. The reason for discontinuation from the study and the end of study status are missing in the DS dataset and the date/time of end of participation in the DM dataset for 22 subjects (b) (6) in 020. Please explain and update datasets if possible.
2. You indicate that the variables RFSTDTC, RFENDTC, RFXSTDTC, RFXENDTC in the DM dataset are null for several subjects because these subjects are screen failures. However, we have found that the USUBJID count for screen failures does not match among the DM, IE and DS datasets. Please explain and update datasets if needed:
 - a. In study 019, we found 32 subjects in DM, 37 in IE and 28 in DS (out of total 1234 subjects in DM)
 - b. In study 020 we found 122 subjects in DM, 131 in IE and 109 in DS (out of total of 2455 subjects in DM)
 - c. In study 017 we found 500 subjects in DM, 512 in IE and 495 in DS (out of total of 2012 subjects in DM)
 - d. In study 021 we found 77 subjects in DM, 83 in IE and 59 in DS (out of total of 1274 subjects in DM)

- e. In study 016 we found 23 subjects in DM, 27 in IE and 22 in DS (out of total 674 subjects in DM)
- f. In study 018 we found 81 subjects in DM, 86 in IE and 81 in DS (out of total of 383 subjects in DM)
3. In study 020 we have found 4 subjects that have reported AEs yet have only been randomized (no further information such as completed, lost to follow-up, etc.). Please explain.
4. In study 021 we have found 1 potential unreported death for subject (b) (6) . Please provide any additional updates you have on this subject and correct the dataset(s) if needed.
5. The AE datasets are missing MedDRA coding data (AESOC and AESOCCD) for all clinical trials. Please provide a rationale for not including these variables. In addition, we found that AEPTCD, AELLTCD, AEHLTCD, AEHLGTCD, AEBDSYCD, AESOC, and AESOCCD are not included in the ISS. We recommend that the codes be provided in the ISS to allow easier analysis. Please comment.
6. In future submissions, please ensure that the severity of ongoing reactogenicity events, i.e., the severity of the event after the solicited event assessment period, be reported in the AE dataset.

On Feb 12, 2021- Merck requested clarification on the 4 subjects referenced in comment 3. We responded on Feb 16, 2021 with the clarification: In study 020 we have found 22 subjects that have been randomized (no further information such as completed, lost to follow-up, etc.). Of the 22 subjects, 3 subjects (b) (6) had unsolicited AEs (n=4). Please explain and update datasets where needed.

On Feb 26, 2021 Merck responded in amendment 15 to the Feb 12, 2021 IR:

1. V114-020's final study visit (telephone contact at 6 months) for the above referenced 22 subjects coincided with the onset of the global SARS-CoV-2 pandemic. As a result of the pandemic, Site 3005 personnel were unable to complete the 6-month follow-up telephone contact for these participants. However, each of the 22 participants had remained in the study for at least 6 months (180 days) after study vaccination and all study participants had been provided the necessary information and instructions to contact the study site with any concerns or should any serious adverse events have occurred during the study. Given the uncertainty and heavy strain on medical institutions at the time, and the judgment that the small quantity of missing data would not jeopardize participant safety, data integrity, or data quality, the Applicant decided to move forward with close out activities without the final study status for these participants. Therefore, the corresponding end of study status and reason for discontinuation are missing in the DS dataset and date/time of end of participation are missing in the DM dataset. No updates to the datasets are needed.

2. The variables RFSTDTC, RFENDTC, RFXSTDTC, RFXENDTC in the DM dataset are null for participants who did not receive study vaccination. This includes participants who: Failed screening and did not enroll, successfully completed screening but did not enroll, or successfully completed screening, enrolled, but were not vaccinated. The number of subjects in the various domains provided by the agency represent different combinations of these participants and in some cases includes other participants with reference start and end dates in the DM domain.

The IE domain includes participants that did not meet inclusion criteria or met exclusion criteria. This domain includes all participants who failed screening, with the exception of 3 subjects in V114-017 that didn't provide the corresponding inclusion/exclusion criteria associated with the screen failure.

The DS domain contains the status of "SCREEN FAILURE" for participants selecting this option for their study status. Nearly all participants that did not enroll have DSTERM = "SCREEN FAILURE" in this domain, though there are a few subjects where another choice for study status was more appropriate (for example, screen failure was not selected for subjects who were not able to be enrolled due to technical issues with the interactive randomization technology, the randomization cap having been met, if study enrollment was closed before the screening results were available, if the subject withdrew consent, or if the subject was lost-to-follow-up following the screening visit). In addition to the participants not enrolled, there is one subject with a study status of screen failure who was enrolled (in error) after failing screening.

3. All 22 subjects received the study vaccine and thus the 3 subjects (b) (6) with AEs is allowed.
4. Merck indicated that no updates to the datasets are need as the death did not meet the criteria for reporting, i.e., subject (b) (6) died (b) (6) day after his final study visit was completed (b) (6) days after receipt of V114 and Fluarix, and (b) (6) days after receipt of study placebo), and the death was considered by the Investigator as not related to the study vaccine.
5. Merck now understands that these variables (AESOC and AESOCCD) are preferred and is working to update the internal process to ensure that all four variables (AESOC, AESOCCD, AEBODSYS, and AEBDSYCD) contain the MedDRA primary system organ class and associated code for future submissions. As requested, we will update the ISS ADAE analysis dataset (and corresponding documentation: define.xml and define.pdf) to include the

AEPTCD, AELLTCD, AEHLTCD, AEHLGTCD and AEBDSYCD variables. The Applicant will include these variables in analysis datasets in future submissions.

6. Future submissions of reactogenicity data from the V114 program will be consistent with this approach and the agreements made with the Agency in the March 11, 2020 teleconference. In future submissions (for new programs that started Phase 2 after Mar-2020), reactogenicity data will be captured in the Clinical Event domain with the maximum severity during the assessment period. If the reactogenicity event continued beyond the assessment period, the event will be captured in the AE domain along with the event's maximum severity.

Reviewers comment: *Their explanation and agreements are acceptable.*

Additionally, a comment was sent on March 17, 2021 to Merck in which we noted that discrepancies were observed in myalgia and arthralgia rates between the results reported from the subjects diary and results reported in the CRF from the investigator, with concordance across collection methods of ~40-50% for some studies. One contributing factor in the observed differences may have been that the VRC reviews by the site investigators were conducted on Day 15 (telephone contact). We requested that Merck revise the draft PI documents to include solicited adverse reactions based solely on clinical events data reported only on the VRC.

We also provided guidance for future studies that include the collection of solicited adverse reactions safety data over a pre-specified time period:

- If your study protocol includes provisions for investigator assessment or review of clinical events data reported by participants on the VRC, then to mitigate concerns about recall bias we recommend that these reviews occur either during the reporting period post-vaccination or at time points that are temporally closer to when these clinical events are more likely to occur. For example, more timely reviews could be included with reminder phone calls every 2-3 days.
- In order to mitigate concerns about differences in assessment methods across sites/investigators, we recommend that all sites adhere to a uniform set of instructions/criteria to adjudicate clinical data and that an appropriately worded script is followed to guide investigators/staff while reviewing clinical events reported on the VRC or reported elsewhere (i.e., medical records or verbally communicated) that are subsequently captured in the CRF.

Merck submitted a response in amendment 22, dated March 24, 2021 and expressed concern that the use of VRC data only may risk introduction of misclassification bias. Merck stated that no specific instructional text was provided on the VRC, whereas measures were put in place to ensure uniformity and reduce variability and bias from investigators. Therefore, Merck maintains the position that the

most unbiased assessment of solicited adverse reactions is based on investigator-assessed AEs and proposes to retain data summaries based on investigator assessed AEs in the draft V114 PI.

We held an internal meeting on Mar 29, 2021 to discuss their response. During this meeting, the concerns and issues were discussed with the division and office management and the following conclusions were reached:

1. Merck's response is acceptable.
2. Solicited adverse reactions data that reflect the study investigators assessments will be included in the draft PI. In the draft PI, CBER will include the data collection method, including the review of the VRC by the site investigators on Day 15 post vaccination.
3. For future protocols, CBER will reiterate their recommendation that the investigator assessment or review of clinical events data reported by participants on the VRC occur either during the reporting period post-vaccination or at time points that are temporally closer to when these clinical events are more likely to occur, for example, reminder phone calls every 2-3 days.