Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

**BLA 125814 Data validation Report Summary and Subsequent follow-up with Merck**

**Our Reference:** BLA 125814 (studied under IND 19316)

**Sponsor:** Merck

**Product:** Pneumococcal 21-valent Conjugate Vaccine conjugated to CRM197 carrier protein ()

**Proposed Indication**: active immunization for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older

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**Previous data standardization** discussion included:

- V114 Data standards discussion regarding reporting solicited reactogenicity events in March 2020
- Amendment 14 submission of the SDSP/CBER Appendix and aCRF for study p001V116 on September 24, 2020. Comments were provided on June 29, 2021
- Amendment 31 received on August 13, 2021, with a response to the comments provided on June 29, 2021. A follow-up comment regarding the medical assessment of the VRC was sent to Merck on August 26, 2021
- Amendment 35 received on October 8, 2021, for an EOP2 meeting. Several comments regarding their data standardization were conveyed in the WRO sent on December 2, 2021.
- Amendment 42 received on April 8, 2022, with a response to the EOP2 meeting comments sent on the SDSP dated December 2, 2021
- Amendment 141 received on September 13, 2023. No response was provided to Merck since this BLA was submitted too soon after.

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On October 18, 2023, Merck submitted the biologics license application (BLA) to support licensure of the Pneumococcal 21-valent Conjugate Vaccine conjugated to CRM197 carrier protein. The BLA included results from 5 clinical trials p001v116, p003v116, p004v116, p005v116 and p006v116. Clinical trial datasets were submitted for all 5 as well as an ISS and ISE; however, only one will be reviewed under this BLA (p003v116):

- **Study p001v116** - Phase 1/2 – Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity in Adults - SDTMv1.4 – initiated Sep 23, 2020 – completed Jul 12, 2021 – locked Jul 29, 2021

- **Study p003v116** - Phase 3 – Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults – SDTM1.7 – initiated Jul 13, 2022 – completed Jun 21, 2023

- **Study p004v116** - Phase 3 – Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age – SDTMv1.7 – initiated Aug 12, 2022 – completed Jul 3, 2023

- **Study p005v116** - Phase 3 – Randomized, Double-blind, Placebo- Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older – SDTMv1.7 – initiated Sep 23, 2022 – completed Jun 28, 2023

- **Study p006v116** - Phase 3 – Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older – SDTMv1.7 – initiated Jul 12, 2022 – completed Jun 22, 2023

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**General notes on the data to be found in the p003 datasets and the objectives of the clinical trial**:

Cohort 1 (≥50 years of age) and/or Cohort 2 (18 to 49 years of age). For the objectives in this study, the serotypes are categorized as follows:

• 10 common serotypes in V116 and PCV20 (3, 6A, 7F, 8, 10A, 11A, 12F, 19A, 22F, and 33F)
• 11 unique serotypes in V116 (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, and 35B)
• 2 cross-reactive serotypes (6C and 15B)

- Primary safety – Solicited AEs from Day 1 through Day 5 postvaccination (injection site swelling, pain, erythema; fever, fatigue, headache, myalgia); Vaccine-related SAEs from Day 1 through the duration of participation in the study
- Primary efficacy
  - Cohort 1 - compare the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V116 versus PCV20
  - Cohort 1 - compare the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days post-vaccination with V116 versus PCV20 for the unique serotypes in V116

- Cohort 2 - To compare the serotype-specific OPA GMTs in adults 18 to 49 years of age from Cohort 2 to adults 50 to 64 years of age from Cohort 1 at 30 days postvaccination with V116
- Cohort 1 and 2 - To evaluate serotype-specific cross-reactive OPA responses at 30 days postvaccination with V116 in adults ≥50 years of age from Cohort 1 and adults 18 to 49 years of age from Cohort 2 for serotypes within a serogroup
- Cohort 1 - To evaluate the serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with V116 compared with PCV20

**P003v116 Datasets**:

- BE dataset – 5297 records in 2665 subjects – contains when specimens were obtained
- CM dataset – 9694 records in 2162 subjects – 1 category (Prior or concomitant medication) they use SCAT to differentiate prevention vs treatment (which they actually provide the drug and dosage)

| CMSCAT (3) | |
|---|---|
| ??? | 9503 |
| ANALGESIC/ANTIPYRETIC FOR PREVENTION | 2 |
| ANALGESIC/ANTIPYRETIC FOR TREATMENT | 189 |

  - Prespecified? – no
  - Suppcm – 44223 records in 2162 subjects
- CO dataset – 469 records in 49 subjects – further descriptions of AEs
- DD dataset – 19 records in 6 subjects
  - Count matches AE (6), DM (6) and DS (6)
  - Dates/days provided
  - Cause of death included? – yes as DDTEST=primary cause of death
  - Suppdd – 38 records in 6 subjects – provides the vaccine administered in QVAL

| DDTEST (4) | |
|---|---|
| Autopsy Determined Cause of Death | 1 |
| Autopsy Indicator | 5 |
| Information Source for Cause of Death | 7 |
| Primary Cause of Death | 6 |

- DM dataset – 2754 records in 2754 subjects
  - 98 RFSTDTC is null - ARMNRS used to break it down
  - Subjects enrolled more than once? Not evident
  - Suppdm – 22069 records in 2754 subjects

| ARMNRS (4) | |
|---|---|
| ??? | 2656 |
| ASSIGNED, NOT TREATED | 7 |
| NOT ASSIGNED | 19 |
| SCREEN FAILURE | 72 |

- DS dataset – 14015 records in 2754 subjects – 3 categories – 2663 were randomized and 77 were screen failures, 33 lost to follow-up and 15 subject withdrawn

| DSCAT (3) | |
|---|---|
| DISPOSITION EVENT | 2754 |
| OTHER EVENT | 2760 |
| PROTOCOL MILESTONE | 8501 |

  - 6 Deaths
  - Suppds – 28139 records in 2754 subjects - 5 QLABELS – one was additional details on the 33 discontinuations
- DV dataset – 263 records in 222 subjects – 5 categories – SCAT of clinically important, not clinically important or N/A
  - Suppdv – 620 records in 222 subjects

| DVCAT (5) | |
|---|---|
| Inclusion/ Exclusion Criteria | 22 |
| Prohibited Medications | 14 |
| Safety Reporting | 2 |
| Study Intervention | 52 |
| Trial Procedures | 173 |

- EX dataset – 2656 records in 2656 subjects – 1 category (compliance)
    - Dose number - 1
    - Suppex – 13280 records in 2656 subjects – not useful
- HO dataset – 61 records in 44 subjects – 0 categories – hospitalization only info provided with days/dates
    - Suppho – 122 records in 44 subjects
- IE dataset – 129 records in 95 subjects
    - Matches DM screen failures? – no
    - Suppie – 495 records in 95 subjects
- IS dataset – 250835 records in 2658 subjects – 1 category (serology)
    - 48 tests (AB and IgG AB for each of the 21 strains except15C IgG AB missing; and added 6C and 15B both tests, and 20B AB test, d15B IgG AB test and S. pneumo Ab (neg or pos))
    - 9343 null results in 2419 subjects – with range of 1 to 51 tests missing for each of the subjects

| ISREASND (3) | |
|---|---|
| IND | 2833 |
| SII (SAMPLE INTEGRITY ISSUE) | 36 |
| TERMINATION OF REPEATS | 6474 |

    - Suppis – 1239601 records in 2658 subjects
- LB dataset – 1394 records in 26 subjects – 1 category (supplementary labs)
    - Tests – misc chemistry and hematology
    - NRIND used? - yes
    - Supplb – 13753 records in 26 subjects – they provide the conventional units data in the supplemental – this should be reported in another dataset LC
- MB dataset – 70 records in 54 subjects – 1 category (supplemental labs)
    - Tests for SARS-CoV-2, Influenza, RSV and Strep pyogenes
    - Suppmb – 282 records in 54 subjects
- MH dataset – 40988 records in 2686 subjects – 2 categories
    - Events occurring after treatment? 8 are on day 1 so it is unclear if they happened before or after vaccination

| MHCAT (3) | |
|---|---|
| ??? | 48 |
| CONDITIONS ASSOCIATED WITH INCREASED PNEUMOCOCCAL DIS... | 32172 |
| GENERAL MEDICAL HISTORY | 8768 |

    - Prespecified events? Yes – the increased pneumo conditions – 897 events occurred (MHOCCUR=Y)
    - Suppmh – 24 records in 8 subjects – they provide description of element (EPOCH), element code (SCR) and start day rel to EPOCH (1) for the 8 subjects – it would be more helpful if they provide the complete ISO8601 don to the min /sec in MH to help show that the events occurred before vaccination
- PE dataset – not provided
- PR dataset – 134 records in 30 subjects
    - Supppr – 1596 records in 30 subjects
    - FAPR dataset – 132 records in 30 subjects – interpretation of the test as either normal or abnormal
    - Suppfapr – 384 records in 29 subjects
- RP dataset – not provided (page 11-12 and 25-28 of the aCRF provided for collection of this information)

- SC dataset – 2730 records in 2730 subjects - 1 test of gender identity
    - Suppsc – 5456 records in 2728 subjects
- SU dataset – 6165 records in 2677 subjects – 2 categories (E-liquid use, Tobacco use)
    - Suppsu – 849 records in 824 subjects – flag if former or current
- SV dataset – 13236 records in 2754 subjects – 0 categories
    - SVCNTMOD used? Yes
    - 5 VISITS with 5 VISITDY (1,7,30,90 and 180)
    - Suppsv – 5405 records in 2754 subjects - contact location (all are onsite for the in person visits on days 1 and 30)
- VS dataset – 13280 records in 2656 subjects – 1 category (vital signs) – temperature is the only test – 5 records/subject for days 1-5
    - 432 records are null (VSREASND is NOT DONE – that terminology should only be used for VSSTAT)
    - 47 temperature records ≥38.0°C in 38 subjects - matches the 38 in CE
    - Suppvs – 39840 records in 2656 subjects
- AE dataset – 1074 records in 608 subjects
    - 5 Categories – see snapshot – need to provide comment on the desired categories

| AECAT (5) | |
|---|---|
| CLINICAL AE | 922 |
| CLINICAL AE,WORSENING OF MEDICAL HISTORY | 35 |
| INJECTION SITE AE | 108 |
| LABORATORY AE | 1 |
| REACTOGENICITY | 8 |

    - Reactogenicity – doesn't appear to be ongoing – these should be included in CE and suppce (if not already)

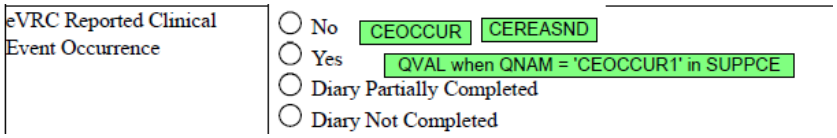
| USUBJID | AETERM | AECAT | AESEV | AESER | AETOX | AESTDY | AEENDY | AEDUR | AEELTM |
|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | mild erythema around injection site | REACTOGENICITY | | N | MILD | 1 | • | PT5H18M | P1D |
| | Pain/Tenderness at Injection Site | REACTOGENICITY | | N | MILD | 1 | • | PT23H | P1D |
| | Fatigue | REACTOGENICITY | | N | MILD | 1 | • | PT0H40M0S | P1D |
| | Tenderness Injection Site | REACTOGENICITY | | N | MILD | 1 | • | PT0H10M0S | P1D |
| | tenderness injection site | REACTOGENICITY | | N | MILD | 1 | • | PT5H50M0S | P1D |
| | Headache | REACTOGENICITY | | N | MILD | 1 | • | PT7H5M | P1D |
| | Injection Site pain | REACTOGENICITY | | N | MILD | 1 | • | PT8H30M | P1D |
| | Injection Site Pain or Tenderness | REACTOGENICITY | | N | MILD | 1 | 2 | | P1D |

    - 6 events are synonymous solicited events (AECAT=Clinical AE) and begin in the 5 day assessment period
        - 2 events with AECAT=clinical AE should be reported as part of an ongoing event (subject (b) (6) headache days 6-17 should be added to the event in CE beginning on day 4 and subject (b) (6) headache days 1-48 should be included in the event in CE on day 2)
    - Injection site AE – appears to mostly be non-solicited reactions and solicited reactions that begin after day 5
    - 67 SAEs –
        - 62 are Y for SHOSP (45 subjects) [does not match HO with 61 records in 44 subjects]
        - 7 are Y for SDTH
        - 1 (subject (b) (6) ) had "Involved Cancer" flagged yet AESER=N
    - No events occur prior to treatment

    - Deaths? – 7 AEOUT=fatal in 6 subjects
    - AEACNOTH not used to flag medically attended events
    - They use AEDUR to provide hours/mins of duration only
    - AEELTM is used – but not needed since it is only 1 dose
    - Suppae – 11615 records in 608 subjects – 17 QLABELS
- FAAE dataset – 45 records in 4 subjects – 3 QLABELS – unclear the necessity of this dataset
- FACE dataset – 84686 records in 2656 subjects
    - 1 Category (reactogenicity)
    - 2664 Null records
    - FAEVAL not used – supposedly this dataset only includes subject diary data
    - Suppface – 254058 records in 2656 subjects – 3 QLABELS - pointless
- FAEF dataset – not provided
- CE dataset – 18592 records in 2656 subjects (Merck only includes investigator assessment in this dataset – safety phone call is on day 7 and 30)
    - 1 category - reactogenicity
    - flat model is used
    - 123 "Unrelated" events – all are systemic
        - Some events are considered "related" even though CEOCCUR is null
        - Some events are considered "related" even though CEOCCUR=N
    - all solicited reactions are included for each subject – 2656 records for each event
    - fever is reported in 38 subjects but severity is missing for all
    - Severity also missing for 200 injection site swelling and 169 injection site erythema
    - 155 ongoing reactogenicity events (flagged in CEENRTPT -1 event ended on day 1 and 46 events ended on day 5) whereas in CEENDY only 108 records are day 6 or greater – does not match number in AE (8) because the events in AECAT=reactogenicity are not ongoing
    - CECONTRT=Y for 186 records (in CM they have 189 records for treatment and 2 for prevention)
    - Diary completion reported in CEREASND (see snapshot)

| QLABEL (22) | |
|---|---|
| Description of Element | 18592 |
| Element Code | 18592 |
| Invest/Subject Overall Assmnt Differ | 15936 |
| Focus of Study-Specific Interest | 7968 |
| Start Day Rel to Epoch | 2910 |
| Relationship to Blinded Study Med | 2871 |
| Stop Day Rel to Epoch | 2871 |
| Study Medication - Blinded | 2871 |
| Symptom of Other Diagnosis Indicator | 1776 |
| Reason Investigator Changed Assessment | 1453 |
| Clinical Event Occurrence 1 | 1337 |
| Medical History Association | 1189 |
| Longest Diameter | 367 |
| Longest Diameter Unit | 367 |
| Severity/Intensity 1 | 108 |
| Onset Date/Time of Event 1 | 66 |
| Maximum Temperature | 38 |
| Maximum Temperature Day | 38 |
| Maximum Temperature Location | 38 |
| Maximum Temperature Unit | 38 |
| Related VAE Event | 14 |
| Reconstructed Data | 4 |

| CEREASND (3) | |
|---|---|
| ??? | 18318 |
| DIARY NOT COMPLETED | 26 |
| DIARY PARTIALLY COMP... | 248 |




    - Diary not completed for 2 subjects (14 records) – CEOCCUR was null - the remaining 12 records were fevers from 12 subjects (odd that the other solicited events were collected)

- Diary partially completed are also null for CEOCCUR – majority are fever – probably because investigator couldn't take the temperature when contacting the subject and so couldn't fill in the diary results

- Suppce –79444 records in 2656 subjects – 22 QLABELS (see snapshot)
  - Investigator/subject overall assessment differ – 1453 records have QVAL=Y, 36 records = unable to confirm with subject
    - Flag not always accurate – CE usually has more days for event occurrence than FACE so they seem to error on the side of overreporting

| QLABEL (22) | |
|---|---|
| Description of Element | 18592 |
| Element Code | 18592 |
| Invest/Subject Overall Assmnt Differ | 15936 |
| Focus of Study-Specific Interest | 7968 |
| Start Day Rel to Epoch | 2910 |
| Relationship to Blinded Study Med | 2871 |
| Stop Day Rel to Epoch | 2871 |
| Study Medication - Blinded | 2871 |
| Symptom of Other Diagnosis Indicator | 1776 |
| Reason Investigator Changed Assessment | 1453 |
| Clinical Event Occurrence 1 | 1337 |
| Medical History Association | 1189 |
| Longest Diameter | 367 |
| Longest Diameter Unit | 367 |
| Severity/Intensity 1 | 108 |
| Onset Date/Time of Event 1 | 66 |
| Maximum Temperature | 38 |
| Maximum Temperature Day | 38 |
| Maximum Temperature Location | 38 |
| Maximum Temperature Unit | 38 |
| Related VAE Event | 14 |
| Reconstructed Data | 4 |

| USUBJID | IDVAR | IDVARVAL | QNAM | QLABEL | QVAL | QORIG |
|---|---|---|---|---|---|---|
| (b) (6) | CESEQ | (b) (6) | CEISOADF | Invest/Subject Ov... | N | CRF |

| USUBJID | CESEQ | CETERM | CEOCCUR | CEDY | CESTDY | CEENDY | CEDUR |
|---|---|---|---|---|---|---|---|
| (b) (6) | 438066 | Injection site pain | Y | 5 | 1 | 2 | P2D |

| USUBJID | FAOBJ | FAORRES | FALAT | FADY | FATPT |
|---|---|---|---|---|---|
| (b) (6) | Pain or Tenderness | Y | LEFT | 1 | DAY1 POST-VACCINATION |
| | Pain or Tenderness | N | LEFT | 2 | DAY2 POST-VACCINATION |
| | Pain or Tenderness | N | LEFT | 3 | DAY3 POST-VACCINATION |
| | Pain or Tenderness | N | LEFT | 4 | DAY4 POST-VACCINATION |
| | Pain or Tenderness | | LEFT | 5 | DAY5 POST-VACCINATION |
| | Pain or Tenderness | MILD | LEFT | 1 | DAY1 POST-VACCINATION |

  - Reason investigator changed assessment – 2 choices as per aCRF – Updated per verbal discussion with subject, or updated per investigator medical judgement
  - FOCID – SITEAL (left arm) or SITEAR (right arm)
  - Severity/Intensity 1 – is from subject diary
  - Clinical Event Occurrence 1 (see aCRF picture above) – Y, N, or flags the same info as in CEREASND
  - 4 records with reconstructed data

| STUDYID | RDOMAIN | USUBJID | IDVAR | IDVARVAL | QNAM | QLABEL | QVAL | QORIG |
|---|---|---|---|---|---|---|---|---|
| V116-003 | CE | (b) (6) | CESEQ | (b) (6) | CERECON | Reconstructed Data | Y | Derived |
| V116-003 | CE | | CESEQ | | CERECON | Reconstructed Data | Y | Derived |
| V116-003 | CE | | CESEQ | | CERECON | Reconstructed Data | Y | Derived |
| V116-003 | CE | | CESEQ | | CERECON | Reconstructed Data | Y | Derived |

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On November 17, 2023, the eDATA team discussed the validation results for studies p003, p004, -005 and p006 with the review committee for STN 125814.

Based on the initial validation results (beginning page 18 below) and a deeper dive into the study datasets for study p003, the following issues were identified and conveyed on November 27, 2023 (IR Request #3):

1. We have found the following number of subjects that were screen failures in the datasets: 72 in DM (ARMNRS), 77 in DS and 95 in IE. Pleas provide a rationale for these discrepancies and correct any that are erroneous.
2. We note that you are reporting the SI unit results in LB and the conventional unit data in supplb. Unfortunately, this will be difficult to analyze. We request that you either add the columns (US results/findings, US units, US lower range, and US upper range) to the existing LB dataset or provide an additional dataset named "LC" which is identical in format to LB but provides US conventional units instead of SI units.
3. In the MH dataset, we note that 8 events are reported as beginning on day 1. As it is unclear if the event began before or after vaccine administration, please provide the hour/minute in the date (MHSTDTC).
4. In the VS dataset, 432 temperature records are null with VSREASND=NOT DONE. We recommend in any future submission that only VSSTAT = "Not Done" and that VSREASND provide the reason that the event was not recorded. Please acknowledge.
5. We have the following comments regarding the AE dataset:
    a. Please ensure that categories are used to aid in our review, e.g., in the AE dataset we recommend using: Immediate Adverse Event, Non-solicited Reactogenicity Event, Post-exposure Procedure Related, PIMMC, NOCD, Exacerbation of Chronic Disease. Please note that the category should not be the same as the domain name.
    b. You include a category of "Reactogenicity"; however, it doesn't appear that the events in this category are ongoing solicited reactogenicity events, and it is unclear why they were included in AE. We request that the records be removed from AE and instead be included in the CE dataset as part of the summary, with suppce indicating if it changes the summary and why (using the currently used supplemental QVALs).
    c. It appears that two of the events that are synonymous with solicited events, but with AECAT=clinical AE, should be reported as part of an ongoing event in CE (subject (b) (6) headache days 6-17 should be added with the headache in CE beginning on day 4 and subject (b) (6) headache days 1-48 should be included with the headache in CE). Please correct if erroneous.
    d. Of the 67 SAEs, 62 are Y for SHOSP (in 45 subjects). This does not match the HO dataset with 61 records in 44 subjects. Please explain or correct those records that are erroneous.
    e. Subject (b) (6) had a breast carcinoma reported in AE which was flagged with "Involved Cancer" yet AESER=N. Please explain and correct if erroneous.
    f. We recommend that in any future BLA or sBLA that AEACNOTH be used to flag medically attended events.

6. Please provide the following compliance summaries for the 5-day reporting period for solicited reactions by study group following each dose:
    a. Proportion of participants who completed eDiary entries:
        i. for all solicited reactions for all 5 days
        ii. for each reporting day (i.e., Day 1, Day 2, etc.) for each solicited reaction
        iii. for each solicited reaction by consecutive days of completion:
            1. Days 1 through 2 post-vaccination,
            2. Days 1 through 5 post-vaccination.
7. We have the following comments concerning the CE dataset:
    a. 2379 fevers are considered “related” even though CEOCCUR=N and 239 fevers are considered “related” even though CEOCCUR is null. Please explain how a non-occurring event or unknown event occurrence can be related. Please correct the records that are erroneous.
    b. Fever is reported in 38 subjects, but the severity is missing for all. Please update the CE dataset to include the severity.
    c. Severity is also missing for 200 injection site swelling records and 169 injection site erythema records. Please include the severity for each record in the CE dataset. If the measurement is below the minimum length to be considered “mild” we recommend that you report the severity as “below mild.”
    d. We note that 155 reactogenicity events are flagged as ongoing in CEENRTPT; however, of those events, 47 appear to end by day 5 (1 event ended on day 1 and 46 events ended on day 5) which would indicate they are not ongoing. Please correct those records that are erroneous whether it be the day or flag.
    e. We note that CECONTRT=Y for 186 records yet in CM you have 189 records for treatment and 2 for prevention. Please explain and correct those that are erroneous.
    f. Please ensure that in any future BLA or sBLA that the reactogenicity terms between FACE and CE match.

We additionally have the following specific comments concerning datasets from the other studies:

8. In study p004v116 we have found 1891 fevers considered “related” even though CEOCCUR=N and 207 fevers are considered “related” even though CEOCCUR is null. Please explain how a non-occurring event or unknown event occurrence can be related. Please correct the records that are erroneous.

9. In study p005v116 we have found 7 SAEs which were flagged as “Involved Cancer”, yet they were not flagged as serious in AESER. Please explain and correct if erroneous.
10. In study p005v116 we have found 1,778 fevers considered “related” even though CEOCCUR=N and 311 fevers are considered “related” even though CEOCCUR is null. Please explain how a non-occurring event or unknown event occurrence can be related. Please correct the records that are erroneous.
11. In study p006v116 we have found 650 fevers considered “related” even though CEOCCUR=N and 49 fevers are considered “related” even though CEOCCUR is null. Please explain how a non-occurring event or unknown event occurrence can be related. Please correct the records that are erroneous.

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Merck provided a response in amendment 5 (sequence 6) on December 12, 2023. Revised datasets were provided (these were not revalidated) for studies p003, p004, p005 (CE, DM, suppce and suppdm), and p006 (CE, suppce).

<u>In response to comment 1</u>: Merck confirms there are 72 screen failures in the DM domain and 77 screen failures in the DS domain. The difference is attributed to a misclassification for 5 participants in the DM domain ARMNRS; 5 participants were marked as "NOT ASSIGNED" instead of "SCREEN FAILURE" in DM. For IE in which 23 additional subjects were reported as not meeting an inclusion/exclusion criteria, 5 will be updated from “Not assigned” to “Screen failure”, 2 were not randomized due to administrative reasons, 3 never received the vaccine, and 13 were randomized and vaccinated, but later found to have violated one or more IE criteria.

> **Reviewer’s thoughts**: they corrected this by updating the ARMNRS in the DM domain to "SCREEN FAILURE" for these 5 participants in V116-003. This issue was also identified and will be updated in V116-004 and V116-005 (this issue was not identified in V116-006).

<u>In response to comment 2</u> – Merck is aware of the requirement of LC to provide the US conventional units of lab values and is working on updating the internal technical standards to incorporate this requirement.

> ***Reviewer’s thoughts****: They propose to maintain the current dataset. This is acceptable at this time since both of the units and values are provided.*

<u>In response to comment 3</u> - Queries were issued for these events and were confirmed by the site to be accurately reported as medical history and thus, these events commenced prior to vaccination.

> ***Reviewer’s thoughts****: collection date/time needs to be reported in the CRF as well as start date/time (especially for those events that begin on day 1).*

In response to comment 4 – Merck acknowledges the recommendation provided and will update internal technical standards such that VSREASND will provide the reason that the event was not recorded. As this information is provided by the participant, this change is unable to be applied for studies ongoing or completed at the time of this response.

In response to comment 5a – Merck describes that in the V116 studies the AE dataset contains the categories: Reactogenicity, Clinical AE, Laboratory AE, Injection Site AE, Pregnancy Event, and Clinical AE, Worsening of Medical History. They provide a table comparing CBER recommended categories and categories used in V116 AE datasets.

> ***Reviewer's thoughts**: Events that are not protocol specified solicited reactions and appear to be consistent with a local or systemic reactogenicity event should be reported in AE with AECAT= Non-solicited reactogenicity event (not adverse events with the same preferred term as a reactogenicity (solicited) event and an onset of Day 6 or later which should be categorized as Solicited Event Delayed Onset).*

In response to comment 5b - The events with a category of "Reactogenicity" in the AE domain are immediate reactions (events that occurred within 30 minutes of vaccine administration). Merck reported immediate reactions in both the AE domain and the CE domain because time is collected on the VAE eCRF and not on the VCET eCRF. As such, reporting of these events on the VAE eCRF to reside in the AE domain allows for identification of immediate reactions. Duplicate reporting is avoided in the ADaM dataset where one single event record is created.

> ***Reviewer's thoughts**: we disagree with this approach. Immediate solicited reactions which are specifically prespecified, for example, those occurring within 1 hour following administration, and generally collected separately from the reactogenicity events occurring during the subject diary assessment period, should be reported on separate line(s) in CE and categorized using "Immediate Solicited Reaction" in CECAT. If the immediate reaction is not individually solicited, it should be reported in AE with an AECAT of "Immediate Adverse Event." The –EVINTX should be utilized to report the timing post-vaccination. The event should not be reported in both AE and CE. Please correct the datasets as initially requested.*

In response to comment 5c – Merck states that the two events of headache, although synonymous with solicited events, were documented by the investigator as being separate events. Specifically,

> Subject (b) (6) : The participant reported a solicited event of headache occurring over study days 4-5. The investigator assessed the event to be related to study vaccine and that the event resolved on study day 5. The investigator then reported

that a new event of headache began on study day 6 and resolved on study day 17 (after the reactogenicity period) and reported as an AE. The investigator assessed this event to be not related to study vaccine.

Subject (b) (6) : The participant reported the solicited event of headache over study days 1-2. The investigator assessed the event to be related to study vaccine. The participant sought medical attention from a neurologist for a separate event and was diagnosed as having a tension headache. The investigator determined that this was a separate adverse event and not considered to be the same as the reactogenicity/ solicited event of headache. For this reason, the participant has events of headache and tension headache (PT=headache) in the CE and AE domains respectively.

***Reviewer's thoughts**: We disagree with these assessments as the events either overlap or are continuous (ongoing). We request that the headaches be removed from the AE dataset and instead be reported in FACE with a summary in CE.*

In response to comment 5d - Participant (b) (6) experienced an SAE of neutropenia which was reported to the site at the final study contact which was also the last patient last visit date for the trial. The site made all efforts but was unable to obtain hospital records and thus the dates of the hospitalization in the HO domain. Due to this, there is a one-participant difference for hospitalization between the AE and HO domains.

In response to comment 5e - cancer is not serious per ICH definition. For this event involving cancer that was not flagged as an SAE, it was confirmed that serious criteria were not met. Therefore, the Sponsor proposes to retain the current AE dataset.

***Reviewer's thoughts**: response is acceptable.*

In response to comment 5f – ACNOTH will be used to flag medically attended events.

In response to comment 6 – diary compliance summaries were provided as requested (they note that subjects are required to respond to all 6 solicited events before they can submit the daily diary, therefore the compliance rates for all 6 solicited events are expected to be the same).

***Reviewer's thoughts**: no notable differences were found between the 2 arms*

In response to comment 7a – Merck acknowledges the comment and has updated the CE and SUPPCE domains in V116-003, V116-004, V116-005, and V116-006 to remove the default causality where CEOCCUR='N' or Null.

In response to comment 7b – Merck notes that the Intensity Grade for the 38 events of pyrexia are present in the ADaM dataset. They propose to maintain this approach.

**Reviewer's thoughts**: we disagree with the approach and again request that the severity be included in CE.

In response to comment 7c - For the 200 injection site swelling records and 169 injection site erythema records, the Intensity Grade is populated in the ADaM dataset. If an event of injection site erythema or injection site swelling was reported to the site outside of the eVRC, the investigator assesses the Intensity Grade of the event (functional assessment) and only severity (not size) is present in the CE domain.

**Reviewer's thoughts**: we disagree with the approach and again request that the severity be included in CE.

In response to comment 7d - The variable CEENRTPT for the 47 events identified were erroneously entered as ONGOING by the site. It is the sites' responsibility to enter and update the source data, but they were not corrected prior to database lock. The variable CEENDTC variable is used in our analysis and was reported correctly for all 47 events. They state that since these errors did not impact the analysis, they propose to retain the current CE dataset.

***Reviewer's thoughts**: They do indicate that for studies that have not yet started enrollment, CEENRTPT will be derived, instead of having this data field entered by the site. However, they need to correct the CE dataset for these studies as it does impact our analysis.*

In response to comment 7e – Merck acknowledge that there is not always a 1 to 1 correspondence between CECONTRT='Y' in the CE domain and CMSCAT in the CM domain. In some instances, a participant reported using an analgesic/antipyretic medication to treat multiple solicited events; in some instances, a participant reported that more than one analgesic/antipyretic medication was used to treat a single event; finally in other instances, an analgesic/antipyretic medication was used to treat another condition which is not a solicited event.

In response to comment 7f – Merck acknowledges the recommendation provided and will update internal technical standards such that the reactogenicity terms in the FACE and CE domains match. The updated internal standards will allow this change to be applied to studies which have not yet started enrollment.

***Reviewer's thoughts**: updated standard should be applied to any study in which they intend to submit to the FDA not just those that haven't started enrollment.*

In response to comment 8 - see response to 7a

In response to comment 9 – see response to 5e

In response to comment 10 – see response to 7a

In response to comment 11 – see response to 7a

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With the above concerns an additional IR was sent to Merck on March 25, 2014 (IR#16).

1. In response to comment 3 you indicate that queries were issued for the noted events and were confirmed by the site to be accurately reported as medical history and thus, these events commenced prior to vaccination. While we understand that you confirmed these events to have occurred prior to vaccination the dataset does not clearly show it. We request that in any future dataset you implement the following:
    a. Any future study performed by or for Merck should include the time of the event for any report of an event that begins on the day of the first vaccination.
    b. Any future study should include instructions that full dates (i.e., month, day, and year and possibly hours/minutes) be collected on each of the CRF pages.

2. In response to comment 5a you describe that in the V116 studies the AE dataset contains the categories: Reactogenicity, Clinical AE, Laboratory AE, Injection Site AE, Pregnancy Event, and Clinical AE, Worsening of Medical History. A table is additionally provided comparing CBER recommended categories and categories used in the V116 AE datasets. We request that you not use AECAT= "Non-solicited reactogenicity event" for events with the same preferred term as a protocol specified solicited reactions and an onset of Day 6 or later events. Instead, we request that you use the category of "Solicited Event Delayed Onset." The AECAT= "Non-solicited reactogenicity event" should be used for those events that are not protocol specified solicited reactions, but appear to be consistent with a local or systemic reactogenicity event.

3. In response to comment 5b, you indicate that the events with a category of "Reactogenicity" in the AE domain are immediate reactions (events that occurred within 30 minutes of vaccine administration) and that you reported immediate reactions in both the AE domain and the CE domain because time is collected on the VAE eCRF and not on the VCET eCRF. You also indicate that duplicate reporting is avoided in the ADaM dataset where one single event record is created. We disagree with this approach. Immediate solicited reactions which are specifically prespecified, for example, those occurring within 1 hour following administration, and generally collected separately from the reactogenicity events occurring during the subject diary assessment period, should be reported on separate line(s) in CE and categorized using "Immediate Solicited Reaction" in CECAT. If the immediate reaction is not individually solicited, it should be reported in AE with an AECAT of "Immediate Adverse Event." The –EVINTX should be utilized to report the timing post-vaccination. The event should not be reported in both AE and CE. Please correct the datasets as initially requested.

4. In response to comment 5c you provide a rationale why the two events of headaches in subjects (b) (6) and (b) (6), although synonymous with solicited events, were documented by the investigator as being separate events. We disagree with these assessments as the events either overlap or are continuous (ongoing). We request that the headaches be removed from the AE dataset and instead be reported in FACE with a summary in CE.

5. In response to comment 7b you note that the Intensity Grade for the 38 events of pyrexia are present in the ADaM dataset. You propose to maintain this approach of only reporting severity in the analysis dataset. We disagree with the approach and again request that the severity be included in CE.

6. In response to comment 7c you indicate that for the 200 injection site swelling records and 169 injection site erythema records, the Intensity Grade is populated in the ADaM dataset. If an event of injection site erythema or injection site swelling was reported to the site outside of the eVRC, the investigator assesses the Intensity Grade of the event (functional assessment) and only severity (not size) is present in the CE domain. We disagree with the approach and again request that the severity be included in CE.

7. In response to comment 7d you state that the variable CEENRTPT results were erroneously entered as ONGOING by the site for the 47 events identified. You indicate that it is the sites' responsibility to enter and update the source data, but that the data were not corrected prior to database lock. While you do indicate that for studies that have not yet started enrollment, CEENRTPT will be derived, instead of having this data field entered by the site; you also indicate that since these errors did not impact the analysis, you propose in this submission to retain the current CE dataset. As the variable is used in our analysis and was reported incorrectly for all 47 events, we disagree and again request that the correction be made in the CE dataset for the studies in this submission.

8. In response to comment 7f you acknowledge the recommendation provided such that the reactogenicity terms in the FACE and CE domains match and will update internal technical standards. You indicate that the updated internal standards will allow this change to be applied to studies which have not yet started enrollment. The updated standard should be applied to any study in which you intend to submit to the FDA not just those that haven't started enrollment. Please acknowledge.

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Merck provided a response in Amendment 21 (sequence 24) on April 8, 2024, as well as updated datasets for studies P003, P004, P005 and P006 (AE, CE, suppae, suppce). The revised datasets were not validated.

**In response to comment 1**, Merck acknowledges the request to provide this information more discretely in the datasets and agrees to do so in future studies. They also clarify that time is already required to be collected on the VAE eCRF for adverse events that begin on Day 1 to ensure appropriate categorization (after screening but before vaccination or after vaccination.

**In response to comment 2**, Merck acknowledges the request and has updated the AECAT category to use "Solicited Event Delayed Onset" for events with the same preferred term as a protocol specified solicited reaction and an onset of Day 6 or later. Merck also will use the AECAT= "Non-solicited reactogenicity event" for events that are not protocol specified solicited reactions but appear to be consistent with a local or systemic reactogenicity event.

| AECAT (8) | |
|---|---|
| CLINICAL AE | 815 |
| CLINICAL AE, IMMEDIATE ADVERSE EVENT | 3 |
| CLINICAL AE, SOLICITED EVENT DELAYED ONSET | 102 |
| CLINICAL AE, WORSENING OF MEDICAL HISTORY | 35 |
| INJECTION SITE AE | 42 |
| INJECTION SITE AE, SOLICITED EVENT DELAYED ONS... | 66 |
| LABORATORY AE | 1 |
| REACTOGENICITY, IMMEDIATE ADVERSE EVENT | 1 |

> *<u>Reviewer's thoughts</u>: Merck was unclear on how to categorize these events other than local events that occur at the injection site so they provided tables broken down into injection site as well as systemic. In the future only injection site reactions need to be flagged this way.*

**In response to comment 3**, Merck has updated the datasets and categories such that prespecified solicited reactions occurring within 30 minutes following vaccine administration (immediate reactions) are reported in CE with a CECAT of "Reactogenicity, Immediate Solicited Reaction" and CESTDTC including full dates (i.e., month, day, year, and time). Immediate reactions that are not prespecified terms are reported in AE with an AECAT including "Immediate Adverse Event". -EVINTX is not utilized if specific time has been provided in -STDTC for an event that begins on the day of vaccination. This change has been applied to the four studies (V116-003, V116-004, V116-005, and V116-006) included in the BLA.

**In response to comment 4**, Merck removed the two events of headache from the AE dataset and instead summarized them in the CE dataset as requested. Merck did not make changes to the FACE dataset as this domain contains participant's original daily report of solicited complaints in the eVRC and our company standard is that these records will be presented exactly as reported by the participant. Even with these changes they still disagreed that this is the best approach since the investigator utilized their medical expertise and judgement to assess each distinct event.

> *<u>Reviewer's thoughts</u>: Even though they didn't provide the data in FACE the changes are acceptable since Merck only uses CE to report the investigator assessment.*

**In response to comment 5**, Merck has included severity for the 38 events of pyrexia in the CE domain for V116-003. This change has also been applied to the other three studies (V116-004, V116-005, and V116-006) included in the BLA.

**In response to comment 6**, Merck has included severity for the 200 injection site swelling records and 169 injection site erythema records in the CE domain for V116-003. This change has also been applied to the other three studies (V116-004, V116-005, and V116-006) included in the BLA.

**In response to comment 7**, Merck has updated the records for the 47 events that were erroneously identified as ONGOING. The CEENRTPT has been updated based on the end date of each solicited event as reported in CEENDY for single dose studies or suppce SPDYRLEP (Stop Day Rel to Epoch) for multi-dose studies.

**In response to comment 8**, Merck acknowledges the request to update the FACE and CE domains so that the reactogenicity terms match. The internal technical standards will be updated for any study to be submitted to the Agency.

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**Final Conclusion**: the datasets are adequate for review.