BLA 125761 Data validation Report Summary and Subsequent follow-up with Emergent

Our Reference: BLA 125761 (studied under IND 14451)

Sponsor: Emergent Product Development

Product: Anthrax Vaccine Adsorbed, Adjuvanted with CpG7909 (AV7909; CYFENDUS)

Proposed Indication: for use as a post-exposure prophylactic vaccine following suspected or confirmed exposure to Bacillus anthracis in persons 18 through 65 years of age when administered in conjunction with the recommended antibacterial regimen.

Previous data standardization comments were provided on May 20, 2019, regarding the SDSP/CBER Appendix v1.0 for studies EBS.AVA.201, EBS.AVA.208, EBS.AVA.210 and EBS.AVA.212 submitted in amendment 100 on December 17, 2018, and the aCRF for EBS.AVA.212 submitted in amendment 111 on April 25, 2019; on September 23, 2019, in response to their SDSP question on not using CE to report reactogenicity data posed in amendment 127 (submitted August 1, 2019); on October 5, 2021 in response to the preBLA WRO question concerning the SDSPv3.0 submitted in amendment 222 on May 12, 2021.

Emergent is seeking licensure of AV7909 via FDA's Animal Rule pathway under 21 CFR Part 601, Subpart H. AV7909 is stockpiled in the United States Strategic National Stockpile for the purposes of emergency preparedness

On December 14, 2021, the sponsor submitted the part 1 of the biologics license application (BLA) to 125761/0 and on April 20, 2022, part 2 was submitted which included Module 5 and clinical datasets. The sBLA included reports for five clinical studies: V011, EBS.AVA.201, EBS.AVA.208, EBS.AVA.210 and EBS.AVA.212. Four clinical trial datasets were submitted (201, 208, 210, 212) and an ISS:

- **V011** - Phase 1 proof-of-concept – immunogenicity and safety of BioThrax and CpG7909 (AVA7909) – initiated Sep 27, 2004, date of report Jul 31, 2006

- **EBS.AVA.201** - Phase 1 parallel-arm, double-blind, randomized, placebo-controlled, dose-ranging clinical trial evaluating the safety, tolerability, and immunogenicity of AV7909 in healthy adults – initiated Dec 27, 2010 – date of report Oct 19, 2012

- **EBS.AVA.208 (DMID 11-0055)** - Phase 2 randomized, parallel-group, active-controlled, double-blind study to evaluate the safety and immunogenicity of AV7909 for post-exposure prophylaxis of anthrax using three immunization schedules and two dose levels in healthy adult volunteers – initiated Jan 16, 2013 – date of report Sep 24, 2014

- **EBS.AVA.210** - Phase 2 Drug-Vaccine Interaction Study to Examine Whether Co-administering AV7909 with Ciprofloxacin or Doxycycline Affects Antibiotic

Pharmacokinetics or AV7909 Immunogenicity in Healthy Adults – initiated Aug 22, 2019 – date of report Dec 24, 2020

- **EBS.AVA.212** - Phase 3 Randomized, Double-blind, Parallel-group Trial to Evaluate the Lot Consistency, Immunogenicity, and Safety of AV7909 for Postexposure Prophylaxis of Anthrax in Healthy Adults – initiated Mar 15, 2019 – date of report May 6, 2021 (addendum 3 report was Nov 10, 2022)

<u>General notes on the data to be found in their datasets and the endpoints/objectives of the phase 3 clinical trial:</u>

212 Endpoints included:
Primary:
- To demonstrate lot consistency following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults
- To demonstrate immunogenicity under the US FDA's Animal Rule on Day 64 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults
- To demonstrate immunogenicity using the US FDA's Animal Rule on Day 64 based on the non-inferiority of a two-dose schedule of AV7909 (Days 1 and 15) administered IM to the licensed three-dose schedule of BioThrax (Days 1, 15, and 29) administered SC in healthy adults
- To evaluate the safety of AV7909 in healthy adults following a two-dose schedule (Days 1 and 15) administered IM
Secondary:
- To demonstrate immunogenicity under the US FDA's Animal Rule on Day 29 following a two-dose schedule of AV7909 (Days 1 and 15) administered IM in healthy adults

210 and 212 Dataset issues unless otherwise noted

- o CE dataset– 3 categories (not applicable, potential AESI, reactogenicity)
  - start and end date/day not provided nor is duration
  - variables to flag ongoing (CEENTPT and CEENRTPT) were provided but no event was marked as ongoing – really problematic since can't identify without the dates of event
  - Fever was only reported on 21239 rows whereas all the other events had 21831 rows – each subject should have 1 row/event/vaccine administration (study 212)
  - Reactions occurring within 30 minutes were not flagged in CECAT with "Immediate Reaction" - Flagging immediate reactions was conveyed under IND on 10-12-21
  - Suppce not provided to report differences between investigator and subject

CETERM (13)	
ARM MOTION LIMITATI...	21831
BRUISING	21831
ERYTHEMA/REDNESS	21831
FEVER	21239
HEADACHE	21831
INDURATION	21831
ITCHING	21831
MUSCLE ACHE	21831
PAIN	21831
SWELLING	21831
TENDERNESS	21831
TIREDNESS	21831
WARMTH	21831

- TPT was not used appropriately in CE as it appears they are reporting the last day an event was collected (End Day 1 through 14 and 30M post-dose) (TPTREF has vaccination 1, 2 or 3) – if used it should be End Day 7 for these datasets (since the protocol included a 7 day assessment) - 30M post-dose was ok
  - FA dataset – they don't provide all the days of assessment which is what they are supposed to do. I'm wondering if they only reported the days that were reported in the diary and not the ones that were not. We made them correct their datasets under 125597/123 back in 2020 so they were well aware of this.
  - VS dataset–
    - QC of temperature recording is problem and/or don't match anticipated result in CE
      - (study 210) 19 readings range from 114 to 988 – because decimal point missing or C or F got switched – standardized result contained both F and C (these were not reported as fevers in CE)
      - (study 212) 1618 readings are 0 to 95.0 F (I wasn't quite sure where to cut it off for a normal reading) and 98 readings are 107.6 to 999.9 F - also subjects that appear to have a fever as evidenced by an elevated temperature in VS are not reported as having a fever in CE (look at subject US(b) (6) treatment 2)
  - AE dataset– 3 categories
    - reactogenicity events are in this dataset which are not always ongoing nor SAEs (but have AECAT= reactogenicity) – these results sometimes are in conflict with the result in CE (and FACE) – no explanation provided (look at US(b) (6) itching).

AECAT (3)	
Not Applicable	2313
Potential AESI	18
Reactogenicity	807

USUBJID	AETERM	AECAT	AESHOSP	AETOXGR	AESTDTC	AEENDTC	AESTDY	AEENDY	AERFTDTC
EBS.AVA.212/US(b) (6)	LEFT UPPER ARM ITCHING	Reactogenicity		1	2019-05-10	2019-05-15	30	35	2019-05-09T15:43

	USUBJID	CETERM	CEOCCUR	CETOXGR	CEDY	CETPT	CERFTDTC
504	EBS.AVA.212/US(b) (6)	ITCHING	N	Grade 0 (Absent)	1	30M POST-DOSE	2019-04-11T10:13
505	EBS.AVA.212/US	ITCHING	N	Grade 0 (Absent)	15	30M POST-DOSE	2019-04-25T17:48
506	EBS.AVA.212/US	ITCHING	N	Grade 0 (Absent)	29	30M POST-DOSE	2019-05-09T15:43
507	EBS.AVA.212/US	ITCHING	Y	Grade 2 (Modera...	20	END DAY 6	2019-04-25T17:48
508	EBS.AVA.212/US	ITCHING	Y	Grade 3 (Severe)	35	END DAY 7	2019-05-09T15:43
509	EBS.AVA.212/US	ITCHING	Y	Grade 1 (Mild)	14	END DAY 14	2019-04-11T10:13

	USUBJID	FATESTCD	FAOBJ	FAORRES	FASTRESC	FAEVAL	FADY	FATPT
1646	EBS.AVA.212/US(b) (6)	TOXGR	Itching	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	15	END DAY 1
1647	EBS.AVA.212/US	TOXGR	Itching	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	16	END DAY 2
1648	EBS.AVA.212/US	TOXGR	Itching	Moderate: Some ...	Grade 2 (Modera...	STUDY SUBJECT	17	END DAY 3
1649	EBS.AVA.212/US	TOXGR	Itching	Moderate: Some ...	Grade 2 (Modera...	STUDY SUBJECT	18	END DAY 4
1650	EBS.AVA.212/US	TOXGR	Itching	Moderate: Some ...	Grade 2 (Modera...	STUDY SUBJECT	19	END DAY 5
1651	EBS.AVA.212/US	TOXGR	Itching	Moderate: Some ...	Grade 2 (Modera...	STUDY SUBJECT	20	END DAY 6
1652	EBS.AVA.212/US	TOXGR	Itching	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	29	END DAY 1
1653	EBS.AVA.212/US	TOXGR	Itching	Moderate: Some ...	Grade 2 (Modera...	STUDY SUBJECT	30	END DAY 2
1654	EBS.AVA.212/US	TOXGR	Itching	Severe: Prevents ...	Grade 3 (Severe)	STUDY SUBJECT	31	END DAY 3
1655	EBS.AVA.212/US	TOXGR	Itching	Severe: Prevents ...	Grade 3 (Severe)	STUDY SUBJECT	32	END DAY 4
1656	EBS.AVA.212/US	TOXGR	Itching	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	33	END DAY 5
1657	EBS.AVA.212/US	TOXGR	Itching	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	34	END DAY 6
1658	EBS.AVA.212/US	TOXGR	Itching	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	35	END DAY 7
1659	EBS.AVA.212/US	TOXGR	Muscle Ache	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	1	END DAY 1

Another example (this one appears to be ongoing from info on the induration reported in AE, but not from CE):

	USUBJID	AETERM	AECAT	AESHOSP	AETOXGR	AESTDTC	AEENDTC	AESTDY	AEENDY
2358	EBS.AVA.212/US (b) (6)	1CM INDURATION RIGHT DELTOID (AT INJEC...	Reactogenicity		1	2019-06-11T09:09	2019-07-10T09:15	15	44

	USUBJID	CETERM	CEOCCUR	CETOXGR	CEDY	CETPT	CERFTDTC
10334	EBS.AVA.212/US (b) (6)	INDURATION	N	Grade 0 (Absent)	1	30M POST-DOSE	2019-05-28T10:53
10335	EBS.AVA.212/US	INDURATION	N	Grade 0 (Absent)	15	30M POST-DOSE	2019-06-11T09:09
10336	EBS.AVA.212/US	INDURATION	N	Grade 0 (Absent)	29	30M POST-DOSE	2019-06-25T10:28
10337	EBS.AVA.212/US	INDURATION	Y	Grade 1 (Mild)	21	END DAY 7	2019-06-11T09:09
10338	EBS.AVA.212/US	INDURATION	Y	Grade 1 (Mild)	35	END DAY 7	2019-06-25T10:28
10339	EBS.AVA.212/US	INDURATION	Y	Grade 1 (Mild)	7	END DAY 7	2019-05-28T10:53
10340	EBS.AVA.212/US	ITCHING	N	Grade 0 (Absent)	1	30M POST-DOSE	2019-05-28T10:53

	USUBJID	FATESTCD	FAOBJ	FAORRES	FASTRESC	FAEVAL	FADY	FATPT
29431	EBS.AVA.212/US (b) (6)	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	7	END DAY 7
29432	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	15	END DAY 1
29433	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	16	END DAY 2
29434	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	17	END DAY 3
29435	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	18	END DAY 4
29436	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	19	END DAY 5
29437	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	20	END DAY 6
29438	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	21	END DAY 7
29439	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	29	END DAY 1
29440	EBS.AVA.212/US	TOXGR	Induration	Mild: No interfer...	Grade 1 (Mild)	STUDY SUBJECT	30	END DAY 2
29441	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	31	END DAY 3
29442	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	32	END DAY 4
29443	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	33	END DAY 5
29444	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	34	END DAY 6
29445	EBS.AVA.212/US	TOXGR	Induration	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	35	END DAY 7
29446	EBS.AVA.212/US	TOXGR	Itching	Absent: Sympto...	Grade 0 (Absent)	STUDY SUBJECT	1	END DAY 1

- Of the 807 reactogenicity events in AE:
  - 130 caused the drug to be withdrawn (these can be reported in CEACN/CEACNOTH)
  - 3 discontinuations – 4 events – 1 of the events in (b) (6) was worsening of back pain which should not be considered reactogenicity
  - 0 SAEs
- Suppae – provides whether each AE is medically attended and AESI status
- Events (AEDECOD) that don't belong under reactogenicity as they are not solicited – injection site haemorrhage (2), injection site mass (12), injection site nodule? (1), muscoskeletetal procedural complication (66)
- Events that began during the assessment period should be reported in FACE and then summarized with the event in CE – follow the example provided (e.g., US(b) (6) headache on Day 2 and 3) otherwise the result in CE may be inaccurate or result in AE may be a duplication
- Some of the events may be ongoing but since not summarized with the subject data it is hard to tell, e.g., those events starting on D8 or D22 or D37

Analysis Datasets

- ADAE - directly from AE which normally would be ok but they include the reactogenicity events which may/may not match diary
- ADFACE –
  - multiple rows for each event because using FACE (Not CE) – each row is a day that was collected
  - duration may not be determined correctly based on this

- Appears to be duplicate days but with different severities (unclear where grade 3 came from)

	USUBJID	ADY	ATPT	PARAM	ATOXGR	EVAL
2240	EBS.AVA.212/US (b) (6)	18	END DAY 4	Itching (Study Subject)	Grade 2	STUDY SUBJECT
2241	EBS.AVA.212/US	19	END DAY 5	Itching (Study Subject)	Grade 2	STUDY SUBJECT
2242	EBS.AVA.212/US	20	END DAY 6	Itching (Study Subject)	Grade 2	STUDY SUBJECT
2243	EBS.AVA.212/US	20	END DAY 6	Itching (Study Subject)	Grade 2	STUDY SUBJECT
2244	EBS.AVA.212/US	29	END DAY 1	Itching (Study Subject)	Grade 1	STUDY SUBJECT
2245	EBS.AVA.212/US	30	END DAY 2	Itching (Study Subject)	Grade 2	STUDY SUBJECT
2246	EBS.AVA.212/US	31	END DAY 3	Itching (Study Subject)	Grade 3	STUDY SUBJECT
2247	EBS.AVA.212/US	32	END DAY 4	Itching (Study Subject)	Grade 3	STUDY SUBJECT
2248	EBS.AVA.212/US	33	END DAY 5	Itching (Study Subject)	Grade 1	STUDY SUBJECT
2249	EBS.AVA.212/US	34	END DAY 6	Itching (Study Subject)	Grade 1	STUDY SUBJECT
2250	EBS.AVA.212/US	35	END DAY 7	Itching (Study Subject)	Grade 0	STUDY SUBJECT
2251	EBS.AVA.212/US	35	END DAY 7	Itching (Study Subject)	Grade 3	STUDY SUBJECT
2252	EBS.AVA.212/US	1	END DAY 1	Pain (Study Subject)	Grade 1	STUDY SUBJECT

On June 7, 2022, the eDATA team discussed the validation results with the review committee for 125761. Two study datasets were validated – AVA.210 and AVA-212. Based on the validation results (beginning page 16 below) and a deeper dive into the study datasets, the following issues were identified:

Comments:

1. Regarding the CE dataset:
   a. Please update to include start and end date/day for each event if it occurred (CESTDTC, CESTDY, CEENDTC, CEENDY). If you are deriving the dates, you can provide an explanation in the cSDRG.
   b. Please update to include duration of each event during the solicited assessment period if it occurred (CEDUR). If you are deriving the duration, please provide an explanation in the cSDRG.
   c. In study EBS.AVA.212, fever was reported on 21239 rows in CE whereas all the other solicited events had 21831 rows. Each subject should have 1 row/event/vaccine administration. Please update the dataset to ensure that each subject has a result reported for occurrence of fever with either Y/N/null.
   d. CETPT (planned time point) was not used appropriately for the solicited events collected after the 30-minute post-dose assessment. Specifically, the time points reported in CE range from "End Day 1" to "End Day 14" and the protocol specified that each of the subjects have a 14-day assessment period, therefore CETPT should be "End Day 14." Please comment why a subject would have days of assessment that are less than "End Day 14." Please correct if other entered values are erroneous.
   e. As communicated in PreBLA WRO dated October 12, 2021, please ensure that solicited reactions occurring within 30 minutes are flagged in CECAT with "Immediate Reaction."
2. Regarding the AE dataset: You include 807 "Reactogenicity Events" in the AE dataset, most of which are not necessarily ongoing nor SAEs but have AECAT= reactogenicity. Please ensure that only ongoing or serious solicited events are included in AE. The other solicited events should be reported in FA (with FAEVAL= investigator) and summarized with the subject's diary data in CE. An example of how to report these events is provided in the appendix at the end of comments.

3. Regarding the FA dataset: It appears that this dataset does not provide all the days of assessment for each subject for each event per vaccine administration. For each of the 14 days of assessment each day of each event should be reported in this dataset even if the subject did not complete the diary on a given day (in which case the result would be null). As an example, subject 212/US(b) (6) had bruising reported on Days 1-7, 15-19 and 30-34. As per your protocol the subjects were to record the solicited events for 14 days after each vaccine administration, i.e., Days 1-14, 15-29 and 30-44. Please update the FA dataset accordingly.

4. Regarding the VS dataset:
   a. Many temperatures reported in the VS dataset are clearly not accurate/realistic, i.e., they range from 0 to 999.9. This may include 1716 recordings in study EBA.AVA.212 and 19 recordings in study EBS.AVA.210. Please clarify if the subject had the capability to correct an erroneous entry in the eDiary and if so, what that procedure included.
   b. Temperature results appear to be recorded in both °C and °F including in the standardized results. Please ensure that either °C or °F is used in the standardized results, but not both.
   c. In the cases where the temperature was potentially accurate and elevated, you did not indicate in CE that the subject had a fever (e.g., subject US(b) (6) treatment 2). Please ensure that all subjects with fevers are reported in the CE dataset.

5. The ADAE does not need to contain the solicited events as these should be incorporated into the ADFACE dataset (except if they are an SAE). Please correct.

6. ADFACE:
   a. The dataset contains multiple rows for each event/subject/administration in which it appears that each row constitutes each day reported in FA. Because of this structure, we believe duration may have been determined based on the total number of days that an event was reported instead of the total span of days, e.g., if an event occurred on Day 2 and 5 you may have tabulated the duration to be 2 days instead of 4 days. If so, the duration will need to be recalculated and clearly shown in a column of the dataset.
   b. Some results appear to be semi-duplications (see comment 6.iii. below).
   c. It is unclear where some of the results are derived from as they don't match results in the FACE dataset, e.g., subject 212/US(b) (6) appears to have two rows for itching on Day 35 (ADY), one with ATOXGR= Grade 0 and the other Grade 3 in ADFACE yet FACE has only the Grade 0 result reported. Please ensure that traceability is not an issue and that we can clearly follow the tabulations through to the analysis and finally to the Clinical Study Report and the tables/figures.

7. 411 of 1,379 (29.8%) screen failure subjects (in 212) and 2 of 119 (1.7%) (in 210) do not have information in Inclusion/Exclusion Criteria Not Met (IE) domain. Although it is not uncommon for some screen failures to not have information in the IE domain, when a significant portion is missing, it is difficult to exclude bias in subject selection. Please provide additional information on these subjects.

8. We note that a few events began after a subject's first vaccine exposure yet were reported in the Medical History (MH) dataset. Please provide additional details for

the events reported in MH for subjects EBS.AVA.212 -US(b) (6)   US(b) (6)
US(b) (6)   , US(b) (6)   and US(b) (6)   .

9. In LB some of the records where LBTESTCD=LBALL and LBSTAT=Not Done, are either duplicated or triplicated. Since the visit information is missing it is unclear why there are multiple results. Please explain.

10. In 212, it appears that other lab results in LB are also potential duplicates with one result providing the range of the original result and one result providing the actual result, e.g., 15-30/NPF is on one row and 24/NPF is on the next row. Please explain what each result represents, and which result is correct.

11. In study EBS.AVA.212, 2,429 of 205,000 (1.2%), and in study EBS.AVA.210, 11 of 9872 (0.1%) observations are missing Reference Range Upper Limit in Standard Units (LBSTNRHI). Please update the dataset to include an upper limit for each reference range. If no upper limit exists for a reference range, the value should be "null".

12. You provide two ADaM define.xml files in study EBS.AVA. 212: define-1.xml and define-2.xml, neither open correctly and both are named incorrectly. Please change the file name from 'define2-0-0-1.xsl' or 'define2-0-0-2.xsl' to 'define2-0-0.xsl' to get them to display properly and resubmit.

13. Two sets of ADaM datasets were provided for study EBS.AVA.212 to differentiate those that were created to exclude subjects from Site 1027 from any potential analysis population. Since it is hard to analyze with the datasets together in one folder, please separate into two folders and resubmit.

14. Please provide the algorithm for the actual derivation of SAFFL and ITTFL which were not included in the define.xml file for EBS.AVA.212.

On June 10, 2022, we requested an informal teleconference regarding Studies EBS.AVA.210 and EBS.AVA.212 clinical datasets. A teleconference was held on June 13, 2022, with Emergent. On June 14, 2022, we sent Emergent the above comments under IR#1 (along with an example showing how to report investigator obtained solicited reactogenicity events in the datasets). On June 15, 2022, Emergent requested a follow-up teleconference and provided an initial response to the IR on June 16, 2022, as amendment 2 (sequence 3). The amendment includes the document shared during the June 16, 2022, teleconference with Emergent.

In response to comment 1, Emergent will update the CE dataset as requested. They will update CETPT to be 'End Day 7'. If an event was ongoing past Day 7, the subjects were to continue to record the presence/absence of the event in the e-diary. Emergent also noted that the information used to create the flag for immediate reactions is included in the CETPT variable. When CETPT='30M POST-DOSE' the record represents an immediate reaction. They indicated they could include this specification in CECAT.

> *Reviewer's thoughts: we agree that CETPT should be set to "End Day 7." They need to confirm that if an event lasted beyond the 14 days of the final vaccination that it was assessed until resolution.*

In <u>response to comment 2</u>, Emergent states that if based on the investigator's assessment, the solicited event was considered 'serious' (i.e., Grade 4 or Grade 3 event that meets any of the SAE criteria), resulted in discontinuation of vaccination or withdrawal from the study, or remained unresolved for 14 days or more, it was to be recorded as an AE. Emergent considers these events from the AE dataset as important safety information and were recorded as per the protocol instructions.

Reviewer's thoughts: the approach is not adequate. Solicited events that begin during the 7-day assessment period should only be reported in the FACE dataset and summarized in the CE dataset; this includes assessments (scheduled and unscheduled) by the investigator. If they separate the event into the CE and AE datasets as proposed instead of reporting the event as a whole, data can potentially be duplicated, missed or the total duration inaccurate in the solicited events analysis. Some of the events may also be ongoing but since they are not summarized with the subject data it is hard to tell they are ongoing, e.g., those events starting on Day 8, 22 or 37. For these reasons, the solicited events should not be included in the AE dataset and should instead be summarized with the subject's data. They should use the example previously provided in the appendix sent as part of IR#1 on June 14, 2022. For those solicited events which caused discontinuation of vaccination or withdrawal from the study you can use CEACN and or CEACNOTH to flag them. Events that are not specifically solicited, e.g., injection site haemorrhage, should still be reported in AE; however, a flag other than "reactogenicity" should be used as that implies a solicited event to us. Please also ensure that the AE dataset contains ongoing events past Day 7 instead of Day 14. See additional discussion below on the resubmitted AE datasets.

In <u>response to comment 3</u>, Emergent stated that the protocol specified the e-diary to be continued for any ongoing event continuing past Day 7 until they had no event for 2 consecutive days. Because of this, not all subjects will have CE records complete through Day 14, but they will update the FA dataset for the 7 days post injection.

In <u>response to comment 4</u>, As part of the e-diary functionality, the subjects had the capability to correct a possibly erroneous entry via a prompt for the subject to verify the value before submitting it. While the ability to correct invalid body temperatures was possible prior to submitting, the responses still contained some unrealistic values submitted by the subjects. After submission of the data in the e-diary, there was no capability to correct the data. As per protocol training, if the temperature value met Grade 3 or 4 criteria, the site would have been notified via the e-Pro system and the site staff would contact the subject to inquire about values that met grade 3 or 4 criteria and would further assess the subject, if required. Regarding the unit, if it was noted as C, then the standardized result was unchanged from the raw data; if it was entered as F, then the temperature was converted to C for the standardized result. The issue with mixed temperature units were identified but unresolvable as they originated from the subject e-diaries. For this reason, the invalid body temperatures were handled in analysis. They will ensure that all subjects with fevers will be reported in the CE dataset.

Reviewer's thoughts: Their rationale is not valid regarding the standard unit. While I agree that the diary unit cannot be changed, the standard unit can be as it is generally derived (if changed).

In <u>response to comment 5</u>, As Emergent considers all data in ADAE important safety data, the ongoing and Grade 3/4 reactogenicity (as confirmed by the investigator) data should remain in the ADAE dataset for incorporation into the analyses.

Reviewer's thoughts: We disagree. The solicited reactogenicity data reported in CE is also safety data; however, it should not be included with the unsolicited data even if it is grade 3 or 4. It should be included in AE only if it is an SAE. They will need to acknowledge this for future submissions.

In <u>response to comment 6</u>, Presently duration is not derived in any SDTM or ADaM dataset. Per our response to 1, CEDUR will be derived, added to the CE dataset, and calculated as the span from start to end date. In ADFACE, there is an additional summary row that includes the worst toxicity grade for each event per assessment period and ADY for the summary record is set to the latest day in the assessment period. In this example, there is a row with ADY=35 for the individual day record (where itching was Grade 0) and the summary row also with ADY set to 35 as the latest day in the assessment period. The 'Grade 3' record in ADFACE in the example is the summary record (identified by the 'MAXIMUM' entry in the variable DTYPE). 'Grade 3' comes from the two Grade 3 records dated May 11 and May12, 2019 in FACE.

Reviewer's thoughts: The datasets were updated accordingly.

In <u>response to comment 7</u>, As presented in DS domain, these subjects were screen failed due to reasons other than eligibility criteria not met, including reasons such as withdrawal of consent, individual not reachable to come back for randomization, subjects screening period expired, etc.

Reviewer's thoughts: Explanation is acceptable. They additionally provided the reason for screen failure in updated suppdm datasets in amendment 6.

In <u>response to comment 8</u>, the events were related to newly diagnosed pre-existing conditions or procedures associated with pre-existing conditions; Subject US(b) (6) had a newly diagnosed Hashimoto's' disease, subject US(b) (6) had tooth extraction, subject US(b) (6) had a gum graft and frenectomy due to acquired ankyloglossia, and subject US(b) (6) was diagnosed of Type 2 diabetes mellitus. As a result, it was required that this be provided on the MH CRF.

In <u>response to comment 9</u>, in LB some records were created from unscheduled visits when only specific lab tests were requested by the Investigator. For the tests not done, the visit information is missing in the raw data, so these appear as duplicates.

Reviewer's thoughts: They provide an explanation, but they already have some records with "unscheduled" visits. My question really did not pertain to unscheduled visits as it appears many of them were to be done at screening. Nonetheless, an update to the data is not needed.

In <u>response to comment 10</u>, Some results are from Urinalysis RBC single test, some are from Urinalysis RBC test. We will update LBSCAT to distinguish between the tests.

> *Reviewer's thoughts: Although we only requested an explanation, Emergent provided a subcategory to distinguish the tests in LB (revised LB dataset submitted in amendment 6). They have included anti-HIV 1/2 (n=4998), Categorial value (n=923), continuous value (n=1669), HIV 1/2 confirmation (n=16), Macrocytosis (n=25) and Microcytosis (n=96). This also removes 7728 null subcategories.*

In <u>response to comment 11</u>, in LB the reference ranges are not available in the raw vendor data. However, for these tests with no upper limit, we will assign the value as 'null'.

> *Reviewer's thoughts: although not ideal they have included a new variable in LB called LBSTNRC (Reference range for char-results std unit) and provided a result of "null" if the limits are not available (revised LB dataset submitted in amendment 6).*

In <u>response to comment 12</u>, Due to the technical rejection criteria, Emergent is unable to provide the addendum 2 ADaM dataset files in an entirely separate STF as originally attempted. Emergent was instructed by the FDA CBER eSubmissions office to provide the Study EBS.AVA.212 Addendum 2 ADaM datasets under the primary STF within the existing ADaM dataset section.

> *Reviewer's thoughts: they need to change define2-0-0-1.xsl to define2-0-0.xsl and remove define2-0-0-2.xsl.*

In <u>response to comment 13</u>, Emergent would like to recommend that the addendum dataset be filed under the existing STF in the ADaM Legacy or the Miscellaneous dataset folder to correct the issue.

> *Reviewer's thoughts: We agree that the addendum datasets can be filed in the Miscellaneous dataset folder and removed from the ADaM dataset folder for Study EBS.AVA.212.*

In <u>response to comment 14</u>, Emergent provided the following: SAFFL= 'Y' if subject was randomized and received at least one vaccination; otherwise SAFFL= 'N'. ITTFL= 'Y' if the inform consent date, randomization date, and randomization ID for a subject are not missing; otherwise ITTFL= 'N'.

On June 27, 2022, a second round of comments was sent to Emergent (IR#3).

1. We agree that CEENTPT should be set to "End Day 7." Please confirm that if an event lasted beyond the 14 days of the final vaccination that it was assessed until resolution.
2. Upon further review of your preliminary response, we have determined that your approach is not adequate. <u>Solicited events</u> that begin during the 7-day assessment period should only be reported in the FACE dataset and summarized in the CE dataset; this includes assessments (scheduled and unscheduled) by the investigator. If you separate the event into the CE and AE

datasets as proposed instead of reporting the event as a whole, data can potentially be duplicated, missed or the total duration inaccurate in the solicited events analysis. Some of the events may also be ongoing but since they are not summarized with the subject data it is hard to tell they are ongoing, e.g., those events starting on Day 8, 22 or 37. For these reasons, the solicited events should not be included in the AE dataset and should instead be summarized with the subject's data. Please use the example previously provided in the appendix sent as part of IR#1 on June 14, 2022. For those solicited events which caused discontinuation of vaccination or withdrawal from the study you can use CEACN and or CEACNOTH to flag them. Events that are not specifically solicited, e.g., injection site haemorrhage, should still be reported in AE; however, we recommend that you use a flag other than "reactogenicity" as that implies a solicited event to us. Please also ensure that the AE dataset contains ongoing events past Day 7 instead of Day 14.

3. Your preliminary response does not seem to match our request under comment 12. To ensure that we can use the ADaM define.xml file for Study EBS.AVA.212 please change define2-0-0-1.xsl to define2-0-0.xsl and remove define2-0-0-2.xsl.

4. We agree that the addendum datasets can be filed in the Miscellaneous dataset folder and removed from the ADaM dataset folder for Study EBS.AVA.212.

On June 30, 2022, Emergent requested clarification for comment 2 IR3 (and IR1 solicited event comments). Specifically, they had 5 questions in which we provided responses on July 6, 2022.

A. For the specifically solicited events removed from the AE dataset and added to the CE domain in steps 1 and 2, do we also need to create matching FACE records (if they do not exist), for each day in the date range of the originally removed AE? If we are to add matching records to FACE, we assume that we need to pad 'NOT DONE' records in FACE after any inclusion in FACE from the original AE date range. Does CBER concur with this interpretation?

> *CBER Response: If a solicited event according to the investigator, e.g., occurred on days 2-5 it should be reported in FACE ideally on 4 rows with each row indicating the severity and the person reporting the event in FAEVAL (= study staff or investigator). You do not need to pad or include the other days (1, 6 and 7 in this example) in FACE*

B. The records to be newly added to the AE domain (solicited events continuing beyond Day 7 but not beyond Day 14) may not have all the attributes collected as part of the typical AE eCRF collection (e.g., relationship, outcome, action taken, etc.). Is CBER in agreement to leave these variables "null" in the corresponding AE record being newly created?

> *CBER Response: We agree that relationship, outcome and action taken, etc. do not need to be reported in AE for those solicited events that are ongoing. Please note that "ongoing" is any event that continues beyond day 7. If the event continues beyond day 14 it should still be included, e.g., if a subject has*

erythema that occurred from day 1 through day 21 it should be reported as such in both CE and AE with duration being 7 days in CEDUR and 14 days in AEDUR. In this example the highest level of severity during days 1 through 7 should be reported in CESEV/CETOXGR and the highest level of severity during days and the highest level of severity during days 8 through 21 should be reported in AESEV/ AETOXGR.

C. For the solicited events that continue past Day 7 but were not already in AE because they did not continue past Day 14, should Emergent remove the FACE records for Days 8-14 where OCCUR='Y'? Emergent's assumption is that we <u>should not</u>, but we would like to confirm.

> ***CBER Response****: You are correct. Daily records of solicited reactogenicity events should remain in FACE. This would include any days up to time of resolution of an ongoing solicited event.*

D. The OVRR guidance clearly states that the CEENDTC should be the end date associated with the full duration of the event past Day 7 and into the AE domain and that we should set CEDUR to be only the period during the assessment interval through Day 7, with CEENRTPT noted as 'Ongoing' for these newly revised cases. Does CBER concur with this interpretation?

> ***CBER Response****: We concur with this interpretation. Please see response above in 2B regarding duration.*

E. For item #4 above (events that are not specifically solicited), Emergent will update the AE dataset to assign AECAT= 'Un-prespecified Solicited Events' for such records. If CBER prefers that Emergent use a different term, would you kindly indicate which term is preferred?

> ***CBER Response****: We recommend using "Non-solicited reactogenicity event."*

On July 19, 2022, Emergent submitted amendment 6 (sequence 4). Emergent made the changes outlined below to the submission backbone:
- The Study EBS-AVA-212 Addendum ADaM datasets have been deleted from the primary ADaM dataset folder and resubmitted as new in a standalone Study Tagging File (STF) called "EBS-AVA-212 Addendum Study Tagging File". This change is made to resolve Comment 13 of IR #1. It contains all of the original tabulation and analysis datasets.
- To resolve rejection criteria validation error 1734, which states TS XPT file with the study start date must be included in every STF in Section 5.3.5.1. A standalone STF called EBS-AVA-212-Addendum includes an identical copy of the Study EBS-AVA-212 SDTM dataset package originally provided in the primary Study EBS-AVA-212 STF. Additionally, to resolve another aspect of validation error 1734 the TS dataset file in EBS-AVA-212- Addendum STF is modified to include the SPREFID data field.

The amendment includes the following amended datasets: Study EBS.AVA.210 – LB, suppdm, supplb, and accompanying define package and Study EBS.AVA.212 – TS, LB and suppdm and accompanying define package. These datasets were validated, and results provided on August 6, 2022. The results were essentially the same as the initial validation.

On September 9, 2022, amendment 15 (sequence 13) was received. In this amendment, Emergent submitted responses to CBER Comments 1, 2, 3, 4(iii), 5 and 6(i) to complete the requests from IR #1 and all CBER Comments provided in IR #3. Due to the changes made to SDTM.LB to address FDA Comments 9 through 11, ADLB dataset for both studies were run based on the revised SDTM.LB. Emergent has also included the EBS.AVA.212 Addendum 2 ADaM datasets for ADAE, ADFACE and ADLB which excludes Site 1027 from the analysis. Several datasets for both studies 210 and 212 were revised and resubmitted in this amendment including: CE, suppce, FACE, AE, suppae, ADAE (and addendum for 212), ADFACE and ADLB. These datasets were also validated, and results were obtained on December 2, 2023.

The following was noted in looking at the revised datasets for 212:

- AE dataset – now contains 3822 records (originally had 3138 – 684 record difference – numbers add up)

AECAT (5)	
Non-solicited reactogenicity event	21
Not Applicable	2313
Potential AESI	18
Reactogenicity	263
Solicited events added to AE domain	1207

  - o the "solicited events added to the AE domain" from FACE/CE are literally just added they don't put it together -see example

USUBJID	AETERM	AEDECOD	AECAT	AESER	AETOXGR	AESTDY	AEENDY	AETPTREF
EBS.AVA.212/US (b) (6)	BRUISING	Injection site brui...	Solicited events a...		1	1	11	Dose 1
EBS.AVA.212/US	INDURATION	Injection site ind...	Solicited events a...		2	2	14	Dose 1
EBS.AVA.212/US	INDURATION AT ...	Injection site ind...	Reactogenicity	N	1	14	20	Dose 1
EBS.AVA.212/US	ITCHING	Injection site prur...	Solicited events a...		1	7	9	Dose 1

  - o Suppae – now contains 6523 records (from 6362)
- CE dataset – now contains 288249 records (from original 283211)
  - o CETPT variable was removed
  - o CESTDY/CESTDTC and CEENDY/CEENDTC were added
  - o CECAT – immediate reaction was added (n=147953) (in addition to reactogenicity) – most of these events were already present and were

USUBJID	CETERM	CECAT	CEO C...	CETOXGR	CES TDY	CEE NDY	CETPTREF	CEENRTPT
EBS.AVA.212/US (b) (6)	INDURATION	REACTO...	Y	Grade 1 (...	2	14	VACCINATION 1	ONGOING
EBS.AVA.212/US	INDURATION	REACTO...	Y	Grade 2 (...	16	20	VACCINATION 2	
EBS.AVA.212/US	INDURATION	REACTO...	Y	Grade 2 (...	29	35	VACCINATION 3	

    differentiated from the other events by CETPT= 30M Post-Dose (n=147361)
  - o CEENTPT was changed from "End day 14" to "End day 7" - see new example of induration (AE dataset example also provided for this subject) – as we are changing our requirements for ongoing events we will not request that they revise again – the CE dataset (or FACE) should have the most accurate records
  - o CEDUR was added – it was reported as per the guidance (with AEDUR containing the remaining duration)
  - o CEACN was added to report "Dose not changed" and "Drug Withdrawn"
  - o Suppce dataset included now – see the 2 QLabels

QLABEL (2)	
Duration reported by subject	343
Severity/Intensity reported by subject	191

    - o Fever – 252 records now where CEOCCUR=Y (previously it was 240)

- FACE dataset – now contains 1009149 records (from original 839579) – this was due to adding records with null results – they still are missing some null results as the records are not equal
  - FAEVAL records are now 2689 (initially they had 130)
- ADAE – contains all ongoing events (including the duplications) and unsolicited events – number of rows = updated AE dataset rows
- ADFACE – 1209433 records in addendum dataset
  - 546900 records in non-addendum – data is missing as the original FACE dataset has 1009149 records – it appears that any subjects after US(b) (6) were removed (FACE also has subjects US(b) (6) through US(b) (6) and they don't include results that are null in FACE – however the in-clinic reactogenicity data is reported

FATPT (15)	
30M POST-DOSE	130
END DAY 1	140480
END DAY 2	140796
END DAY 3	140820
END DAY 4	140741
END DAY 5	140663
END DAY 6	140594
END DAY 7	140537

In response to comment 1 IR#3, Emergent confirmed that events lasting beyond the 14 days of the final vaccination were assessed by the Principal Investigator or designee at the next scheduled visit to fully assess the reactogenicity event and followed-up on the event until resolution.

A major amendment was implemented on September 9, 2022.

After reviewing the responses in amendment 2 and 15 and the updated datasets, the following additional comments were sent to Emergent on June 2, 2023:

1. In <u>response to comment 4 in amendment 2</u>, you indicate that for the e-diary functionality, the subjects had the capability to correct a possibly erroneous entry before submitting it. Regarding the unit, you indicate that if it was noted as C, then the standardized result was unchanged from the raw data; and if it was entered as F, then the temperature was converted to C for the standardized result. The issue with mixed temperature units were identified but unresolvable as they originated from the subject e-diaries. For this reason, the invalid body temperatures were handled in analysis. *While we agree that the original temperature and original unit obtained from the diary cannot be changed, the standard temperature and unit in the tabulation dataset can be as it is generally derived (if changed). Please acknowledge and confirm that this will be implemented in any future submission.*

2. In <u>response to comment 5 in amendment 2</u>, you indicated that you consider all data in ADAE important safety data, and as such the ongoing and Grade 3/4 reactogenicity (as confirmed by the investigator) data should remain in the ADAE dataset for incorporation into the analyses. *We disagree. The solicited reactogenicity data reported in CE is also safety data; however, it should not be included with the unsolicited data even if it is grade 3 or 4. It should be included in AE only if it is an SAE. Please acknowledge and confirm that this will be implemented for any future submission.*

3. Please note that we no longer require that ongoing solicited reactogenicity events be reported in AE. The CE dataset is the only dataset that needs to have the summary of these events. The entire duration should be reported in CEDUR. This does not need to be implemented in these datasets, but we wanted to make you aware of this change.

A response was received on July 3, 2023 (amendment 56, sequence 54). Emergent acknowledged the advice and agrees to implement in future submissions.

Final conclusion: The datasets were adequate for review after they revised the datasets.