Data Fitness Findings Report

BLA125761

Emergent BioSolutions, Inc, May 2022

Findings	Notes
EBS.AVA.210 **Title:** *A Phase 2 Drug-Vaccine Interaction Study to Examine Whether Coadministering AV7909 with Ciprofloxacin or Doxycycline Affects Antibiotic Pharmacokinetics or AV7909 Immunogenicity in Healthy Adults*	

Document / Standard	Version	Notes
annotated CRF		Seems fine
SDTM Implementation Guide	SDTM-IG v3.2	
SDTM Controlled Terminology	2020-05-08	
SDTM define.xml	V2.0	Derivations reference raw data not received. For example, for RFENDTC: Set to latest date and time from EX1.EX1STDAT_RAW and EX1STTIM, EX2.EX2STDAT_RAW and EX2STTIM, EX3.EX3STDAT_RAW and EX3STTIM, EX4.EX4STDAT_RAW and EX4STTIM, EX5.EX5STDAT_RAW and EX5STTIM, EOMED1. EOMEDTMSTP_RAW and EOMED3, EOMED2. EOMED2TMSTP_RAW and EOMED2_3, ORALLATE. ORALLATEQ1 and ORALLATEQ2. For ACTARMCD = 'NOTTRT' set to the latest DS.DSSTDAT_RAW date. Set to null for screen failures or unassigned subjects.
Medications Dictionary	WHOGLOBAL_202003_B3	
Medical Events Dictionary (MedDRA)	V22.0	
SDTM Reviewer's Guide	PhUSE template	File named 'sdrg.pdf' instead of 'csdrg.pdf'

EBS.AVA.212

Title: *A Phase 3, Randomized, Double-blind, Parallel-group Trial to Evaluate the Lot Consistency, Immunogenicity, and Safety of AV909 for Postexposure Prophylaxis of Anthrax in Healthy Adults.*

Document / Standard	Version	Notes
annotated CRF		Seems fine
SDTM Implementation Guide	SDTM-IG v3.2	
SDTM Controlled Terminology	2019-06-28	
SDTM define.xml	V2.0	Derivations reference raw data not received. For example, for RFSTDTC: Set to date part of CDM.RND.RANDOMIZED_AT_RAW and concatenated with the converted time portion of RANDOMIZED_AT_RAW to local 24 hour time using the file EBS.AVA.212_Time Zones by Site_29Sep2020.xlsx merged onto to RND by SITE. If timezone=Eastern then convert time -18000, else if timezone=Central then convert time-21600, else if timezone=Mountain then convert time -25200, else if timezone=Pacific then convert time - 28800 and format time in HH:MM:SS.
ADaM define.xml	V2.0	There are two ADaM define.xml files: define-1.xml and define-2.xml. Neither open correctly because they provided two stylesheet files, but both are named incorrectly. You need to 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.
Medications Dictionary	WHOGLOBAL_202003_B3	
Medical Events Dictionary (MedDRA)	V22.0	
SDTM Reviewer's Guide	PhUSE template	Seems fine

ISS

Title: *AV7909 BLA - 2021*

Document / Standard	Version	Notes
annotated CRF		N/A
SDTM Implementation Guide	SDTM-IG v3.2	
ADaM Implementation Guide	ADaM-IG v1.1	
SDTM Controlled Terminology	2020-06-26	
SDTM define.xml	V2.0	
ADaM define.xml	V2.0	
Medications Dictionary	WHODD GLOBALB3Mar21	
Medical Events Dictionary (MedDRA)	V24.1	
Reviewer's Guides	PhUSE template	

From ADRG: All AV7909 treatment groups with all regimen and formulation in the four AV7909 clinical studies (EBS.AVA.201, EBS.AVA.208, EBS.AVA.210, and EBS.AVA.212) will be pooled and presented in the ISS.

Data Issues	

Two sets of ADaM datasets provided for study EBS.AVA.212
• All provided in the same folder, differentiated with '-1' or '-2' appended to the filename
    ○ For example, there is an ADAE-1.xpt dataset and an ADAE-2.xpt dataset. There are two versions of every ADaM dataset
    ○ The ADDD-1.xpt dataset is exactly the same as ADDD-2.xpt
    ○ For the other datasets, it seems that the datasets are the same, except the values differ for the following variables:
        ▪ SAFFL
        ▪ ITTFL
        ▪ PPROTFL
        ▪ COMP12FL
        ▪ RANDFL
        ▪ SCRNFL
        ▪ IMMUFL
        ▪ COMPLTFL
        ▪ COMPLSFL
        ▪ CONMEDFL
    ○ Note that they do not list an actual derivation in the define.xml for these variables. For example:
        ▪ The algorithm listed in the define.xml for SAFFL is: "Safety Population Flag"
        ▪ The algorithm listed in the define.xml for ITTFL is: "Intent-To-Treat Population Flag"
        ▪ Etc.
    ○ Therefore, it is not possible to tell (as far as I can see) what the different derivations between the two versions of the datasets are.
    ○ From the adrg-2.pdf file: This document corresponds to a second set of ADaM files that were created to exclude subjects from Site 1027 from any potential analysis population. Due to concerns associated with Site 1027, a decision was made in Nov2021 to create a second version of ADaM files that would retain all data for Site 1027 but exclude those records from any outputs produced from the associated set of ADaM files. This convention allowed all source data from SDTM to be included in ADaM files for transparency. <mark>All populations variables for Site 1027, including the screened population flag, were set to 'N' in ADSL and all subsequent ADAM datasets were run using the modified ADSL file. Records for subjects not associated with Site 1027 were confirmed as unchanged from the original ADaM.</mark>
	Potentially
	Critical Issue

Inconsistent coding of the exact same AETERM across/within studies • Affects two terms across the two studies	

aeterm	aellt	aedecod	aehlt	aehlgt	aebodsys	STUDYID	count_of_aes	meddrav
ELEVATED BLOOD GLUCOSE	BLOOD GLUCOSE INCREASED	BLOOD GLUCOSE INCREASED	CARBOHYDRATE TOLERANCE ANALYSES (INCL DIABETES)	METABOLIC, NUTRITIONAL AND BLOOD GAS INVESTIGATIONS	INVESTIGATIONS	EBS.AVA.212	2	22.0
ELEVATED BLOOD GLUCOSE	HYPERGLYCEMIA	HYPERGLYCAEMIA	HYPERGLYCAEMIC CONDITIONS NEC	GLUCOSE METABOLISM DISORDERS (INCL DIABETES MELLITUS)	METABOLISM AND NUTRITION DISORDERS	EBS.AVA.210	1	22.0
FEVER	POST PROCEDURAL FEVER	POST PROCEDURAL FEVER	NON-SITE SPECIFIC PROCEDURAL COMPLICATIONS	PROCEDURAL RELATED INJURIES AND COMPLICATIONS NEC	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	EBS.AVA.210	2	22.0
FEVER	FEVER	PYREXIA	FEBRILE DISORDERS	BODY TEMPERATURE CONDITIONS	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	EBS.AVA.212	5	22.0

Inconsistent coding of the exact same AETERM in ISS
- Affects three terms across the two studies

aeterm	aellt	aedecod	aehlt	aebodsys	STUDYID	count_of_aes	meddrav
ELEVATED BLOOD GLUCOSE	BLOOD GLUCOSE INCREASED	BLOOD GLUCOSE INCREASED	CARBOHYDRATE TOLERANCE ANALYSES (INCL DIABETES)	INVESTIGATIONS	EBS.AVA.212	2	24.1
ELEVATED BLOOD GLUCOSE	HYPERGLYCEMIA	HYPERGLYCAEMIA	HYPERGLYCAEMIC CONDITIONS NEC	METABOLISM AND NUTRITION DISORDERS	EBS.AVA.210	1	24.1
FEVER	FEVER	PYREXIA	FEBRILE DISORDERS	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	AVA.208	2	24.1
FEVER	FEVER	PYREXIA	FEBRILE DISORDERS	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	EBS.AVA.201	12	24.1
FEVER	FEVER	PYREXIA	FEBRILE DISORDERS	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	EBS.AVA.212	5	24.1

FEVER	POST PROCEDURAL FEVER	POST PROCEDURAL FEVER	NON-SITE SPECIFIC PROCEDURAL COMPLICATIONS	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	EBS.AVA.210	2	24.1	
GENERALIZED MUSCLE ACHES	GENERALIZED MUSCLE ACHES	MYALGIA	MUSCLE PAINS	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	EBS.AVA.201	1	24.1	
GENERALIZED MUSCLE ACHES	MUSCULOSKELETAL PROCEDURAL COMPLICATION	MUSCULOSKELETAL PROCEDURAL COMPLICATION	MUSCULOSKELETAL PROCEDURAL COMPLICATIONS	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	EBS.AVA.210	1	24.1	

CEENDTC not provided for reactogenicity data
- Affects both studies
- Unable to determine if events should be considered adverse events or not