STATISTICAL ANALYSIS PLAN

CDPH
Protocol rBV A/B-CL-002
Tolerability and Immunogenicity of a Single 40-µg Dose of Recombinant Botulinum Vaccine A/B (rBV A/B) for the Production of BabyBIG® in Volunteers with Existing Botulinum Immunity

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Title: **Tolerability and Immunogenicity of a Single 40-µg Dose of Recombinant Botulinum Vaccine A/B (rBV A/B) for the Production of BabyBIG® in Volunteers with Existing Botulinum Immunity**

Protocol: **rBV A/B-CL-002**

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LIST OF ABBREVIATIONS

AE	adverse event
BabyBIG	CDPH proprietary name for Botulism Immune Globulin Intravenous (Human) (BIG-IV)
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
DSMB	data and safety monitoring board
eCRF	electronic case report form
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NAC	neutralizing antibody concentration
NOCI	new onset chronic illness
PBT	pentavalent botulinum toxoid
PP	per protocol
rBV A/B	recombinant botulinum vaccine A/B
SAE	serious adverse event

1.0 STUDY INTRODUCTION

1.1 BACKGROUND

Botulism Immune Globulin Intravenous (Human) (BIG-IV; BabyBIG®) has been demonstrated to significantly shorten hospital stay and improve outcomes in infant botulism patients. It is currently produced from antibodies collected from persons with existing botulinum immunity including individuals previously immunized with investigational pentavalent botulinum toxoid (PBT) for occupational protection and/or boosted with investigational recombinant botulinum vaccine A/B (rBV A/B).

Previously, PBT was distributed through the Centers for Disease Control and Prevention (CDC) under BB-IND-0161 for occupational safety. The toxoid was administered to naïve recipients and was also administered as a booster in persons who had been previously immunized. PBT-immunized individuals who have circulating antibodies against botulinum toxin type A and type B are eligible to donate plasma for manufacture of BabyBIG. Donated plasma is fractionated and treated to yield a purified immunoglobulin G product that provides passive immunity to patients with infant botulism.

However, the CDC no longer provides investigational PBT for immunization of laboratory workers at risk for occupational exposure to botulinum serotypes A, B, C, D, and E. Specifically, on the basis of evidence of declining immunogenicity, increasing reactogenicity, and the age of the product, the CDC ceased distribution of PBT after 30 November 2011. Thus, a new immunogen against botulinum toxins is needed.

A recombinant botulinum vaccine for the toxin serotypes A and B (rBV A/B) has been developed and is being proposed as a replacement immunogen for boosting individuals who previously received the PBT for occupational protection. This study is the second phase 2 study under IND 15155 being conducted by the California Department of Public Health (CDPH) to determine if rBV A/B will stimulate production of neutralizing antibodies against botulinum toxin types A and B in participants previously immunized with PBT (or PBT and rBV A/B). Participants with a range in neutralizing antibody titers against the toxin types would be candidates for plasma collection for BabyBIG production under IND 15155.

This protocol has as its ultimate goal the production of additional lots of the approved orphan drug BabyBIG for the treatment of the rare disease infant botulism. To enable production of BabyBIG, a group of high-titer immunized persons are needed who are willing to donate their hyperimmune plasma as a starting agent (i.e., Source Plasma) for BabyBIG. This protocol is designed to determine botulinum toxin type A and type B neutralizing antibody levels in healthy participants who were previously immunized with PBT (or PBT and rBV A/B) for occupational protection and who receive rBV A/B (or an rBV A/B boost). A Phase 2b study conducted by CDPH (rBV A/B-CL-001) from 2013 to 2015 demonstrated a single 40-µg dose of rBV A/B was well tolerated and resulted in a significant increase in neutralizing antibodies against botulinum toxins type A and B in participants previously immunized with PBT. The proposed study (rBV A/B-CL-002) will continue to evaluate the immunogenicity and tolerability of a single dose of the rBV A/B vaccine in this population of individuals with existing botulinum immunity. This study design is similar to rBV A/B-CL-001. However, in this study a single 40-µg dose of rBV A/B will be used to stimulate the production of neutralizing antibodies against botulinum toxin type A and type B in participants that are either rBV A/B naïve or in participants that volunteered for the rBV A/B-CL-001 clinical study and received one dose of rBV A/B.

1.2 STUDY OBJECTIVES

1.2.1 Immunogenicity

The immunogenicity objective of this study is to evaluate the effects of a single 40-µg dose of rBV A/B on botulinum toxin type A and type B neutralizing antibody concentrations (NAC) over a 12-week period following vaccination in participants previously immunized with PBT (or PBT and rBV A/B) for occupational protection.

1.2.2 Safety

The safety objective of this study is to obtain safety information during the 12-week study period and at 6 months post-vaccination on the use of rBV A/B in a population of participants previously immunized with PBT (or PBT and rBV A/B) for occupational protection.

1.2.3 Exploratory

The exploratory objective of this study is to collect source plasma from participants that contains neutralizing antibodies against botulinum toxin type A and type B for the production of BabyBIG.

1.3 STUDY DESIGN

This will be an open-label, uncontrolled study to evaluate the safety and immunogenicity of a single intramuscular injection of 40 μg of rBV A/B in participants who were previously immunized with PBT (or PBT and rBV A/B) for occupational protection. Participants will receive the rBV A/B injection and may elect to undergo plasmapheresis at a maximum of two times per week for up to 12 weeks post-vaccination. Participants continue plasmapheresis for up to 14 weeks post-vaccination as long as they continue to meet source plasma donor acceptance criteria.

The study period is defined as the 12-week period that includes the clinic visits and plasmapheresis visits. The study period will end at Week 4 for participants who opt not to participate or who have been determined to be ineligible for donation for the entire study. Participants undergoing plasmapheresis will also have an additional hematology specimen collected at Week 4 and will have a final on-site study visit at Week 12. All participants will have a final phone call for safety follow-up at Week 26.

1.4 SAMPLE SIZE

No formal power calculations were performed for this study. The sample size will consist of up to 50 participants. On the basis of prior Sponsor-Investigator experience, this sample size is considered adequate for fulfilling the study objectives.

1.5 RANDOMIZATION

This is an open-label study, and no randomization or blinding will take place.

1.6 STUDY PROCEDURES

The study will begin with a 7-day screening period (Days -7 to -1), during which participant eligibility will be determined. Screening must occur 1 to 7 days before the Vaccination Visit (Day 0).

Participants will enter either a 4-week treatment period (for non-plasma donors) or a 12-week treatment period (for plasma donors). At the Vaccination Visit (Day 0), the first day of the treatment period for all subjects, participant eligibility will be reviewed and blood collection will be performed to determine baseline NAC. After these assessments, a single rBV A/B injection will be administered to stimulate the production of antibodies against botulinum toxin type A and type B. Safety assessments will be performed before and after the injection, and a diary will be distributed to the participant to record injection site information, systemic reactions, and concomitant medications over the next seven days.

Study personnel will call all participants at Week 1 (± 3 days) to review the diary, injection site reactions, and any potential serious adverse events (SAEs) or new onset chronic illnesses (NOCIs) occurring over the past week.

Participants who receive the rBV A/B vaccination may elect to participate as source plasma donors if they meet the donor eligibility criteria of the sponsor-approved licensed source plasma collection site. Participants who elect to donate source plasma may begin following the Week 1 safety phone call and may donate up to twice per week through Week 12, with the possibility of continuing through Week 14 post-vaccination if they continue to meet source plasma donor eligibility criteria. The assessments to be completed at the visits to the plasma collection center are listed in the protocol and include a blood collection for NAC determination.

Safety assessments for non-plasma donors are scheduled on Week 0, Week 1 (± 3 days) (by phone), and Week 4 (± 3 days) (final on-site visit). Safety assessments for plasma donors are scheduled at Week 0 with follow-up phone calls at Weeks 1 (± 3 days), 4 (± 3 days) and 10 (± 3 days), and a final on-site study visit at Week 12 (± 7 days) to assess general health status and query for the interim occurrence of SAEs or NOCIs, if any.

Within 1 week of Week 26, site personnel will contact all participants by phone to assess their general health status. Interim occurrence of any SAEs or NOCIs will be queried for and recorded. Any concomitant medications used to treat SAEs or NOCIs will be recorded.

NAC sample collections are required for all participants at Week 0 and Week 4. For plasma-donating participants, NAC sample collection is required with each donated unit.

2.0 STUDY POPULATIONS

For this study, up to 50 participants are anticipated to be enrolled. Eligibility will be established by the investigator(s) on the basis of the inclusion and exclusion criteria.

2.1 DEFINITIONS OF POPULATIONS FOR ANALYSIS

2.1.1 Immunogenicity Population

The immunogenicity population will include all participants who receive the vaccine dose, have a baseline NAC, and have at least one post-vaccination immunogenicity assessment up to and including 4 weeks after administration of rBV A/B.

This population will be used for all immunogenicity endpoints.

2.1.2 Per Protocol Population

The per protocol (PP) population will include all participants who receive the vaccine, have a baseline NAC, and have the relevant immunogenicity assessments completed within the protocol-specified timelines (including visit windows) for the time point(s) being summarized and who do not have any major protocol violations expected to affect immunogenicity.

For all summaries and analyses using the PP population, values collected outside the visit windows and values associated with a major protocol violation expected to affect immunogenicity will be excluded from the specific time point being summarized or analyzed.

This population will be used in the case that any sensitivity analyses are deemed necessary.

2.1.3 Safety Population

The safety population will include all participants enrolled into the study who receive the vaccine dose and have at least one post-baseline safety assessment [this assessment can include a response from a participant that no adverse events (AEs) occurred].

2.1.3 Plasma-Donating Population

The plasma-donating population will include all participants who receive the vaccine and donate at least one plasma unit. This population will be used for the exploratory endpoint described in Section 9.0.

2.2 PROTOCOL VIOLATIONS

Determination of major protocol violations expected to affect immunogenicity for each participant (and hence affecting the PP population) will be performed by the Sponsor-Investigator before reviewing the immunogenicity data for the applicable participant.

All protocol deviations will be documented and listed in an appendix listing of the clinical study report.

3.0 SPECIFICATIONS FOR STATISTICAL ANALYSES

3.1 GENERAL INFORMATION AND DATA COLLECTION METHODS

All statistical analyses will be performed and data displays will be created using SAS® Release 9.4 or newer.

Summary tables of data will be provided as appropriate, showing the number of participants with non-missing data (n), mean, standard deviation, median, minimum and maximum for continuous variables, and counts and percentages for categorical variables. Appendix listings will also be provided for the clinical study report.

Data will be recorded in electronic case report forms (eCRFs). Clinical laboratory data and NAC data will come from external vendors.

For all summaries and analyses, including those involving change from baseline endpoints or baseline covariates, a participant's baseline value will be defined as the last non-missing value prior to vaccination.

3.2 ENDPOINTS

3.2.1 Immunogenicity Endpoints

The primary immunogenicity endpoint is the proportion of participants achieving a four times or greater increase in NAC by Week 4 compared with Week 0. A positive response will be defined as achieving this level of increase in at least 50% of the participants for botulinum toxin type A and type B.

The secondary immunogenicity endpoints are as follows:

- The proportion of participants achieving a two times increase in the area under the plasma concentration-time curve between Week 0 and Week 12 in NAC in comparison to a straight-line extension of the Week 0 NAC to Week 12. A positive response will be defined as achieving this level of increase in at least 50% of the participants for botulinum toxin type A and type B.

- The proportion of participants achieving a three times or greater increase in NAC by Week 4 compared with Week 0. A positive response will be defined as achieving this level of increase in at least 50% of the participants for botulinum toxin type A and type B.

3.2.2 Safety Endpoints

Safety endpoints will be as follows:

- Frequency of injection site reactions and systemic reactions that are characterized as severe during the 0-7 day diary collection period
- Frequency of injection site reactions and systemic reactions that are characterized as SAEs
- Participant incidence of treatment-related SAEs
- Participant incidence of serious NOCIs
- Clinically significant changes from baseline health resulting in SAEs
- Clinically significant changes in hematology between screening and Week 4 resulting in severe or serious adverse events

3.2.3 Exploratory Endpoints

The exploratory endpoint will be the volume of source plasma containing neutralizing antibodies against botulinum toxin type A and type B collected by plasmapheresis for use in BabyBIG manufacture.

3.3 METHODS FOR HANDLING DROPOUTS AND MISSING DATA

No imputation will be made for missing data, with the exception that partially missing dates will be imputed to the least favorable date. For example, AEs with partially missing dates that occur in the same month as dose administration will be considered treatment emergent.

Participant dropouts will not be replaced.

3.4 VISIT WINDOWS

Immunogenicity values (NAC values) will be assigned to weeks/visits according to the visit windows listed in Section 7.3. For displays using the per protocol population, immunogenicity assessment values which are collected outside the visit windows for the relevant time points will be excluded from per protocol analyses.

Safety values will be evaluated and displayed as belonging to the intended visit, regardless of the actual study day on which they were collected.

3.5 DISPLAY SPECIFICATIONS

Displays will be produced by using the Courier New 8-point font. Headers will also be in Courier New 8-point font.

All displays are intended to be printed as landscape on 8.5-in × 11-in paper. The top and bottom margins will be 0.50 in, and the left and right margins will be 0.75 in.

Relative to the number of digits after the decimal in the original data, summary statistics will have the following number of digits after the decimal: mean, median, and percentiles - one more digit; standard deviation and standard error - two more digits; minimum, maximum, and range - same number of digits. Summary statistics will not exceed four digits after the decimal. Some laboratory parameters or other data may require judicious deviation from this rule.

Percentages will be displayed with one digit after the decimal.

3.6 DATA AND SAFETY MONITORING BOARD

A data and safety monitoring board (DSMB) meeting will take place quarterly throughout the study and as needed. Details regarding the displays to be provided for the DSMB meetings will be determined separately from this statistical analysis plan.

4.0 ENROLLMENT AND DISPOSITION

Participant enrollment, inclusion in analysis populations, number of participants discontinuing before study completion, and reasons for premature discontinuation will be summarized with frequencies and, where appropriate, percentages of enrolled participants. Data will also be provided in an appendix listing of the clinical study report.

5.0 EVALUATION OF BASELINE VALUES

5.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristic data will be collected prior to vaccination. All demographic and baseline characteristic data will be summarized and listed.

5.2 MEDICAL HISTORY

Medical history is collected during Screening (Days -7 to -1). Medical history data will be listed.

6.0 EVALUATION OF TREATMENT EXPOSURE AND COMPLIANCE

A single dose of the rBV A/B vaccine will be administered to each participant at the Vaccination Visit (Day 0). The vaccine formulation is 40 µg total antigen (20 µg Antigen A and 20 µg Antigen B) with 100 mM sodium chloride, 15 mM sodium phosphate, and 50 mM sodium acetate with Alhydrogel™ (0.2% weight per volume) balanced to a pH of 5.5 for a total dose volume of 0.5 mL. Vaccine administration and exposure data, including whether or not each participant received the injection, will be provided in an appendix listing of the clinical study report.

7.0 EVALUATION OF IMMUNOGENICITY PARAMETERS

The immunogenicity population will be used for all immunogenicity endpoints. The PP population will be used in the case that any sensitivity analyses are deemed necessary.

All immunogenicity endpoints will be performed for both botulinum toxin type A and type B.

7.1 ANALYSIS OF PRIMARY IMMUNOGENICITY ENDPOINT

The primary immunogenicity endpoint is the proportion of participants achieving a four times or greater increase in NAC by Week 4 compared to Week 0. The cut-off value for determining whether the increase is achieved for each subject will be calculated as [(Week 0 value) x 4] + (Week 0 value). A positive response will be defined as achieving this level of increase in NAC in at least 50% of participants. The proportion of participants who achieve this level of increase in NAC will be provided along with a 95% confidence interval. Graphs may be used to show corresponding participant-level data.

This primary analysis will be performed for both botulinum toxin type A and type B. In the event that the primary endpoint is not met for neutralizing antibodies against botulinum toxin type A or type B, the Sponsor-Investigator will determine if the plasma collected during the study contains sufficient antibody titers for meeting specifications for BabyBIG production. If so, the trial will still be considered successful.

Details regarding the collection schedule for blood samples for NAC can be found in Section 7.3.

7.2 ANALYSIS OF SECONDARY IMMUNOGENICITY ENDPOINTS

All secondary immunogenicity endpoints will use the immunogenicity population.

The first secondary immunogenicity endpoint is the proportion of participants achieving a two times increase in the estimated area under the plasma concentration-time curve in the period between Week 0 to Week 12 in comparison to straight-line extension of the Week 0 NAC to Week 12. The cut-off value for determining whether

the increase is achieved for each subject will be calculated as (Week 0 value) x (total number of days from Week 0 to Week 12 collection) x 2. A positive response will be defined as achieving this level of increase in at least 50% of the participants. If a participant does not have NAC collections through Week 12, the date of the last NAC collection will be used in place of the Week 12 date for both the concentration-time curve and the straight-line extension. In the cases where there are multiple NAC values on the same date for a particular subject, the mean of those values will be used in calculating the estimated area under the plasma concentration-time curve.

The second secondary immunogenicity endpoint is the proportion of participants achieving a three times or greater increase in NAC above baseline by Week 4 compared to Week 0. The cut-off value for determining whether the increase is achieved for each subject will be calculated as [(Week 0 value) x 3] + (Week 0 value). A positive response will be defined as achieving this level of increase in at least 50% of the participants.

Proportions will be provided for both secondary endpoints along with 95% confidence intervals.

Further details regarding the collection schedule for blood samples for NAC can be found in Section 7.3.

7.3 NEUTRALIZING ANTIBODY CONCENTRATION (NAC) VALUES

NAC determinations will be performed at Battelle Biomedical Research Center (Columbus, Ohio) by using a fully validated mouse neutralization assay used for all NAC determinations in the BabyBIG program.

Blood collection for determination of NAC values will be performed prior to vaccination at the Vaccination Visit (Day 0), for non-plasma donating participants at the Week 4 visit, and for plasma-donating participants at plasmapheresis visits and the Week 12 final study.

For summary tables involving NAC values, the week numbers will be assigned as described below. Week 4 and Week 12 have larger windows than other weeks in order to facilitate collection of NAC values during the time periods of primary interest.

Week 1 - values collected from Day 4 through Day 10

Week 2 - values collected from Day 11 through Day 17
Week 3 - values collected from Day 18 through Day 23
Week 4 - values collected from Day 24 through Day 32 [Day 28 (±4 days)]
Week 5 - values collected from Day 33 through Day 38
Week 6 - values collected from Day 39 through Day 45
Week 7 - values collected from Day 46 through Day 52
Week 8 - values collected from Day 53 through Day 59
Week 9 - values collected from Day 60 through Day 66
Week 10 - values collected from Day 67 through Day 73
Week 11 - values collected from Day 74 through Day 79
Week 12 - values collected from Day 80 through Day 88 [Day 84 (±4 days)]
Week 13 - values collected from Day 89 through Day 94
Week 14 - values collected from Day 95 through Day 101

8.0 EVALUATION OF SAFETY PARAMETERS

The safety population will be used for all safety analyses.

8.1 SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF INTEREST

Only SAEs and AEs of special interest will be evaluated for this study. AEs of special interest will include a) severe localized injection site reactions and severe systemic reactions that occur from Day 0 to Day 7 and b) severe clinically significant changes in hematology between screening and Week 4. SAEs will be recorded from administration of the investigational product at the vaccination visit through the follow-up phone call at Week 26. AE data will be coded using MedDRA v22.0.

Severe localized injection site reactions and severe systemic reactions that occur from Day 0 to Day 7 will be summarized by category (localized or systemic) and maximum severity. An overall summary with point estimates of incidence and 95% confidence intervals will be provided for severe localized injection site reactions and severe systemic reactions, along with average durations for each. Clinically significant changes in hematology between screening and Week 4 and related SAEs will also be summarized by maximum severity.

A summary of all SAEs by system organ class and preferred term will be produced. A similar summary will be produced for SAEs that are categorized as NOCIs (serious NOCIs). Summaries by maximum severity and strongest relationship to vaccine will be produced for all SAEs. SAEs, serious NOCIs, severe localized injection site reactions and severe systemic reactions, clinically significant changes in hematology between screening and Week 4, AEs resulting in death, and AEs leading to discontinuation from the study will be provided in appendix listings of the clinical study report.

When calculating the incidence of AEs, each AE will be counted only once for a given participant within a MedDRA category (e.g., overall, system organ class, or preferred term). When AEs are summarized within levels of another AE assessment (e.g., causality or severity), AEs will be counted once per participant at the worst level of the assessment (e.g., strongest relationship to study drug or greatest severity).

8.2 CLINICAL LABORATORY EVALUATIONS

Samples for hematology, serum chemistry, and urinalysis will be collected at screening. Hematology samples will also be collected at Week 4.

Treatment-emergent abnormal hematology values at Week 4 will be summarized. Hematology laboratory abnormalities will be assessed for relatedness and may be presented by relatedness in tables based on the investigator's assessment.

8.3 PRIOR AND CONCOMITANT MEDICATIONS

All prior and current medications taken within 60 days prior to Screening will be collected and recorded in the eCRF. Concomitant medications will be queried for at each visit. Concomitant medication data will be listed.

8.4 VITAL SIGNS AND OTHER PHYSICAL EXAMINATIONS

Vital sign measurements will include temperature, blood pressure, heart rate, and respiratory rate. These measurements will be provided in an appendix listing of the clinical study report.

Physical examinations will be performed during screening and at the initial plasmapheresis visit. Physical examination findings will be recorded with medical history or AEs.

8.5 PARTICIPANT DIARIES

Participants will complete a home diary on a daily basis for 7 days post-vaccination, as well as during the study period to report any adverse events and concomitant medications. Significant data from the diaries will be additionally recorded with adverse event data or concomitant medication data, so there will be no separate summaries or listings of diary data.

9.0 ANALYSIS OF EXPLORATORY ENDPOINT

The exploratory endpoint will be the volume of source plasma containing neutralizing antibodies against botulinum toxin type A and type B collected by plasmapheresis.

This exploratory endpoint will use the plasma-donating population.

Plasmapheresis data will be summarized and provided in an appendix listing of the clinical study report. Further details regarding the collection schedule for blood samples for NAC can be found in Section 7.3.

10.0 SCHEDULE OF TIME AND EVENTS

The schedule of time and events is presented in Table 1.

Table 1. Schedule of Time and Events

				Study Period				
Measurements/Evaluations	**Screening**	**Vaccination Visit**	**Telephone Call**	**Telephone Call**	**Telephone Call**	**Plasmapheresis**	**Final Study Visit**	**Follow-up Call**
	Day -7 to -1	**Week 0, Day 0**	**Week 1[a]**	**Week 4[a, b]**	**Week 10[a]**	**Week 2- 14[c]**	**Week 12[d]**	**Week 26[e]**
Informed consent	X					X[f]		
Physical examination	X					X[g]		
Medical history	X							
Prior medication history	X							
Urine pregnancy test	X	X[h]					X	
Inclusion/exclusion criteria	X	X						
Vital signs	X	X[i]				X		
Informed consent for plasma collection	X							
HIV, HBV, and HCV tests[j]						X		
Hematology	X[k]			X[l]				
Serum chemistry	X[k]							
Urinalysis	X[k]							
NAC sample collection		X[m]		X[n]		X	X	
Plasmapheresis[o]						X		
rBV A/B injection		X						
Injection site evaluation		X[p]		X			X	
Diary distribution[q]		X						
Diary review			X					
Serious adverse event collection[r]		X	X	X	X		X	X
Concomitant medication information	X[t]		X[s]	X[s]	X[s]		X[s]	X[s]
Phone call			X	X	X			X

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NAC = neutralizing antibody concentration; rBV A/B = recombinant botulinum vaccine A/B.

a. Week 1, Week 4, and Week 10 Follow-up Calls must occur with ±3 days of the scheduled time.
b. Final Study Visit will be an on-site visit at Week 4 for participants who opt not to participate or who have been determined to be ineligible for donation for the entire study. All final assessments occurring at Week 12 will occur at Week 4 for these participants.
c. Extension of plasmapheresis for up to 14 weeks post-vaccination is optional
d. Final on-site Study Visit must occur within ± 7 days of the scheduled time.
e. Final follow-up call for safety must occur within ±1 week of the scheduled time.
f. Plasmapheresis-specific informed consent forms will be signed at the source plasma center.

g. Physical examination will be performed as part of source plasma donor screening at the plasma collection center
h. Female participants of childbearing potential must have a negative pregnancy test within 24 hours prior to vaccination.
i. Participants will have vital signs taken twice at Visit 1: prior to injection, and 30 minutes (± 5 minutes) after receiving the injection.
j. HIV, HBV, and HCV tests will be performed on each donated source plasma unit
k. Results from screening tests must be available before Vaccination Visit
l. Study participants will go to central lab or plasma center for this draw (not an on-site visit).
m. Baseline NAC sample must be collected before rBV A/B injection and before plasmapheresis
n. Participants not donating plasma must go to site for NAC collection within ±3 days of the scheduled time.
o. May occur up to twice a week for up to 14 weeks (if hemoglobin and total protein remain within acceptable range) following vaccination with rBV A/B.
p. At this visit, participants will be monitored for at least 30 minutes after injection for a possible reaction.
q. In the diaries, participants record adverse events in order to determine SAE, oral temperature and injection site information.
r. Only serious adverse events and new onset chronic illnesses are to be queried for and collected
s. All concomitant medication used to treat a severe injection site or systemic reaction from Week 0-1 as well as any SAEs or serious NOCIs throughout the study (through Week 26) will be queried for and collected.
t. All prior and current medications taken within 60 days prior Screening will be queried for and collected.