CONFIDENTIAL

CLINICAL PROTOCOL

Protocol rBV A/B-CL-003

Recombinant Botulinum Vaccine A/B (rBV A/B)	
Protocol rBV A/B-CL-003	

TITLE OF STUDY:

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.

Date of issue: 02 Jul 2024

Sponsor: **California Department of Public Health**
Infant Botulism Treatment and Prevention Program
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Signatures of approval for protocol (Version 2.0)

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Medical Monitor:	John Edward Swartzberg, M.D., F.A.C.P	DocuSigned by: John Edward Swartzberg AE732FC1725849E...	7/3/2024

This study is to be performed in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations, Part 50 (Protection of Human Subjects), Part 56 (Institutional Review Boards), Part 312 (Investigational New Drug Application) and the International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

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STUDY SYNOPSIS

Name of sponsor company: California Department of Public Health (CDPH)

Name of investigational product: Recombinant Botulinum Vaccine A/B (rBV A/B)

Names of active ingredients: Recombinant Botulinum Antigen A and Antigen B adsorbed to 0.2% (wt/vol) Alhydrogel™

Title of study: 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

Sponsor-Investigator: Dr. Jessica M. Khouri

Number of sites: 2

Study period: 18 months

Phase of development: Phase 2

Objectives and Endpoints:

Immunogenicity Objective	Immunogenicity Endpoints
To evaluate the effects of a single 40-µg dose of rBV A/B on botulinum toxin type A and type B neutralizing antibody concentration (NAC) over a 12-week period following vaccination in participants previously immunized with PBT (or PBT and rBV A/B) for occupational protection.	Primary: • The proportion of participants achieving a four times or greater increase (point estimate) 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. Secondary: • The proportion of participants achieving 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 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 in at least 50% of the participants for botulinum toxin type A and type B.
Safety Objective	**Safety Endpoints**
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.	Primary safety endpoints collected over the 12-week study period and will be as follows: • Frequency of injection site reactions and systemic reactions that are characterized as severe during the diary reporting period (Days 0-7); • Frequency of injection site reactions and systemic reactions that are characterized as SAEs as defined in the protocol; • Participant incidence of treatment-related SAEs as defined in Appendix B; • 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

STUDY SYNOPSIS (continued)

Name of sponsor company: California Department of Public Health (CDPH)

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	severe or serious AEs.
Exploratory Objective	**Exploratory Endpoint**
To collect source plasma from participants that contain neutralizing antibodies against botulinum toxin type A and type B for the production of BabyBIG (BIG-IV).	The volume of source plasma containing neutralizing antibodies against botulinum toxin type A and type B collected by plasmapheresis for use in BabyBIG manufacture.

AE = adverse event; BIG-IV = Botulism Immune Globulin Intravenous (Human); NAC = neutralizing antibody concentration; NOCI = new onset chronic illness; PBT = pentavalent botulinum toxoid; rBV A/B = recombinant botulinum vaccine A/B; SAE = serious adverse event.

Number of participants (planned):
It is anticipated that up to 30 participants who were previously immunized with pentavalent botulinum toxoid (PBT) (or PBT and recombinant botulinum vaccine [rBV A/B]) for occupational protection will be enrolled in this study.

Patient Selection Criteria:

Inclusion criteria:
Participants are qualified for the study if they:

1. Have received PBT (or PBT and rBV A/B) for occupational protection under BB-IND-0161 (or BB-IND-0161 and IND 15155)
2. Are 18 to 69 years old at the time of consent
3. Are healthy and have an acceptable medical history (defined as individuals who are free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, infective, muscular, infectious, rheumatic, immunological, or psychiatric diseases, as determined at screening) that will not interfere with the objectives of the study
4. Meet the participant suitability requirements and recommendations for source plasma donors
5. Participants of childbearing potential:
    - Must have negative pregnancy test at screening and within 24 hours prior to vaccination
    - Must agree to not become pregnant until after the last plasma donation or until after the Week 12 visit (whichever occurs last)
    - Must agree to use at least one form of highly effective birth control starting 30 days prior to rBV A/B administration through the end of the study
        - Acceptable forms of contraception include intrauterine device, birth control pills, injectable birth control, implantable birth control device, or any other United States Food and Drug Administration (U.S. FDA) approved contraceptive method or a monogamous relationship with partner who has been vasectomized for at least 6 months prior to participant's enrollment or sexual abstinence
6. To be considered of non-childbearing potential, participants must be menopausal (no menstrual period for at least 12 months prior to screening) or be surgically sterile
7. Are able to understand the requirements of the study, have provided written informed consent as evidenced by signature on an informed consent form (ICF) approved by the appropriate Institutional Review Board (IRB), and have agreed to abide by the study restrictions and return for the required assessments

STUDY SYNOPSIS (continued)

Name of sponsor company: California Department of Public Health (CDPH)

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8. Agree to complete the participant home diary on a daily basis for 7 days post-vaccination, as well as report any severe adverse events (AEs) and serious AEs (SAEs), including serious new onset chronic illnesses (NOCIs) and concomitant medications during the study period
9. Have provided written authorization for use and disclosure of protected health information
10. Agree not to donate blood or blood products (outside of study procedures) until after the last plasma donation or until the Week 12 visit (whichever occurs last)
11. Have personal health insurance

Exclusion criteria:

Participants will be excluded if they:

1. Are pregnant or nursing
2. Have a history of laboratory evidence of syphilis, acquired immunodeficiency syndrome (AIDS), Creutzfeldt-Jakob disease (CJD), or infection with human immunodeficiency viruses (HIV) 1 or 2, human T-cell lymphotropic virus 1, hepatitis B virus (HBV), or hepatitis C virus (HCV)
3. Have had a prior severe (Grade 3 or higher) local or severe (Grade 3 or higher) systemic reaction to last immunization with PBT
4. Have had a prior severe immediate hypersensitivity reaction or severe systemic reaction on Day 0 to last vaccination with rBV A/B
5. Have a known allergy to aluminum compounds, yeast, or other components of the vaccine
6. Have donated one or more units of blood or undergone plasmapheresis within 49 days prior to enrollment
7. Have received a blood product or immunoglobulin within 6 months prior to enrollment or plans to receive such products during the study period (exclusive of returned red blood cells as part of the plasmapheresis procedure). For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last)
8. Have received licensed nonliving vaccine within 14 days prior to enrollment, or licensed live vaccine within 60 days prior to enrollment
9. Have received nonliving vaccine authorized for emergency use only within 14 days prior to enrollment, or living vaccine authorized for emergency use only within 60 days prior to enrollment
10. Have received investigational products (drugs, biologics, vaccines [except for those authorized for emergency use only per exclusion criterion 9], or implantable devices) within 60 days prior to enrollment or plans to receive experimental products at any time during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last)
11. Have received prescription immunosuppressive or immunomodulatory agents, including parenteral, inhaled, or oral corticosteroids within 3 months of enrollment or plans on receiving such therapy at any time during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last) with the exceptions mentioned below:
    - Participants who have used prescription topical steroids may be enrolled 2 weeks after the therapy is completed
    - Intra-articular, bursal, or tendon injectable steroids are permitted
    - Any over-the-counter topical steroid use is permitted
    - Ophthalmic and intranasal steroids are permitted
12. Have received cytotoxic therapy at any time in the previous 5 years before enrollment

STUDY SYNOPSIS (continued)

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13. Have an active systemic or recurrent disease that would place the participant at unacceptable risk of injury, require hospitalization, or require surgical intervention (This includes active mental illness or history of mental illness not responsive to treatment.)
14. Have a history of alcohol or drug abuse or dependence within 12 months of enrollment
15. Have past, present, or suspected illicit injection drug use
16. Have inflammatory, vasculitic, or rheumatic disease, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, or scleroderma (Stable osteoarthritis treated with physical therapy and nonsteroidal anti-inflammatory drugs is not an exclusion criterion.)
17. Have any acute or chronic neuromuscular or neurologic disorder
18. Have clinically confirmed hepatic or renal insufficiency
19. Have uncontrolled hypertension, as defined as systolic blood pressure greater than 160 mmHg and diastolic blood pressure greater than 90 mmHg
20. Have moderate to severe asthma, chronic obstructive pulmonary disease, or other significant pulmonary disease
21. Have a seizure disorder
22. Have moderate or severe illness or oral temperature of 100.4°F or greater within 3 days prior to enrollment.
23. Have any positive result for SARS-CoV-2 (COVID-19) using an FDA-cleared or FDA-authorized test within 14 days of enrollment
24. Be unsuitable for participation in this study for any reason, as assessed by the investigator

Test product, dose, and mode of administration:
The rBV A/B vaccine contains 40-µg of total antigen (20 µg of Antigen A and 20 µg of Antigen B) adsorbed to 0.2% (wt/vol) Alhydrogel™, in a total dose volume of 0.5 mL. The vaccine will be administered by intramuscular (IM) injection in the deltoid muscle, preferably in the nondominant arm.

Reference therapy, dose, and mode of administration:
No reference therapy will be employed**.**

Participant Duration:
Vaccine administration for all enrolled participants will occur at Day 0, and participants may elect to undergo plasmapheresis up to two times a week for up to 12 weeks post-vaccination, with the final on-site visit at Week 12 (± 7 days) and follow-up phone call for safety assessment at Week 26 (± 7 days) after vaccination. Participants can elect to continue plasmapheresis up to 14 weeks post-vaccination so long as they continue to meet source plasma donor eligibility requirements.

Study design:
This will be a Phase 2, open-label, uncontrolled study to evaluate the safety and immunogenicity of a single 40-µg intramuscular injection of rBV A/B in participants who were previously immunized with PBT (or PBT and rBV A/B) for occupational protection for collection of source plasma for potential use in the production of BabyBIG (Botulism Immune Globulin Intravenous [Human] [BIG-IV]).

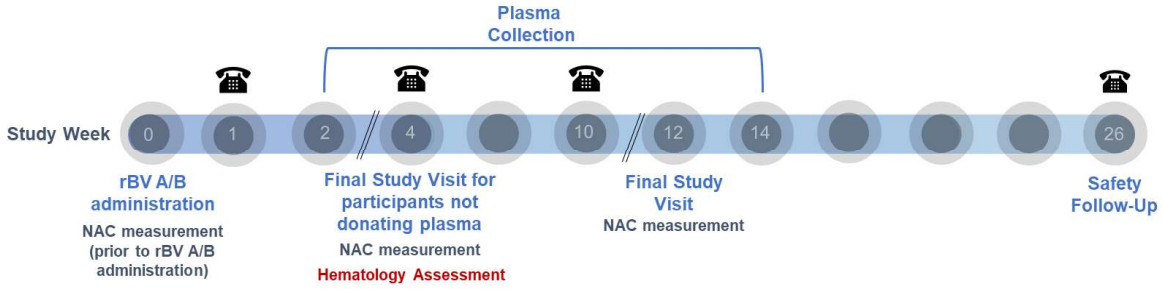
A flow diagram providing an overview of the study design is provided below:

STUDY SYNOPSIS (continued)

Name of sponsor company: California Department of Public Health (CDPH)

Name of investigational product: Recombinant Botulinum Vaccine A/B (rBV A/B)

Names of active ingredients: Recombinant Botulinum Antigen A and Antigen B adsorbed to 0.2% (wt/vol) Alhydrogel™



Participants must sign the ICF prior to any screening-related procedures. Participants will undergo a screening period of up to 1 week (Day -7 to Day -1) prior to administration of the study vaccine. Eligibility will be determined based on screening-related procedures according to the Schedule of Time and Events. Participants who meet inclusion criteria and do not meet any exclusion criteria will be considered eligible for the study. Participants will be enrolled into the study on Day 0 (Vaccination Visit) following confirmation of eligibility and prior to administration of the investigational product. Participants who meet certain exclusion criteria may be re-screened for study enrollment under the following conditions:

- Participants who have received a non-living vaccine or live vaccine (licensed or emergency use authorized) within 14 days or 60 days of scheduled Vaccination Visit (Day 0), respectively, and no other exclusion criteria may be permitted to re-screen for study enrollment following the conclusion of the appropriate time period.
- Participants presenting with moderate or severe illness or oral temperature of 100.4°F or greater within 3 days of scheduled Vaccination Visit and no other exclusion criteria may be permitted to re-screen for study enrollment following resolution of illness/temperature for at least three consecutive days.
- Participants presenting with any positive result for SARS-CoV-2 (COVID-19) using an FDA-cleared or FDA-authorized test within 14 days of scheduled Vaccination Visit and no other exclusion criteria may be permitted to re-screen for study enrollment at least 20 days after performance of laboratory-based positive test as long as the individual remains symptom free.
- Participants presenting while currently taking medications that are included on the Blood and Plasma Donation Medication Deferral List who wish to be a donor as a part of the study may be permitted to enter the study if, under the supervision of their physician, they elect to discontinue the medication(s) for the length of the study. The exact length of time between last dose of medication and Vaccination Visit will be determined per standard operating procedures for plasma donor requirements.

Participants will receive a single IM rBV A/B injection on Week 0, Day 0 (Vaccination Visit). All participants will be provided a diary and will report on localized injection site reactions, including diameter of any swelling and redness around the injection site, and systemic reactions, including generalized symptoms, that occur within the first 7 days following vaccination as well as any concomitant medications administered during this time period. All participants will receive a telephone call at Week 1 (± 3 days) for diary review. All severe localized injection site reactions and severe systemic reactions and SAEs, including serious NOCIs, will be recorded in the electronic case report form (eCRF). Any concomitant medications used as treatment for these events will also be recorded.

STUDY SYNOPSIS (continued)

Name of sponsor company: California Department of Public Health (CDPH)
Name of investigational product: Recombinant Botulinum Vaccine A/B (rBV A/B)
Names of active ingredients: Recombinant Botulinum Antigen A and Antigen B adsorbed to 0.2% (wt/vol) Alhydrogel™

Study participants who consent to plasma donation may report to the licensed plasma collection center after the Week 1 phone call where they will be assessed by the center for donor eligibility. Once donor eligibility has been confirmed, the participant may choose to donate plasma up to twice weekly through Week 14 post-vaccination. Prior to each donation, a serum sample will be collected for neutralizing antibody concentration (NAC) determination. If the participant fails to meet donor criteria at any time during the plasmapheresis period, the participant will continue to be followed for safety according to the Schedule of Time and Events.

If participants opt not to participate in plasma collections or have been determined to be ineligible to donate plasma for the entire study, they will have a final on-site visit at Week 4 for safety and immunogenicity determinations in lieu of the Week 4 safety follow up phone call; at the final Week 4 study visit, participants will provide a serum sample for NAC determination and a blood sample for the Week 4 hematology assessment. Serum and blood samples collected at Week 4 from participants undergoing plasmapheresis will be used for NAC determination and hematology assessment, respectively; if a donor is not scheduled for plasmapheresis within the Week 4 study window, they will have a scheduled blood draw to provide a serum sample for NAC determination and a sample for the Week 4 hematology assessment.

Participants opting to not participate in plasma collections will undergo safety assessment during the final on-site visit at Week 4. Only participants who consent to plasma donation will receive a safety phone call at Week 4 (± 3 days) and at Week 10 (± 3 days). All donor and non-donor participants will be queried for occurrence of SAEs and serious NOCIs, which will be recorded in the eCRF. All concomitant medication used as treatment for these events will be recorded. The Week 4 hematology assessment will be used to determine clinically significant changes in parameters between screening and Week 4. All clinically significant changes in hematology classified as a severe AE or SAE will be recorded in the eCRF.

Study participants participating in plasma donations will have a final on-site study visit at Week 12 (± 7 days). Assessments include inspection of the injection site, collection of serum sample for NAC determination, urine pregnancy test for participants of childbearing potential, and recording of SAEs, including serious NOCIs, and any concomitant medications used as treatment for these events in the eCRF.

All study participants will have a final phone call for safety follow-up at Week 26 (± 7 days) and will be queried for occurrence of SAEs and serious NOCIs. Serious adverse events, including any serious NOCIs, and any concomitant medications used as treatment for these events will be recorded in the eCRF.

STUDY SYNOPSIS (continued)

Name of sponsor company: California Department of Public Health (CDPH)

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Names of active ingredients: Recombinant Botulinum Antigen A and Antigen B adsorbed to 0.2% (wt/vol) Alhydrogel™

Statistical methods:

Analysis Populations:

Immunogenicity Population: All participants who have received the study vaccine at the assigned dosage and for whom at least one post-baseline NAC was collected within 4 weeks of vaccination.

Per Protocol Population: All participants who received the vaccine dose, have a baseline NAC, and have all immunogenicity assessments completed within the protocol-specified timelines (including visit windows) for the time periods summarized and do not have major protocol violations expected to affect immunogenicity. (Note: It is possible for a participant to be included in the primary per protocol analysis for Week 4, even if the subsequent blood draws occur outside of the study windows.)

Safety Population: All participants enrolled into the study who received the vaccine dose and had at least one post-baseline safety assessment (this assessment can include a response from a participant that did not experience AEs).

Plasma-donating Population: All participants who receive the vaccine and donate at least one plasma unit.

Analyses:
Detailed methodology for summary and statistical analyses of the data collection in the study will be documented in the Statistical Analysis Plan (SAP). All AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

The data will be summarized in tables listing the mean, standard deviation, or standard error, median, minimum, maximum, and number of participants for continuous data, or in tables listing count and percentage for categorical data, where appropriate.

The immunogenicity parameters are NACs for botulinum toxin type A and type B. These NAC parameters will be analyzed using a validated mouse neutralization assay.

Summaries of local and systemic severe AEs and SAEs related to vaccination (collected in the 7-day diaries) will be produced in tables, by category and severity.

Summaries of clinically significant changes in hematology between screening and Week 4 resulting in a severe AE or SAE will be listed.

SAE data will be listed individually and summarized by system organ class and preferred terms and by severity and relatedness.

SAE data of NOCIs will be listed individually and summarized by system organ class and preferred terms and by severity and relatedness.

No formal sample size calculations will be done.

Table 1. Schedule of Time and Events

	Study Period							
Measurements/Evaluations	**Screening**	**Vaccination Visit**	**Study Assessments**			**Plasmapheresis**	**Final On-Site Study Visit**	**Follow-up Call**
	Day -7 to -1	**Week 0, Day 0**	**Week 1 (± 3 days)**	**Week 4[a] (± 3 days)**	**Week 10 (± 3 days)**	**Week 2 - 14**	**Week 12[a] (± 7 days)**	**Week 26 (± 7 days)**
Informed consent	X[b]					X[c]		
Physical examination[d]	X							
Medical history[e]	X							
Prior medication history[f]	X	X						
Urine pregnancy test	X[g]	X[g]		X[h]			X	
Inclusion/exclusion criteria	X	X						
Vital signs[i]	X	X[j]						
Hematology[k]	X			X[l,m]				
Serum chemistry[k]	X							
Urinalysis[k]	X							
NAC sample collection		X[n]		X[l]		X[n]	X	
rBV A/B injection		X						
Injection site evaluation		X[o]		X[l,m]			X	
Diary distribution[p]		X						
Diary review			X					
Plasmapheresis[q]						X		
Adverse event collection[r]		X	X	X	X		X	X
Concomitant medication information[s]			X	X	X		X	X
Safety phone call			X	X[a]	X[t]			X[u]

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = calcium; eCRF = electronic case report form; Hgb = hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; K = potassium; NAC = neutralizing antibody concentration; NOCI = new onset chronic illness; rBV A/B = recombinant botulinum vaccine A/B; SAE = serious adverse event; WBC = white blood cell.

a. Participants not donating plasma must go to the site for a Final Study Visit at Week 4 in lieu of a safety follow-up phone call at Week 4. All assessments listed under Week 12 will be completed at this time.
b. Participants will sign ICF for study participation and a separate ICF for plasmapheresis if willing to participate in plasma collection.
c. Plasmapheresis-specific informed consent form and testing consent form will be signed during plasmapheresis screening at the source plasma collection center.
d. Physical examination includes evaluation of weight and height; head, eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; extremities; skin; neurologic and mental status evaluations.
e. Evaluation of total medical history for the previous 5 years.

STUDY SYNOPSIS (continued)

f. All prior and current medications taken within 60 days prior to Screening Visit will be queried for and collected.
g. Participants of childbearing potential must have a negative pregnancy test within 24 hours prior to vaccination. If urine test is positive, a confirmatory blood test must be performed.
h. Participants of childbearing potential who are non-plasmapheresis donors must have a negative pregnancy test performed at the Final On-Site Study Visit at Week 4.
i. Vital sign measurements consist of temperature, blood pressure, heart rate, and respiratory rate.
j. Participants will have vital signs taken twice at Vaccination Visit: prior to injection, and 30 minutes (± 5 minutes) after receiving the injection.
k. Results from screening tests must be available before Vaccination Visit. Hematological assessments consist of Hgb, WBC count (with absolute count of lymphocytes, neutrophils, and eosinophils), and platelets; serum chemistry assessments consist of ALT, AST, ALP, bilirubin, BUN, creatinine, glucose, Ca, and K; urinalysis assessments (by dipstick testing of clean-catch sample) consist of protein, glucose, blood, ketones, and leukocyte esterase.
l. Week 4 NAC and hematology collection must occur within ±3 days of the scheduled time. For non-plasmapheresis donors or participants not scheduled for plasma donation within the Week 4 study window, NAC and hematology specimens will be collected at the study site or clinical laboratory. Plasma donors will have Week 4 hematology and NAC specimens collected at the plasma center if the plasma donation occurs within the Week 4 study window.
m. Hematology assessment and injection site evaluation will be performed at Final On-Site Study Visit at Week 4 for participants not donating plasma.
n. Baseline NAC sample must be collected before rBV A/B injection. Post-vaccination NAC samples will be collected at each plasmapheresis visit.
o. Participants will be monitored for at least 30 minutes immediately following injection for possible reactions.
p. Participants will record AEs in diaries through Day 7 post-vaccination to determine occurrence of any severe AEs and SAEs (includes local and systemic reactions).
q. Participants may donate plasma up to twice weekly through Week 14 following vaccination with rBV A/B based on source plasma donor eligibility criteria (including physical examination, vital signs, and donor screening laboratory assessments, including finger prick tests for hemoglobin and total protein. All source plasma units must be tested for HIV, HBV, and HCV).
r. All SAEs, including serious NOCIs, will be recorded in the eCRF throughout the study. All severe localized injection site reactions and severe systemic reactions will be recorded in the eCRF based on 7-day diaries; only localized injection site or systemic reactions classified as serious will be recorded in eCRF thereafter. Clinically significant changes in hematology parameters classified as a severe AE or SAE based on Week 4 assessment will be recorded in the eCRF.
s. All concomitant medication used to treat a severe localized injection site or severe systemic reaction from Week 0-1 as well as any SAEs (including serious NOCIs) throughout the study (through Week 26) will be recorded in the eCRF.
t. Only participants donating plasma will receive this safety follow-up call.
u. All study participants (including non-plasma donors) will receive the Week 26 final safety follow-up phone call.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (continued)

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BabyBIG	CDPH proprietary name for Botulism Immune Globulin Intravenous (Human) (BIG-IV)
BoNT	botulinum neurotoxin
BUN	blood urea nitrogen
Ca	calcium
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CJD	Creutzfeldt Jakob Disease
DSMB	data and safety monitoring board
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
ISF	investigator site file
K	potassium
MedDRA	Medical Dictionary for Regulatory Activities
Na	sodium
NAC	neutralizing antibody concentration
NOCI	new onset chronic illness
PBT	pentavalent botulinum toxoid
rBV A/B	recombinant botulinum vaccine A/B
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse events
TSG-DA	The Surgeon General – Department of the Army
ULN	upper limit of the normal range
U.S. FDA	United States Food and Drug Administration
WBC	white blood cell

1.0 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. BabyBIG 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 also boosted with investigational recombinant botulinum vaccine A/B (rBV A/B).

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.[1] Thus, a new immunogen against botulinum toxins was needed. A recombinant botulinum vaccine for the toxin serotypes A and B (rBV A/B) has been developed and was proposed as a replacement vaccine for boosting participants who previously received PBT for occupational protection for Study rBV A/B-CL-002, which was conducted under IND 15155 from 2019-2020. This study (rBV A/B-CL-003) is the third 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 under IND 15155 for BabyBIG production under BLA 125034.

1.2 STUDY RATIONALE

This protocol has as its ultimate goal the production of additional lots of the approved orphan drug Botulism Immune Globulin Intravenous (Human), (BIG-IV; BabyBIG®) for the treatment of 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 rBV A/B boost). Two Phase 2b studies conducted by CDPH (rBV A/B-CL-001 and rBV A/B-CL-002) 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 or PBT and rBV A/B. The proposed study will continue to evaluate the immunogenicity and safety of a single dose of the rBV A/B vaccine in this previously immunized population. This study design is similar to rBV A/B-CL-002. 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 rBV A/B naïve or in participants that volunteered for the rBV A/B-CL-001 and/or rBV A/B-CL-002 clinical trials and received one dose of rBV A/B.

1.3 DOSE RATIONAL

An rBV A/B dose of 40-µg of total antigen (20-µg of Antigen A and 20-µg of Antigen B) with Alhydrogel™ has been shown in Phase 1 and Phase 2 studies in healthy participants to be effective in stimulating a strong antibody response and has an acceptable safety profile. Most treatment-emergent adverse events (TEAEs) were mild and transient. Furthermore, the safety and immunogenicity of the rBV A/B vaccine in a naïve population was investigated in 372 participants using the same dose level and a three-dose schedule (under BB-IND 11756). Two Phase 2b studies conducted by CDPH (rBV A/B-CL-001 and rBV A/B-CL-002) demonstrated a single 40-µg dose of rBV A/B was well tolerated, and no safety concerns were identified during the study. In addition, the single 40-µg dose resulted in a significant increase in neutralizing antibodies against botulinum toxin types A and B in participants previously immunized with PBT. Therefore, the proposed dose in this study is expected to have an acceptable safety profile and be

effective in stimulating antibody response in persons previously immunized with PBT or PBT and rBV A/B for occupational protection.

2.0 OBJECTIVES AND ENDPOINTS

The immunogenicity objective of this Phase 2b study is to evaluate the effects of a single 40-µg dose of rBV A/B on botulinum toxin type A and type B NAC over a 12-week period following vaccination in participants previously immunized with PBT or PBT and rBV A/B for occupational protection. The safety objective 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 these participants. The exploratory objective is to collect source plasma from participants that contain neutralizing antibodies against botulinum toxin type A and type B for the production of BabyBIG (BIG-IV).

Table 2 outlines the objectives and endpoints for this study.

Table 2. Study rBV A/B-CL-003 Objectives and Endpoints

Immunogenicity Objective	**Immunogenicity Endpoints**
To evaluate the effects of a single 40-µg dose of rBV A/B on botulinum toxin type A and type B neutralizing antibody concentration (NAC) over a 12-week period following vaccination in participants previously immunized with PBT (or PBT and rBV A/B) for occupational protection.	Primary: • The proportion of participants achieving a four times or greater increase (point estimate) 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. Secondary: • The proportion of participants achieving 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 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 in at least 50% of the participants for botulinum toxin type A and type B.
Safety Objective	**Safety Endpoints**
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.	Primary safety endpoints collected over the 12-week study period and will be as follows: • Frequency of injection site reactions and systemic reactions that are characterized as severe during the diary reporting period (Days 0-7); • Frequency of injection site reactions and systemic reactions that are characterized as SAEs

	as defined in the protocol; • Participant incidence of treatment-related SAEs as defined in Appendix B; • 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 AEs.
Exploratory Objective	**Exploratory Endpoint**
To collect source plasma from participants that contain neutralizing antibodies against botulinum toxin type A and type B for the production of BabyBIG (BIG-IV).	The volume of source plasma containing neutralizing antibodies against botulinum toxin type A and type B collected by plasmapheresis for use in BabyBIG® manufacture.

AE = adverse event; BIG-IV = Botulism Immune Globulin Intravenous (Human); NAC = neutralizing antibody concentration; NOCI = new onset chronic illness; PBT = pentavalent botulinum toxoid; rBV A/B = recombinant botulinum vaccine A/B; SAE = serious adverse event

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

This will be an open-label, uncontrolled study to evaluate the safety and immunogenicity of a single 40-µg intramuscular injection of rBV A/B in participants who were previously immunized with PBT (or PBT and rBV A/B) for occupational protection for collection of source plasma for potential use in the production of BabyBIG. Participants will receive the rBV A/B injection and may elect to undergo plasmapheresis up to twice weekly through Week 14 post-vaccination, so long as they meet donor eligibility requirements. Prior to each donation, a serum sample will be collected for NAC determination. Participants will be evaluated for safety and immunogenicity at each study visit with longer-term follow-up safety data collected at 6 months.

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. All participants, including donors undergoing plasmapheresis, will also have an additional hematology specimen collected at Week 4. Study participants participating in plasma donations 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.

3.2 STUDY POPULATION

For this study, up to 30 participants are anticipated to be enrolled. Eligibility will be established by the investigator(s) on the basis of the inclusion and exclusion criteria.

3.2.1 Inclusion Criteria

Participants are qualified for the study if they:

1. Have received PBT (or PBT and rBV A/B) for occupational protection under BB IND 0161 (or BB-IND-0161 and IND 15155)

2. Are 18 to 69 years old at the time of consent

3. Are healthy and have an acceptable medical history (defined as individuals who are free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, infective, muscular, infectious, rheumatic, immunological, or psychiatric diseases, as determined at screening) that will not interfere with the objectives of the study

4. Meet the participant suitability requirements and recommendations for source plasma donors (see Appendix A)

5. Participants of childbearing potential:

    a. Must have negative pregnancy test at screening and within 24 hours prior to vaccination

    b. Must agree to not become pregnant until after the last plasma donation or until after the Week 12 visit (whichever occurs last)

    c. Must agree to use at least one form of highly effective birth control starting 30 days prior to rBV A/B administration through the end of the study

        i. Acceptable forms of contraception include intrauterine device, birth control pills, injectable birth control, implantable birth control, or any other U.S. FDA approved contraceptive method or a monogamous relationship with partner who has been vasectomized for at least 6 months prior to participant's enrollment or sexual abstinence

6. To be considered of non-childbearing potential, participants must be menopausal (no menstrual period for at least 12 months prior to screening) or be surgically sterile

7. Are able to understand the requirements of the study, have provided written informed consent as evidenced by signature on an informed consent form (ICF) approved by the appropriate Institutional Review Board (IRB), and have agreed to abide by the study restrictions and to return for the required assessments

8. Agree to complete the participant home diary on a daily basis for 7 days post-vaccination, as well as to report any severe adverse events (AEs) and serious AEs (SAEs), including serious new onset chronic illnesses (NOCIs) and concomitant medications during the study period

9. Have provided written authorization for use and disclosure of protected health information

10. Agree not to donate blood or blood products (outside of study procedures) until after the last plasma donation or until the Week 12 visit (whichever occurs last)

11. Have personal health insurance

3.2.2 Exclusion Criteria

Participants will be excluded if they:

1. Are pregnant or nursing

2. Have a history of laboratory evidence of syphilis, acquired immunodeficiency syndrome (AIDS), Creutzfeldt-Jakob disease (CJD), or infection with human immunodeficiency viruses (HIV) 1 or 2, human T-cell lymphotropic virus 1, hepatitis B virus (HBV), or hepatitis C virus (HCV)

3. Have had a prior severe (Grade 3 or higher) local or severe (Grade 3 or higher) systemic reaction to last immunization with PBT

4. Have had a prior severe immediate hypersensitivity reaction or severe systemic reaction on Day 0 to last vaccination with rBV A/B

5. Have known allergy to aluminum, yeast, or other components of the vaccine

6. Have donated one or more units of blood or undergone plasmapheresis within 49 days of enrollment

7. Have received blood product or immunoglobulin within 6 months prior to enrollment or plans to receive such products during the study period (exclusive

of returned red blood cells as part of the plasmapheresis procedure). For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last)

8. Have received licensed nonliving vaccine within 14 days prior to enrollment or licensed live vaccine within 60 days prior to enrollment

9. Have received nonliving vaccine authorized for emergency use only within 14 days prior to enrollment, or living vaccine authorized for emergency use only within 60 days prior to enrollment

10. Have received investigational products (drugs, biologics, vaccines [except for those authorized for emergency use only per exclusion criterion 9], or implantable devices) 60 days prior to enrollment or plans to receive experimental products at any time during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last)

11. Have received prescription immunosuppressive or immunomodulatory agents, including parenteral, inhaled, or oral corticosteroids within 3 months of enrollment or plans on receiving such therapy at any time during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last), with the exceptions mentioned below:

    - Participants who have used prescription topical steroids may be enrolled 2 weeks after the therapy is completed

    - Intra-articular, bursal, or tendon injectable steroids are permitted

    - Any over-the-counter topical steroid use is permitted

    - Ophthalmic and intranasal steroids are permitted

12. Have received cytotoxic therapy at any time in the previous 5 years before enrollment

13. Have an active systemic or recurrent disease that would place the participant at unacceptable risk of injury, require hospitalization, or require surgical intervention (This includes active mental illness or history of mental illness not responsive to treatment.)

14. Have a history of alcohol or drug abuse or dependence within 12 months of enrollment

15. Have past, present, or suspected illicit injection drug use

16. Have inflammatory, vasculitic, or rheumatic disease, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, or scleroderma (Stable osteoarthritis treated with physical therapy and nonsteroidal anti-inflammatory drugs is not an exclusion criterion.)

17. Have any acute or chronic neuromuscular or neurologic disorder

18. Have clinically confirmed hepatic or renal insufficiency

19. Have uncontrolled hypertension, as defined a systolic blood pressure greater than 160 mmHg and diastolic blood pressure greater than 90 mmHg

20. Have moderate to severe asthma, chronic obstructive pulmonary disease, or other significant pulmonary disease

21. Have a seizure disorder

22. Have moderate or severe illness or oral temperature of 100.4°F or greater within 3 days prior to enrollment

23. Have any positive result for SARS-CoV-2 (COVID-19) using an FDA-cleared or FDA-authorized test within 14 days of enrollment

24. Be unsuitable for participation in this study for any reason, as assessed by the investigator

3.3 REEVALUATION OF PARTICIPANT ELIGIBILITY

Participants who meet certain exclusion criteria may be re-screened for study enrollment under the following conditions:

- Participants who have received a non-living or live vaccine (licensed or emergency use authorized) with 14 days or 60 days of scheduled Vaccination Visit (Day 0), respectively, and no other exclusion criteria may be permitted to re-screen for study enrollment following the conclusion of the appropriate time period.

- Participants presenting with moderate or severe illness or oral temperature of 100.4°F or greater within 3 days of Vaccination Visit and no other exclusion criteria may be permitted to re-screen for study enrollment following resolution of illness/temperature for at least 3 consecutive days.

- Participants presenting with any positive result for SARS-CoV-2 (COVID-19) using an FDA-cleared or FDA-authorized test within 14 days of Vaccination Visit and no other exclusion criteria may be permitted to re-screen for study enrollment at least 20 days after performance of laboratory-based positive test as long as the individual remains symptom free.

- Participants presenting while currently taking medications that are included on the Blood and Plasma Donation Medication Deferral List who wish to be a donor as part of the study may be permitted to enter the study if, under the supervision of their physician, they elect to discontinue the medication(s) for the length of the study. The exact length of time between last dose of medication(s) and Vaccination Visit (Day 0) will be determined per standard operation procedures for plasma donor requirements.

3.4 RANDOMIZATION AND BLINDING

There will be no randomization or blinding of participants for safety assessments in this study.

3.5 REPLACEMENT OF DROPOUTS

Dropouts will not be replaced in this study.

4.0 DRUGS AND DOSAGES

4.1 IDENTIFICATION AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

4.1.1 Investigational Product

The rBV A/B program is currently overseen by The Surgeon General, Department of the Army (TSG-DA) under IND 11756. TSG-DA has authorized CDPH to use rBV A/B in the Study rBV-A/B-CL-003 clinical trial. The procedure used to manufacture the active ingredient of rBV A/B is described below.

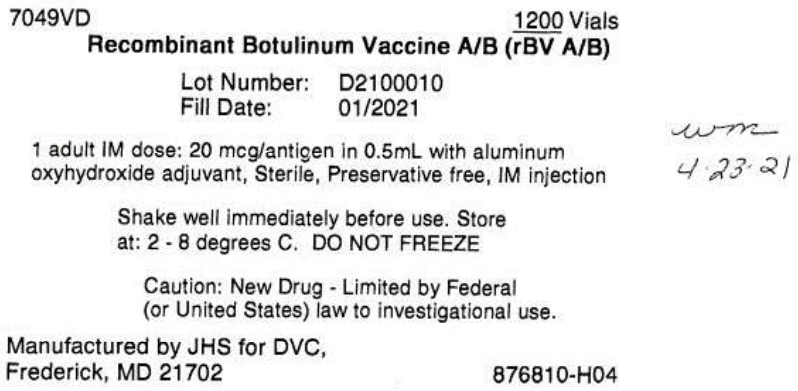
The recombinant botulinum neurotoxin antigens are expressed from synthetic genes encoding the carboxy-terminal region of the botulinum neurotoxins (BoNT) heavy-chains [rBoNT(Hc)] of BoNT/A and BoNT/B, designated Antigen A and Antigen B. These fragments are from the binding domain of the heavy-chain and do not have neurotoxic activity. Antigen A and Antigen B are expressed in the methylotrophic yeast *Pichia pastoris* as 50 kDa and 52 kDa proteins, respectively. Antigen A is derived from the BoNT/A1 expressed by *Clostridium botulinum* strain NCTC 2916 (Group I, proteolytic), and Antigen B is derived from BoNT/B1 expressed by *C. botulinum* strain Danish (Group I, proteolytic). These proteins have been expressed individually by using a methanol induction system from synthetic genes introduced into *P. pastoris*. The bulk antigens were manufactured at high purity (each antigen purified drug substance is >95% pure), formulated and combined in a 1:1 ratio based on mass (in micrograms) to produce the final drug product.

The formulation used for this study will have 40 micrograms (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.

4.1.2 Labeling

Each vial in Lot D2100010 (produced under IND 11756 in 2021 according to cGMP standards) will be labeled as shown in Figure 1.

Figure 1. Sample vial label.



4.2 DOSING INSTRUCTIONS AND SCHEDULE

Participants will receive a 0.5 mL intramuscular injection of rBV A/B in the deltoid muscle, preferably in the nondominant arm. The injection will be administered by the investigator or delegated site personnel. Site personnel will document the time of the injection in the electronic case report form (eCRF). Each vial should be visually inspected for particulate matter, discoloration, signs of adulteration, or contamination before administration. If the product appears discolored or has visible particulate matter, it should not be used, and both the study monitor, and principal investigator should be notified. If the investigational product in the vial is suspect, it should not be dispensed or administered. Instead, a new dose should be obtained, inspected, and the dose withdrawn then administered. The occurrence of such an event should be recorded in the ISF (investigator site file).

Each vial will be prepared by swirling gently immediately before use. Approximately 0.5 to 0.6 mL of investigational product will be drawn into a sterile, 1 mL latex-free tuberculin syringe (Becton Dickinson & Co.) or equivalent with a sterile, 21-gauge, 1-inch BD PrecisionGlide™ Needle (Becton Dickinson & Co.) or equivalent. To ensure a full dose is able to be drawn from each vial, the vial may need to be inverted with the bevel of the needle inserted just above the rubber

stopper. The date, time, and administrator's initials will be recorded in the participant's source record and on the Investigational Product Accountability Log upon administering the investigational product to the participant. In addition, the site of vaccination (e.g., deltoid muscle of left arm) will be recorded in the participant's source medical record.

4.3 STORAGE AND HANDLING OF INVESTIGATIONAL PRODUCT

All vials will be stored at 2°C to 8°C (35.6°F to 46.4°F) in a secure storage location. The refrigerator temperature will be recorded continuously and monitored daily. The investigational product must not be frozen. A copy of the temperature logs for the storage refrigerator must be filed in the site study files to document appropriate storage conditions.

The principal investigator must ensure that accurate records of receipt of all vaccine, including date of receipt, are maintained throughout the study. In addition, accurate records must be kept regarding when and how much vaccine was used.

Study personnel must not destroy or throw away any vial of vaccine, including empty, damaged, or partially used ones. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all vaccine will be reconciled, and the study monitor will verify that the remaining vials have been either returned to designee as determined by the sponsor-investigator or destroyed following the sponsor-investigator's instructions.

4.4 DOSE STOPPING RULES

4.4.1 Individual Participant Stopping Rules

Because only one dose of vaccine is administered per participant, there will be no individual participant stopping rules to preclude further vaccination.

Participants who develop a Grade 3 (or higher) immediate hypersensitivity reaction to the vaccine will be counselled by the investigator that future exposure to rBV A/B would not be advisable.

4.4.2 Study Stopping Rules

For this study, the following are the dose stopping rules; and, if they occur, all dosing will stop, the DSMB (Section 6.10) will convene, review the data collected, and make a recommendation for continued dosing.

- If any participant has an SAE (see Section 6.1 for a definition) considered possibly, probably, or definitely related to the vaccine
- Two or more participants with a Grade 3 (severe) or higher similar hematologic abnormality, considered possibly, probably or definitely related to the vaccine
- Two or more participants with neuromuscular AEs considered possibly, probably or definitely related to the vaccine

If the DSMB determines that an SAE was a vaccine-related SAE, then the sponsor-investigator will provide the DSMB's recommendation along with the SAE report to the FDA and seek the Agency's guidance on resuming the study.

4.5 CONCOMITANT MEDICATIONS

There are no restrictions on concomitant medications for the treatment of adverse events. 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 study visit. Any concomitant medication used to treat a severe injection site or systemic reaction during the diary reporting period (first 7 days after injection) as well as any SAEs or serious NOCIs throughout the study (through Week 26) will be recorded in the eCRF.

Enrolled participants should not receive licensed preparations of botulinum toxin A or B used to treat spastic disorders because they are already immune to the therapeutic benefits.

Enrolled participants should not receive any additional vaccines during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last).

Participants should not receive prescription immunosuppressive agents, including corticosteroids (systemic and inhalational), during the study period. For participants who choose to donate plasma, this will apply until their last plasma donation or at the Week 12 visit (whichever occurs last). Intra-articular, bursal or tendon injectable steroids are permitted. Ophthalmic and intranasal steroids are permitted. Over-the counter topical steroids are permitted.

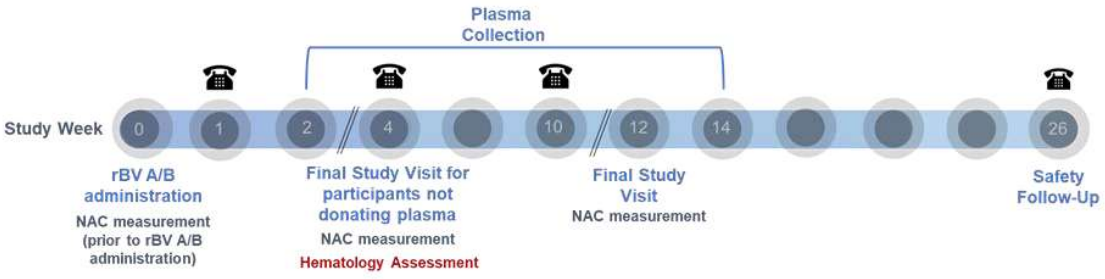
5.0 EXPERIMENTAL PROCEDURES

5.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

For this clinical trial there is a 7-day screening period (Days –7 to –1) in which participant eligibility will be determined (see Section 3.2 for further description). Participants will be enrolled in the study following confirmation of eligibility on Day 0 prior to administration of rBV A/B. Participants will enter either a 4-week (non-plasma donors) or a 12-week (plasma donors) treatment period in which a single rBV A/B injection will be administered on Day 0 to stimulate the production of antibodies against botulinum toxin type A and type B. Participants will be able to donate plasma starting 1 week after injection with rBV A/B at a frequency of up to two times a week through to 14 weeks post-vaccination in accord with FDA plasma donation regulations and guidelines.[2] NAC sample collections are required for all participants at Week 0 and Week 4. NAC sample collection is required for plasma donors with each donated unit and at Week 12. Safety assessments for non-plasma donors are scheduled on Week 0, Week 1 (by phone), and Week 4 (final on-site visit). Safety assessments for plasma donors are at Week 0 with follow-up phone calls at Weeks 1, 4 and 10, and a final on-site study visit at Week 12 to assess general health status and query for the interim occurrence of any SAEs or serious NOCIs. All participants will have a final phone call for safety follow-up at Week 26. Concomitant medications will be queried for at each study visit. Any 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 will be recorded in the eCRF.

The schedule of events is presented in **Error! Reference source not found.**. A schematic of the overall study design for rBV A/B-CL-003 is presented in Figure 2.

Figure 2. rBV A/B-CL-003 Schematic



5.2 MEASUREMENTS AND EVALUATIONS

This section details the visits that occur during the study and the assessments that are conducted at each visit. Details of the assessments performed during the study are provided at the visit at which they are first performed.

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

5.2.1 Screening Period (Day –7 and –1)

Before the initiation of screening assessments, the participant will be given a complete explanation of the purpose and evaluations of the study. Subsequently, the participant must sign and receive a copy of the institutional review board (IRB) approved ICF (Section 9.1) that includes authorization for use and disclosure of protected health information (Section 9.1). Once the ICF has been obtained, the baseline screening assessments will be performed, and the eligibility of the participant will be determined. Each participant will be assigned a unique participant number once the ICF is signed. A separate plasmapheresis ICF must be obtained for participants donating plasma.

Screening must occur between 1 and 7 days before Visit 1 (i.e., Vaccination Visit [Day 0]). The following evaluations will be performed to assess the participant's eligibility for the study:

- Total medical history for the previous 5 years
- Physical examination, including weight and height; head, eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; extremities; skin; neurologic and mental status evaluations
- Vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Urine pregnancy test (if positive, a confirmatory blood test must be performed)
- Listing of prior and current medications for past 60 days

- Hematology panel (hemoglobin [Hgb], white blood cell [WBC] count [with absolute count of lymphocytes, neutrophils, and eosinophils], and platelets)

- Serum chemistry panel (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin, blood urea nitrogen [BUN], creatinine, glucose, calcium [Ca], and potassium [K])

- Urinalysis (by dipstick testing of clean-catch sample; protein, glucose, blood, ketones, and leukocyte esterase)

The investigator may use clinical judgment when determining the clinical relevance of laboratory parameter findings throughout the study. Depending on study criteria, the medical monitor maybe consulted before enrollment about a potential participant with abnormal laboratory values. Guidance on abnormal laboratory values is given in Appendix B.

Total blood volume collected at this visit will be approximately 10 mL (approximately 5 mL each for the hematology and serum chemistry). Total urine volume collected will be approximately 30 mL for the urinalysis and for participants of childbearing potential, a urine pregnancy test.

5.2.2 Treatment Period (12 weeks, plasma donors; 4 weeks non-plasma donors)

During this period, participants will have visits and phone calls as outlined below. If the participant discontinues, effort should be made to conduct the assessments of the Week 12 visit or end-of-study visit for the participant at Week 4.

5.2.2.1 Vaccination Visit (Week 0, Day 0)

During this visit, the following activities will occur:

- Review of baseline health assessment and inclusion and exclusion criteria to confirm study eligibility

- Urine pregnancy test for participants of childbearing potential, performed within 24 hours preceding receipt of the study vaccine (if positive, a confirmatory blood test must be performed)

- Collection of 20 mL of blood to determine NAC
- Vital signs (temperature, blood pressure, heart rate, and respiratory rate) assessed before the injection and 30 minutes (± 5 minutes) after the injection
- Injection of rBV A/B
- Participant monitored for at least 30 minutes after injection for localized and systemic reactions, including vital signs taken at the end of the 30-minute period
- Reaction Recording Sheet – Participant Home Diary distributed to the participant to record injection site information and systemic reactions for 7 days post-vaccination, if any, as well as concomitant medications taken for potential reactions (copy of diary is in Appendix C)
- Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events distributed to the participant to record adverse events throughout the study (copy of recording sheet is in Appendix E)
- Home Concomitant Medications form distributed to the participant to record concomitant medications administered in association with severe or serious adverse events throughout the study (copy of concomitant medications form is in Appendix F)

Total blood volume collected at this visit will be 20 mL for NAC. Total urine volume collected at this visit will be approximately 5-10 mL for urine pregnancy test.

5.2.2.2 Plasma Donation Period (up to 14 weeks)

After receiving the rBV A/B vaccination, the participant may participate as a source plasma donor if they choose. A screening physical exam will be performed at the plasma collection center. Donor eligibility will be determined at the sponsor-approved, licensed source plasma collection center. Once donor eligibility has been confirmed, the participant may begin donating plasma beginning 1 week after vaccination up to twice weekly through Week 14 post-vaccination, consistent with FDA plasma donation regulations and guidelines.[2] Procedures associated with evaluation of donor eligibility at the plasmapheresis center are not associated with data collection in rBV A/B-CL-003 and will not be reported in the Clinical Study Report.

A 20 mL whole blood sample will be collected from the participant at each visit to the plasma collection center for NAC determination prior to plasmapheresis. Antibody titers against both botulinum toxin type A and type B will be recorded in the eCRF. The source plasma from plasmapheresis that has been fully tested and meets all requirements for use in manufacturing will be retained and is eligible for use in the production of BabyBIG.

Participants will be able to complete plasma donations at a maximum of twice a week up to 14 weeks after the rBV A/B injection so long as they continue to meet required eligibility criteria (see Appendix A). If a participant fails to meet donor criteria at any time during the plasmapheresis period, the participant will continue to be followed for safety according to the Schedule of Time and Events.

During the first visit to the plasma collection center, the following activities (associated with general FDA plasma donor requirements) will occur:

- Brief physical examination by a licensed physician or otherwise authorized designee at the plasma collection center (the medical exam for plasmapheresis is repeated on an annual basis)
- Measurement of vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Obtaining informed consent for plasma donation and procedures

COMPLETION OF DONOR HISTORY QUESTIONNAIRE (

- Appendix D)

- Finger prick for hemoglobin measurement and total serum protein measurement
- Approximately 10 mL of whole blood collected for atypical antibody measurements, serologic test for syphilis, and serum protein electrophoresis at 4-month intervals
- Plasma donation (takes approximately 1 to 1.5 hours) per the donation site's procedures
- Each donated unit will be tested for infectious markers using nucleic acid testing

During each subsequent visit to the plasma collection center, the following activities (associated with general FDA plasma donor requirements) will occur:

- Completion of the donor history questionnaire
- Measurement of vital signs (temperature, blood pressure, heart rate, and respiratory rate)
- Finger prick for hemoglobin measurement and total serum protein measurement
- Plasma donation (takes approximately 1 to 1.5 hours) per the donation site's procedures
- Each donated unit will be tested for infectious markers using nucleic acid testing

At 4-month intervals, the participant will have an additional tube of whole blood drawn at the plasmapheresis center for atypical antibody measurements and serum protein electrophoresis. These additional blood draw results are associated with general FDA plasma donor requirements and, therefore, will not be included among the study data.

5.2.2.3 Telephone Call (Week 1)

Study personnel will call participants at Week 1 (± 3 days) to review the Reaction Recording Sheet – Participant Home Diary injection site and systemic reactions, as well as any potential SAEs occurring over the past week including any serious NOCIs and any concomitant medications used to treat SAEs and serious NOCIs.

Study personnel should inquire about participants overall well-being and any concomitant medications. Participants should use the provided Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events form (Appendix E) and the Home Concomitant Medications form(Appendix F) between phone calls to assist during the inquiry. The information recorded by the delegated site personnel during the phone call will serve as the source documentation. All severe localized injection site reactions and severe systemic reactions and SAEs, including serious NOCIs, will be recorded in the eCRF; any concomitant medications used as treatment for these events will also be recorded.

5.2.2.4 Week 4 Final On Site Visit for Non-Donors and Week 4 Laboratory Draws

Participants not participating in plasma donation must return to the site at Week 4 (± 3 days) for their final study visit. During this visit, the following activities will occur:

- Injection site inspection
- Review of serious adverse events
- Review of any new onset chronic illnesses
- Collection of concomitant medication information, if any
- Collection of 20 mL of blood to determine NAC
- Urine pregnancy test for participants of childbearing potential
- Collection of approximately 5 mL blood for repeat hematology conducted at screening (Section 5.2.1)
- Completion of final on-site study record

Participants should use the provided Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events form (Appendix E) and the Home Concomitant Medications form (Appendix F) between visits to assist during the inquiry. The information recorded by the delegated site personnel during the visit will serve as the source documentation. Total blood volume collected at this visit will be approximately 25 mL (20 mL for NAC and approximately 5 mL for

hematology). Total urine volume collected will be approximately 5-10 mL for the urine pregnancy test.

All participants continuing in the study will go to a central lab or plasma center for hematology and NAC serum sample collection at Week 4. If a participant continuing in the study is not scheduled for plasmapheresis within the Week 4 study window, they will have a scheduled blood draw to provide a blood sample for NAC determination and an additional blood sample for the Week 4 hematology assessment.

5.2.2.5 Telephone Calls (Weeks 4 and 10)

Study personnel will call plasma donating participants at Weeks 4 (± 3 days) and 10 (± 3 days) to inquire about participants overall well-being, SAEs including serious injection site or systemic reactions and any serious NOCIs, if any, that occurred since the last visit or phone call, any concomitant medication used. SAEs, including serious NOCIs, serious injection site or systemic reactions and concomitant medication used as treatment will be recorded in the eCRF. Participants should use the provided Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events form (Appendix E) and the Home Concomitant Medications form (Appendix F) between phone calls to assist during the inquiry. The information recorded by the delegated site personnel during the phone call will serve as the source documentation.

5.2.2.6 Week 12 Visit

For all participants participating in plasma donation, the final on-site study visit must occur within 1 week of Week 12. During this visit, the following activities will occur:

- Injection site inspection
- Review of serious adverse events or serious NOCIs
- Collection of concomitant medication information used for treatment of any SAEs or serious NOCIs, if any
- Collection of 20 mL of blood to determine NAC

- Urine pregnancy test for participants of childbearing potential
- Completion of final on-site study record

Participants should use the provided Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events form (Appendix E) and the Home Concomitant Medications form (Appendix F) between visits to assist during the inquiry. The information recorded by the delegated site personnel during the visit will serve as the source documentation. Total blood volume collected at this visit will be 20 mL for NAC determinations. Total urine volume collected will be approximately 5-10 mL for the urine pregnancy test.

5.2.3 Final Study Follow-up (Week 26)

Within 1 week of Week 26, site personnel will contact all participants by phone to assess each participant's general health status. Interim occurrence of any SAEs or serious NOCIs will be queried for and recorded. Any concomitant medications used to treat SAEs or serious NOCIs will be recorded and entered in the eCRF.

Participants should use the provided Adverse Event Recording Sheet for Identification of Possible Serious Adverse Events form (Appendix E) and the Home Concomitant Medications form (Appendix F) between phone calls to assist during the inquiry. The information recorded by the delegated site personnel during the phone call will serve as the source documentation.

6.0 PROCEDURES FOR HANDLING SERIOUS ADVERSE EVENTS

6.1 DEFINITION OF A SERIOUS ADVERSE EVENT

In this clinical trial, a *serious adverse event* is defined as an AE that meets any of the following criteria:

- Results in death
- Is life-threatening

  The term *life-threatening* in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event. *Life-threatening* does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalization or a prolongation of an existing hospitalization

  In general, hospitalization signifies that the participant has been detained at the hospital or emergency department for observation or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs, but not necessarily SAEs. An occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a preexisting condition that did not worsen from its original baseline level is not considered an SAE.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  This definition is not intended to include AEs of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- A congenital anomaly or birth defect

- Other important medical events

  Medical or scientific judgment should be exercised in deciding whether reporting is appropriate for other important medical events that may not result in death, be life threatening, or require hospitalization but still may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An SAE requires additional detailed reports and follow-up. The content of these detailed reports must address the investigator's estimate of causality. The medical monitor will review the SAE to determine if it is an expected SAE (i.e., whether or not the SAE is identified in nature, severity, or frequency in the Investigator's Brochure).

The investigator is responsible for performing periodic and specific assessments for SAEs at study visits. The investigator and clinical staff will note all SAEs mentioned by the participant during and after administration of the investigational product until the end of the study. All clinical complaints volunteered by, or elicited from, the participant during the study will be recorded on the appropriate page of the source documentation for the indicated study period. Information related to serious adverse events will be recorded on the eCRF. The participant will receive appropriate treatment guidance for any SAE that occurs.

All SAEs judged to be clinically significant, including clinically significant laboratory abnormalities, will be followed until resolution or considered stable by the investigator. All SAEs will be summarized in the annual report or more frequently, if requested by the regulatory agency. Serious adverse events require special reporting in addition to documentation in the eCRF as described in Section 6.2.

6.2 RECORDING SERIOUS ADVERSE EVENTS

When an SAE occurs, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relevant to the event(s). The investigator will record all relevant information about

the SAEs on the SAE page of the eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of the properly completed SAE pages of the eCRF. These types of documents should not be sent unless they are specifically requested by pharmacovigilance. If this request occurs, all participant identifiers and protected health information will be blinded on the copies of the medical records before submission to the appropriate authorities.

The investigator will also attempt to report a diagnosis versus signs, symptoms, or other clinical information for the SAE. The diagnosis, not the individual signs and symptoms, should be documented on the appropriate page of the eCRF as the SAE. In addition, SAEs need to be reported on the SAE report form.

6.3 ASSESSMENT OF SEVERITY

The investigator will assess the severity for each SAE reported during the study. The assessment will be based on the investigator's clinical judgment.

The classifications in Table 3 should be used in assigning severity of each AE recorded in the eCRF. Additional guidance is provided in Appendix B for specific AEs, laboratory abnormalities, and changes in vital signs.

Table 3. Classification of AEs by Severity

Severity	Definition
Grade 1 Mild AE	Transient or mild discomfort (<48 hours); no medical intervention or therapy required
Grade 2 Moderate AE	Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention or therapy required
Grade 3 Severe AE	Marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization possible
Grade 4 Life-threatening AE or Death	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

AE = adverse event.

Any SAE that changes in severity during its course will be recorded in the eCRF at the highest level experienced by the participant.

Severity of an AE is graded as follows: Mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening or death (Grade 4). An AE that is assessed as severe should not be confused with an SAE. An event may be of relatively minor medical significance, such as a severe headache, but not be considered an SAE. Both AEs

and SAEs can be assessed as severe. An AE is defined as serious when it meets one of the predefined outcomes as described in Section 6.1.

6.4 ASSESSMENT OF CAUSALITY

The investigator must estimate the relationship between the investigational product and the occurrence of each SAE by using his or her best clinical judgment. Elements to consider include the history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product. The investigator will also consult the Investigator's Brochure or product-labeling information for marketed products in estimating the relationship.

Because of reporting timelines, the investigator might have minimal information to include in the initial SAE report. However, the investigator must always assess causality for every event prior to the transmission of the SAE report. The investigator may change their opinion of the causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank. Table 4 provides the definitions to use in the assessment.

Table 4. Assessment of Causality of Adverse Events

Term	Definition
Definitely	The AE follows a reasonable temporal sequence from treatment and is consistent with the Investigator's Brochure.
Probably	• The AE follows a reasonable temporal sequence from the administration of the investigational drug. • The AE cannot be easily explained from the participant's clinical condition, environmental or toxic factors, or other therapy administration. • The AE disappears or diminishes on cessation or reduction in dose, except in case of irreversible damage (positive de-challenge). • The AE follows a known pattern or response of the investigational drug. • The AE reappears upon re-administration of the investigational drug (positive re-challenge).
Possibly	• The AE follows a reasonable temporal sequence from the administration of the investigational drug. • The AE cannot easily be explained from the participant's clinical condition, environmental or toxic factors, or other therapy administration. • The AE follows a known pattern or response of the investigational drug. • The AE disappears or diminishes on cessation or reduction in dose, except in case of irreversible damage (positive de-challenge).
Unlikely	• The AE follows a reasonable temporal sequence from administration of the investigational drug. • The AE can be easily explained from the participant's clinical condition, environmental or toxic factors, or other therapy administration. • The AE does not follow a known response pattern of the investigational drug.
Not Related	• The AE does not follow a reasonable temporal sequence from administration of the investigational drug and occurrence of the AE. • The AE could readily have been produced by the participant's clinical state, environmental or toxic factors, or other therapy administration. • The AE does not follow a known response pattern to the investigational drug. • The AE does not reappear or worsen when the investigational drug is re-administered (negative re-challenge).

AE = adverse event.

6.5 EXPECTEDNESS OF ADVERSE EVENTS

An expected AE is one that is consistent with the known risk information described in the current Investigator's Brochure. An AE is considered unexpected if it is not listed the in the Investigator's Brochure or it is not listed at the specificity or severity that has been observed. This will be assessed by the medical monitor or sponsor-investigator upon receipt of the initial AE report.

6.6 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest that are particularly specific to this study will be collected, assessed and recorded in the eCRF as an AE. These events of special interest will be collected in addition to the SAEs described in Section 6.1 and include the following clinical situations (see safety endpoints in Section 2.0):

- Frequency of injection site reactions and systemic reactions among the study participants that are assessed as severe between Days 0 and 7 will be captured as an AE

- Clinically significant changes in hematology between screening and Week 4 that are assessed as severe will be captured as an AE

6.7 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE occurring after the participant has been vaccinated with rBV A/B must be reported to the medical monitor and sponsor-investigator by phone, fax, or e-mail within 24 hours of the time the investigator becomes aware of the SAE (Table 5). Urgent reporting of SAEs is required for the following reasons:

1. To enable the sponsor-investigator to fulfill the reporting requirements to the appropriate regulatory authority

2. To facilitate the sponsor-investigator's rapid dissemination of information about SAEs to other investigators or sites in a multicenter study

3. To facilitate reporting unanticipated and/or serious problems involving risk to participants to the IRB within 48 hours

Table 5. Timeline for Reporting Serious Adverse Events to Medical Monitor and Sponsor-Investigator

Initial SAE Report		Follow-up SAE Report	
Time Frame	**Documents**	**Time Frame**	**Documents**
24 hours	SAE report	7 days	Updated SAE report

SAE = serious adverse event.

The SAE report form will be completed as thoroughly as possible, including the following information:

- Participant identification information
- All available details about the event
- Causality of each SAE
- Signature of the investigator

The SAE report will be forwarded to the DSMB within the designated time frames. If the investigator does not have all information about an SAE, the investigator will NOT wait to receive additional information before notifying the DSMB of the SAE and completing the form. The form will be updated when additional information is received.

IND Safety Reports: The investigator will report a suspected adverse reaction that is both “serious” and “unexpected” to FDA in accordance with the timeframe outlined in 21 CFR 312.32. FDA and all participating investigators will be notified of potentially serious risks identified from any source within 15 calendar days after the sponsor-investigator receives the safety information and determines that it is reportable [21 CFR312.32 (c) (1)]. The sponsor-investigator must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor-investigator’s initial receipt of the information.

6.8 FOLLOW-UP OF SERIOUS ADVERSE EVENTS

All SAEs (as well as clinically significant changes in hematology that result in a severe or serious adverse event) will be followed until the occurrence of one of the following:

- The event resolves
- The condition stabilizes
- The event is otherwise explained
- The participant is lost to follow-up

The appropriate SAE report form will be updated for SAEs only once the SAE resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up. The investigator will also ensure that additional updates include any supplemental data that may explain causality of the event(s).

New or updated information will be recorded on a copy of the initially completed SAE report, with all the changes signed and dated by the investigator or designee. The updated SAE report will then be signed by the investigator and resubmitted to the DSMB as outlined in Table 5.

6.9 INJECTION SITE AND SYSTEMIC REACTIONS

Commonly seen injection site reactions for rBV A/B are consistent with reactions in participants vaccinated with other recombinant protein vaccines that include Alhydrogel™. The majority of reactions at the injection site seen to date with rBV A/B have been mild or moderate in severity and included erythema, pain, pruritus, and swelling. Participants will be actively monitored for localized and systemic reactions to the injections and an anaphylaxis (epinephrine) kit will be available at the time of injections.

The definitions to be used to determine severity of injection site reactions are provided in Table 6.

Table 6. Protocol Definitions for Severity of Injection Site, i.e., Local Reactions

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Injection site pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Injection site tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Injection site erythema (redness)[a]	2.5-5.0 cm	5.1-10.0 cm	>10.0 cm	Bullae, necrosis, or exfoliative dermatitis
Injection site swelling (induration)[b]	2.5-5.0 cm and does not interfere with activity	5.1-10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis

ER = emergency room.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration (swelling) should be evaluated and graded using the functional scale as well as the actual measurement.

Systemic reactions collected in the diary are severity of muscle weakness, malaise, rash, headache, nausea, chest discomfort, breathing difficulties, anxiety, feelings of depression, and neuromuscular TEAEs. For systemic reactions, use the guidance provided in Appendix B.

6.10 DATA AND SAFETY MONITORING BOARD

The DSMB will meet quarterly throughout the study and as needed as described in Section 4.4. The specific information that will be reviewed to make its recommendation will be safety data and neutralizing antibody concentrations.

In addition, the DSMB will convene at any time during the study if a stopping rule is met (see Section 4.4.2)

6.11 PREGNANCY

If a participant becomes pregnant at any time after receipt of the study vaccine, they should report the pregnancy via telephone to the study investigators within 24 hours

of being made aware of it; study investigators will then promptly complete the pregnancy report form and forward the form to the medical monitor and sponsor-investigator. The participant will be discontinued from further study procedures, including plasmapheresis. The pregnancy will be followed until there is an outcome, and the outcome is reported to the study investigators.

7.0 STUDY OR SITE TERMINATION AND PARTICIPANT DISCONTINUATION

7.1 PARTICIPANT DISCONTINUATION

Participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation of the reason for discontinuation in a source document, which will be transcribed to the appropriate eCRF page. If a participant withdraws before completion, every effort should be made to complete the assessments scheduled during the final on-site study visit. In addition, the participant will be offered safety follow-up for the planned duration of the study (through the Week 26 telephone contact) regardless of the reason for discontinuation.

A participant may be removed from the study for the reasons described in Section 7.1.1 through Section 7.1.5.

7.1.1 Adverse Event

If a participant suffers an AE that, in the judgment of the investigator, the sponsor-investigator, or the medical monitor, presents an unacceptable consequence or risk to the participant, the participant may be discontinued from the study.

7.1.2 Intercurrent Illness

A participant may be discontinued from the study if, in the judgment of the investigator, the participant develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study.

7.1.3 Noncompliance

After consultation among the investigator, the medical monitor, and study/data monitor, a participant may be discontinued from the study for failure to comply with protocol requirements. Upon being discontinued from the study, the participant will be notified by study personnel and the reason for discontinuation documented in the appropriate eCRF page and on study source documents.

7.1.4 Refusal of Investigational Product Administration

Any participant refusing vaccination with rBV A/B for any reason will be discontinued from the study, and the reason(s) will be documented on the appropriate eCRF page. No further assessments will be performed on participants who refuse vaccination with rBV A/B.

7.1.5 Withdrawal of Consent

Any participant that withdraws consent for any reason at any time during the study will be discontinued from the study, and the reason(s) will be documented on the appropriate eCRF page.

7.2 PREMATURE STUDY OR SITE TERMINATION

If the sponsor, investigator, medical monitor, study/data monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the site should be terminated, this action may be taken after appropriate consultation among the sponsor-investigator, medical monitor, and study/data monitor. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the participants enrolled in the study

- A decision on the part of the sponsor-investigator or product manufacturer to suspend or discontinue testing, evaluation, or development of the product

A study conducted at a single site in a multicenter study may also warrant termination under the following conditions:

- Failure of the investigator to enroll participants into the study at an acceptable rate

- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities

- Submission of knowingly false information from the site to the sponsor-investigator, study/data monitor, or appropriate regulatory authority

- Insufficient adherence to protocol requirements

Study termination and follow-up will comply with the conditions set forth in the ICH E6 Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

8.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

8.1 DATA COLLECTION AND PROCESSING

eCRFs will be used to capture study assessments and data. The study investigator or other delegated study personnel will enter data from source documents into the eCRFs. All eCRFs and their data will be reviewed, and source verified by the study/data monitor. The medical monitor may examine the eCRFs for preliminary medical review. Once the eCRFs are completed and source-verified, the study investigator will sign and date all required pages, thereby verifying the accuracy of all data contained in the eCRFs.

8.2 STATISTICAL ANALYSIS

8.2.1 General Overview

The data will be summarized in tables listing the mean, standard deviation, or standard error, median, minimum, maximum, and number of participants for continuous data or in tables listing count and percentage for categorical data, where appropriate. Data will be listed by "participant ID." All statistical analyses will be performed, and data appendices will be created using SAS.

8.2.2 Populations of Interest

8.2.2.1 Immunogenicity Population

The immunogenicity population defines participants who have received 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.

8.2.2.2 Per Protocol Population

The per protocol population defines participants who have received the vaccine dose, have a baseline NAC, and have the relevant immunogenicity assessments completed within the protocol-specified timelines (including visit windows) for the time point(s) summarized and who do not have major protocol violations expected to affect immunogenicity. Determination of a major protocol violation expected to

affect immunogenicity will be done by the sponsor-investigator before reviewing the immunogenicity data for the applicable participant. The precise reasons for excluding participants from the per protocol population will be fully defined and documented. (Note: It is possible for a participant to be included in the primary per protocol analysis for Week 4, even if the subsequent blood draws occur outside of the study windows.)

8.2.2.3 Safety Population

The safety population comprises all participants enrolled into the study who received the vaccine dose and had at least one post-baseline safety assessment (this assessment can include a response from a participant that no adverse events occurred).

8.2.2.4 Plasma-Donating Population

The plasma-donating population will include all participants who receive the vaccine and donate at least one plasma unit.

8.2.3 Baseline Comparability

No formal baseline comparability testing is planned for this study.

8.2.4 Immunogenicity Analysis

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

The immunogenicity parameters are concentrations of neutralizing antibodies against botulinum toxin type A and toxin type B. These parameters will be analyzed by using NAC data from a validated mouse neutralization assay.

For the primary endpoint, a positive response will be defined as achieving a greater than or equal to four times increase (point estimate) above baseline in NAC by Week 4 compared with Week 0 in at least 50% of the participants in the immunogenicity population for botulinum toxin type A and type B, respectively. A

point estimate and two-sided 95% confidence interval for the proportion of participants who achieve this endpoint will be provided.

For the first secondary immunogenicity endpoint, a positive response will be defined as achieving a two times increase above baseline in the estimated area under the plasma NAC-time curve in the period from Week 0 to Week 12 in comparison to a straight-line extension of the Week 0 antibody concentration to Week 12 NAC in least 50% of the participants in the immunogenicity population for botulinum toxin type A and type B, respectively.

For the second secondary immunogenicity endpoint, a positive response will be defined as is achieving a three times or greater increase in NAC above baseline by Week 4 in at least 50% of the participants in the immunogenicity population for botulinum toxin type A and type B, respectively. A point estimate and two-sided 95% confidence interval for the proportion of participants who achieve this endpoint will be provided.

Further details of the analysis will be provided as needed in a separate statistical analysis plan.

In the event that the primary endpoint is not met for neutralizing antibodies against botulinum toxin type A and 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 the immune responses meet specifications to permit the production of BabyBIG, then the trial will still be considered successful. Also, a second booster dose of rBV A/B vaccine may be considered; however, this will require operational modifications (e.g., a protocol amendment and updated consent form).

8.2.5 Safety Analysis

The safety analysis will use the safety population.

Localized and systemic severe AEs and SAEs collected from the Week 1 telephone call will be summarized by category and severity. A point estimate of incidence, with 95% confidence limits will be computed and reported (not coded into the Medical Dictionary for Regulatory Activities [MedDRA] terminology or assessed for relatedness). The time period summarized will include throughout the study as

a whole and again within Days 0 through 7. For tables summarizing severity, the highest reported severity grade will be used. In addition, the average duration, by category, will be summarized.

All other SAE data will be listed individually and summarized by system organ class and preferred terms for each treatment group. When calculating the incidence of SAEs, each SAE based on preferred terminology from MedDRA will be counted only once for a given participant. If the same SAE occurs on multiple occasions in a participant, the occurrence with the highest severity and highest causality relationship to the vaccine will be reported. If two or more SAEs are reported as a unit, the individual terms will be reported as separate experiences.

Summaries of clinically significant changes in hematology between screening and Week 4 resulting in a severe AE or SAE will be listed. Treatment-emergent abnormal laboratory values that occur prior to the end of the study will be summarized. Laboratory abnormalities will be assessed for relatedness. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

Presentation of relatedness in tables will be based on the investigator's assessment.

8.2.6 Sample Size

No formal power calculations will be performed for this study. The sample size will consist of up to 30 participants. On the basis of prior sponsor-investigator experience, this sample size is considered adequate for fulfilling the study objectives.

9.0 CLINICAL STUDY ADMINISTRATION

9.1 INFORMED CONSENT WITH AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written informed consent with authorization of use and disclosure of protected health information must be obtained from each participant before performing any study-specific screening/baseline period evaluations. The informed consent form that includes authorization for use and disclosure of protected health information must have been reviewed and approved by the sponsor-investigator, the study/data monitor, and the investigator's IRB prior to the initiation of the study. The ICF will conform to the 20 elements of informed consent described in ICH E6, Section 4.8 and will include the elements required by Title 45 of the Code of Federal Regulations, Section 164.508(b), and any local regulations for valid authorizations. One copy of the signed ICF with authorization for use and disclosure of protected health information form will be given to the participant, and the investigator will retain the original in the Investigators' Study Files.

9.2 STUDY DOCUMENTATION

9.2.1 Investigator Information

Investigator information is included in the study procedure manual, which is updated as needed.

9.2.2 Investigators' Study Files

Documentation about the investigator and study staff, the IRB, and the institution is required before study site initiation. Copies of these documents will be kept on-site in study site–specific binders or files, along with the following supplemental information: a list of investigator's obligations; the current Investigator's Brochure; the clinical trial protocol and amendments; safety information; information about investigational product, biological samples, and the laboratory; the study procedure manual and study logs; and records of monitoring activities.

The investigator is responsible for ensuring frequent backup of all electronic data systems used for primary documentation or source documentation. Electronic

(eCRF) data will be backed up periodically as described in the EDC vendor's standard operating procedures.

9.2.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the study/data monitor, other authorized representatives of the sponsor-investigator, and the appropriate regulatory authority inspectors. The eCRF for each participant will be checked against source documents at the study site by the study/data monitor, and a final copy of the eCRF will be signed by the investigator with an electronic signature. A copy of the final eCRFs will be provided to the investigator in portable document format on computer disc after study closure to be kept in the investigator's study files.

9.2.4 Retention of Study Documents

According to ICH E6, Section 4.9, all eCRFs, as well as supporting paper and electronic source documentation and administrative records, must be retained by the investigator until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product in the United States. The sponsor-investigator is responsible for informing the investigator and institution as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the sponsor-investigator. If the investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to a designee approved by the sponsor-investigator, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the participant electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

9.3 CONFIDENTIALITY

9.3.1 Data

The investigator shall keep all information about the nature of the proposed investigation provided by the sponsor-investigator or study monitor to the investigator confidential (with the exception of information required by law or regulations to be disclosed to the IRB, the participant, or the appropriate regulatory authority). Additionally, de-identified data (safety and immunological) will be disclosed to JPEO-CBRND on behalf of TSG-DA for possible safety reporting required by regulatory authorities.

9.3.2 Participant Anonymity

The anonymity of participating participants must be maintained. Participants will be identified by an assigned participant number on eCRFs and other documents retrieved from the site or sent to the study/data monitor, sponsor-investigator, regulatory agencies, central laboratories, or blinded reviewers. Documents that identify the participant (e.g., the signed ICF) must be maintained in strict confidence by the investigator and designated study staff, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study/data monitor, or sponsor-investigator representatives.

9.4 PROTOCOL COMPLIANCE AND AMENDMENT PROCEDURES

Substantive changes in the protocol include changes that affect the safety of participants or changes that meaningfully alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of participants treated, or the participant selection criteria. Such changes must be prepared as a protocol amendment by the sponsor-investigator and implemented only upon joint approval of the sponsor-investigator and the IRB. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes to the ICF, the revised ICF prepared by the investigator must also be approved by the sponsor-investigator, study/data monitor, and the IRB before implementation.

Deviations from the protocol are allowed only in situations for which the deviation would eliminate an immediate risk to a participant and that are deemed crucial for the safety and well-being of that participant. The investigator or the attending physician also will contact the medical monitor as soon as possible in the case of such a deviation. These deviations do not require preapproval by the IRB; however, the IRB and medical monitor must be notified in writing or via e-mail as soon as possible after the deviation occurs. In addition, the investigator will document in the participant's eCRF the reasons for the protocol deviation and the ensuing events.

9.5 STUDY/DATA MONITOR FUNCTIONS AND RESPONSIBILITY

The study/data monitor, in accordance with the sponsor-investigator's requirements, will ensure that the clinical trial is conducted and documented properly by carrying out the activities outlined in ICH E6, Section 5.18.4.

10.0 REFERENCES

1. Centers for Disease Control and Prevention. Notice of CDC's discontinuation of investigational pentavalent (ABCDE) botulinum toxoid vaccine for workers at risk for occupational exposure to botulinum toxins. MMWR 2011;60(42):1454-1455.

2. U.S. Department of Health and Human Services, Food and Drug Administration. Code of Federal Regulations Title 21, Part 630 Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use. Revised 22 May 2015; Available at: eCFR :: 21 CFR Part 630 -- Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use.

APPENDICES

APPENDIX A

CODE OF FEDERAL REGULATIONS PART 630: REQUIREMENTS FOR BLOOD AND BLOOD COMPONENTS INTEDED FOR TRANSFUSION OR FOR FURTHER MANUFACTURING USE AND PART 640: ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

CODE OF FEDERAL REGULATIONS PART 630.10: GENERAL DONOR ELIGIBILITY REQUIREMENTS AND PART 640 SUBPART G: SOURCE PLASMA

630.10 General donor eligibility requirements:

(a) What factors determine the eligibility of a donor? You, an establishment that collects blood or blood components, must not collect blood or blood components before determining that the donor is eligible to donate or before determining that an exception to this provision applies. To be eligible, the donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes in this subchapter. A donor is not eligible if the donor is not in good health or if you identify any factor(s) that may cause the donation to adversely affect:

(1) The health of the donor; or

(2) The safety, purity, or potency of the blood or blood component.

(b) What educational material must you provide to the donor before determining eligibility? You must provide educational material concerning relevant transfusion-transmitted infections to donors before donation when donor education about that relevant transfusion-transmitted infection, such as HIV, is necessary to assure the safety, purity, and potency of blood and blood components. The educational material must include an explanation of the readily identifiable risk factors closely associated with exposure to the relevant transfusion-transmitted infection. You must present educational material in an appropriate form, such as oral, written or multimedia, and in a manner designed to be understood by the donor. The educational material must instruct the donor not to donate blood and blood components when a risk factor is present. When providing educational material to donors under this section, you may include in those materials the information required to be provided to donors under paragraph (g)(2)(ii)(E) of this section.

(c) When must you determine the eligibility of a donor? You must determine donor eligibility on the day of donation, and before collection. Except:

(1) When a donor is donating blood components that cannot be stored for more than 24 hours, you may determine the donor's eligibility and collect a sample for testing required under §610.40 of this chapter, no earlier than 2 calendar days before the day of donation, provided that your standard operating procedures address these activities.

(2) In the event that, upon review, you find that a donor's responses to the donor questions before collection were incomplete, within 24 hours of the time of collection, you may clarify a donor's response or obtain omitted information required under paragraph (e) of this section, provided that your standard operating procedures address these activities.

(d) How must you determine the eligibility of a donor? You must determine the donor's eligibility before collection of blood or blood components, by the following procedures:

(1) You must consult the records of deferred donors maintained under §606.160(e)(1) and (2) of this chapter. Exception: If pre-collection review of the record described in §606.160(e)(2) of this chapter is not feasible because you cannot consult the cumulative record at the collection site, you must consult the cumulative record prior to release of any blood or blood component prepared from the collection.

(2) Assure that the interval since the donor's last donation is appropriate;

(3) Assess the donor's medical history; and

(4) Perform a physical assessment of the donor.

(e) How do you assess the donor's medical history? Before collection you must conduct a medical history interview as described in this section to determine if the donor is in good health; to identify risk factors closely associated with exposure to, or clinical evidence of a relevant transfusion-transmitted infection; and to determine if there are other conditions that may adversely affect the health of the donor or the safety, purity, or potency of the blood or blood components or any product manufactured from the blood or blood components. Your assessment must include each of the following factors:

(1) Factors that make the donor ineligible to donate because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection. A donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection if that risk of exposure is still applicable at the time of donation. Information and evidence indicating possible exposure to a relevant transfusion-transmitted infection include:

(i) Behaviors associated with a relevant transfusion-transmitted infection;

(ii) Receipt of blood or blood components or other medical treatments and procedures associated with possible exposure to a relevant transfusion-transmitted infection;

(iii) Signs and/or symptoms of a relevant transfusion-transmitted infection;

(iv) Institutionalization for 72 hours or more consecutively in the past 12 months in a correctional institution;

(v) Intimate contact with risk for a relevant transfusion-transmitted infection; and

(vi) Nonsterile percutaneous inoculation.

(2) Other factors that make the donor ineligible to donate. A donor is ineligible to donate when donating could adversely affect the health of the donor, or when the safety, purity, or potency of the blood or blood component could be affected adversely. Your assessment of the donor must include each of the following factors:

(i) Symptoms of a recent or current illness;

(ii) Certain medical treatments or medications;

(iii) Travel to, or residence in, an area endemic for a transfusion-transmitted infection, when such screening is necessary to assure the safety, purity, and potency of blood and blood components due to the risks presented by donor travel and the risk of transmission of that transfusion-transmitted infection by such donors;

(iv) Exposure or possible exposure to an accidentally or intentionally released disease or disease agent relating to a transfusion-transmitted infection, if you know or suspect that such a release has occurred;

(v) Pregnancy at the time of, or within 6 weeks prior to, donation;

(vi) Whether, in the opinion of the interviewer, the donor appears to be under the influence of any drug, alcohol or for any reason does not appear to be providing reliable answers to medical history questions, or if the donor says that

the purpose of donating is to obtain test results for a relevant transfusion-transmitted infection; and

(vii) The donor is a xenotransplantation product recipient.

(f) How do you perform a physical assessment of the donor? You must determine on the day of donation, and before collection that the donor is in good health based on the following, at a minimum:

(1) Temperature. The donor's oral body temperature must not exceed 37.5 °C (99.5 °F), or the equivalent if measured at another body site;

(2) Blood pressure. The donor's systolic blood pressure must not measure above 180 mm of mercury, or below 90 mm of mercury, and the diastolic blood pressure must not measure above 100 mm of mercury or below 50 mms of mercury. A donor with measurements outside these limits may be permitted to donate only when the responsible physician examines the donor and determines and documents that the health of the donor would not be adversely affected by donating.

(3) Hemoglobin or hematocrit determination. You must determine the donor's hemoglobin level or hematocrit value by using a sample of blood obtained by fingerstick, venipuncture, or by a method that provides equivalent results. Blood obtained from the earlobe is not acceptable.

(i) Allogeneic donors must have a hemoglobin level or hematocrit value that is adequate to assure donor safety and product potency. The following minimum standards apply.

(A) Female allogeneic donors must have a hemoglobin level that is equal to or greater than 12.5 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 38 percent. Recognizing that lower levels are also within normal limits for female donors, you may collect blood from female allogeneic donors who have a hemoglobin level between 12.0 and 12.5 grams per deciliter of blood, or a hematocrit value between 36 and 38 percent, provided that you have taken additional steps to assure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation, in accordance with a procedure that has been found acceptable for this purpose by FDA.

(B) Male allogeneic donors must have a hemoglobin level that is equal to or greater than 13.0 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 39 percent.

(ii) An autologous donor must have a hemoglobin level no less than 11.0 grams of hemoglobin per deciliter of blood, or a hematocrit value no less than 33 percent.

(4) Pulse. The donor's pulse must be regular and between 50 and 100 beats per minute. A donor with an irregular pulse or measurements outside these limits may be permitted to donate only when the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.

(5) Weight. The donor must weigh a minimum of 50 kilograms (110 pounds).

(6) Skin examination.

(i) The donor's phlebotomy site must be free of infection, inflammation, and lesions; and

(ii) The donor's arms and forearms must be free of punctures and scars indicative of injected drugs of abuse.

(g) Are there additional requirements for determining the eligibility of the donor? You must obtain the following from the donor on the day of donation:

(1) Proof of identity and postal address. You must obtain proof of identity of the donor and a postal address where the donor may be contacted for 8 weeks after donation; and

(2) Donor's acknowledgement.

(i) Prior to each donation, you must provide information to the donor addressing the elements specified in paragraphs (g)(2)(ii)(A) through (E) of this section and obtain the donor's acknowledgement that the donor has reviewed the information. You must establish procedures in accordance with § 606.100 of this chapter to assure that the donor has reviewed this material and provide for a signature or other documented acknowledgement.

(ii) The donor acknowledgement must not include any exculpatory language through which the donor is made to waive or appear to waive any of the donor's legal rights. It must, at a minimum clearly address the following:

(A) The donor has reviewed the educational material provided under paragraph (b) of this section regarding relevant transfusion-transmitted infections;

(B) The donor agrees not to donate if the donation could result in a potential risk to recipients as described in the educational material;

(C) A sample of the donor's blood will be tested for specified relevant transfusion-transmitted infections;

(D) If the donation is determined to be not suitable under § 630.30(a) or if the donor is deferred from donation under § 610.41 of this chapter, the donor's record will identify the donor as ineligible to donate and the donor will be notified under § 630.40 of the basis for the deferral and the period of deferral;

(E) The donor has been provided and reviewed information regarding the risks and hazards of the specific donation procedure; and

(F) The donor has the opportunity to ask questions and withdraw from the donation procedure.

(h) What must you do when a donor is not eligible? You must not collect blood or blood components from a donor found to be ineligible prior to collection based on criteria in §§ 630.10 or 630.15, or deferred under § 610.41 of this chapter or § 630.30(b)(2), unless this subchapter provides an exception. You must defer donors found to be ineligible and you must notify the donor of their deferral under § 630.40.

Part 640 Subpart G—Source Plasma

The proper name of the product shall be Source Plasma. The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

640.64 – Collection of blood for Source Plasma

(a) [Reserved]

(b) Blood containers. Blood containers and donor sets must be pyrogen-free, sterile, and identified by lot number.

(c) The anticoagulant solution. The anticoagulant solution must be sterile and pyrogen-free. Anticoagulant solutions must be compounded and used according to a formula that has been approved for the applicant by the Director, Center for Biologics Evaluation and Research.

(d) Donor identification. Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) Prevention of contamination of the blood and plasma. The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

640.65 Plasmapheresis

(a) Procedure-general. The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the biologics license application.

(b) Procedures-specific requirements. The plasmapheresis procedure shall meet the following requirements:

(1)

(i) Except as provided under § 630.25 of this chapter, the responsible physician must draw a sample of blood from each donor on the day of the initial physical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent

test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: Provided, That no longer than 6 months has elapsed since the last sample was collected, and the responsible physician approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4–month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as prescribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)

(i) Except as provided under § 630.25 of this chapter, the responsible physician must review the accumulated laboratory data, including any tracings of the plasma or serum protein electrophoresis pattern, the calculated values of the protein composition of each component, and the collection records within 14 calendar days after the sample is drawn to determine whether or not the donor should be deferred from further donation. If a determination is not made within 14 calendar days, the donor must be deferred pending such a determination. The responsible physician must sign the review. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein level is less than 6.0 grams per deciliter or more than 9.0 grams per deciliter in a plasma sample or serum sample, the donor must be deferred from donation until the protein composition returns to acceptable levels. Reinstatement of the donor into the plasmapheresis program when the donor's protein composition values have returned to an acceptable level must first be approved by the responsible physician.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b)(2) (iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: Provided, That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-

positive reaction and indicates that the responsible physician has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: Provided, That the responsible physician approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,400 milliliters.

(6) No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case no more than 600 milliliters of whole blood shall be removed from the donor at one time.

(7) The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

(8) The volume of plasma collected during an automated plasmapheresis collection procedure shall be consistent with the volumes specifically approved by the Director, Center for Biologics Evaluation and Research, and collection shall not occur less than 2 days apart or more frequently than twice in a 7-day period.

640.66 Immunization of Donors

If specific immunization of a donor is to be performed, the selection, scheduling and administration of the antigen, and the evaluation of each donor's clinical response, shall be by the responsible physician. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

640.67 Laboratory Tests

Each unit of Source Plasma shall be tested for evidence of infection due to relevant transfusion-transmitted infections as required under § 610.40 of this chapter.

APPENDIX B

TOXICITY TABLES FROM GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT PARTICIPANTS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Table 7. Clinical Abnormalities from Vital Signs

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b] (°F)[b]	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40.0 102.1-104.0	>40.0 >104.0
Tachycardia (beats per minute)	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia[c] (beats per minute)	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension: systolic (mm Hg)	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension: diastolic (mm Hg)	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension: systolic (mm Hg)	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17-20	21-25	>25	Intubation

ER = emergency room.

a Participant should be at rest for all vital sign measurements.

b Oral temperature should be taken, and there should be no consumption of recent hot or cold beverages or smoking.

c Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example conditioned athletes.

Table 8. Systemic Clinical Abnormalities

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity, or 1 to 2 episodes per 24 hours	Some interference with activity or >2 episodes per 24 hours	Prevents daily activity, requires outpatient intravenous hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools or <400 g per 24 hours	4 to 5 stools or 400 to 800 g per 24 hours	6 or more watery stools or >800 g per 24 hours or requires outpatient intravenous hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event	No interference with activity	Some interference with activity, but not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

ER = emergency room.

Table 9. Modified Table for Laboratory Abnormalities

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Glucose: hypoglycemia (mg/dL)	65–69	55–64	45–54	<45
Glucose: hyperglycemia fasting (mg/dL); random (mg/dL)	100–110 110–125	111–125 126–200	>125 >200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen (mg/dL)	23–26	27–31	>31	Requires dialysis
Creatinine (mg/dL)	1.5–1.7	1.8–2.0	2.1–2.5	>2.5 or requires dialysis
Alkaline phosphate: increase by factor	1.1–2.0 × ULN	2.1–3.0 × ULN	3.1–10 × ULN	>10 × ULN
Liver function tests: ALT, AST, increase by factor	1.1–2.5 × ULN	2.6–5.0 × ULN	5.1–10 × ULN	>10 × ULN
Bilirubin: when accompanied by any increase in liver function test, increase by factor	1.1–1.25 × ULN	1.26–1.5 × ULN	1.51–1.75 × ULN	>1.75 × ULN
Bilirubin: when liver function test is normal, increase by factor	1.1–1.5 × ULN	1.6–2.0 × ULN	2.0–3.0 × ULN	>3.0 × ULN
Potassium - Hyperkalemia (mEq/L)	5.1–5.2	5.3–5.4	5.5–5.6	>5.6
Potassium - Hypokalemia (mEq/L)	3.5–3.6	3.3–3.4	3.1–3.2	<3.1
Calcium - Hypocalcemia (mg/dL)	8.0–8.4	7.5–7.9	7.0–7.4	<7.0
Calcium - Hypercalcemia (mg/dL)	10.5–11.0	11.1–11.5	11.6–12.0	>12.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the normal range.

a The laboratory values provided in the table serve as guidelines and are dependent on institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that the laboratory values are appropriate.

b The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low potassium value that falls within a Grade 3 parameter should be recorded as a Grade 4 hypokalemia event if the participant had a new arrhythmia event associated with the low potassium value.

Table 10. Modified Hematology Clinical Abnormalities

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin: female (g/dL)	11.0-12.0	9.5-10.9	8.0-9.4	<8.0
Hemoglobin: male (g/dL)	12.5-13.5	10.5-12.4	8.5-10.4	<8.5
WBC increase (cell/mm^3)	10.800-15,000	15,001-20,000	20,001-25,000	>25,000
WBC decrease (cell/mm^3)	2,500-3, 500	1,500-2,499	1,000-1,499	<1,000
Lymphocytes decrease (cell/mm^3)	750-1,000	500-749	250-499	<250
Neutrophils decrease (cell/mm^3)	1,500-2,000	1,000-1,499	500-999	<500
Eosinophils (cell/mm^3)	650-1,500	1,501-5,000	>5,000	Hypereosinophilic
Platelets decrease (cell/mm^3)	125,000-140,000	100,000-124,999	25,000-99,999	<25,000

WBC = white blood count.

a The laboratory values provided in the table serve as guidelines and are dependent on institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that the laboratory values are appropriate.

Table 11. Clinical Abnormalities from Urinalysis Values

Urine[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic): red blood cells per high-power field	1-10	11-50	>50 and/or gross blood	Hospitalization or packed red blood cells transfusion

a The laboratory values provide in the table serve as guidelines and are dependent on institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that the laboratory values are appropriate.

Table 12. Neuromuscular Toxicities

Neurological Event	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially Life Threatening Grade 4
Muscle Weakness[a]	subjective weakness with no objective symptoms or signs	mild objective signs or symptoms and no decrease in function	objective weakness function limited	paralysis
Ophthalmoplegia / Diplopia (double vision)	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not with interfering with ADL; mild objective signs or symptoms; intervention not indicated	Symptomatic and interfering with function and ADL; objective weakness; medical intervention indicated	Disabling; Paralysis; medical intervention indicated
Vision – blurred vision Vision - photophobia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL; mild objective signs or symptoms	Symptomatic and interfering with function and ADL; objective weakness;	Disabling
Voice changes / dysarthria (e.g., hoarseness, loss, or alteration of voice)	Mild or Intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability	Disabling; non-understandable voice or aphonic;
Dyspnea (shortness of breath)	Dyspnea on exertion, but can walk one flight of stairs without stopping	Dyspnea on exertion, but unable to walk one flight of stairs without stopping	Dyspnea interfering with ADL	Dyspnea at rest; intubation may be indicated
Neuro-Cerebellar (lack of coordination, tremor)	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Cranial neuropathy	Asymptomatic, detected on examination	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening, disabling

[a] Check for generalized, cranial muscles (see sentence below), extremities (upper and lower), and specific areas (extra ocular, facial, ocular, and trunk). Symptoms or signs of cranial muscle involvement are disruption of the appearance or functioning of the senses, facial muscles, pharynx, larynx, and neck.

APPENDIX C

REACTION RECORDING SHEET - PARTICIPANT HOME DIARY

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

Reaction Recording Sheet – Participant Home Diary

Study Site/Location*: _____ /_____ Participant Study ID Number*: _____

Participant Name: _____

Recombinant vaccine given: Date: _____/_____/_____ Time: ___ AM/PM

	1 day 24 hrs		2 days 48 hrs		3 days 72 hrs		4 days 96 hrs		5 days 120 hrs		6 days 144 hrs		7 days 168 hrs	
Local reactions:														
Soreness?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Itching?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Erythema? (mm)[a]	_____		_____		_____		_____		_____		_____		_____	
Induration? (mm)[a]	_____		_____		_____		_____		_____		_____		_____	
Systemic reactions:														
General malaise?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Fatigue?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Lethargy?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Chills, fever?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Lumps, soreness? (not local)	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Stiff back, stiff neck?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Nausea, vomiting, or diarrhea?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Other GI symptoms?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Itching, hives?	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N

[a] Please use tool provided to measure. Please list any medications used to treat the potential reactions above:

If you answered ***yes*** to any of the above potential reactions, please record additional comments i.e., date/time of reaction, symptoms, on the back of this form.

Please retain the completed form and return to study staff at the final study visit (Week 4 for non-donors and Week 12 for plasma donors.)

*to be filled in by study staff

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

Reaction Recording Sheet – Participant Home Diary

Study Site/Location*: _____ /_____ Participant Study ID Number*: _____

Reaction Recorded as "Y on previous page	Date/Time started	Date/Time ended	Medications used to Treat reaction	Other comments

*to be filled in by study staff

APPENDIX D

DONOR HISTORY QUESTIONNAIRE

This document is one component of the PPTA donor history questionnaire documents to be used by source plasma organizations. The PPTA abbreviated donor history questionnaire documents must be used collectively.

PPTA Abbreviated Donor Health Questionnaire
For Frequent Plasma Donors

Current Health	Yes	No
1. Are you feeling healthy and well today?	☐	☐

Please Read the Medication List

2. Since you last donated plasma have you taken any medications on the medication list in the time frames indicated?	☐	☐

Changes in Health

Since you last donated plasma:

	Yes	No
3. Have you been pregnant or are you pregnant now?	☐	☐
4. Have you had any new medical problems or diagnoses?	☐	☐
5. Have you had any new medical treatments, vaccinations or medications?	☐	☐
6. Have you had contact with someone who had a smallpox vaccination?	☐	☐
7. Have you donated whole blood, platelets, or plasma at another center?	☐	☐

Risk Activities

Please review our Risk Poster	Yes	No
8. Did you review the Risk Poster?	☐	☐
9. Do you have any questions about anything mentioned on the Risk Poster?	☐	☐
10. Since you last donated plasma, does anything on the Risk Poster apply to you in the time frames indicated?	☐	☐

PPTA Abbreviated Donor Health Questionnaire
For Frequent Plasma Donors

Since you last donated plasma:	**Yes**	**No**
11. Have you had a tattoo applied or had one touched up?	☐	☐
12. Have you had an ear or body piercing?	☐	☐

	Yes	**No**
Optional Question A. Since you last donated plasma, have you had surgery or a diagnostic, medical or dental procedure?	☐	☐
Optional Question B. Since you last donated plasma, have you had acupuncture?	☐	☐

Additional Questions:

Acknowledgment:

1. I have reviewed the educational materials regarding infections that can be transmitted by my donation, such as, Syphilis, HIV, and Hepatitis B and C.
2. I agree not to donate if my donation could result in a potential risk to people who receive plasma products.
3. A sample of my blood will be tested for infections that can be transmitted by my donation, such as Syphilis, HIV, and Hepatitis B and C.
4. I understand you will attempt to notify me if for any reason I cannot donate, and records will be maintained indicating the reason for the deferral and the deferral time period.
5. I have reviewed the information regarding the potential risks and hazards of donating Source Plasma.
6. I have been given the opportunity to ask questions and understand that I may withdraw from the donation procedure at any time.

Donor Signature: _____Date: _____

APPENDIX E

ADVERSE EVENT RECORDING SHEET FOR IDENTIFICATION OF POSSIBLE SERIOUS ADVERSE EVENTS (SAEs) (V2.0, JULY 2024)

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

Adverse Events Recording Sheet for Identification of Possible Serious Adverse Events (SAEs)

Recombinant vaccine given: Date: __/_____/_____Time: _____ AM / PM

You may or may not experience any adverse events. The purpose of this recording sheet is for you to document at home any severe and/or serious adverse events (SAEs) as well as serious new onset chronic illnesses (NOCIs) during the course of the study if such should occur. An SAE is defined as an adverse event which may result in a life-threatening situation such as inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect or death.

- In addition to any SAEs, please record any new concomitant medications taken to treat the SAEs and serious NOCIs.
- The information you document on this form will be queried for by study staff during on-site study visits and phone call follow-up for safety at Weeks 1, 4, 10, 12 and 26. Only plasma donors will receive follow up phone calls at Weeks 4 and 10 in addition to a final on-site study visit at Week 12.
- Please describe the SAE or serious NOCI in column 2 and whether the event is newly occurring.
- Please indicate the date and time (if relevant) of each event's occurrence, as well as the date/time of the event's resolution.
- Please record any concomitant medications taken to treat each SAE or serious NOCI event in the Treatment column and additionally on the Home Concomitant Medication form provided to you.
- Please proceed to confidentially destroy this form after the Week 26 phone call follow up.

Note: If you experience severe, life-threatening or any of the following neuromuscular symptoms (blurred or double vision, drooping of eyelids, drooping of the mouth, dry mouth, difficulty swallowing, difficulty speaking, weakness of an arm or leg, lack of coordination, shallow breathing, sensitivity to sunlight, or inability to perspire), **please seek medical attention <u>immediately</u> and notify Dr. Khouri (24/7/365 phone # 925-408-5935 or at 510-231-7600 which is answered 24/7/365) as soon as possible.**

Please categorize the severity of the adverse event as:

severe = you have a marked limitation in activity, some assistance is needed, medical intervention or therapy is likely required

life threatening = you have an extreme limitation in activity, significant assistance is required and/or significant medical intervention or therapy are required, the event requires hospitalization or hospice is probable.

#	Reaction or Event Description	New Event? (Y/N)	Date / Time Started	Date / Time Ended	Severity (see definitions above)	Treatment	Comments

Additional Comments, if any:

APPENDIX F

HOME CONCOMITANT MEDICATIONS FORM (V2.0, JULY 2024)

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

Home Concomitant Medications

- Please record the medication name, dates taken (started and stopped), the amount taken each time, the frequency taken, the route of administration, and the reason for use for all medications used to treat severe AEs, SAEs and serious NOCIs recorded in the Adverse Events Recording Sheet.
- The information you document on this form will be queried for by study staff during on-site study visits and phone call follow-up for safety at Weeks 1, 4, 10 and 26. Only plasma donors will receive follow up phone calls at Weeks 4 and 10.
- Please proceed to confidentially destroy this form after the Week 26 phone call follow up.

Medication Name (generic or trade) *Do not include hospital administered medications	**Start date**	**Stop date**	**Dosage**	**Frequency**	**Route** (e.g., oral, topical)	**Reason for use**

Medication Name (generic or trade) *Do not include hospital administered medications	**Start date**	**Stop date**	**Dosage**	**Frequency**	**Route** (e.g., oral, topical)	**Reason for use**