A Phase 1, Randomized Double-Blind, Placebo-Controlled, Single Ascending Dose Safety, Tolerability, and Pharmacokinetics Study of SAB-176 in Healthy Adults

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CRIS	Clinical Research Information System
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HA	Hemagglutinin
HAC	Human Artificial Chromosome
HAI	Hemagglutination Inhibition
hIgG	Human Polyclonal IgG
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin
IVIg	Immunoglobulin for Intravenous Use
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
K	Potassium
LDH	Lactate Dehydrogenase
MN	Microneutralization
Na	Sodium
NIH	National Institutes of Health
OTC	Over-the-Counter
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event/Serious Adverse Experience
SRCP	Safety Review and Communication Plan
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TBD	To Be Determined
Tc	Transchromosomic
TKO	Triple Knockout
UDS	Urine Drug Screen
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

PROTOCOL SUMMARY

Full Title:	A Phase 1, Randomized Double-Blind, Placebo-Controlled, Single Ascending Dose Safety, Tolerability, and Pharmacokinetics Study of SAB-176 in Healthy Adults
Short Title:	SAB-176
Clinical Phase:	1
IND Sponsor:	SAB Biotherapeutics, Inc.
Conducted by:	PPD
Principal Investigator:	Rebecca N. Wood-Horrall, M.D.
Sample Size:	27 subjects
Accrual Ceiling:	150 (up to 150 subjects screened to randomize a total of 27 subjects)
Study Population:	Healthy Volunteers aged 18 to 60 years
Accrual Period:	Start Date: *TBD* End Date: *TBD*
Study Duration:	Start Date: *TBD* End Date: *TBD*
Study Design:	Randomized, Double-Blind, Placebo-Controlled, Dose-escalating
Study Agent:	Active: SAB-176 Control: Normal (0.9%) saline
Primary Objective:	To evaluate the safety and tolerability of SAB-176 in healthy adults, following single intravenous administration at escalating dose-levels
Secondary Objectives:	• To evaluate the pharmacokinetics of intravenously administered SAB-176 in healthy adults, following single intravenous administration at escalating dose-levels • To determine the ability of serum levels of SAB-176 to neutralize Type A and Type B influenza viruses • To evaluate the immunogenicity of SAB-176
Primary Endpoint:	Type and frequency of adverse events experienced by subjects receiving SAB-176 at escalating dose-levels, as compared to control saline
Secondary Endpoints:	• Pharmacokinetic profile of intravenously administered SAB-176 in healthy adults • Serum Type A and B Hemagglutination Inhibition (HAI) Assays • Serum Type A and B Microneutralization (MN) Assays • Frequency and concentrations of antibodies caused by SAB-176, as measured by: o Anti-IgG antibodies using rheumatoid factor o Anti-SAB-176

PRÉCIS

The administration of convalescent plasma or hyperimmune immunoglobulin G (IgG) is often used for treatment of infectious diseases. However, production of large quantities of anti-pathogen human plasma and/or immunoglobulin with high affinity and avidity antibodies currently requires donations by convalescent humans, a process that can limit availability for a number of reasons. One novel alternative source is transchromosomic (Tc) bovine that produce fully human polyclonal IgG (hIgG) de novo and mount a robust antibody immune response after vaccination.

This study will evaluate the safety, tolerability, and immunogenicity of SAB-176, a fully human polyclonal anti-Influenza IgG produced from transchromosomic bovine. Beginning with a low single-dose, subjects are randomized to receive either SAB-176 or a normal saline control, and evaluated on Study Days 1, 3, 7, 21, 42, and 90. The safety and tolerability is evaluated using symptoms, clinical laboratory tests, pharmacokinetics, and immunogenicity assays. Utilizing a series of stopping rules and a medical monitor, the dose will be escalated as safety and tolerability are established.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

Influenza causes substantial morbidity and mortality worldwide despite available antivirals and vaccines. Influenza is responsible for 226,000 excess hospitalizations and 30,000 to 50,000 deaths each year in the United States alone (*1*). Effective therapeutics are needed to prevent mortality or morbidity in those afflicted with severe influenza. Human plasma (delivered as Fresh Frozen Plasma units) or human intravenous immunoglobulin (hIVIg) with anti-influenza antibodies have been proposed as treatments for severe influenza (*2*). A limitation with plasma or hIVIg is that large numbers of human plasma donors/units must be screened to identify those few with a higher-than-average hemagglutination inhibition (HAI) titers to multiple strains of influenza. However, recent clinical trials have not shown benefit to hospitalized patients with severe Type A influenza infections treated with human-derived anti-influenza plasma or hIVIg (*3, 4*).

SAB Biotherapeutics, Inc., has developed SAB-176 to address the production limitations and lack-of-clinical efficacy of human-derived plasma or hIVIg. SAB-176 is a unique anti-influenza hIgG containing fully human polyclonal IgG antibodies with extremely high HAI and microneutralization (MN) titers against past, current, and potentially future strains of Type A influenza (H1N1/H3N2) and both lineages of Type B influenza (Yamagata/Victoria). SAB-176 is purified from the plasma of immunized transchromosomic (Tc) bovines that were immunized with a quadrivalent recombinant hemagglutinin (HA) protein vaccine produced in insect cells. The HA antigens match the four influenza strains recommended yearly for the Northern hemisphere by the Center for Disease Control and Prevention (CDC).

Furthermore, Tc bovine hIgGs have an IgG1 subclass content of approximately 80-90% versus approximately 60% for human-derived IVIg. IgG1 strongly activates complement and effector cells (NK cells, neutrophils, monocytes, etc.) of the innate immune system. SAB-176 is therefore much different than human-derived anti-influenza hIVIgs. SAB Biotherapeutics believes that SAB-176's distinct attributes, in combination with early treatment of severe influenza disease, could demonstrate that the product reduces morbidity and mortality in patients with Type A and/or B influenza.

The genome of Tc bovines contains a human artificial chromosome (HAC) comprising the entire human Ig gene repertoire (human Ig heavy chain [IgH] and human kappa light chain) that reside on 2 different human chromosomes (hChr), specifically the IgH locus from hChr14 and the Immunoglobulin kappa (Igk) locus from hChr2. The system maintains the ability to use the genetic information provided by the immunoglobulin gene repertoires for generating the seemingly unlimited diversity of human polyclonal antibodies (pAbs).

Fully hIgG (hIgG/hIgκ) can then be produced in these Tc bovines after vaccination with suitable antigens, and these animals produce up to 15 g/L of IgG antibodies in their plasma (similar to humans which have 7-16 g/L IgG). SAB-176 is an anti-influenza hIgG prepared in this system.

Tc bovines receive repeated doses of a quadrivalent recombinant HA protein vaccine produced in insect cells. Just prior to immunization of the Tc bovine, the HA proteins are mixed with adjuvants.

Plasma is collected using an automated plasmapheresis system. After collection of sufficient volume, plasma undergoes Quality Control testing, is frozen and stored. Once it is ready to be processed, qualified frozen plasma is thawed, pooled, fractionated by caprylic acid (CA) and clarified by depth filtration in the presence of filter aid. The clarified sample containing hIgG is further purified by affinity chromatography, first using an anti-human IgG kappa affinity column to capture hIgG pAbs and remove residual non-hIgG and bovine plasma proteins (BPP). The sample is subsequently passed through an anti-bovine IgG (bIgG) heavy chain specific affinity column to further remove residual IgG molecules that contain a bovine heavy chain. The hIgG fraction is then subjected to a Q Sepharose chromatography polishing step to further reduce impurities, nanofiltration, final buffer exchange, concentration and sterile filtration. Finally, the product is terminally filtered and filled into vials.

The drug product will be administered intravenously and will be diluted in saline per the clinical protocol.

1.2 Rationale

This study will evaluate the safety and pharmacokinetics of SAB-176. This will both advance treatments for Type A and Type B influenza viruses, as well as establish the safety of the platform that could be used to quickly develop therapeutics for other emerging infectious diseases.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of SAB-176 in healthy adults, following single intravenous administration at escalating dose-levels

2.2 Secondary Objectives

- To evaluate the pharmacokinetics of intravenously administered SAB-176 in healthy adults, following a single intravenous administration at escalating dose-levels
- To determine the ability of serum levels of SAB-176 to neutralize Type A and Type B influenza viruses
- To evaluate the immunogenicity of SAB-176, as measured by:
  - Anti-IgG antibodies using rheumatoid factor
  - Anti-SAB-176

3 INVESTIGATIONAL PLAN

3.1 General

Study size: 27 subjects (up to 150 subjects screened to randomize a total of 27 subjects)
Study duration: 1 year
Study duration of individual subjects (not including screening): 90 days
Sex distribution: males and females
Age range: 18 to 60 years

3.2 Study Design

This safety and tolerability study of intravenous (IV) SAB-176 consists of up to 4 single dose-levels or cohorts (cohort 1–4) in a double-blind, randomized, placebo-controlled dose-escalating cohort design. Four cohorts of 2-10 subjects each will be administered a single IV dose of SAB-176 or saline placebo. At very low doses, the concern is primarily allergic or T-cell activation/cytokine storm, so small cohort sizes should be utilized. As the target dose is approached, the sample size will increase to increase the likelihood of detecting toxicity events. The cohorts and dose levels are outlined in Table 1.

Table 1: Cohorts and Dose Levels

Cohort	Number of Subjects Receiving SAB-176				Number of Subjects Receiving Saline Control
	1 mg/kg	10 mg/kg	25 mg/kg	50 mg/kg	
1	2				1
2		4			2
3			6		2
4				8	2

The number of subjects dosed will follow the limitations below:

- The first three subjects of each cohort will be dosed every other day (48-hour interval).
- For Cohorts 2-4, 48 hours after the third subject is dosed, up to 3 subjects may be dosed per day, until the cohort is completed, and no more than 8 subjects will be dosed per week.
- For cohorts 2, 3, and 4, additional dosing in the cohort may continue only after the safety committee recommends continuation after reviewing the safety data from the 3 initial subjects of the cohort.
- After the first three in each cohort, subsequent subjects will be observed for at least 4 hours before beginning the next infusion in the next subject.

Table 2. Example of dosing timeline

	Infusion Day								
	1	2	3	4	5	6	7	8	9
Subject 1	X								
Subject 2			X						
Subject 3					X				
Subject 4							X*		

Table 2. Example of dosing timeline (con't)

	Infusion Day								
	1	2	3	4	5	6	7	8	9
Subject 5							X (≥4 hrs post Subject 4)		
Subject 6							X (≥4 hrs post Subject 5)		
Subject 7								X	
Subject 8								X (≥4 hrs post Subject 7)	
Subject 9								X (≥4 hrs post Subject 8)	
Subject 10									X

* Additional enrollment in the cohort may continue only after the safety committee recommends continuation after reviewing the safety data from the three initial subjects of the cohort.

NOTE: Only 1 subject should be infused at any given time. An infused subject should be observed for at least four hours prior to beginning the next infusion.

Beginning with a low single-dose, subjects are randomized to receive either SAB-176 or placebo on Day 0. Subjects are then evaluated on Study Days 1, 3, 7, 21, 42, and 90.

3.3 Definitions for the Purpose of this Study

Definitions for the Purpose of this Study:

Enrolled

For the purpose of collecting data and samples and reporting adverse events (AEs), a subject will be considered enrolled beginning from when the informed consent form is signed until the subject is considered "screen failure", "discontinued", or "completed".

Randomized

Subjects are considered randomized when they meet all of the following criteria:

- Enrolled (as defined above)
- Confirmation that the inclusion and exclusion criteria are met
- Randomization number is assigned

Screen Failures

Subjects are considered screen failures when they meet one or more of the following criteria after signing consent:

- Screening tests reveal that the subject is ineligible
- Subject withdraws consent before being randomized

Discontinued

Subjects are considered discontinued when they meet one or more of the following criteria:

- Subject withdraws consent after being randomized and prior to the completion of Day 90 (see Section 4.6)
- Subject is withdrawn after enrollment by Investigator (see Section 4.7) including lost to follow-up

Completed

Subjects are considered completed when they are followed through Study Day 90 and complete the final study follow-up visit (Study Day 90).

4 STUDY POPULATION

4.1 Research Subject Selection

Healthy volunteers will be recruited for this study.

4.2 Recruitment

Volunteers will be recruited through the posting of advertisements or via a pre-existing registry of potential subjects. All flyers and advertisements will be submitted to the Institutional Review Board (IRB) for approval.

4.3 Inclusion Criteria

1. Age ≥18 years and ≤60 years
2. Body mass index (BMI) of 19-32 kg/m^2
3. Subjects must have values in normal ranges for basic labs (i.e., CBC, PT/INR, Chem-7, and LFTs), unless deemed not clinically significant by the PI.
4. Estimated glomerular filtration rate ≥85 mL/min at screening, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
5. Subjects must agree to:
    - Not take any prescription or over-the-counter (OTC) medications with the exception of acetaminophen, ibuprofen, vitamins, seasonal allergy medications, and/or contraceptive medications, or others unless approved by the study investigator, for a period 7 days prior to study drug administration (i.e., Day 0)

    1) Use one of the following in order to avoid pregnancy:

        - Females who are able to become pregnant (i.e., are not postmenopausal, have not undergone surgical sterilization, and are sexually active with men) must agree to use at least 2 effective forms of contraception from the date of the subject's signing of the informed consent form through 60 days after the last dose of study drug. At least one of the methods of contraception should be a barrier method.

- Males who have not undergone surgical sterilization and are sexually active with women must agree to use condoms plus have a partner use at least one additional effective form of contraception from the date of the subject's signing of the informed consent form through 60 days after the last dose of study drug.
- Neither females or males should donate oocysts or sperm for use in artificial insemination through 60 days after the last dose of study drug.

4.4 Exclusion Criteria

1. Any history of allergy, anaphylaxis, or severe reaction to beef products (including milk and gelatin)
2. Any history of allergy, anaphylaxis, or severe reaction to IVIg or human blood products
3. Any chronic medical problem/condition that require medications needed to maintain the subject's health. Exceptions to this restriction can be allowed for minor health conditions that are treated with Tylenol, over-the-counter non-steroidal anti-inflammatories, vitamins, seasonal allergy medications, or oral/transdermal/IUD contraceptives, etc. The study investigator will make a determination to exclude a subject based upon their medical history and the type and frequency of the drug substance.
4. History of cardiovascular disease, cardiomyopathy, heart failure, or unexplained syncope
5. Abnormal clinically significant 12-lead electrocardiogram (ECG), per PI discretion
6. Subjects who have been laboratory confirmed or clinically diagnosed with influenza within seven days prior to infusion (by subject history) will be deferred from infusion. Any subject with signs and symptoms of an active respiratory infection on the day of infusion will be deferred until the infection is cleared in the opinion of the investigator. Subjects that present with an active upper respiratory infection on the day of infusion will be tested with an FDA licensed Influenza A/B Antigen Test. Signs and symptoms constituting an upper respiratory infection include cough, sore throat, or rhinorrhea with or without fever.
7. Enrollment will be delayed for all patients who have other intercurrent infections (e.g., gastroenteritis, abscess, etc.).
8. Women who are breast-feeding
9. Positive urine or serum pregnancy test
10. Positive urine drug screen (UDS)
11. Clinically significant results, including laboratory results, as determined by study investigator
12. Positive rheumatoid factor
13. IgA deficiency (defined as IgA < 7 mg/dL)

14. Participation in another research study with receipt of any investigational drug within 5 half-lives or 30 days, whichever is longer, prior to study drug administration (i.e., Day 0) and until completion of the study
15. Participation in any other research study until the completion of the study
16. Receipt of blood products within 2 months prior to study drug administration (i.e. Day 0)
17. Receipt of any vaccination within 30 days prior to study drug administration (i.e. Day 0)
18. Any acute or chronic condition that, in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in this clinical study

4.5 Justification of Exclusions of Pregnant Women and Children

4.5.1 Exclusion of Pregnant and Breastfeeding Women

Pregnant women are excluded from this study because the effects of SAB-176 on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events (AEs) in nursing infants secondary to treatment of the mother with SAB-176, women that are breastfeeding will also be excluded from the study.

4.5.2 Exclusion of Children

Because there are insufficient data regarding dosing or AEs events available in adults to judge the potential risk in children, children are excluded from this study.

4.6 Subject Withdrawal

Subjects (or their legal surrogates if subjects become unable to make informed decisions) can terminate study participation at any time without prejudice. If a subject terminates participation before completing the study, the reason for this decision will be recorded in the study record.

Best efforts will be made to follow withdrawn subjects who have received study drug administration for safety. Subjects who withdraw from the study after study drug administration will not be replaced.

4.7 Discontinuation of Subject by Investigator

The Investigator has the right to withdraw subjects from the study. Subjects may be withdrawn from the study for any of the following reasons:

- The subject is lost to follow-up.
- The Investigator believes that continuation in the study would be detrimental to the subject. In general, subjects withdrawn for AEs will still be followed for safety follow-up if possible.
- If, in the Investigator's best judgment, discontinuation is in the subject's best interest.

The reason for withdrawal from the study is to be recorded in the study record. All subjects should be followed for safety assessments. If a non-serious AE is unresolved at the time of discontinuation, efforts should be made to follow up until the event resolves or stabilizes, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow all serious adverse events (SAEs) to resolution.

Subjects withdrawn from the study after study drug administration will not be replaced.

4.8 Discontinuation of Study

SAB Biotherapeutics as the study sponsor, the study site IRB, and the Food and Drug Administration (FDA) may terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of an AE in this or other studies indicates a potential health hazard to subjects.
- If there is one death, irrespective of attribution by the investigator/medical monitor. Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study.

4.9 Emergency Unblinding

If a subject experiences a SAE, and the treating clinician requests unblinding of the study treatment, the Principal Investigator (PI) or designee will be contacted. If the PI or designee is in agreement that unblinding is necessary, the PI or designee will contact the PPD Phase 1 Clinic Pharmacy for release of the randomization code for the subject to the treating clinician. For individual subject unblinding, the site will follow their unblinding procedures per SOP-AUSCLN-506. The sponsor and Medical Monitor will be informed within one business day that unblinding was necessary. In this case, the subject is still considered enrolled in the study, and the data is still used for analysis.

5 TREATMENT

5.1 Randomization and Blinding

The randomization schedule will be generated using SAS Version 9.4 or later (SAS Institute Inc, Cary, North Carolina), which will link sequential volunteer randomization numbers to treatment codes. The randomization schedule and the volunteer-specific emergency unblinding documentation will be provided to the unblinded pharmacist(s) at the clinic site.

Study participants and study team (PI and associate Investigators and study staff) will be blinded throughout the entire study. The study team will be unblinded after the Study Day 90 visit, all laboratory (and immunogenicity) results are available, and the final monitoring visits has occurred.

The infusion will be provided in an opaque bag to obscure the bag, since SAB-176 may develop bubbles similar to what is seen with IVIg, if the product is agitated. This process has been used in other studies (INSIGHT influenza IVIG) and was successful in maintaining blinding of the study team.

5.2 Formulation, Packaging and Labeling

5.2.1 SAB-176

SAB-176 is a purified human immunoglobulin G (hIgG) designed to specifically bind to Type A and Type B influenza viruses. The product is in development for use as a therapeutic agent to treat patients who are infected with Type A and Type B influenza viruses. The hIgG is purified from the plasma of immunized transchromosomic (Tc) bovines that were immunized with a quadrivalent recombinant hemagglutinin (HA) protein vaccine produced in insect cells.

The product is in a sterile liquid form formulated in 10 mM glutamic acid monosodium salt, 262 mM D-sorbitol, 0.05 mg/mL Tween 80, pH 5.5. The drug product will be administered intravenously and will be diluted in saline per the clinical protocol.

5.2.1.1 Label

SAB-176 anti-Influenza
Human Immunoglobulin Intravenous (Tc Bovine-Derived)
70.12mg/ml (701.2mg in 10mL) For Intravenous Use Only
Lot No: PD2001010QR Manufacture Date: 03 Feb 2020
Store at 2-8°C
Mfr: SAB Biotherapeutics, Inc. Sioux Falls, South Dakota, USA
Caution: New Drug--Limited by Federal law to investigational use.

Figure 1: SAB-176 Vial Label

5.2.1.2 Storage

Store SAB-176 at 2-8° C

5.2.2 Saline Control

Subjects randomized to the control infusion will receive normal (0.9%) saline in approximately the same volume as they would have received if randomized to the active arm.

5.3 Dosing and Administration

The NIH clinical center guidelines for administration of a standard human 10% IVIg (10g/100mL) are for the initial rate to be 0.6 mL/kg/hr, and the rate can be increased gradually to a maximum of 4.8 mL/kg/hr, if tolerated.

SAB-176 will be prepared in the following dilutions:

- Cohort 1 will be prepared as a solution 1mg/1ml (0.1% solution by weight), which is 1/100th the concentration of standard human IVIg (e.g. Gammunex).
- Cohort 2 will be prepared as a solution 4mg/1ml (0.4% solution by weight), which is 1/25th the concentration of standard human IVIg.
- Cohorts 3&4 will be prepared as a solution 20mg/1ml (2% solution by weight), which is 1/5th the concentration of standard human IVIg.

The dose of study drug will be calculated based on the subject's dose cohort and weight (up to a maximum weight of 100 kg). The pharmacy will prepare a bag containing the dose of SAB-176 plus as much normal (0.9%) saline as is needed to reach the above listed concentrations. The infusion will be provided in an opaque bag to obscure the bag (as the SAB-176 may develop

bubbles like IVIg if agitated). The drip chamber will also be covered, but accessible if needed by nursing staff for verification of flow rate, etc.

Table 3: Dosing and Administration

Cohort	Dose (mg/kg)	Concentration	Start Rate (mL/kg/hr)	End Rate (mL/kg/hr)	Start Rate (mg/kg/hr)	End Rate (mg/kg/hr)	Proportion of Human IVIG Rate	Duration (mins) *(approx.)*
1	1	1 mg/mL (0.1%)	0.5	2	0.5	2	$1/120^{th}$ – $1/240^{th}$	53
2	10	4 mg/mL (0.4 %)	0.5	3	2	12	$1/30^{th}$ - $1/40^{th}$	85
3	25	20 mg/mL (2 %)	0.5	1	10	20	$1/6^{th}$ - $1/12^{th}$	83
4	50	20 mg/mL (2 %)	0.5	2	10	40	$1/6^{th}$ - $1/10^{th}$	97

The infusion will be started at of 0.5 mL/kg/hr, escalating by 0.5 mL/kg/hr increments every 15 minutes to a maximum specified above (end rate).

It is anticipated that the infusion is prepared the morning of the infusion. Since the study drug has been shown stable for 24 hours when mixed in saline, the infusion should be started within 6 hours of preparation in order to assure completion within normal working hours.

The dosing of an individual subject will be slowed and or stopped (depending on clinical assessment) for the following:

- hypotension (systolic or mean blood pressure decreases by 20 mmHg)
- shortness of breath, wheezing, or desaturation
- pain, tenderness, erythema, or swelling around the infusion site
- fevers, chills
- Other adverse reactions not specified, that are concerning for infusion related adverse events

After clinical assessment, and resolution or improvement of the event of concern, the infusion may be resumed. If the event is not resolving in a reasonable amount of time, the infusion will not be resumed.

However, in order to establish absolute criteria for stopping an infusion – the treatment should be immediately stopped should any of the following occur:

- Profound hypotension (systolic blood pressure < 85 mmHg)
- Shortness of breath, wheezing, or sustained (i.e., ≥ 10 seconds) oxygen saturation < 92% on room air
- Severe (Grade ≥ 3) local infusion site reactions, including pain, tenderness, erythema, or swelling as defined in the protocol-specified toxicity grading scale
- Body core temperature exceeding 38.5°C
- Suspected sepsis
- Severe chest pain
- Suspected anaphylaxis

The subject's actual time of drug administration will be recorded in the source documents.

5.4 Justification of Dose

The proposed starting dose for this Phase 1 study is 1 mg/kg administered as a single IV infusion. Based on the non-clinical toxicology results in New Zealand white rabbits, the no observed adverse effect level was considered to be 725.30 mg/kg/day or higher. The 725.30 mg/kg dose was the maximum dose available to test due to dose volume limitations for the species. Using body surface area calculations (*5*) and 5X safety factor, a 50 mg/kg dose (The maximum therapeutic target dose for SAB-176) is equivalent to 770.8 mg/kg in rabbits. The planned 1 mg/kg starting dose for humans is approximately 47X lower than the maximum recommended starting dose.

5.5 Study Drug Accountability

The study pharmacist is unblinded, and will maintain accurate drug accountability records. This log will not be shown to the study Investigators. When the study is completed, copies of the study drug accountability records will be returned to the sponsor, and the originals will be maintained at the study site. Copies of the drug accountability records must be maintained with the rest of the documentation for the study. All unused study drug must be disposed of upon authorization by SAB or its designee. All records regarding the disposition of study drug must be available for inspection by the study monitors and regulatory authorities.

5.6 Concomitant Medications

Subjects will be monitored throughout the study for use of concomitant medications. Any prescription medications, OTC preparations, herbal remedies, and/or nutritional supplements taken during the study period must be recorded in the research record.

5.7 Prohibited Medications

Subjects will refrain from receipt of any investigational drug within 5 half-lives or 30 days, whichever is longer, prior to Day 0 and during the entire study.

6 STUDY PROCEDURES

6.1 Personnel for Study Procedures

The physical examination (excluding vital signs) will be performed by a physician, nurse practitioner, or physician's assistant. All other assessments may be performed by other appropriately trained members of the investigative team as noted on the Delegation of Responsibilities form.

6.2 Screening

Screening evaluations may be done up to 28 days before Day 0.

6.2.1 Informed Consent

The Investigator or designated staff will review informed consent with the subject. One informed consent form will be used for both screening and enrollment into this protocol.

6.2.2 Demographics

The following information should be recorded:

- Age

- Sex
- Ethnicity
- Race

6.2.3 Medical History

The following information should be recorded:

- Medical history including any chronic medical conditions
- Current use of prescription and OTC medications within the last 7 days
- History of allergies
- Current or recent participation in any other research protocols

6.2.4 Clinical Data

- Vital signs (See Section 7.1.3)
- 12-lead ECG (See Section 7.3)

6.2.5 Physical Exam

A brief physical exam to ensure there are not medical conditions that would increase a subject's risk for participation in this study (Section 7.1.2)

6.2.6 Laboratory Testing

The following tests will be performed the day of screening:

- CBC with differential
- Reticulocyte count
- Prothrombin Time (PT) and Partial Thromboplastin Time (PTT)
- Chemistry panel
- Quantitative Immunoglobulins
- Routine urinalysis
- Urine biomarkers
- Serum or urine pregnancy test (females of childbearing potential only)
- Rheumatoid factor

(Elements of each panel are listed in Section 7.1.1)

6.2.7 Determination of Eligibility

Once the screening evaluation is complete, eligibility will be determined based on the inclusion and exclusion criteria. Eligible subjects will be contacted, and if still interested in participating, will be scheduled to return to the Clinical Center for randomization and study drug administration. The period of time between screening evaluation visit and administration of study drug should not exceed 28 days.

Subjects that are found to be ineligible will be contacted (or told directly if found ineligible during screening evaluation), and the reason for ineligibility will be discussed. If desired by the subject, and if applicable for the reason for ineligibility, the results will be shared with their

health care provider and/or the subject will be assisted in finding definitive medical care for said condition.

6.3 Detailed Description of Assessments

6.3.1 Schedule of Assessments

The schedule of assessments is described in Table 3. The day when the subject is randomized is denoted as Study Day 0, the first day after enrollment is Study Day 1, etc.

Table 4: Schedule of Assessments

	Screen	*Baseline*							
Day +/- Window	**−28 to -1**	**-1 to 0**	**1**	**2**	**3 (+1)**	**7 ± 1**	**21 ± 2**	**42 ± 3**	**90 ± 7**
Evaluation/Procedure		**Prior to infusion**							
ELIGIBILTY									
Informed consent	X								
Demographics	X								
Medical history	X								
RANDOMIZATION/ STUDY DRUG									
Randomize subject		X							
Study drug administration		X							
STUDY PROCEDURES									
Assess Symptoms		X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Review of concomitant medications	X	X	X	X	X	X	X	X	X
Physical exam	X		*if needed to assess AEs*						
ECG	X								
Adverse events		X	X	X	X	X	X	X	X
SAFETY LABORATORY [a]									
CBC	X	X		X	X	X		X	X
PT/PTT	X	X		X	X	X		X	X
Reticulocyte Count	X	X		X	X	X		X	X
Chemistry Panel	X	X		X	X	X		X	
Urinalysis	X	X		X	X	X		X	
Quantitative Immunoglobulin	X	X		X	X	X	X	X	X
Rheumatoid factor	X	X		X	X	X	X	X	X
Urine biomarkers	X	X		X	X	X		X	
Pregnancy test (urine or serum)	X	X							
UDS	X	X							
REFERENCE PROCEDURE									
Stored serum for pharmacokinetics		X[b]	X	X	X	X	X	X	X
Stored serum for immunogenicity[c]		X				X	X	X	X

Notes. a) Elements of each panel are listed in Section 7.1.1
b) PK sample on Day 0 includes baseline (pre-infusion), 1 hour (+/- 15 min) after the end of the infusion, and 6 hours (+/- 30 min) after the end of the infusion.
c) Serum will be collected for immunogenicity assessment for subjects at the time of an AE suggestive of hypersensitivity reaction (including serum sickness) even if the AE does not coincide with a visit in which immunogenicity assessment is planned.

6.3.2 Location of Study Drug Administration

The study drug will be administered in the PPD Phase 1 Clinic in Austin, Texas. Subjects will be asked to arrive on the unit at least 60 minutes prior to scheduled time of study drug administration.

6.3.3 Randomization

An order for randomization to SAB-176 or placebo will be entered into CRIS. A blinded treatment allocation is determined by the pharmacy as discussed in Section 5.1.

6.3.4 Study Day -1 to Day 0 - Baseline Evaluation

Prior to study drug administration, a baseline evaluation will be performed, including the following:

6.3.4.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions since screening visit
- Any new medications since screening visit
- Allergies
- Participation in any other research protocols within the last month or since the screening visit, whichever is longer

6.3.4.2 Assessment of Baseline Symptoms

The presence of any baseline symptoms will be elicited and documented.

6.3.4.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte Count
- PT/PTT
- Chemistry panel
- Urinalysis
- Urine biomarkers
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Serum or urine pregnancy test for women of child-bearing potential
- Stored serum for pharmacokinetics and immunogenicity (16 ml blood)

(Elements of each panel are listed in Section 7.1.1)

Only the pregnancy test must be resulted prior to initiation of study drug infusion.

6.3.5 Study Day 0: Study Drug Administration

SAB-176 or placebo will be prepared as noted in Section 5.3. The blinded bag of SAB-176 diluted in sterile normal saline or placebo (sterile normal saline) will be provided to blinded study staff for dose administration.

A peripheral IV will be placed. The dose will be administered as an IV infusion. For each dose, the subject's actual administration time will be recorded in the source documents.

6.3.6 Study Day 0: Peri-Administration Assessments

After study drug administration, subjects will remain in the trial unit for 6 hours after the end of infusion. Monitoring will be performed in a setting with emergency medications, resuscitation equipment and appropriately trained personnel to intervene if needed. The following procedures will occur:

- Vital signs: prior to start of infusion, and then approximately 15 and 30 minutes after the start of the infusion, and every 30 minutes thereafter until the end of the infusion
- Pharmacokinetic Evaluation approximately 1 hour (+/- 15 min) after the end of the infusion. The PK sample (8 ml blood) will be obtained from a separate venipuncture (i.e. not through the infusion IV).
- Vital signs post-dosing will be captured hourly for 6 hours and again at 12h.
- Pharmacokinetic Evaluation approximately 6 hours (+/- 15 min) after the end of the infusion. The PK sample (8 ml blood) will be obtained from a separate venipuncture (i.e. not through the infusion IV).
- Any adverse events occurring during the infusion will be recorded

6.3.7 Study Day 1

6.3.7.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.7.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.7.3 Laboratory Testing

- Stored serum for pharmacokinetics (8 mL blood)

6.3.8 Study Day 2

6.3.8.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.8.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.8.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte count
- PT/PTT
- Chemistry panel
- Urinalysis
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Urine biomarkers
- Stored serum for pharmacokinetics

(Elements of each panel are listed in Section 7.1.1)

6.3.9 Study Day 3 (+1)

6.3.9.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.9.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.9.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte count
- PT/PTT
- Chemistry panel
- Urinalysis
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Urine biomarkers
- Stored serum for pharmacokinetics (8 mL blood)

(Elements of each panel are listed in Section 7.1.1)

6.3.10 Study Day 7 (+/-1)

6.3.10.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.10.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.10.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte count
- PT/PTT
- Chemistry panel
- Urinalysis
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Urine biomarkers
- Stored serum for pharmacokinetics & immunogenicity (16 mL blood)

(Elements of each panel are listed in Section 7.1.1)

6.3.11 Study Day 21 (+/- 1)

6.3.11.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.11.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.11.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Stored serum for pharmacokinetics & immunogenicity (16 mL blood)

6.3.12 Study Day 42 (+/- 2)

6.3.12.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.12.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.12.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte count
- PT/PTT
- Chemistry panel
- Urinalysis
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Urine biomarkers
- Stored serum for pharmacokinetics & immunogenicity (16 mL blood)

(Elements of each panel are listed in Section 7.1.1)

6.3.13 Study Day 90 (+/- 7)

6.3.13.1 Interval History and Exam

An interval medical history will be performed. This will include:

- Any new medical conditions
- Current prescription and OTC medications
- Vital signs
- Physical exam as needed to evaluate new symptoms/complaints

6.3.13.2 Assessment of Symptoms

The presence of any symptoms will be elicited and documented.

6.3.13.3 Laboratory Testing

The following clinical laboratory tests will be performed and documented:

- CBC with differential
- Reticulocyte count

- PT/PTT
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor
- Stored serum for pharmacokinetics & immunogenicity (16 mL blood)

7 MEASURES OF SAFETY, EFFICACY, AND COMPLIANCE

7.1 Safety Evaluations

7.1.1 Laboratory Evaluations

All laboratory evaluations (except reference endpoint assays) will be performed at a CLIA-certified clinical laboratory. Blood samples will be collected from subjects as noted in the schedule of assessments. Abnormal labs thought to be erroneous may be repeated once.

On the designated days, the following laboratory tests will be performed:

- CBC with differential: white cell count (to include absolute neutrophil, and lymphocyte counts), hemoglobin, hematocrit, and platelet count
- Reticulocyte count
- Prothrombin Time (PT) and Partial Thromboplastin Time (PTT)
- Chemistry panel: Na, K, total CO2, BUN, creatinine, glucose, ALT, AST, total bilirubin, LDH, CPK, and estimated GFR by the CKD-EPI equation)
- Routine urinalysis (includes protein, glucose, ketones, hemoglobin, urobilinogen, leukocyte esterase, nitrite, pH, specific gravity, RBCs, WBCs)
- Urine biomarkers (quantitative albumin, quantitative protein, β2-microglobulin, and creatinine)
- Serum or urine pregnancy test (females of childbearing potential only)
- Quantitative Immunoglobulins (IgG level)
- Rheumatoid factor

7.1.2 Physical Examinations

A brief physical examination will be conducted at screening to ensure there are no medical conditions that would increase a subject's risk for participation in this study. Symptom-targeted physical examinations will be conducted at all other visits as needed to evaluate new complaints and possible AEs.

7.1.3 Vital Signs, Including SaO_2

At each visit, vital signs assessments (BP, HR, temperature, respiration rate, oxygen saturation).

7.2 Measures of Pharmacokinetics and Immunogenicity

As noted in the schedule and text above, 8 mL or 16 mL of blood will be obtained for evaluation of pharmacokinetics and immunogenicity. It is anticipated this will be in a serum separator tube (this tube may change without amending the protocol). Serum will be collected for immunogenicity assessment for subjects at the time of an AE suggestive of hypersensitivity reaction (including serum sickness) even if the AE does not coincide with a visit in which immunogenicity assessment is planned.

Pharmacokinetics evaluations will be performed by PPD. As SAB-176 cannot be differentiated from human IgG, the pharmacokinetics evaluations will use Hemagglutination Inhibition assays.

This protocol will evaluate immunogenicity in several assays:

1. anti-IgG antibodies using rheumatoid factor
2. Anti-Drug (anti-SAB-176) Antibody (performed at SAB Biotherapeutics)

7.3 12-Lead ECG

A 12-lead ECG will be obtained according to the Schedule of Assessments.

The ECGs will be measured using and ECG machine that calculates the heart rate and measures PR, QRS, QT, and QTcF.

Subjects will be required to lie quietly in a supine position for at least 5 minutes.

8 RISKS AND BENEFITS

8.1 Potential Risks

8.1.1 Risks of SAB-176

The risks of SAB-176 are largely unknown. However, a previous Phase 1 study of SAB-301 (anti-Middle Eastern Respiratory Syndrome virus immunoglobulin) derived from Tc bovines was shown to be safe and well tolerated at the highest dose of 50 mg/kg proposed in this study. It is anticipated that the risks will be similar to SAB-301 and human derived IVIg with some unique considerations for proteins of animal origin as discussed below.

Based on human IVIg, common side effects may include:

- Headache
- Injection site reaction
- Nausea
- Urticaria
- Fatigue
- Arthralgia
- Pyrexia

Less common side effects may include:

- Vomiting
- Back pain
- Rash

Serious side effects seen with human IVIg that could be seen with SAB-176 include:

- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IVIg therapy (*6*). Humans routinely receive up to 1-2 grams/kg of human-derived IVIg to treat Guillain-Barre syndrome and other immune related neuropathies. Therefore, the addition of 50 mg/kg IgG as SAB-176 is a relatively

small amount and is unlikely to cause AEs related to increased viscosity.

- Aseptic Meningitis Syndrome (AMS) has been reported with IVIg treatments, especially with high doses or rapid infusion. This risk is anticipated to be minimized given the low amount of protein and relatively slow infusion.
- Hemolysis, either intravascular or due to enhanced RBC sequestration, can be seen with human IVIG. This risk is anticipated to be low given the lack of exposure of the cows to human RBC antigens.
- Volume overload has been reported with human IVIg. This risk is anticipated to be minimized given the low amount of protein and small total volumes administered.

There may be unique risks given the animal origin of the IVIg. SAB-176 is a human IgG so it is anticipated the risk with SAB-176 would be less, though there may be residual animal proteins. The most similar product would be an animal polyclonal antibodies to non-human proteins e.g. Horse Heptavalent Botulism Antitoxin. (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf)

There is the risk of off-target binding of the IVIg. In the worst case, this could cause immune activation (cytokine storm). The tissue cross reactivity assays do not predict any off-target binding, and this has not been seen in any other animal IVIg (of Fab fragment) preparations, so this risk is considered low.

For Horse Heptavalent Botulism Antitoxin, the most common adverse reactions in all healthy subjects were headache (9%), pruritus (5%), nausea (5%), and urticaria (5%). Other adverse reactions reported in less than 4% of subjects included pyrexia and throat discomfort. All reported adverse reactions were considered mild or moderate. No serious adverse reactions were reported. Two moderate acute allergic reactions that required premature termination of the infusion and treatment were reported. Reactions were predefined as mild if the subject was aware but could tolerate the symptoms. Moderate reactions were predefined as discomfort enough to interfere with normal daily activity.

The development of antibodies to bovine proteins and potential for food allergies is a theoretical concern. There is precedent for animal antibodies (or Fab fragments) being obtained from animal plasma and given to humans.

- Rabbit Anti-thymocyte Globulin [Thymoglobulin] (http://products.sanofi.ca/en/thymoglobulin.pdf)
- Horse Anti-thymocyte Globulin [Atgam] (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM199603.pdf)
- Horse Heptavalent Botulism Antitoxin (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf)
- Sheep Digoxin Immune Fab [DigiFab] (http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm117626.pdf)

- Sheep Digoxin Immune Fab [DigiBind] (http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=19044)
- Sheep Crotalidae Polyvalent Immune Fab [CroFab] (http://www.crofab.com/documents/CroFab-Prescribing_Information.pdf)

Upon review of these package inserts, the development of anti-drug antibodies was noted only in Horse Heptavalent Botulism Antitoxin (11 of 271 subjects). There was no warning in any of these products concerning the development of allergies to other animal proteins, nor of any food allergies. As SAB-176 is a transgenic human IgG, the risk should be even further minimized. However, given the American diet is often heavy in bovine products (milk and/or beef, including derivatives), there is the risk of development of anti-bovine antibodies that is stimulated with repeated exposure. Given the data above and the lack of precedent for the development of food allergies after exposure to similar products, it is anticipated this risk with SAB-176 is very small.

Patients exposed to topical bovine thrombin products (previously used in surgical procedures e.g. fibrin glue) have developed antibodies towards bovine thrombin and contaminating bovine factor V; these antibodies can cross react with human clotting factors and may cause coagulopathy (*7*). In that series, postoperative coagulation abnormalities were more common in patients with antibodies to human coagulation proteins. SAB-176 clinical lots contain less than 5 ppm (parts per million) of bovine plasma proteins, but the clinical significance of this level of bovine contaminants is not known. Regardless, the serial assessment of PT/PTT in the study will monitor for any coagulation abnormalities in the subjects receiving SAB-176.

As SAB-176 is bovine derived, it may contain galactose-alpha-1,3-galactose (alpha-Gal) glycosylation of the IgG. In other products, the alpha-Gal glycosylation has been shown to be the source of immune based hypersensitivity reactions. For example, the epidermal growth factor receptor (EGFR) inhibitor cetuximab is a monoclonal antibody with alpha-Gal glycosylation. Cetuximab, while a marketed product, has been associated with hypersensitivity reactions, including anaphylaxis. In most subjects that had hypersensitivity reaction to cetuximab, IgE antibodies were present in pretreatment samples (*8*). This study is designed to start with very small doses, with close monitoring for similar hypersensitivity reactions.

Lastly, SAB's Tc-bovine production system and the US cattle population have a negligible risk for transmissible bovine spongiform encephalopathy (BSE), also known as "Mad Cow Disease". Only three reported cases of BSE infection in cattle have been documented in the US in the last decade. Risk assessments for infectious diseases were completed on the production herd, and documented procedures are in place to reduce or eliminate certain infectious diseases in the production animals. All inputs (feed, medications, and vaccines) have been evaluated for the transmission of viral and BSE agents. The manufacturing process was also evaluated for the clearance and removal of viruses and BSE. Virus removal has been validated. The BSE Western blot analysis was done to demonstrate clearance and removal of prions.

There may be additional risks not apparent or predicted by preclinical testing.

8.1.2 Risk of Intravenous Catheter

The primary risks of the placement of an intravenous catheter include local discomfort; occasional bleeding or bruising of the skin at the site of needle puncture; hematoma; and, rarely, infection or fainting. To reduce the risk of injury from a fall, the subject will be closely monitored and asked about these symptoms before being allowed to stand up.

8.1.3 Risks of Phlebotomy

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, hematoma and, rarely, infection or fainting. At the time of enrollment and during study visits, each subject will be asked about participation in other research studies, to ensure that blood draws do not exceed 450 mL over any 8-week period for adults, for all research protocols combined.

8.2 Potential Benefits

Subjects will not benefit directly from participation in this protocol.

8.3 Alternatives

As there is no benefit to the subject for enrollment in this protocol, the alternative to participating in this protocol is not to participate.

9 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, AND DATA

9.1 Intended Use of the Samples/Specimens/Data

Samples and data collected under this protocol will be used to determine the safety and pharmacokinetics of SAB-176.

9.2 Storage of Samples/Specimens/Data

Samples will be stored for the reasons noted above.

9.3 Storage of Genetic Samples

No samples are being stored for genetic testing on the subjects.

9.4 Tracking Samples

Samples will be tracked by a commercial software program.

9.5 Use of Samples/Specimens/Data at the Completion of the Protocol

Samples will be maintained for further laboratory testing for up to 5 years after completion (or closure) of the protocol for the purpose stated in Section 9.1. No long-term storage of samples will occur in this study.

9.6 Reporting Loss or Destruction of Samples/Specimens/Data

Any loss or unanticipated destruction of locally maintained samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) will be reported to the site IRB.

10 ASSESSMENT OF SAFETY

Regulatory requirements, including FDA regulations and ICH Guideline for Good Clinical Practice, set forth safety monitoring and reporting responsibilities of Sponsors and Investigators to ensure the safety and protection of human subjects participating in clinical trials.

10.1 Toxicity Scale

All AEs that occur during the study should be assessed according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1 (July 2017).

Some grade 1 laboratory parameters on the DAIDS Toxicity Table may fall within the lab reference range for normal values. If so, these normal values will not be reported as grade 1 adverse events.

10.1.1 Causality

Causality (likelihood that the event is related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related:

- Reasonable temporal relationship
- Follows a known response pattern
- Clear evidence to suggest a causal relationship
- There is no alternative etiology

Probably Related:

- Reasonable temporal relationship
- Follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology

Possibly Related:

- Reasonable temporal relationship
- Little evidence for a more likely alternative etiology

Unlikely Related:

- Does not have a reasonable temporal relationship

OR

- Good evidence for a more likely alternative etiology

Not Related:

- Does not have a temporal relationship

OR

- Definitely due to an alternative etiology

Note: Causality assessment is based on available information at the time of the assessment of the AE. The Investigator may revise the causality assessment as additional information becomes available.

10.2 Recording/Documentation

At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations and will be immediately recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools, and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable AEs that are identified will be recorded in Medidata Rave. The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AEs relationship to the study agent/intervention will also be recorded in Medidata Rave.

10.3 Definitions

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, that includes any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR): An adverse event that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction, which implies a higher degree of certainty.

Serious adverse event (SAE): Any adverse event that results in one or more of the following outcomes:

- Death
- Life-threatening (i.e. an immediate threat to life) event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Medically important event*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is a suspected adverse reaction that is both serious and unexpected.

Unanticipated Problem (UP): Any incident, experience, or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to
   a. The research risks that are described in the IRB-approved research protocol, informed consent document, Investigator's Brochure, or other study documents; and
   b. The characteristics of the subject population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the Investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data.

Protocol Deviation: Any change, divergence, or departure from the IRB-approved study procedures in a research protocol. Protocol deviations are designated serious or non-serious and further characterized as:

1. Those that occur because a member of the research team deviates from the protocol
2. Those that are identified before they occur, but cannot be prevented
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a SAE or compromises the safety, welfare, or rights of subjects or others.

Non-Compliance: The failure to comply with applicable SAB policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that:
   a. Increases risks or causes harm to participants
   b. Decreases potential benefits to participants
   c. Compromises the integrity of the study
   d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that is neither serious nor continuing

10.4 Adverse Event Reporting

10.4.1 Expedited Reporting to the site IRB

Unanticipated problems that are either AEs or non-AEs (as defined by Section 10.3) and Serious Protocol Deviations will be reported within seven calendar days of Investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be

reported to the site IRB within seven calendar days of Investigator's awareness, regardless of expectedness.

10.4.2 Annual Reporting to the site IRB

The following items will be reported to the site IRB in summary at the time of Continuing Review:

- Serious and non-serious unanticipated problems
- SAEs that are possibly, probably, or definitely related to the research
- SAEs that are not related to the research
- All AEs.
- Serious and Non-Serious Protocol deviations
- Serious, continuing, and minor non-compliance
- Any trend or event that, in the opinion of the Investigator, should be reported

10.4.3 Investigator Reporting Responsibilities to the Sponsor

Adverse Events: Line listings, frequency tables, and other summary AE data will be submitted to the IND Sponsor when needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and in the preparation of final study reports.

SAEs (whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported within one business day after the site becomes aware of the event. All other SAEs must be reported within three business days of site awareness.

SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:

SAB Biotherapeutics, Inc.
ATTN: Clinical Safety Office
2301 E. 60th St. North
Sioux Falls, SD 57104

Phone: 605-679-6980
Fax: 888-680-0864
E-mail: safetyreporting@sabbiotherapeutics.com

Non-Serious AEs that are UPs must also be reported on the SERF and sent to the CSO by fax or e-mail attachment no later than seven calendar days of site awareness of the event. The UPs that are not AEs are not reported to the Sponsor CSO.

Pregnancy: Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (e.g., congenital anomaly/birth defect) are reportable on the SERF. Pregnancy and pregnancy outcome data (e.g. delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within three business days of the site's awareness via email or fax.

10.5 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs that occur following enrollment of the subject (by signing the informed consent) are followed until the final outcome is known or until the end of the study follow-up period.

SAEs that have not resolved by the end of the follow-up period are followed until the final outcome is known. If it is not possible to obtain the final outcome for an SAE (e.g. the subject is lost to follow-up), the reason that a final outcome could not be obtained will be recorded by the Investigator on the AE case report form (CRF), if the CRF is still open, and the SERF as applicable.

SAEs that occur after the study follow-up period that are reported to the Investigator and are assessed to be possibly, probably, or definitely related to the study agent must be reported to the CSO, as described above.

10.6 Sponsor's Reporting Responsibilities

Serious, unexpected, suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 will be reported to FDA and all participating Investigators as IND Safety Reports. The sponsor will also submit a brief report of the progress of the investigation to the FDA on an annual basis as defined in 21 CFR 312.33.

11 CLINICAL MONITORING STRUCTURE

11.1 Site Monitoring Plan

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. Study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines" or similar guideline currently in use. Monitors under contract to SAB or CRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be:

1) To verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject;
2) To verify the prompt and accurate recording of all monitored data points and prompt reporting of all SAEs;
3) To compare Medidata Rave data abstracts with individual subject records and source documents (subject charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information);
4) To help ensure Investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), FDA, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the Investigator (and/or designee) and other study personnel will be available to discuss the study progress and findings of the monitoring visit.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

11.2 Data and Safety Monitoring

11.2.1 Investigator Safety Monitoring

The Investigator or designee may interrupt the administration of study drug to an individual subject, or enrollment into this study if indicated for unanticipated problems or AEs. In addition, the Investigators are responsible for:

- Protecting the safety and welfare of subjects
- Evaluating subject safety, including physician assessment of AEs for seriousness, severity, and causality
- Notifying the sponsor of SAEs and immediately-reportable events
- Providing detailed written reports, including confirmatory tests promptly following immediate initial reports
- Informing the IRB of SAEs

11.3 Safety Review and Communications Plan (SRCP)

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the IND Sponsor Clinical Safety Office (CSO), which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

11.4 Safety Monitoring Plan

PPD has established through their Safety Monitoring Plan a process that defines a committee charged with reviewing the accumulating data as the trial progresses to monitor safety, effectiveness and trial conduct. The Safety Monitoring Plan will be developed by a safety specialist from PPD's pharmacovigilance group. This plan then would be reviewed by the principle investigator, a medical monitor from PPD, as well as medical monitors and subject matter experts (e.g. pharmacokinetic, biostatistics, etc.) identified by the sponsor. While the committee could have up to ten members, including project and study managers, there will be a core committee designated of at least four members that are charged with authorizing study advancement. The plan will be included in the Trial Master File at the end of the study.

11.5 Sponsor Medical Monitor

A Medical Monitor representing the IND Sponsor will be appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP).

11.6 Treatment Interruption or Discontinuation

A subject's study drug infusion may be discontinued at any time at the subject's request or at the discretion of the Investigator or the Sponsor. The following may be justifiable reasons for the Investigator to discontinue a subject from SAB-176 infusion:

- The subject was erroneously included in the study (i.e., was found to not have met the eligibility criteria)
- The subject experiences an intolerable AE
- The subject is unable to comply with the requirements of the protocol

- The subject participates in another investigational study without the prior written authorization of the Sponsor

The criteria for slowing or stopping a given infusion is discussed in Section 5.3

11.7 Pausing Rules

If any of the following criteria are met at any time the study will be paused to further enrollment until assessed by the sponsor medical monitor:

- Any SAE as defined in Section 10.3 that can be possibly, probably, or definitively attributed to the study drug
- Three or more subjects in the same cohort experiencing the same Grade 2 or higher adverse effect that can be possibly, probably, or definitively attributed to the study drug
- Two or more subjects develop the same or clinically similar Grade 3 AE or laboratory abnormality
- Two or more subjects develop a serum creatinine ≥Grade 2 toxicity (≥1.8 mg/dL)
- Two or more subjects develop ≥1.5-fold increase in serum creatinine level from baseline
- Two or more subjects develop GFR <70 mL/min, irrespective if serum creatinine is normal range or Grade 1
- Two or more subjects develop a serum creatinine ≥Grade 2 toxicity in PT and/or PTT (i.e. one grade 2 PT and one grade 2 PTT would meet this pausing rule)

The sponsor medical monitor can request information needed (such as a listing of graded AEs) and unblinded randomization scheme (directly from the site investigational pharmacy group) to evaluate the data. For individual subject unblinding, the site will follow their unblinding procedures per SOP-AUSCLN-506. The sponsor medical monitor will ultimately make the decision to either resume the study or stop the study.

If the trial is stopped due to unacceptable adverse events or stopping criteria, the IRB will be notified.

11.8 Dose Escalation Rules

When the results from the Day 7 visit for the last subject in a cohort (e.g., Cohort 1) are available safety parameters will be analyzed to determine the overall safety of that dose-level (e.g., 1 mg/kg). If any of the following criteria are met, the corresponding dose-level is not considered "acceptably safe", and the study will not proceed to the next higher dose group (as the review is blinded, this will be across treatment arms).

- Any SAE that can be possibly, probably, or definitively attributed to the study drug
- Any immediate hypersensitivity or cytokine storm events
- Two or more subjects with asymptomatic positive anti-IgG (rheumatoid factor)
- One or more subjects with positive anti-IgG (rheumatoid factor) with associated rheumatologic symptoms (i.e. arthralgia, myalgia, etc.)
- Two or more subjects across all cohorts experience the same Grade 3 or higher adverse effect that can be possibly, probably, or definitively attributed to the study drug

- Three of the first 10 subjects (30%) experience the same grade 2 or higher adverse effect that can be possibly, probably, or definitively attributed to the study drug or any time thereafter 30% of enrolled subjects have the same grade 2 or higher 'related' AE.
- Two or more subjects across cohorts develop a serum creatinine ≥ Grade 2 toxicity (≥1.8 mg/dL) or doubled from baseline (whichever is lower)

If any of the above criteria are met at any time, then the medical monitor will evaluate unblinded study data and make a determination about continuation of the study and/or amendment of the protocol.

11.9 Study Endpoints

11.9.1 Primary Endpoint

- Type and frequency of AEs experienced by subjects receiving SAB-176 at escalating dose-levels, as compared to placebo

11.9.2 Secondary Endpoints

- Pharmacokinetic profile of intravenously administered SAB-176 in healthy adults
- Hemagglutination Inhibition (HAI)
- Microneutralization (MN)
- Frequency and concentrations of antibodies caused by SAB-176, as measured by:
  Anti-IgG antibodies using rheumatoid factor
  Anti-SAB-176

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers about the essential information about the study, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions of essential information about the research will include the study's purpose, duration, experimental procedures, alternatives, risks, and benefits. Subjects will have the opportunity to ask questions and have their questions answered.

The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. Study monitors and other authorized representatives of the Sponsor may inspect all documents and

records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, or the sponsor's designee.

13 DATA MANAGEMENT AND MONITORING

13.1 Data Management Responsibilities

The Investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected in the electronic data system**,** and must be signed and dated by the person recording and/or reviewing the data. All data should be reviewed by the Investigator and signed as required electronic signature.

13.2 Data Capture Methods

Study data will be collected at the study site and maintained in an electronic data system (Medidata Rave). This data will be completed on an ongoing basis during the study. Data will be entered into electronic data systems by authorized individuals. Corrections to electronic data systems will be tracked electronically (password protected or through an audit trail) with time, date, individual making the correction, and what was changed.

13.3 Types of Data

Source documents include, but are not limited to, the subject's medical records, laboratory reports, ECG tracings, x-rays, radiologist's reports, subject's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

13.4 Source Documents and Access to Source Data/Documents

Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Data from Medidata Rave will be collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. The subject's medical record must record his/her participation in the clinical trial and, after unblinding, study treatment/vaccination (with doses and frequency) or other medical interventions or treatments administered, as well as any adverse reactions experienced during the trial.

13.5 Record Retention

The Investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects are to be maintained by the Investigators in a secure storage facility for a minimum of three years. The FDA requires study records to be retained for up to two years after marketing approval or disapproval (21 CFR 312.62), or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB, state, and federal medical

records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

14 REFERENCES

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