A Phase 2 randomized blinded single dose comparison of the safety pharmacokinetics and pharmacodynamics of rabies immune globulin, and SYN023 in healthy adult subjects receiving rabies vaccines

Investigational Product: **SYN023**

Protocol Number: **SYN023-002**

US FDA IND Number: **BB-IND-121522**

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Version Superseded **Version 1.0 (12 May 2016)**

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol and agree to conduct this protocol in accordance with Good Clinical Practices (ICH-GCP), the ethical principles set forth in the Declaration of Helsinki, and with local regulatory requirements.

Signature Date

Printed Name

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ADCC	antibody directed cellular cytotoxicity
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	area under the curve time 0 to last time point
$AUC_{0\text{-inf}}$,	area under the curve time 0 to infinity
βHCG	beta human chorionic gonadotropin
BUN	blood urea nitrogen
BP	blood pressure
HIV	human immunodeficiency virus
ICI	immune complex illness
CBC	complete blood count
CDC	Centers for Disease Control
C_{max},	maximum concentration
Clp	plasma clearance
CFR	code of federal regulations
Cr	creatinine
CRF	case report form
CPK	creatinine phosphokinase
CV	coefficient of variation
ECG	electrocardiogram
eCRFs	electronic case report form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
HASYN023	human anti-SYN023 antibodies
HIV	human immunodeficiency virus
IEC	independent ethics committee
IgA	Immunoglobulin A
IgG1κ	Immunoglobulin G type 1 kappa
IM	intramuscular
IRB	Institutional review board
IU	International units
λ_z	terminal elimination rate constant
LLN	lower limit of normal
kg	kilogram
MedDRA	medical dictionary for regulatory activities
mL	milliliter

mAb	monoclonal antibody
PD	pharmacodynamic
PEF	peak expiratory flow
PK	pharmacokinetic
PEP	post-exposure prophylaxis
PT(INR)	prothrombin time (international normalized ratio)
PTT	partial thromboplastin time
RFFIT	rapid fluorescent foci inhibition test
RVNA	rabies virus neutralizing activity
RIG	rabies immune globulin
RVa	RabAvert®
RVi	Imovax®
SAE	serious adverse event
SAP	statistical analysis plan
SMC	safety monitoring committee
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse event
T_{max}	time till maximum concentration
$t_{1/2}$	half-life
ULN	upper limit of normal
WHO	World Health Organization

STUDY ABSTRACT

TITLE: A Phase 2 randomized blinded single dose comparison of the safety pharmacokinetics and pharmacodynamics of rabies immune globulin, and SYN023 in healthy adult subjects receiving rabies vaccines

RATIONALE:
The lowest dose of SYN023 tested in Protocol SYN023-001(0.3 mg/kg) exceeded rabies virus neutralizing activity (≥ 0.5 IU/mL) in the serum for at least 35 days. The two higher doses of 1.0 mg/kg and 3.0 mg/kg exceeded rabies virus neutralizing activity for 84 days. This means that the lowest dose of SYN023 administered to humans will likely produce a bridge of rabies neutralizing activity until the rabies neutralizing response to vaccination becomes therapeutic, usually in two to three weeks after vaccination. Since high levels of antibody have the potential to impair the immune response to the rabies vaccine it is important to evaluate the potential of 0.3 mg/kg SYN023 to inhibit the immune response of the two licensed rabies vaccines Imovax® and Rabavert®.

OBJECTIVES:
Primary Objective
Compare the rabies virus neutralizing activity induced by licensed rabies vaccines Imovax® (RVi) and Rabavert® (RVa) co-administered with human rabies immune globulin (RIG) or 0.3 mg/kg of SYN023.

Secondary Objective(s)
- Compare the safety RVi and RVa administered with RIG or SYN023
- Determine the pharmacokinetics of SYN023
- Determine the immunogenicity of SYN023

DESIGN:
This is a Phase 2 single site, randomized, blinded comparison of the immunogenicity, of RVi and RVa when administered RIG or SYN023. After sentinel subjects are evaluated for each regimen subjects will be randomized into one of four dose regimens with a ratio of 1:1:1:1 (Table 2.1-1). The trial is planned at one site. All injections will be given intramuscularly

Table 2.1-1Treatment Allocation

Treatment Allocation	Number of subjects
RVi + RIG	40
RVa + RIG	40
RVi + SYN023 0.3 mg/kg	40
RVa + SYN023 0.3 mg/kg	40
Total	160

The labeled RVi and RVa regimens for post exposure prophylaxis are both five dose regimens. The initial dose of RVi and RVa will be co-administered with Study Drug (either RIG or 0.3 mg/kg SYN023) on Study Day 0. Rabies virus neutralizing activity (RVNA) and blood levels of SYN023 will be measured for the remainder of the trial while the rest of the post-exposure RVi and RVa doses are given. It is anticipated that RVNA will remain high during RVi and RVa administration and through the end of the study at Study Day 112. Pharmacodynamic efficacy will be defined as RVNA measured above 0.5 IU/mL with RVi and RVa for the duration of the trial. SYN023 concentrations and anti-SYN023 antibodies will also be measured.

ANALYSIS OF SAFETY

Safety monitoring will include vital signs (blood pressure, temperature, pulse, oximetry and respiration rates), physical examination, electrocardiogram (ECG) and clinical laboratory tests (serum chemistry, hematology, troponins, creatinine phosphokinase [CPK], human anti-SYN023 antibodies [HASYN023], and urinalysis). Adverse events will be recorded throughout the study and will be coded using MedDRA (Medical Dictionary for Regulatory Activities) terminology. Visual assessment of the injection site will be performed prior to and 30 minutes post-injection after all injections. Solicited local (induration, pain, redness and swelling) and systemic reactions are reviewed over follow-up visits during the twenty eight (28) days following administration. Adverse events are captured and recorded from the time of first administration through Day 42. Serious adverse events (SAEs) are captured and recorded from the time of administration through Day 112.

Safety analyses will be performed using the Safety Population, as defined in section 7.1. Both count and percent summaries will be presented by treatment group for all subjects. Descriptive statistics (number of subjects, mean, standard deviation, percent coefficient of variation, median, minimum, and maximum) will be used to summarize all safety and laboratory data.

ANALYSIS OF EFFICACY

RVNA of >0.5 IU/mL will be used as a pharmacodynamic surrogate of efficacy.

ANALYSIS OF IMMUNOLOGY

Anti-SYN023 antibodies (i.e., anti-CTB011 and anti-CTB012 antibodies) will be determined on Study Days 0, and 7 through 112, or the last blood specimen available for subjects who leave the study prior to Day 112. The development of anti-SYN023 antibodies will be analyzed as a continuous measure across categorical groups by treatment assignment, with descriptive statistics. Exploratory immunological analyses may be conducted on any collected sera.

ANALYSIS OF PHARMACOKINETICS

All PK analyses of serum SYN023 concentrations will be based on subjects who received study drug. Individual analyses will be performed and descriptive statistics will be used to describe the results of individual analyses. PK parameters for SYN023 mAb will be estimated using non-compartmental analysis. Cmax, Tmax, AUC0-last, AUC0-inf, t1/2, Clp, and λz will be calculated when possible.

1 INTRODUCTION

1.1 Background

Rabies is an acute lethal zoonotic disease transmitted from animals to humans. Rabies is known to be present in more than 150 countries and territories and on every continent except Antarctica, and all mammals are believed to be susceptible to infection with the virus. In the US, multiple rabies virus variants are maintained in wild mammalian reservoir populations such as raccoons, skunks, foxes, and bats. Infected domestic and wild animals spread rabies to humans via saliva or scratches (Gompf, 2014). Although the US has been declared free of canine rabies virus variant transmission, in developing countries, the primary route of transmission to humans is via the bite of a rabid dog (Manning et al. 2008). There are currently no known effective rabies antiviral drugs.

Once the clinical signs of rabies manifest, the mortality rate approaches 100%. Therefore, post-exposure prophylaxis against rabies infection is of critical importance. Rabies vaccination alone is used for preexposure prophylaxis (Fishbein, 1989). Studies on the development of rabies virus neutralizing activity through immunization indicate that on Day 7 post vaccination most individuals lack adequate rabies virus neutralizing activity while by Day 14 after immunization virtually all individuals vaccinated with a modern vaccine have adequate rabies neutralizing activity (Grandien 1976, Vodopija 1988a)

The rabies mortality from rabid wolf attacks in Iran in 1955 was 1/24 (4.2%) when both vaccination and rabies antisera were used prior to disease manifestations versus 3/5 (60%) when vaccine alone was employed (Baltazard 1955). A study by the same investigator from 1974 found that a rabies vaccine from human diploid cells combined with mule derived anti-rabies antiserum yielded 0% rabies mortality in 44 bitten individuals without disease manifestations even with delays of up to 14 days (Bahmanyar 1976). Delays of up to 4 days in the initiation of rabies immune globulin after anti-rabies vaccination have demonstrated no inhibition of the RVNA activity in blood (Khawplod 1996). Since those experiences post-exposure prophylaxis through the combined administration of a rabies vaccines and rabies immune globulin (RIG) is the standard of care.

The passive administration of RIG is intended to provide an immediate supply of virus neutralizing antibodies to bridge the gap until the induction of active immunity in response to vaccine administration. The use of RIG provides rapid passive immunity that persists for a short time (half-life of approximately 21 days) (Manning et al. 2008). There is sometimes an interaction between RIG and the immune response elicited by the rabies vaccine thus the dose of rabies immune globulin must be evaluated to insure no significant inhibition (Vodopija 1988b).

Two anti-rabies immunoglobulin (Ig) formulations prepared from hyperimmunized human donors have been approved by the FDA: HyperRab® S/D (Grifols Therapeutics) and Imogam®

Rabies-HT (Sanofi Pasteur). Since both human RIG preparations are considered equivalent HyperRab® S/D will be used as the RIG in this trial.

1.2 Description of SYN023

SYN023 is a mixture of two anti-rabies humanized monoclonal IgG1κ antibodies, CTB011 and CTB012, which bind to distinct and non-overlapping antigenic sites on the rabies glycoprotein. N355 and H389 are the critical binding residues for CTB011 and H289, L290 and V291 are the critical residues for CTB012. As with RIG, the goal of treatment with SYN023 is to rapidly establish protective levels of anti-rabies antibody in individuals exposed to the rabies virus. Since RIG is derived from pooled sera of human donors or horses vaccinated against rabies (human rabies immune globulin and equine rabies immune globulin, respectively), there is a limited supply, particularly in endemic areas. Thus, there is an urgent need for improved approaches to the critical initial treatment period. SYN023, a mixture of two anti-rabies humanized monoclonal IgG1κ antibodies, CTB011 and CTB012, has been shown to neutralize more than 15 contemporary clinical isolates of rabies viruses collected in China, and the 10 predominant strains in the US.

1.3 Nonclinical Experience with SYN023

Nonclinical studies with SYN023 and its component antibodies CTB011 and CTB012 showed that both antibodies exhibited high affinity for the rabies virus glycoprotein target and that the two antibodies bind to distinct, non-overlapping sites on the surface of the virus. SYN023 and the component antibodies exhibited potent neutralizing activity against a wide spectrum of rabies virus strains from both the US and China and importantly, SYN023 did not attenuate or impact the nature or timing of the immune response to rabies vaccine in an established hamster model.

SYN023 provided improved post-exposure prophylaxis (PEP) relative to vaccine alone, and provided early-phase passive immune protection that served as a bridge in both hamster and dog disease models until active immunity was produced by the rabies vaccine.

The antibodies comprising SYN023 both exhibited half-lives of a week or more in rats and dogs, with >90% bioavailability in both males and females. Dose-dependent exposure was observed in both rats and dogs with increasing doses of SYN023.

SYN023 was safe and well-tolerated in male and female rats following three repeated weekly IM doses at up to 10 mg/kg, and no mortality or toxicity were observed. SYN023 and the component antibodies did not bind specifically to any human tissues, and neither CTB011 nor CTB012 exhibited any apparent *in vitro* cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxic activity in normal, non-rabies-infected cells. As anticipated, SYN023 did exhibit potent complement-dependent cytotoxic activity against rabies-infected BSR hamster cells, demonstrating the specificity of SYN023 antibodies for rabies virus and virus-infected cells, and that the antiviral activity likely involves a complement-dependent mechanism. It is important to note that neither of the component SYN023 antibodies bound

specifically to any human tissue, and there is no endogenous target for the SYN023 product in normal, healthy human tissues, such that no specific or non-specific toxicity is anticipated for SYN023.

Animal PEP studies have demonstrated that in hamsters, doses of antibody combinations as low as 0.3 mg/kg provided complete protection against rabies challenge, whereas in dogs, doses of SYN023 as low as 0.03 mg/kg in tandem with rabies vaccine also provided complete protection against lethal rabies challenge. These findings suggest that doses of SYN023 as low as 0.005-0.01 mg/kg, at least in dogs, should produce levels of RVNA of at least 0.5 IU/mL, which are generally considered sufficient for complete protection against lethal rabies challenge when administered in concert with rabies vaccine.

1.4 Clinical Experience with Anti-infective Monoclonal Antibody Preparations

SYN023 is a mixture of monoclonal antibodies that are directed against an infectious agent and do not exhibit cross-reactivity with human tissues. Palivizumab (Synagis, MedImmune Inc.) is a monoclonal antibody that is directed against an infectious agent, respiratory syncytial virus that lacks cross-reactivity with human tissues. Palivizumab has been on the market since1998 and continues to remain effective and exhibit an acceptable safety profile.

1.5 Clinical Experience with SYN023

SYN023 administration exhibited an acceptable safety profile in protocol SYN023-001. There were no SAEs or acute allergic reactions and local toxicity was mild. SYN023 antibody concentrations are pending for Study SYN023-001, however RVNA determinations are final. All five subjects in each dose group of protocol SYN023-100 lacked RVNA prior to SYN023 injection and exhibited measurable RVNA after administration thus, it is reasonable to conclude that the RVNA was the result of SYN023 antibody injection. If this is true then the two higher doses of 1.0 mg/kg and 3.0 mg/kg exceeded rabies virus neutralizing activity for 84 days and the mean level of the lowest dose of SYN023 tested in Protocol SYN023-001 (0.3 mg/kg) exceeded rabies virus neutralizing activity (≥ 0.5 IU/mL) by over five-fold in the serum for at least 28 days (Table 1.5-1). The descriptive statistics including mean, standard error and 95% confidence intervals were calculated by SAS 9.4 (Cary, NC, USA) and figure 1.5-1was generated using Graphpad Prism 5.0 (San Diego, CA, USA

Table 1.5-1 Mean RVNA activity in IU by dose level in Phase I study of SYN023. Five subjects in each group.

Dose Level mg/kg	Study Day							
	0	1	3	7	14	28	35	84
0.3	0.00 ± 0.00	2.70 ±0.43	3.68 ±0.56	4.44 ±1.09	3.78 ±0.41	2.82±0.61	1.82 ±0.93	0.22 ±0.25
1.0	0.00 ± 0.00	8.88 ±3.13	10.02 ±2.07	17.00 ±8.81	11.2 ±3.24	10.3±3.37	11.64 ±3.86	2.22 ±1.06
2.0	0.02 ± 0.00	13.40 ±8.19	27.60 ±3.31	35.00 ±2.40	35.6 ±3.85	13.80 ±7.61	10.14 ±2.12	3.76 ±1.07

These results are graphically presented for the lowest dose group as means ± 95% confidence interval (Figure 1.5-1). Rabies neutralizing activity from IM injection Study Day 0 was measurable and several-fold above the minimum inhibitory level of 0.5 IU/mL on Study Days 1, 3, 7, 14 and 28.

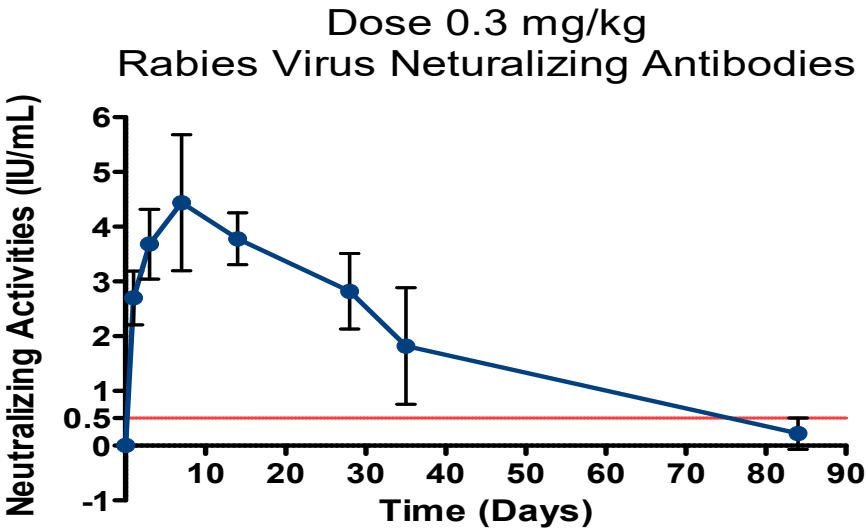

Figure 1.5-1 SYN023 Rabies Virus Neutralizing Activity over time (95% CI)

The lowest dose of SYN023 tested in Protocol SYN023-001(0.3 mg/kg) in humans exceeded 0.5 IU/mL of RVNA in the serum of all volunteers for at least 35 days. The two higher doses of 1.0 mg/kg and 3.0 mg/kg exceeded serum rabies virus neutralizing activity for 84 days (Table 1.5-1). This means that the lowest dose tested in humans will produce a bridge of RVNA long enough for the neutralizing response from vaccination to become therapeutic, usually within 14 days. Since high levels of antibody have the potential to impair the immune response to the rabies vaccine it is important to evaluate the potential of the lowest SYN023 dose active in animal (0.3 mg/kg) to inhibit the immune response of the two licensed rabies vaccines Imovax® and Rabavert®. SYN023-001 was a single dose study. Any effects of anti-SYN023 antibodies on RVNA are reflected in the RVNA values and seem to have a negligible inhibitory effect. The overall RVNA needed for protection will be known with certainty in the current SYN023-002

study. When the human SYN023-001 pharmacokinetic values are available it will be possible to correlate the RVNA provided by a known amount of SYN023 to develop a RVNA-per-mg-SYN023 value that might be useful in the current study to estimate the relative contribution of SYN023 to the overall RVNA induced by vaccination. In any event such as estimation can be made during the Study Day 0 through Study Day 7 interval when vaccine induced RVNA is unlikely to be present.

1.6 Rationale for Study

Monoclonal antibodies (mAbs) offer the advantages of batch-to-batch consistency and large-scale production, and may therefore provide a solution to the current global shortage of RIG. However, as mentioned, there are several strains of the rabies virus that predominate in various regions of the US and the world; their prevalence is tracked by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). A single target epitope may not be present on all strains of the rabies virus. As a result, it is of critical importance for the antibody product to account for the genetic variability of the rabies viruses and offer effective broad spectrum neutralization activities. Accordingly, administration of a mixture of mAbs with complementary specificity and functionality would be preferable to administration of a single mAb.

Consensus definitions of adequate rabies virus neutralizing antibody reference values have been developed to define an appropriate, intact adaptive host response to vaccination: RVNA of 0.5 international units (IU) per milliliter (mL) or complete virus neutralization at a 1:5 serum dilution by RFFIT (Centers for Disease Control and Prevention 1999). The goal of RIG and SYN023 is to rapidly establish protective rabies virus neutralizing levels in the rabies exposed person. RVNA appears to be adequate at the 0.3 mg/kg dose level and since this is clinically important and logically correlated directly with the SYN023 antibody administered the SYN023-002 study may be started despite the ongoing analysis of a RVNA-per-mg-SYN023 value that might be important in the SYN023-002 analysis.

2 STUDY OBJECTIVES AND DESIGN

2.1 Objectives

Primary Objective

Compare the rabies virus neutralizing activity induced by licensed rabies vaccines Imovax® (RVi) and Rabavert® (RVa) co-administered with human rabies immune globulin (RIG) or 0.3 mg/kg of SYN023.

Secondary Objective(s)

- Compare the safety RVi and RVa administered with RIG or SYN023
- Determine the pharmacokinetics of SYN023

- Determine the immunogenicity of SYN023

2.2 Design

This is a Phase 2 single site, randomized, blinded comparison of the immunogenicity, of RVi and RVa when administered RIG or SYN023. Subjects will be randomized into one of four dose regimens with a ratio of 1:1:1:1 (Table 2.2-1). The trial is planned at one site. All injections will be given intramuscularly

Table 2.2-1Treatment Allocation

Treatment Allocation	Number of subjects
RVi + RIG	40
RVa + RIG	40
RVi + SYN023 0.3 mg/kg	40
RVa + SYN023 0.3 mg/kg	40
Total	160

The RVi and RVa regimens for post exposure prophylaxis are both five dose regimens. The initial dose of RVi and RVa will be co-administered with Study Drug (either RIG or 0.3 mg/kg SYN023) on Study Day 0. Rabies virus neutralizing activity (RVNA) and blood levels of SYN023 will be measured for the remainder of the trial while the rest of the post-exposure RVi and RVa doses are given. It is anticipated that RVNA will remain high during RVi and RVa administration and through the end of the study at Study Day 112. Pharmacodynamic efficacy will be defined as RVNA measured above 0.5 IU/mL with RVi and RVa for the duration of the trial and no more than 10% lower for SYN023 compared to RIG at any time point through Study Day 35. SYN023 concentrations and anti-SYN023 antibodies will also be measured.

3 STUDY PROCEDURES

3.1 Schedule of Subject Treatments and Evaluations

A Summary Schedule of Evaluations depicting all visit-specific procedures is provided in Table 3.1-1. All scheduled phlebotomy samples must be collected prior to administration of any study specified vaccine, RIG or SYN023. See Appendix A for a more detailed description of the evaluations.

Table 3.1-1 Summary Schedule of Subject Treatment and Evaluations

Study Visit Day →	Screen	-2	0	1	3	7	14	28	35	42	84	112
Visit Window[d]		0	0	0	0	1	1	3	4	4	8	11
Written informed consent	X											
Eligibility criteria verification	X											
Medical history	X											
Physical examination	X											
ECG[e]	X		X	X	X	X	X	X				X
Urine toxicology screen	X											
Urine βHCG (all females)[e]	X				X	X	X	X				X
Serum βHCG (all females)[a]		5										
Serum Hepatitis B, C tests	3											
Serum HIV-1,2 tests	3											
Rabies Vaccine administration			X		X	X	X	X				
Study Drug Administration			**X**									
Urinalysis[e]	X		X	X	X	X	X	X	X	X		X
Serum Anti-rabies activity[e]			10	10	10	10	10	10	10	10	10	10
Serum chemistry[b,e]	10		10	10	10	10	10	10				10
CBC, differential, platelets[e]	7		7	7	7	7	7	7				7
PT (INR), PTT[e]	5		5			5						5
Serum IgA	7											
SYN023 Pharmacokinetics[e]			14	7	7	7	7	7	7	7	7	
Anti-SYN023 antibodies[e]			5			5	5	5	5	5	5	5
Weight	X		X									X
Vital signs & oximetry	X		X	X	X	X	X	X				X
Interval history			X	X	X	X	X	X	X	X	X	X
Focused physical examination			X	X	X	X	X	X	X	X	X	X
Solicited adverse events (incl. con. meds.)			X	X	X	X	X	X				
Unsolicited adverse events (incl. con. meds.)			X	X	X	X	X	X	X	X		
Serious adverse events (incl. con. meds.)			X	X	X	X	X	X	X	X	X	X
Site of injection examination			X	X	X	X	X	X	X	X		X
Lymphadenopathy			X	X	X	X	X	X	X	X		X
Per visit phlebotomy volume	35	5	51	34	34	39	39	39	22	22	22	37
Cumulative phlebotomy volume[c]	35	40	91	125	159	198	237	276	298	310	332	369

a. Results must be known before Study Drug administration
b. Serum Chemistry: creatinine phosphokinase (CPK), troponin, total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium. Note minimum serum chemistry labs for screening visit are: AST, ALT, ALP and creatinine although other labs monitored for safety may be collected if part of panel.
c. The cumulative phlebotomy volume is approximate.
d. Visit window refers to acceptable variation in days either early or late from scheduled visits in without a protocol violation.
e. Must be obtained on day of visit but prior to any injections.

3.2 Subject Selection

3.2.1 Recruitment and Informed Consent

Various methods of recruitment may be used such as advertising, referrals, or solicitation of subjects previously known to the clinical site. Interested subjects will be invited to participate in the informed consent process. Informed consent will be obtained by the use of a written consent form approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and signed and dated by the subject at the time of consent. Potential subjects will be interviewed to ensure that the subjects meet all entry criteria relating to history. The clinical investigator or designee will conduct the consent discussion on an individual basis with each subject and will allow adequate time for all questions to be addressed. Written informed consent will be obtained prior to conducting any study-related procedures. A copy of the signed consent form shall be given to the subject prior to Study Day 0.

3.2.2 Screening

A sequential site specific volunteer number will be assigned to each subject for identification purposes. Informed consent will then be obtained. Then the subject will be screened to assess eligibility for the study.

A screening log will be maintained by the site that records all subjects for whom consent was obtained and who entered the screening process. The screening log will record the sex, age and racial or ethnic identity of the candidate subjects. Abnormal results and findings resulting in ineligibility will be discussed with the subject, who will be referred for follow-up care with their healthcare provider if necessary. Only screening information from consented, eligible and dosed individuals will be entered into the study database. Eligibility for entry into the study will be based on the inclusion and exclusion criteria described below. The investigator must document confirmation of eligibility prior to randomization. The serum chemistry labs for screening visit that determine eligibility are: AST, ALT, ALP and creatinine. These are a subset of the larger clinical safety laboratory analytes. Other serum chemistry values (total bilirubin, BUN etc.) that are collected for safety monitoring (Table 3.1-1) will be collected for Study Day 0 baseline values but are not part of the inclusion/exclusion criteria as such.

3.2.3 Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria at the time of subject ID assignment:

1. Male or female subjects between 18 and 50 years of age, inclusive
2. Body mass index between 18 and 30 kg/m^2, inclusive
3. Female subjects physically capable of pregnancy (i.e., not sterilized and still menstruating or within 1 year of the last menses if menopausal) must:
    a. Agree to avoid pregnancy from 28 days prior to Study Day 0 through the duration of the study.

b. If in a sexual relationship with a man, use an acceptable method of avoiding pregnancy during this period. Acceptable methods of avoiding pregnancy include: the use of at least two forms of contraception, including use by a partner of a barrier method (e.g., male condom with intravaginal spermicide) as one form of contraception.

4. Women of childbearing potential must have a negative serum pregnancy test within 48 hours preceding receipt of the first dose.

5. Can understand and sign the informed consent document, can communicate with the investigator and provide updated contact information as needed for the duration of the study, has no current plans to move from the study area for the duration of the study, and can understand and comply with the requirements of the protocol.

3.2.4 Exclusion Criteria

Subjects must have <u>none</u> of the following at the time of subject ID assignment:

1. Oral temperature ≥37.5°C at screening

2. Complete blood count (CBC) and platelet count abnormal values (>5% above the upper limit of normal [ULN] or >5% below the lower limit of normal [LLN] per local laboratory parameters) at screening with exception of absolute lymphocyte count.

3. Abnormally elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), or creatinine (Cr) values at screening (however a single test AST, ALT or ALP may be >10% above the ULN per local laboratory parameters)

4. Abnormal PT (INR) PTT

5. Abnormal screening urinalysis result that is, per the investigator, clinically significant, or a screening urine dipstick result of ≥2+ protein

6. Positive screening urine test for illicit drugs (opiates, cocaine, amphetamines methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, PCP, MDMA, and methadone)

7. History or evidence of autoimmune disease

8. History or evidence of any past, present, or future possible immunodeficiency state, including laboratory evidence of human immunodeficiency virus (HIV) 1 or 2 infection

9. History or evidence of chronic hepatitis

10. History or evidence of rabies infection

11. History or evidence of any other acute or chronic disease that, in the opinion of the investigator, may interfere with the evaluation of the safety or immunogenicity of the drug or compromise the safety of the subject; for example a clinically relevant history of respiratory, thyroid, gastrointestinal, renal, hepatic, hematological, lymphatic, oncologic, cardiovascular, psychiatric, neurological, musculoskeletal, genitourinary, infective, inflammatory, immunological, dermatological or connective tissue disease

12. History or evidence of allergic disease or reaction, including adverse responses to therapeutic monoclonal antibodies that, in the opinion of the investigator, may compromise the safety of the subject

13. History of non-compliance that, in the opinion of the investigator, will make it unlikely that the subject will comply with the protocol

14. Previous exposure to rabies vaccine

15. Receipt of an immunoglobulin or blood product within 90 days prior to Study Day 0

16. Receipt of immunosuppressive medications other than inhaled or topical immunosuppressant drugs within 45 days prior to Study Day 0

17. Body weight greater than 90 kg.

18. History or evidence of IgA deficiency

3.2.5 Screening Clinical Assessments and Laboratory Tests

Unless noted otherwise, the window period within which all screening evaluations must be completed, and the results reviewed by the investigator to confirm eligibility of subjects, is 28 days prior to Study Day 0.

Subjects will provide a detailed medical history and subjects will undergo a physical examination. The assessment will include the determination of any surgeries or medically significant procedures planned to occur during the entire study period. Demographic characteristics (date of birth, gender, and race/ethnicity) will also be collected. Any new abnormal findings will be discussed with the subject and referral will be made for follow-up care if necessary.

Screening laboratory tests (See Table 3.1-1) will be performed during the screening process. Results from some of these laboratory tests (HIV, Hepatitis B and C, serum IgA) may serve as study-entry baseline values if not required for Study Day 0. Values from specimens obtained at on or after Study Day -2 will not be required to be redrawn prior to study start on Study Day 0 and the values will serve as baseline values. Eligibility is determined by screening laboratory

tests. All laboratory tests for Study Day 0 must be drawn prior to study drug administration. Abnormal results and findings that make the subject ineligible will be discussed with the subject and the subject will be referred for follow-up care with their healthcare provider if necessary. All screening laboratory specimens will be processed according to laboratory SOPs available from the clinical laboratory(ies) designated for the study. Information about the laboratory(ies), including any instructions for performing and interpreting specific tests, will be maintained in the investigator's study files.

3.2.5.1 Window Period for Select Screening Laboratory Tests

Select laboratory evaluations must be performed on specimens obtained within two days (Study Day -2) prior to study entry on Study Day 0, and the results must be known and eligibility confirmed prior to study entry on Study Day 0. Screening tests that must be obtained ≤ 48 hours prior to receipt of SYN023 or RIG on Study Day 0 include the following: serum βHCG for women only. The results from tests performed on specimens collected within 48 hours prior to study entry on Study Day 0 may serve as both screening and Study Day 0 evaluations.

If blood specimens for serum anti-rabies activity, SYN023 pharmacokinetics (pre dose) and anti-SYN023 antibodies are also taken within two days prior to study entry on Study Day 0, these specimens may be used as the Study Day 0 evaluations for subjects who subsequently are randomized.

3.3 Study Randomization and Sentinel Subjects

Subjects will be randomized to the study based on a randomly-generated sequence of subject identification numbers (randomization schedule). The randomization schedule will be prepared by a statistician who will not be involved in the analysis of the study in order to maintain the blind of the study team. A subject is considered randomized when a subject identification number has been assigned to them on Study Day 0. The first four subjects entered into the study (sentinel subjects) will be randomized such that a subject each receives one of the four possible regimens. Safety information on these sentinel subjects through study day 14 will be collected and reviewed by the medical monitor and principal investigator before the reminder of the trial is enrolled.

Subjects who withdraw from the study or are discontinued may be replaced by modification of the remaining randomization schedule. Unless there is reason to pause the study, based on the study pausing rules as outlined in Section 6.1, then the principal investigators may proceed to enroll all of the subjects.

3.4 Blinding

Because of different volumes for RIG and SYN023 this study is incompletely blinded. In a strict sense it is a single blind study since the subject will not be told which treatment he or she is receiving. The sponsor and the medical monitor are unblinded. The statistician is unblinded.

The other unblinded persons on the study are the study drug manager or pharmacist (and designee, if appointed) and the study monitor(s). All unblinded persons must take care to not reveal individual subject treatment regimen assignments to any other member of the study team. The subject, the principal investigator and most of the study team remain blinded to reduce bias in safety assessment.

The study drug manager or pharmacist (and designee) must have no other clinical or regulatory responsibilities associated with the conduct of the study during the entire study period. With the exception of the medical monitor, unblinded study personnel must not participate in the evaluation of adverse events. A Delegation of Authority Log will be maintained by the site and will identify the individual(s) authorized to function as the study drug manager, i.e., individuals with access to study blinding information.

The randomization schedule will be provided by the unblinded statistician to the study drug manager in a sealed tamper-evident envelope. Access to the randomization schedule during the study will be provided only to the study drug manager (or designee in the pharmacy), the study monitor, and the sponsor's investigational product manager (and/or designee). The randomization schedule and all pharmacy source documents and dose preparation records that can link a subject identification number with a treatment assignment must remain secure (e.g., in the pharmacy with access limited to only unblinded persons) until notification from the sponsor that the study has been unblinded.

Labels accompanying the syringes of prepared study drug doses will not indicate which vaccine is in the syringe. Identical syringes and needles will be used for preparation and administration of each study drug.

3.4.1 Unblinding for Clinical Emergencies

If there is an urgent clinical requirement to know a subject's treatment assignment, the investigator (in consultation with the medical monitor, if possible) will make a written request (handwritten is acceptable) to the Study Drug manager for urgent unblinding of a subject's treatment. The request must include the subject identification number, the date, a brief justification of the clinical requirement to the vaccine manager in the research pharmacy, and the investigator's signature. The request will be kept in the study file.

Upon receipt of proper written request, the vaccine manager or designee will disclose the treatment group to the investigator. The sponsor must be notified immediately of any clinically required break of the study blind on an Immediately Reportable Event Form.

3.5 Medicinal Product and Study Drug Administration

There are four substances administered as part of this study. There are two study drugs SYN023 and rabies immune globulin (RIG): HyperRab ST® Grifols. SYN023 is investigational agent that has been administered previously to human subjects in a Phase 1 trial. RIG is licensed and

commercially available. SYN023 was tolerated acceptably in the initial human study thus enrollment of this study may be parallel between the different study groups. Vaccination will occur within 75 minutes after Study Drug administration. RVi, RVa, SYN023 and RIG will be administered by intramuscular injection. Generally antibodies should be administered on the right side of the body and vaccinations on the left aside of the body to avoid administration in the same site.

3.5.1 SYN023 (Study Drug)

One or more IM injections of the calculated dose of SYN023 should be administered in any of the acceptable injection sites on the RIGHT side of the body on Study Day 0. If for some reason left sided administrations sites must be used a record must be kept of the site and care taken to not administer SYN023 at a rabies vaccination site. SYN023 is supplied at a concentration of 10 mg/mL. For example a dose calculation for a 70 kg person receiving SYN023 at the dose of 0.3 mg/kg would require a dose of 21mg resulting in a dose volume of 2.1 mL. This would need to be administration into injection sites as described below. A needle no smaller than 21-gauge and 1.0 to 3.0 inches in length depending on subject size should be used to draw up the dose of SYN023. Aspiration of SYN023 from the vial should be done gently to avoid foaming.

SYN023 is to be administered as one or more IM injections in one of three possible injection site: the gluteus medius (ventrogluteal injection site/hip), the vastus lateralis (thigh), rectus femoris (thigh) and the deltoid muscle. Doses of up to 5 mL may be given as a single injection into the hip and thigh muscles. Doses up to 3 mL may be given if required in the deltoid muscle. No more than one injection may be administered into each muscle. Only a single deltoid administration is permitted in any subject. Injections into the gluteus maximus (buttocks) will not be performed.

When selecting the site of injection, known paths of nerves, arteries and veins are to be avoided. If available ultrasound assessment of thickness of fat pad and survey of nerve and blood vessel paths may be employed. The needle should be inserted into the skin at a 90° angle. Before SYN023 is administered, aspirate gently by pulling back on the plunger. If blood is drawn into the syringe, the needle is in a blood vessel and must be moved. Remove the needle from the muscle, re-insert it in a new location in the same muscle, and repeat the aspiration step before administering SYN023. If a dose of SYN023 is drawn up and cannot be administered immediately, the syringe may be stored at 2º to 8º C and used within 3 hours.

3.5.2 Rabies Immune Globulin, (HyperRab ST® Study Drug)

RIG should be administered on the Right side of the body. If for some reason left sided administrations sites must be used a record must be kept of the site and care taken to not administer RIG at a rabies vaccination site. The dose of RIG should be calculated based on body weight: 0.133 mL/kg. The calculated dose should be administered as one or more IM injections in one of three possible injection sites: the gluteus medius (ventrogluteal injection site/hip), the vastus lateralis (thigh), rectus femoris (thigh) and the deltoid muscle. For example, a 70 kg person has a calculated dose of 9.31 mL. Since doses of up to 3 mL are recommended for the deltoid muscle, this will require dividing the dose between two injection sites. Doses of up to 5

mL may be given as a single injection into the hip and thigh muscles. Doses up to 3 mL may be given if required in the deltoid muscle. No more than one injection may be administered into each muscle. Only a single deltoid RIG administration is permitted in any subject. Injections into the gluteus maximus (buttocks) will not be performed.

When selecting the site of injection, known paths of nerves, arteries and veins are to be avoided. If available ultrasound assessment of thickness of fat pad and survey of nerve and blood vessel paths may be employed. The needle should be inserted into the skin at a 90° angle. Before RIG is administered, aspirate gently by pulling back on the plunger. RIG should not be administered intravenously. If blood is drawn into the syringe, the needle is in a blood vessel and must be moved. Remove the needle from the muscle, re-insert it in a new location in the same muscle, and repeat the aspiration step before administering RIG. RIG should be administered immediately, as soon as possible after the dose is constituted.

3.5.3 Rabies Vaccine RVa (Chicken Fibroblast Rabies Vaccine RabAvert®)

The 1 mL dose of the chicken fibroblast rabies vaccine should be administered on the LEFT side of the body in Left deltoid muscle or in the Left vastus lateralis (thigh) or rectus femoris (thigh). Five doses of the vaccine should be administered on Study Days 0, 3, 7, 14 and 28. The vaccine should be administered as soon as possible after dose constitution. RVa should be administered within 75 minutes after Study Drug.

3.5.4 Rabies Vaccine RVi (Human Diploid Cell Rabies Vaccine Imovax®)

The 1 mL dose of the human diploid cell rabies vaccine should be administered on the LEFT side of the body in Left deltoid muscle or in the Left vastus lateralis (thigh) or rectus femoris (thigh). Five doses of the vaccine should be administered on Study Days 0, 3, 7, 14 and 28. The vaccine should be administered as soon as possible after dose constitution. RVi should be administered within 75 minutes after Study Drug.

3.6 Study Evaluations

3.6.1 Efficacy Evaluations

This is not an efficacy trial. A pharmacodynamic measurement of serum rabies virus neutralizing activity in international units will be used as a surrogate of protection. Refer to Table 3.11 for the day on which rabies virus neutralizing activity should be drawn. Refer to the Analytical methodology information sheet (provided under separate cover) for further instructions and additional information on specimen collection and processing.

3.6.2 Immunology Laboratory Evaluations

A summary of immunologic assays to be performed on blood specimens is shown in Table 3.6-2. Staff at the clinical research site will refer to the most current version of the analytical methodology information sheet (provided under separate cover) for further instructions and additional information on specimen collection and processing.

Table 3.6-2 Summary of Immunology Laboratory Evaluations

Sample type	Assay	Study Days
Serum for pharmacokinetics	SYN023 concentration	0, 1, 3, 7, 14, 28, 35, 42, 84
Serum for anti-SYN023 antibodies	Anti-SYN023 antibodies	0,7,14, 28, 35, 42, 84, 112

3.6.3 Safety Evaluations

Electrocardiograms are performed to monitor subject safety (Table 3.1-1). Laboratory evaluations for subject safety are clinical chemistry evaluations, CBC, platelet counts and differential counts, PT(INR) an PTT and urinalyses, Please refer to Table 3.1-1 for a list of laboratory tests for monitoring of safety. Additional laboratory tests may be required for evaluation of specific adverse events such as anaphylaxis and immune complex diseases (see chapters 3.6.3.2)

3.6.3.1 Pre-Study Study Drug and Post-Study Drug Administration Clinical Monitoring of Subjects

Hypersensitivity reactions are a potential adverse effect of all medicinal products administered in this protocol including monoclonal antibodies. Allergic reactions to vaccination are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified study team member trained to recognize and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination monitoring period. Appropriate drugs include intravenous fluids, epinephrine, antihistamines, corticosteroids, inhaled oxygen and drugs required for the treatment of cardiac arrest such as antiarrythmics and pressors. Appropriate equipment includes devices for blood pressure monitoring, oximetry, maintenance of airway and intratracheal intubation and, removal of secretions and cardiac defibrillation.

Grade ≥3 hypersensitivity reactions are Immediately Reportable Events.

Subjects will have vital signs and oximetry taken prior to Study Drug administration. Before after and between each medicinal product administration vital signs and oximetry will be monitored every 30 minutes At every clinical contact the subject will be asked how they are feeling and if they have noticed any new adverse symptoms or manifestations.

Subjects will remain in the clinic under close observation for at least 240 minutes after receiving rabies vaccination that is administered after Study Drug. Vital signs and oximetry will be repeated every 30 minutes during the 240 minute monitoring period before subjects leave the clinic.

3.6.3.2 Recognition of Anaphylaxis

When the diagnosis of anaphylaxis is considered the following laboratory tests should be obtained: plasma tryptase, plasma histamine and urinary N-

methyl histamine. Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled (Sampson et al. 2006):

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

  AND AT LEAST ONE OF THE FOLLOWING

  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

- Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

- Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
  - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
  - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

3.6.3.3 Treatment of Anaphylaxis

Epinephrine is the treatment of choice for anaphylaxis. Aqueous epinephrine, 0.01 mg/kg (maximum dose, 1.5 mg) administered intramuscularly every 5 to 15 minutes as necessary, is the recommended dosage for controlling symptoms and maintaining blood pressure. The 5-minute interval between injections can be liberalized to permit more frequent injections if deemed necessary by the clinician. Epinephrine may be administered subcutaneously or intramuscularly.

Intramuscular administration of injectable epinephrine in the anterior lateral thigh is preferred over subcutaneous injection.

Intravenous epinephrine is an option for patients with severe hypotension or cardiac arrest unresponsive to intramuscular doses of epinephrine and fluid resuscitation. Although there is no precisely established dosage or regimen for intravenous epinephrine in anaphylaxis, 5 to 10 mg intravenous bolus (0.2 mg/kg) doses for hypotension and 0.1 to 0.5 mg administered intravenously in the presence of cardiovascular collapse have been suggested. Other treatments should be combined with epinephrine such as: fluid resuscitation, recumbent posture, oxygen, inhaled adrenergic agents, vasopressors, H1 and H2 histamine antagonists, corticosteroids, and glucagon for individuals on β adrenergic blocking agents. (Sampson et al. 2006)

3.6.3.4 Recognition and Evaluation of Immune Complex Illness

Simultaneous presence of antibodies directed at circulating antigens may result in illness. Immune complex illness (ICI) results from the deposition of antibody-antigen complexes on the microvasculature with the resulting activation of compliment and release of inflammatory mediators and tissue injury. These manifestations may result when anti-rabies antibodies such as those in RIG are administered in temporal proximity to rabies vaccine. They may also result when repetitive vaccination induces antibodies to the administered antigens. ICI manifests itself with inflammation and evidence of vascular injury. Syndromes of allergic vasculitis (leukocytoclastic vasculitis or Henoch-schonlein vasculitis in the case of IgA) and glomerular injury may beobserved. Clinical manifestations of headache, anorexia and fever occur early followed by a petechial rash (palpable purpura) or larger purpura and cutaneous edema more frequent in the dependent regions of the body. Joint pain, rash and abdominal pain are common. The urinary findings may reflect an active glomerular process with hematuria, proteinuria and RBC casts. Acute glomerular histologic lesions of hypercellularity, necrosis, crescent formation and leukocyte infiltration are seen. Ultimately a reduction in renal function and elevated serum creatinine reflects this glomerular damage. ICI is treated by the cessation of antigen or antibody administration or the suppression of endogenously produced antigen. Prednisone has been used in the treatment of ICI (Salmon 2012).

3.6.3.5 Clinical Assessments and Laboratory Tests

Abnormal Clinical Assessments and Laboratory Tests

Results from clinical laboratory tests obtained on the study must be reviewed by the investigator (or a designee who is a medically qualified study team member) within 72 hours of receiving the results to determine if abnormalities exist. If the laboratory value is abnormal and has increased in toxicity grade (see Appendix E for toxicity grading scales) from baseline values, it must be reported as an adverse event and repeated promptly to demonstrate resolution. Additional laboratory tests may be performed if the investigator deems them to be necessary to fully evaluate an adverse event. In the event that the investigator elects to order non-protocol-specified laboratory tests, the investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The investigator must keep the medical monitor informed of adverse events of clinical significance.

Abnormal results and findings will be discussed with the subject, or the subject will be referred for follow-up with their healthcare provider if necessary.

3.6.3.6 Adverse Events

The collection periods for adverse events are:
Unsolicited adverse events: 42 days after Study Drug Administration
Solicited adverse events: 28 days after Study Drug Administration
Serious adverse events: Entire study period (i.e., 112 days)

For this study, solicited adverse events are listed in section 5.7.

3.6.3.7 Concomitant Medications

The collection of information on concomitant medications used by subjects following vaccination will coincide with the collection period of adverse events. The collection period for concomitant medications will be through 14 days following the last vaccination. The collection period for concomitant medications associated with the treatment of serious adverse events (SAE) will be Study Days 0-112

Concomitant medication includes prescription and non-prescription drugs or other treatments, and any monoclonal or polyclonal antibodies other than the study antibodies. The name of the medication, treatment start and stop dates (or 'ongoing'), route of administration, and indication must be recorded on the concomitant medications case report form (CRF). The indication recorded on the concomitant medications CRF must correspond to a medical term/diagnosis recorded on the adverse event (AE) CRF, or to a pre-existing condition noted in the subject's medical history, or be noted as prophylaxis, e.g., dietary supplement.

3.6.4 Window Periods for Clinical Laboratory, ECG, Immunology and Pharmacodynamic Blood Specimens

There is no window for clinical laboratory tests earlier than Study Day 7. After Study Day 7 the window is approximately 10% of the Study Day number. For example At Study Day 7 the window is 0.7 days that rounds to 1 day. At Study Day 14 the window is 1.4 days that rounds to 1 day. At Study Day 42 the window is 4.2 days that rounds to 4 days.

3.6.5 Subject Follow-up and Contact

All subjects who are assigned a subject identification number and receive study drug will be followed according to the protocol unless consent is withdrawn. Subjects will be instructed to contact a study team member to report new diagnoses or new or worsening adverse events and to come to the study clinic if medical attention is needed, provided the urgency of the situation permits. For emergencies and other unscheduled visits to a medical facility other than the study clinic, medical records will, to the extent possible, be obtained by the investigator.

During each clinic visit, the subject will be reminded to notify a study team member of the following:

- The occurrence of Aes and SAEs during the respective reporting periods
- Receipt of any concomitant medications during the applicable reporting period
- Plans to move or if contact information changes
- If subject has decided to withdraw from the study
- Change in general health status
- Any other change in status that may affect the subject's participation (e.g., plan to participate in another investigational study)

All deviations from protocol procedures, evaluations, and/or visits must be categorized and documented as they occur. Each deviation must be documented on a Protocol Deviation Form. When possible, missed visits and procedures must be rescheduled and performed at the nearest possible time point to the original schedule.

3.6.6 Loss to Follow-up

If the site's study team members are unable to establish contact with a subject who misses a scheduled study visit, the clinical site must make every possible effort to re-establish contact and document such efforts. If contact is re-established, then the subject will resume participation in the study. If contact with the subject cannot be re-established by the subject's calculated Study Day 112 visit date, then a determination of "lost to follow-up" can be made.

3.6.7 Replacement of Subjects

Subjects who fail to complete the study through Study Day 28 may be replaced at the discretion of the sponsor.

4 STUDY MEDICINAL PRODUCTS

4.1 SYN023

SYN023 will be supplied by Synermore Biologics.

4.1.1 Receipt and Storage

Upon receipt of study drug supplies, the study drug manager must immediately inspect all vials for damage. SYN023 will be shipped with a continuous temperature-monitoring device. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action. SYN023 must be stored upright at 2- 8° C in a secured location with no access for unauthorized personnel. Refer to the most recent version of the Project Specific Procedures or detailed instructions regarding study drug storage.

4.1.2 SYN023 Preparation

After cleaning of the vial top with an alcohol swab, the proper dose of SYN023 is withdrawn slowly from the vial with a 21 gauge needle. After cleaning of the vial top with an alcohol swab, the proper dose of SYN023 is withdrawn slowly from the vial with a 21 gauge needle avoiding foaming. Study drug should be inspected for particulate matter and discarded if present. If more than one vial of SYN023 is required the dose may be accumulated from a second vial. SYN023 must be allowed to sit at room-temperature for at least 15 minutes before intramuscular administration to allow the SYN023 to warm before administration. A constituted SYN023 dose if not administered immediately must be stored at temperature of 2°-8° C and administered within two hours after dose constitution. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug preparation.

4.1.3 Disposal of Unused Supplies

Upon completion of the study, the sponsor must provide authorization for any unused study drug and supplies to be disposed of according to the facility's SOPs. Any disposal of study drug conducted at the clinical site must be documented in the study file.

4.2 RIG (HyperRab ST®)

RIG (HyperRab ST®, Grifols Therapeutics) will be supplied by inVentiv or the sponsor.

4.2.1 Receipt and Storage

Upon receipt of study drug supplies, the study drug manager must immediately inspect all vials for damage. RIG will be shipped with a continuous temperature-monitoring device. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action. RIG liquid will be stored at 2-8° C in a secured location. RIG that has been frozen should not be used. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug storage.

4.2.2 RIG Preparation

RIG is packaged in 2 mL and 10 mL single dose vials. After cleaning of the vial top with an alcohol swab, the proper dose of RIG is withdrawn slowly from the vial with a 21 gauge needle avoiding foaming. Study drug should be inspected for particulate matter and discarded if present. If more than one vial of RIG is required the dose may be accumulated from a second vial. RIG must be allowed to sit at room-temperature for at least 15 minutes before intramuscular administration to allow the RIG to warm before administration. A constituted RIG dose if not administered immediately must be stored at temperature of 2°-8° C and administered within two hours after dose constitution. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug preparation.

4.2.3 Disposal of Unused Supplies

Upon completion of the study, the sponsor must provide authorization for any unused RIG and supplies to be disposed of according to the facility's SOPs. Any disposal of study drug conducted at the clinical site must be documented in the study file.

4.3 RVi (Imovax®)

RVi (Imovax®) will be supplied by inVentiv or the sponsor.

4.3.1 Receipt and Storage

Upon receipt of study drug supplies, the study drug manager must immediately inspect all vials of RVi for damage. The RVi vaccine will be shipped with a continuous temperature-monitoring device. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action. Unreconstituted RVi will be stored at 2-8° C in a secured location. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug storage.

4.3.2 RVi Preparation

RVi (Imovax®) is supplied in a tamper evident unit dose box with:

- One vial of freeze-dried vaccine containing a single dose
- One sterile syringe containing diluent.
- A separate plunger is provided for insertion and use
- One sterile disposable needle for reconstitution.

Cleanse the vaccine vial stopper with a suitable germicide. Do not remove the stopper or the metal seal holding it in place. Attach the plunger and reconstitution needle to the syringe and reconstitute the freeze-dried vaccine by injecting the diluent into the vaccine vial. Gently swirl the contents until completely dissolved and withdraw the total contents of the vial into the syringe. Remove the reconstitution needle and discard. Attach a sterile needle of your choice that is suitable for intramuscular injection of the subject. An RVi dose, once constituted should be allowed to sit at room-temperature for 15 minutes to allow warming and then administered. If unable to be administered immediately after room-temperature warming it should be stored at 2-8° C and should be administered within 2 hours of constitution. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug preparation.

4.3.3 Disposal of Unused Supplies

Upon completion of the study, the sponsor must provide authorization for any unused study drug and supplies to be disposed of according to the facility's SOPs. Any disposal of study drug conducted at the clinical site must be documented in the study file.

4.4 RVa (RabAvert®)

RVa will be supplied by inVentiv or the sponsor.

4.4.1 Receipt and Storage

Upon receipt of study drug supplies, the study drug manager must immediately inspect all vials of RVa for damage. The Rva vaccine will be shipped with a continuous temperature-monitoring device. Any damage or discrepancies from the packing list must be documented and promptly discussed with the sponsor and the study monitor to determine the appropriate action. Unreconstituted RVa will be stored at 2-8° C in a secured location. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug storage.

4.4.2 RVa Preparation

RVa (RabAvert®) is supplied in a tamper evident unit dose box with:

- One vial of freeze-dried vaccine containing a single dose
- One sterile syringe containing diluent.
- A separate plunger is provided for insertion and use
- One sterile disposable needle for reconstitution.

Cleanse the vaccine vial stopper with a suitable germicide. Do not remove the stopper or the metal seal holding it in place. Attach the plunger and reconstitution needle to the syringe and reconstitute the freeze-dried vaccine by injecting the diluent into the vaccine vial. Gently swirl the contents until completely dissolved and withdraw the total contents of the vial into the syringe. Remove the reconstitution needle and discard. Attach a sterile needle of your choice that is suitable for intramuscular injection of the subject. An RVa constituted dose should be allowed to sit at room-temperature for 15 minutes to allow warming and then administered. If unable to be administered immediately after room-temperature warming it should be stored at 2-8° C administered within 2 hours of constitution. Refer to the most recent version of the Project Specific Procedures for detailed instructions regarding study drug preparation.

4.4.3 Disposal of Unused Supplies

Upon completion of the study, the sponsor must provide authorization for any unused study drug and supplies to be disposed of according to the facility's SOPs. Any disposal of study drug conducted at the clinical site must be documented in the study file.

4.5 Accountability

The study drug manager is required to maintain accurate study drug accountability records. Instructions and forms to be completed and kept for accountability will be provided to the study drug manager. If the study drug manager wishes to use site-specific accountability forms, these must be reviewed and approved in advance by the sponsor. Upon completion of the study, all

study drug management records will be copied and the copies returned to the sponsor or its designee. The originals must be maintained at the clinical site with the rest of the study records.

5 SAFETY

5.1 Responsibilities for Ensuring the Safety of Trial Subjects

The national regulatory authority, the sponsor (Synermore), the institution(s) through which the research is performed and all members of the principal investigator's clinical team share responsibility for ensuring that participants in this trial are exposed to the least possible risk of adverse events that may result from participation in this protocol.

5.1.1 Principal Investigator

The principal investigator has a personal responsibility to closely monitor trial subjects and an inherent authority to take whatever measures necessary to ensure their safety. The principal investigator has the authority to terminate, suspend or require changes to a clinical trial for safety concerns and may delay an individual's study drug administration or pause study drug administration in the whole trial if the investigator has some suspicion that the study drug might place a subject at significant risk. The principal investigator determines severity and causality with respect to the study drug for each adverse event. For blinded studies the principal investigator is blinded, in which case the study drug may consist of a placebo, an active control, or the investigational product.

5.1.2 Study Sponsor

The sponsor (Synermore) also has an institutional responsibility to ensure subject safety. This responsibility is vested in a medical monitors and a safety monitoring committee.

5.1.3 Medical Monitor

The local medical monitor is the sponsor's representative and is a licensed physician or surgeon in their country of residence. The local medical monitor reviews the safety of the product for protocols in a specific region and determines expectedness of the adverse event. The local medical monitor may make a sponsor's assessment of severity and causality for adverse events that may upgrade the degree of severity and causality determined by the principal investigator. The local medical monitor, unlike the principal investigator, is unblinded for the study.

5.1.4 Safety Monitoring Committee

If study drug administration is paused (see safety pausing rules in Section 6.1) by the principal investigator, the local medical monitor, or the global medical monitor, an SMC will be convened. The SMC composition is described in an SMC charter. The voting members cannot be directly involved with the conduct of the study. Voting members cannot be employees of the sponsor. Additional subject area experts may be present to provide expertise if requested by the SMC. The SMC may review an individual SAE or it may choose to review adverse events, serious

adverse events, solicited adverse events, and laboratory and vital signs data. The SMC may unblind any amount of safety information needed to conduct their assessment. Only the SMC and the independent statistician responsible for preparing these analyses would be unblinded during these reviews. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented in SMC minutes.

Based on its review and the protocol stopping rules (Section 6) the SMC will make recommendations in the SMC minutes to the sponsor regarding further conduct of the study and further administration of study drug. The conclusions of the SMC will be communicated to the investigators and the Institutional Review Boards/Ethics Committees and the national regulatory authority. The sponsor agrees to abide by the decision of its SMC and any directives issued by the national regulatory authority, the Institutional Review Board or Ethics Committee.

5.1.5 Institutional Review Boards and Ethics Committees

The Institutional Review Board or Ethics Committee has institutional responsibility for the safety of research subjects. The Institutional Review Board or Ethics Committee has the authority to terminate, suspend or require changes to a clinical trial.

5.1.6 National Regulatory Authority

Since the national regulatory authority (such as the FDA for United States) receives all expedited safety reports it also has the authority to terminate, suspend or require changes to a clinical trial.

5.2 Safety Surveillance During the Study

Subjects will be monitored and safety data collected by way of clinical interviews and examinations, evaluations of daily diaries conducted by study team members, and through reports of laboratory evaluations. Time points and the specific data collected for each of these evaluations are described in Section 3 and the protocol appendices. The Medical Monitor will make the SMC aware of new safety data when it becomes available.

5.3 Definition of Adverse Event

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, disease, syndrome, abnormal laboratory finding, or concurrent illness that emerges or worsens after receipt of study drug relative to the subject's pretreatment baseline, whether or not it is considered to be related to the medicinal product.

All conditions that exist prior to administration of the study drug (pre-existing conditions) will be recorded in the subject's medical history to establish baseline. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the subject's status will not necessarily be reported as adverse events.

Any adverse change from the subject's baseline condition (determined from screening evaluations conducted to confirm study eligibility) that occurs following the administration of the study drug will be considered an adverse event. This includes the occurrence of a new adverse event or the worsening of a baseline condition, whether or not considered related to the study drug. Intermittent conditions such as headaches in adults or irritability in infants may be present on Study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following receipt of study drug. Adverse events include but are not limited to: adverse changes from baseline that represent increases in toxicity grade according to the Toxicity Table (see protocol appendices), adverse changes in the general condition of the subject, signs and symptoms noted by the subject after study drug administration; concomitant disease with onset or increased severity after study drug administration, and changes in laboratory safety parameters occurring after study drug administration.

The reporting period for all adverse events is specified in Table 3.1-1. Adverse events will be reported on the Adverse Event CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse event evaluations will be reviewed by the principal investigator or by a designated medically qualified practitioner. Adverse event CRF pages are to be completed by members of the study team designated in writing by the principal investigator. The onset and resolution dates of the event and action taken in response to the event will be documented. All adverse events must be followed until resolution is demonstrated. The resolution date will be recorded on the CRF as the last date on which the subject experienced the adverse event. If an adverse event resolution date is uncertain the principal investigator should estimate the completion date based on medical judgment and interview of the subject. Approximate dates of resolution from interviews may be taken as adverse event resolution dates. Some examples of estimation of adverse event resolution are: 1) an asymptomatic laboratory abnormality on one visit that has not been followed-up between visits but has resolved by the next visit may be assumed to have resolved by the midpoint of the inter-visit interval; 2) A resolved adverse event that was treated may be assumed to have been resolved by the end of treatment. Adverse events that are still present at the end of the trial should be recorded as ongoing. Information recorded on the CRF must be substantiated in the source documents. If an adverse event evolves into a condition that becomes "serious," it will be designated as serious on the Adverse Event CRF and a supplemental SAE report form will be completed.

5.4 Assessing Severity

The safety concepts of "severity" and "seriousness" are distinct concepts (see Section 5.8). Severity refers to a degree of clinical manifestation. "Seriousness" refers to defined outcomes from an adverse event. A severe adverse event is not always serious and a serious adverse event is not always severe.

For all adverse events, the investigator (or designee, who is a healthcare professional; is someone the investigator deems qualified to review adverse event information, to provide a medical evaluation of the event, and to classify the event based upon medical judgment and the severity

categories described below) is responsible for assessing the severity of the event and the causal relationship of the event to the study drug.

The **severity** of all adverse events, including clinical findings and abnormal laboratory values, will be classified as one of the following grades:

1. **Mild**
2. **Moderate**
3. **Severe**

A Toxicity Table is provided in the protocol appendices for the assessment of severity of specified adverse events. The Toxicity Table Adverse Event Grades do not correlate directly with the classical severity grades of mild, moderate and severe. FOR THE PURPOSES OF RECORDING EVENTS ON THE CRF, Toxicity Table Grade 1 events will be considered mild in severity, Toxicity Table Grade 2 events will be considered moderate in severity, and both Toxicity Table Grade 3 and 4 events will be considered as severe. In the Toxicity Table certain local reactions such as erythema (redness) and swelling are graded according to size. Laboratory values are graded according to level of deviation from the normal range.

For adverse events not listed in the Toxicity Table determination of severity requires some level of interpretation as outlined below. The degree of incapacity caused by the adverse event and the level of medical intervention required for treatment may be helpful in assessing the overall severity of the adverse event.
For example:

- "Mild" events are generally regarded as noticeable but have no impact on normal activities; they may or may not require over-the-counter treatment managed by the subject.
- "Moderate" events generally have some impact on an individual's normal activities and may require general symptomatic medical intervention by a healthcare professional or by the subject.
- "Severe" adverse events may be incapacitating, leading to suspension of normal daily activities, and would generally require more immediate medical evaluation and intervention by a healthcare professional.

A change in severity of an adverse event will not be recorded as a new adverse event. Only the highest severity level that occurs during the entire period of the adverse event will be recorded on the CRF with the onset and resolution dates encompassing the entire duration of the event.

5.5 Assessing Causal Relationship (Relatedness)

For all adverse events, the investigator and the sponsor (the medical monitor) will determine a **causal relationship,** to the study drug without knowledge, for the blinded principal investigator, of whether SYN023, placebo, or active control was administered. Serious Adverse Events considered related to other medicinal products administered during the trial such as RIG or the rabies vaccine may occur and are subject to reporting to the manufacturer who will have a post-marketing reporting obligation to the FDA if the event is unexpected. A number of factors will be considered in making this assessment, including: 1) the temporal relationship of the event to

the administration of the study drug 2) whether an alternative etiology has been identified and 3) biological plausibility. The investigator will use the following guidelines to assess the causal relationship of an adverse event to study drug:

- **Not Related** to study drug (i.e., there is no evidence of a causal relationship; another etiology is known to have caused the adverse event. The alternative etiology should be documented in the subject's study record).
- **Unlikely Related** to study drug (i.e., there is less than a reasonable possibility that the adverse event was caused by study drug).
- **Possible** relationship to study drug (i.e., there is a reasonable possibility that the adverse event was caused by study drug. There must be a plausible mechanism for the event to be related to study drug. The evidence is inadequate to accept or reject, or favors rejection of, a causal relationship; an association exists between the event and the study drug but there may also be an alternative etiology, such as characteristics of the subject's clinical status or underlying condition).
- **Probable** relationship to study drug (i.e., it is likely that the adverse event was caused by administration of the study drug. The evidence favors acceptance of a causal relationship; an association exists between the event and receipt of the study drug and there is a plausible mechanism for the event to be related to the study drug, and an alternative etiology is not apparent).
- **Definite** relationship to study drug (i.e., the study drug is known to be the cause of the adverse event. The evidence establishes a causal relationship; an association exists between the event and receipt of the study drug and there is a plausible mechanism for the event to be related to the study drug, and causes other than the study drug have been ruled out).

The principal investigator and the local medical monitor both determine causality. It is expected that communication and consultation may occur in the assessment of the causality of adverse events. The greatest degree of causal relationship (definite > probable > possible > unlikely related > not related) determined by either the investigator or local medical monitor after their discussions will determine the ultimate classification of the adverse event. Definite, probable and possible are considered to be related. Not related and unlikely related are considered to be unrelated.

Every effort should be made by the investigator to determine the existence of any pre-existing conditions (e.g., headache in adults or rashes in infants on Study Day 0 with onset prior to study vaccination) that must be taken into consideration when assessing causal relationship of an adverse event. Pre-existing conditions should be recorded in the CRF as baseline history and substantiated by appropriate source documentation. Intermittent conditions such as headaches in adults or irritability in infants may not be present on Study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following study drug.

5.6 Definition of Adverse Reaction

An adverse reaction is an adverse event judged to be related to study drug (see Section 5.3 for adverse event definition).

Related adverse events (adverse reactions) are defined as those judged by the investigator or local medical monitor to be possibly, probably, or definitely related to study drug.

5.7 Solicited Adverse Events and Injection Site Reactions

Solicited adverse events are events the subject is specifically asked about. These adverse events are commonly observed soon after receipt of study antibody. For this study, solicited adverse events to be collected include: to be collected include the following: injection site (s) pain, tenderness, redness swelling, warmth, skin disruption and regional lymphadenopathy. Non-local solicited symptoms include headache, arthralgia, myalgia, rash, pruritus, urticaria, dyspnea, chest pain, cough, fever and chills. Solicited adverse events of local injection site reactions (i.e., pain at injection site, redness at injection site, or swelling at injection site will be considered causally related to study drug (adverse reaction).

The reporting period during which *solicited* adverse events will be evaluated is specified in Table 3.1-1. The solicited adverse event reporting period begins with the day of vaccination. Adverse events and solicited adverse events including assessment of local injection site reactions will be assessed by the investigator for severity, causal relationship to the study drug, possible etiologies, and whether the event meets criteria as a serious adverse event (and therefore requires immediate notification to the medical monitor).

Presence of ulceration and/or scarring at the site of injection and axillary lymphadenopathy of the injection arm(s) in adults or localized lymphadenopathy (e.g., groin) of the thigh injections are considered to be adverse events that are causally related to the study drug and are of special interest. Site of injection ulceration (including presence of drainage) and axillary lymphadenopathy will be actively evaluated during each clinic visit through study day 28. These events will be recorded on the Adverse Event CRF.

In the event that the clinical presentation meets the definition of a serious adverse event, an SAER form must be completed and the event reported per protocol instructions.

5.8 Assessing "Seriousness" and Serious Adverse Events

Seriousness refers to the outcome of an adverse event. Seriousness is determined by both the principal investigator and the local medical monitor. If either principal investigator or local medical monitor determines an event to be serious, it will be classified as such. If any of the following outcomes are present then the adverse event is serious:

- It results in **death** (i.e., the AE caused or led to the fatality). Serious does not describe an event which hypothetically might have caused death if it were more severe.
- It was immediately **life-threatening** (i.e., the AE placed the subject at immediate risk of dying. It does not refer to an event which hypothetically may have led to death if it were more severe).
- It required inpatient **hospitalization** or prolonged hospitalization beyond the expected length of stay. Hospitalizations for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of study drug, are **not** serious by this criterion. Hospitalization is defined as a hospital admission or an emergency room visit for a period greater than 24 hours.
- It resulted in a persistent or significant **disability/incapacity** (i.e., substantial reduction of the subject's ability to carry out activities of daily living).
- It resulted in a **congenital anomaly or birth defect** (i.e., an adverse finding in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy).
- Other **medically important conditions** that may not result in death, threaten life or require hospitalization (i.e., the AE does not meet any of the above serious criteria) may be considered a serious adverse event when, based on appropriate medical judgment, they may jeopardize the subject and require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A **serious adverse event** is an adverse event meeting the outcome criteria for seriousness regardless of relationship to an administered medicinal product.

5.9 Assessing Expectedness

Expected adverse events are adverse events consistent with the applicable product information provided by the sponsor (the investigator's brochure for an investigational product). The sponsor, in the person of the local medical monitor, determines expectedness. If the assessment is that the adverse event is **expected** no further action is required. If the local medical monitor's assessment is that the adverse event is **unexpected,** then the event may represent a SUSAR or expedited SAE (see Sections 5.10 and 5.11).

5.10 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

When an adverse event is judged to be related to an investigational product, such as SYN023 and also is judged to be serious and unexpected, it is a SUSAR (suspected unexpected serious adverse reaction) and is subject to expedited reporting.

5.11 Reporting of Serious Adverse Events

***Serious adverse events,* which include SUSARs, are reported to the sponsor and to Drug Safety Solutions for the entire study period (see protocol appendices). SUSARs are reported even after the trial is over, if the sponsor, local medical monitor or principal investigator becomes aware of them.** The site will be provided with specific reporting procedures including the Adverse Event CRF and any supplemental reporting forms to be used. Serious adverse events will be reported on the Adverse Event CRF using a recognized medical term or diagnosis that accurately reflects the event.

Serious adverse events will be assessed by the investigator and the local medical monitor according to their roles (as described in Sections 5.1.1 and 5.1.3) for severity, causal relationship to the study drug, and expectedness. The onset and resolution dates of the event and the action taken in response to the event will be documented. If the event has not resolved by the final study visit, it will be documented as "ongoing" on the CRF, however, follow-up of the SAE must continue until resolved. Information recorded on the CRF must be substantiated in the source documents.

The SAE Report form completed for that event must be faxed by the principal investigator or his/her designee, within 24 hours (one calendar day) of the clinical site becoming aware of the event, to the local medical monitor and to Drug Safety Solutions. The AE CRF should be completed with all information known at the time; the Supplemental SAE Report (paper form) should be completed and both forms faxed (even if all information concerning the event is not yet known) within the first 24 hours of awareness of the event.

Fatal or life-threatening serious adverse events that the investigator suspects are related to the study drug should be telephoned to the medical monitor immediately upon the investigator's awareness of the event. If the medical monitor is required by the protocol or chooses to suspend enrollment s/he shall immediately create a written memorandum for record to the study file and telephonically notify the sponsor of this act.

Contact information for all safety personnel are contained in the Team Contact List which will be stored on site in the Site Regulatory Binder and maintained by the study sponsor.

Investigators must not wait to collect additional information to fully document the event before notifying the local medical monitor and Drug Safety Solutions of a serious adverse event. The initial notification should include the following (at minimum):

- Protocol number and name and contact number of the investigator
- Subject ID number (and initials and date of birth, if available)
- Date subject received study drug
- Serious adverse event(s) and date of event onset
- Current status of subject

The sponsor has authorized Drug Safety Solutions to execute its responsibilities for safety report submission to the appropriate regulatory authorities within specific time periods of being notified of the event (within 7 or 15 calendar days depending the character of the SUSAR); therefore, it is important that the investigator submit additional information requested as soon as it becomes available.

The sponsor will notify the SMC of all SUSARs within 3 working days of becoming aware of an event and will provide all follow-up information in a timely manner.

5.12 Other Events Requiring Immediate Reporting

The investigator must report the following events by faxing the appropriate form to the medical monitor within 24 hours of becoming aware of the event:

- Withdrawal of consent during the study (Immediately Reportable Event Form)
- Emergency unblinding (Immediately Reportable Event Form)
- Protocol violation affecting the safety of a subject or involving the vaccination process (Immediately Reportable Event Form)
- Adverse event thought to be an allergic reaction to the study drug (Immediately Reportable Event Form, unless event meets SAE criteria)
- Any event that, in the opinion of the investigator, precludes further administration of the study drug (Immediately Reportable Event Form, unless meets SAE criteria)
- Pregnancy (Immediately Reportable Event Form, and Pregnancy Notification Form)

5.13 Adverse Event Treatment, Follow-up, and Outcome

Treatment of any adverse events will be determined by the investigator using his/her best medical judgment and according to current clinical practice guidelines. All treatments as well as follow-up will be recorded in the appropriate CRF.

Adverse events will be considered resolved when the condition returns to normal or returns to the subject's baseline status as established on Study Day 0, or when the condition has stabilized with the expectation that it will remain chronic.

The investigator will continue follow-up on adverse events, including laboratory abnormalities and solicited adverse events, until the event has resolved, is otherwise satisfactorily explained, or the subject completes the study.

Follow-up for serious adverse events must continue until resolution and the outcome reported to the sponsor, even if this extends beyond the serious adverse event reporting period (i.e., after the final study visit). For analysis purposes, the outcome for serious adverse events will be determined on the final study visit.

Outcome of all adverse events will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

If at any time after completion of the serious adverse event reporting period (the final study visit) the investigator becomes aware of a serious adverse event that is suspected by the investigator to be related to the study drug, the event must be reported to the sponsor.

5.14 Follow-up of Subjects Who Become Pregnant

If a subject becomes pregnant during the study, she should be encouraged to continue in the study for safety follow-up. Follow-up should continue for pregnancy outcome including premature terminations, and data are to be included in the safety reports.

The investigator must notify the local medical monitor of the pregnancy immediately (even if already known to have resulted in spontaneous or elective abortion) by faxing the Pregnancy Notification Form to the medical monitor. At a minimum, the estimated date of conception, the estimated due date, and the date the subject received the study drug should be provided.

If a subject becomes pregnant, she will not have any interventions done as normally mandated by the protocol. The subject will undergo all other evaluations according to the Summary Schedule(s) of Evaluations.

The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be reported to the safety monitor after delivery, using a Pregnancy Notification Form. If delivery occurs before the final study visit, the subject should continue to be followed for SAEs through the final study visit unless withdrawal of consent has occurred. If delivery occurs after the final study visit, the investigator should attempt to maintain contact with the subject to obtain information after delivery.

Pregnancy will not be recorded as an adverse event. However, pregnancy outcomes will be recorded in the World Wide Safety Database. If the pregnancy results in a miscarriage or a planned termination, the event (spontaneous abortion or elective abortion) will be reported as an adverse event or serious adverse event per the investigator's judgment (e.g., if it was a medically important or life-threatening event that meets the definition of a serious adverse event).

A congenital anomaly or birth defect (i.e., an adverse finding in a child or fetus of a subject exposed to the study drug before conception or during pregnancy) must be reported as a serious adverse event.

If it is determined after completion of the study that a subject became pregnant during the study, the subject should notify the investigator. The pregnancy must be reported to the local medical monitor and the status of the mother and child after delivery will be obtained and reported, when possible.

5.15 Subject Daily Temperature Monitoring

Subjects will receive a digital thermometer to be used during the specified post-vaccination. Temperature should be taken and the time recorded as soon as possible after awakening and before the ingestion of hot or cold liquids during the solicited adverse event period after Study Drug administration.

6 PAUSING AND STOPPING RULES

These rules govern the pausing and stopping of study drug administration at any time during the study such as between doses (for multiple dose studies) for an individual, between individuals within a single dose group, and between dose groups.

6.1 Safety Pausing Rules

The principal investigator and/or local medical monitor will pause administration of study drug in the trial if:

1. It is determined that a SUSAR occurred

OR

2. It is determined that a serious adverse event OR a Toxicity Grade 3 or 4 event (except for elevated CPK and visually interpreted urine dipstick findings) OR an adverse event pattern of concern occurred AND is judged to be POSSIBLY, PROBABLY or DEFINITELY related to study drug

If the principal investigator and/or local medical monitor pauses administration of study drug in the study, he or she will record this in a memorandum to the study file and notify the sponsor who will then convene the SMC. The FDA must be notified if the Study is paused for safety reasons. The FDA must be notified if the Study is then resumed. If additional clinical information becomes available that reduces the principal investigator's assessment of causality, severity or toxicity grade such that study pausing is no longer required, then the principal investigator, with the agreement of the local medical monitor, may resume study drug administration, record this in a memorandum to the study file, and notify the sponsor.

Since the medical monitor reviews data from all the sponsor's trials, he or she may become aware of an adverse event pattern of concern not appreciated by the principal investigator or local medical monitor. If the global medical monitor independently determines that an adverse event pattern of concern that is judged to be POSSIBLY, PROBABLY or DEFINITELY related to study drug has occurred, the global medical monitor will pause administration of study drug in the trial, record the study pause in a memorandum to the study file, and notify the local medical monitor, principal investigator and sponsor who will convene the SMC.

6.2 Safety Stopping Rules

The rules for stopping further enrollment and study drug administration by the SMC are below:

- Death in any subject unless the SMC determines it is UNRELATED to SYN023
- An anaphylactic reaction to SYN023 in any subject
- A severe (Toxicity Grade 3 or 4) or serious adverse event (except for CPK elevations and visually interpreted urine dipstick findings) unless the SMC determines it is UNRELATED to SYN023.
- A potentially life-threatening adverse event or serious adverse event unless the SMC determines it is UNRELATED to SYN023.
- A pattern of significant symptoms, physical findings or laboratory abnormalities (adverse events) that, although individually minor, collectively represent a safety concern in the opinion of the investigator or the medical monitor and are judged by the SMC to be DEFINITELY, PROBABLY or POSSIBLY related to SYN023

The SMC may recommend resumption of study drug administration if the study pause was for reasons less severe than those in the SMC stopping rules. The SMC may recommend resumption of enrollment if it judges that changes to the study protocol will eliminate or greatly reduce the safety risks specified in the stopping rules. In the absence of study protocol changes the SMC must follow the SMC study stopping rules.

If a decision to resume study enrollment and study drug administration is made the SMC will record their judgment in a memorandum to the study file and notify the sponsor. The SMC memorandum will be forwarded to the medical monitor and principal investigator. The clinical site will be allowed to resume activities upon receipt of written notification from the sponsor. The U.S. FDA will be informed in writing when:

1. The study is stopped
2. The decision is made by the SMC to resume or discontinue study activities

7 STATISTICAL CONSIDERATIONS

The planned statistical analyses for this study are outlined below. A detailed statistical analysis plan will be created and finalized prior to database lock and preparation of any unblinded preliminary data review and for preparation of the final study report (see Section 8).

7.1 Subject Populations

The safety population will consist of all randomized subjects who received at least one dose of a study drug.

The per-protocol population for efficacy or pharmacodynamic analyses will consist of all randomized subjects who received all scheduled doses of study drug and remained on study for at least 28 days. The intent-to-treat population for efficacy analyses will consist of all randomized subjects who received at least one dose of study drug.

7.2 Demographics and Protocol Compliance

Demographic parameters (age, sex, and race) and other baseline characteristics will be summarized by treatment group for all subjects in the safety population. Detailed demographic descriptions will be provided in the statistical analysis plan (SAP).

Listings of randomized subjects who missed any dose of study drug and of subjects with protocol deviations (to be defined in the statistical analysis plan) will be provided.

7.3 Efficacy or Pharmacodynamic (Serum Rabies Virus Neutralizing Activity) Analyses

Analysis of Pharmacodynamics

Criteria for Pharmacodynamic Similarity Acceptance

Rabies Virus Neutralizing Activity plotted against time will be created. Pharmacodynamic parameters for SYN023 mAb will be estimated using non-compartmental analysis. Cmax, Tmax, AUC0-last, AUC0-inf will be calculated. For the comparison of RIG to SYN023 with RVi and RVa vaccines: The 90% confidence intervals for the ratio of geometric means (RIG/SYN023) must be 80% to 125% . An ANOVA of the in-transformed $AUC_{0\text{-inf}}$ will be run to determine the 90% confidence interval on the difference between treatments. The confidnce interval limits derived on the log scale will be back-transformed to the raw AUC scale for comparison to the acceptance criteria.

To investigate any interference of SYN023 to the immune response generated by the vaccine, a non-inferority test of the $AUC_{14\text{-last}}$ between RIG and SYN023 for each vaccine can be performed. The one-sided 90% confidence interval derived on the log transformed AUC from an ANOVA would be compared to the lower acceptance criterion of 80%.

Additionally, a non-inferiority test of the level of RVNA between RIG and SYN023 for each vaccine at selected time points, such as 14 or 28 days, can be performed using a Wilsoxon rank sum approach with a non-inferiority of 10% of the level associated with RIG. Pharmacodynamic efficacy will be defined as RVNA measured above 0.5 IU/mL with RVi and RVa for the duration of the trial and no more than 10% lower for SYN023 compared to RIG at any time point through Study Day 35.

7.4 Immunogenicity: Anti-SYN023 Antibodies

All immunogenicity analyses will be based on subjects who received at least one dose of Study Drug. Immunogenicity will be summarized for all time points as collected and as available. No imputation for missing data will be performed. Data will be transformed as appropriate prior to analysis. The development of anti-SYN023 antibodies will be analyzed on a continuous scale as a categorical variable by treatment assignment, with descriptive statistics.

7.5 Pharmacokinetic Analyses

All PK analyses of serum SYN023 concentrations will be based on subjects who received study drug. Individual analyses will be performed and descriptive statistics will be used to describe the results of individual analyses. PK parameters for SYN023 mAb will be estimated using non-compartmental analysis. C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{½}$, Clp, and λ_z will be calculated when possible. Anti-SYN023 antibodies (i.e., anti-CTB011 and anti-CTB012 antibodies) will be determined on Study Day 0 and Study Day 7 through 112, or for subjects who leave the study prior to Day 112, the last blood specimen available.

7.6 Safety Analyses

Safety analyses will be performed using the safety population as defined in Section 7.1. Count (percentage) summaries will be presented by treatment group for all subjects in the safety population.

7.6.1 Adverse Events

The safety profile of SYN023 will be described by treatment group. The primary variable for evaluation of the safety profile will be the number and percentage of unsolicited and solicited adverse events recorded at all available post-vaccination time points. For all presentations of adverse events, additional summaries based on reporting period of adverse events following each study vaccination may also be presented.

The number (percentage) of subjects with adverse events will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Additional summaries will present the number (percentage) of subjects with adverse events by severity and by relationship to study drug; each subject will be counted once per preferred term at the greatest severity or most related state recorded for that term.

Separate summaries of the number (percentage) of subjects with solicited adverse events will also be presented. Solicited adverse events will also be summarized by severity and relationship to study drug; each subject will be counted once per preferred term at the greatest severity or most related state recorded for that term.

In addition, dose-safety curves may be produced to examine the proportion of subjects who experience adverse events by treatment regimen.

Serious adverse events will be recorded through the final study visit for all subjects. Listings will be provided for subjects with serious adverse events.

Listings will be provided for subjects who have discontinued prematurely due to an adverse event.

The number (percentage) of subjects with post-vaccination clinical laboratory values or vital sign values recorded as newly abnormal following study vaccination and meeting toxicity mild

criteria (Grade 1) or above as specified in the Toxicity Table (Appendix E) will be tabulated at each post-vaccination time point and overall. Clinical laboratory and vital sign abnormalities will also be reported as adverse events and will be included in the summary of adverse events.

7.6.2 Clinical Laboratory and Vital Sign Parameters

For each clinical laboratory parameter and vital sign parameter prespecified in the protocol, summary statistics for continuous parameters will be presented by treatment regimen for all pre- and post-Study Drug assessments and for change from pre-Study Drug to post-Study Drug assessments.

Statistical methods: Analysis of Safety
Safety analyses will be performed using the Safety Population, as defined in Section 7.1. Count and percent summaries will be presented by treatment group for all subjects.
Descriptive statistics (number of subjects, mean, standard deviation, percent coefficient of variation, median, minimum, and maximum) will be used to summarize all safety and laboratory data.

7.7 Sample Size Considerations

The sample size for this Phase 2 study was selected based on requirement to consider noninferiority of the efficacy parameter, RVNA. The power analysis was performed in SAS 9.2 using the power procedure for noninferiority testing under the assumption of the sample size of 40 per group and likely margin corresponding to SYN023 being no less than 10% lower than RIG. Based on earlier studies, the mean RVNA for 0.3 mg/kg SYN023 of 20 with CV of 15-25% are reasonable. For assumed underlying differences of 0 to1 IU/mL, there is over 80% to conclude non-inferiority of RVNA level at a specified time point. The sample size of 40 per treatment group should be sufficient to address the efficacy objectives of the study.

The assumptions that a difference of 2 or less is considered unimportant (the approximate mean value for 0.3mg/kg SYN023 of 20 was used), with the range in mean difference from -1 to 1, standard deviation of 3 and power of 0.8, the required sample size of 29 is needed to declare that the new treatment (SYN023) is not more tolerably inferior to the previous treatment (RIG). Also, the power analysis was performed for the sample size of 40, standard deviation 3 and the mean difference of 2. This resulted in the power of 0.838. The above results from the sample size and power analysis showed that the sample size of 40 should be sufficiently powered for this study.

Also, a power analysis for non-inferiority of the AUCs was performed using “PowerTOST”, an R CRAN package run under Rstudio version 0.99.491. Under the assumption of a lower non-inferiority bound of 0.9 (corresponding to SYN023 being no less than 10% lower than RIG), the selected sample size of 40 per group would provide over 80% power assuming a CV of 10-20%.

If no SAEs are observed among subjects in each dose group and the 40 subjects in the 3 dose groups combined, the one-sided exact upper 95% confidence bounds on the rate of SAE occurrence will be 45% and 18%, respectively.

7.8 Plan for Statistical Summaries and Analyses

7.8.1 Preliminary Data Reviews

A review of Rabies Virus Inhibitory Activity, anti-SYN023 antibodies, SYN023 pharmacokinetic information and clinical safety data will be conducted following completion of Study Day 42. This review may present individual and aggregate (mean or median [95% CI], as appropriate) and change from pre-study drug to each post administration time point by individual or in aggregate. Study procedures and monitoring practices will not change following this preliminary review. No decision cut points or stopping rules will be stipulated. No hypothesis testing will be performed. The purpose of this review is to obtain preliminary data for use in the decision-making process regarding Study Drug dose level. Personnel at the research site and at the immunology laboratory will remain blinded to all study results and to treatment assignments until after the Study Day 112 data have been collected, reviewed and queries resolved.

7.8.2 Final Study Report

The final study report will include all available safety data, immunogenicity data (including exploratory analyses), clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to preparation of the final study report when all of the above data have been entered, reviewed, and all queries related to the data have been addressed.

Modifications or additions to the analyses described above will be included in the relevant statistical analysis plan(s). Any decisions to deviate from the planned analyses described in the protocol and in the statistical analysis plan will be described in detail in the final study report.

7.9 Computer Methods

Statistical analyses will be performed using SAS® version 9.2 or later under a Windows operating system.

8 DATA COLLECTION, MONITORING, AND RECORD RETENTION

For the purpose of monitoring and auditing the study, source documentation will consist of existing medical records and/or study records developed and maintained by the investigator. Any source document templates provided by the sponsor or its designee will serve as supplements to the subject's study record.

Data recorded on source documents will be transcribed onto case report forms (CRFs) provided by the sponsor or entered using electronic case report forms (eCRFs) using an Electronic Data

Capture (EDC) system provided and approved by the sponsor. Completed, original CRFs will be retrieved by the sponsor or its designee and a copy of each completed CRF will be retained at the clinical site as part of the study records.

The study will be monitored regularly by the sponsor or its designee throughout the study period. For studies of unapproved investigational products, all study records (source documents, signed informed consent forms, copies of CRFs, IRB/IEC correspondence and approval letters, and study drug management records) will be kept secured for a minimum of 2 years following the marketing of the investigational product or for 2 years after the discontinuation of the IND. The investigator will ensure that study records are not disposed of or removed from the clinical site without prior notification and approval from the sponsor or its designee.

9 HUMAN SUBJECTS

9.1 Ethics and Regulatory Considerations

The study will be conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312), and local regulatory requirements.

The protocol and informed consent form will be reviewed and approved by the IRB or IEC of each participating clinical site prior to any protocol-specified procedures being conducted. The investigator will inform the IRB/IEC as to the progress of the study on a regular basis, or at minimum, once a year. The sponsor will also have an independent IRB review and approval of the protocol and informed consent form and will keep the IRB informed of the progress of the study.

Written informed consent will be obtained from each subject prior to any protocol-specified procedures being conducted.

To maintain confidentiality, subject identification numbers will be used to identify the subject's laboratory specimens, source documents, CRF, study reports, etc. All study records will be maintained in a secured location. Clinical information will not be released without written permission from the subject except as necessary for monitoring or auditing of the study by the sponsor or its designee or applicable regulatory authorities.

After the study has been unblinded, the subject should be informed which treatment (Study Drug) the subject received.

9.2 Institutional Review Board or Independent Ethics Committee

All the documents the IRB/IEC may need to fulfill its responsibilities, such as the protocol, protocol amendments, information concerning subject recruitment, payment or compensation procedures, etc., will be submitted to the IRB/IEC by the investigator. The IRB's/IEC's written, unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator/clinical site staff prior to the conduct of any protocol-specified procedures.

Modifications to the protocol may not be implemented without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the modification involves only logistical or administrative aspects of the study. Such logistical or administrative modifications will be submitted to the IRB/IEC in writing by the investigator, and a copy of the correspondence to verify the submission will be maintained.

The investigator must inform the IRB/IEC of modifications to the informed consent form or any other documents previously submitted for review/approval, of any new information that may adversely affect the safety of the subjects or the conduct of the study, provide an annual update and/or request for re-approval, and advise the IRB/IEC when the study has been completed.

Any documents or forms to be provided to the subject (e.g., information cards, form letters from the investigator), and all forms of study advertising (flyers, brochures, print advertisements, radio or television scripts, etc.) must be approved by the sponsor or its designee prior to the clinical site submitting them to the IRB/IEC. Approval from the IRB/IEC must be obtained prior to providing the documents or forms to the subject.

9.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki and ICH-GCP/21 CFR 50.25 should be implemented prior to any protocol-specified procedures being conducted. Informed consent will be documented in writing on a consent form approved by the IRB/IEC.

All relevant information should be provided in both oral and written form in a way that is understandable to the subject. Ample time and opportunity must be given for the subject to inquire about details of the study. The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

The investigator or the investigator's qualified designee will explain the nature of the study and inform the subject that participation is voluntary and that the subject can leave the study at any time, without penalty or loss of benefits to which they are otherwise entitled. The subject must be informed about the study's purpose including why the subject was selected to participate, study goals, expected benefits and risks, potential risks, and that some potential risks are unforeseeable. The subject must be provided with a description of the procedures and the

estimated duration of time required for participation in the study, as well as alternative interventions or courses of treatment, if applicable.

The subject must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they are, where further information may be obtained, and who to contact in the event of a study-related injury. The subject must be told who to contact for answers to any questions related to the study. The extent of the confidentiality of subject records must be defined and the subject must be informed that applicable data protection legislation applies.

The subject must be informed that the monitor(s), auditor(s), IRB/IEC members, and the applicable regulatory authorities will be granted direct access to the subject's original study medical records for verification of protocol-specified procedures and/or data, without violating the confidentiality of the subject to the extent permitted by the applicable laws and regulations. The subject must be informed that his/her signature on the informed consent form indicates that he/she has decided to participate in the study, having read and discussed the information presented.

Modifications made by the investigator to an informed consent form template provided to the investigator by the sponsor or its designee will be reviewed and approved by the sponsor or its designee prior to being submitted to the IRB/IEC.

The original, signed informed consent form for each subject will be maintained by the investigator as part of the subject's study records. A copy of the signed informed consent form will be provided to each subject.

10 STUDY COMPLETION

At the discretion of the sponsor, all materials and supplies provided to the investigator will be returned or disposed of in compliance with local regulatory requirements upon authorization from the sponsor, upon study completion. The investigator or designated clinical site staff will notify the IRB/IEC when the study has been completed.

11 PUBLICATIONS

The final study report will be made available to the principal investigator for purposes of publications. The principal investigator and study staff must send all manuscripts, abstracts, and presentations using data from this study to the sponsor for review prior to their submission. The sponsor reserves the right to delete any part or parts of such materials deemed to be confidential or proprietary.

12 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval from the sponsor. All changes to the protocol must be submitted to the IRB/IEC and must be approved by the IRB/IEC prior to their implementation.

12.1 Changes to Version 2.0 from Version 1.0.

Minor typographical, grammatical or administrative changes are not listed.

Version 1.0 Chapter	Version 2.0 Chapter	Version 2.0 change	Page
1.1 Background	1.1 Background	Discussion of the mortality of rabies vaccination alone compared to combined RIG and vaccination. Discussion of the temporal evolution of rabies virus neutralizing activity.	10
1.4 Clinical Experience with SYN023	1.5 Clinical Experience with SYN023	RVNA data from SYN023-001 presented in rationale for selection of 0.3 mg/kg as dose for current protocol	15
3.1 Schedule of subject treatment and evaluation	3.1 Schedule of subject treatment and evaluation	Table 3.1-1 Additional visit added on Study Day 1 for safety, PD and PK data point	15
3.1 Schedule of subject treatment and evaluation	3.1 Schedule of subject treatment and evaluation	Table 3.1-1 Anti-SYN023 antibody data point added on Study Day 7	15
3.1 Schedule of subject treatment and evaluation	3.1 Schedule of subject treatment and evaluation	Table 3.1-1 CPK and troponin added to safety labs.	15
3.1 Schedule of subject treatment and evaluation	3.1 Schedule of subject treatment and evaluation	Table 3.1-1 Urinalysis added Study Day 1 and 3	15
3.1 Schedule of subject treatment and evaluation	3.1 Schedule of subject treatment and evaluation	Table 3.1-1 ECG added through Study Day 28	15
3.2.3 Inclusion Criteria	3.2.3 Inclusion Criteria	Pregnancy test increased to within 48 hours preceding receipt of the first dose	18
3.2.5 Screening Clinical Assessments and Laboratory Tests	3.2.5 Screening Clinical Assessments and Laboratory Tests	Wording added that eligibility is determined by screening laboratories	19
3.3 Study	3.3 Study	4 sentinel subjects (1 for each	20

Randomization	Randomization and Sentinel Subjects	regimen) will be randomized and Study Day 14 safety data reviewed before enrollment of the remainder of the trial.	
3.5 Medicinal Product and Study Drug Administration	3.5 Medicinal Product and Study Drug Administration	Interval between Study Drug and vaccination lengthened to 75 minutes	22
3.6.2 Immunology Laboratory Evaluations	3.6.2 Immunology Laboratory Evaluations	Added Day 1 data point for PK. Added Day 7 data point for anti-SYN023 antibodies	23
3.6.3 Safety Evaluations	3.6.3 Safety Evaluations	Added ECG, anaphylaxis and immune complex wording	24
3.6.3.1 Pre-Study Study Drug and Post Administration Monitoring of Subjects	3.6.3.1 Pre-Study Study Drug and Post-Study Drug Administration Clinical Monitoring of Subjects	Added wording for clinical monitoring after all medicinal products are administered	24
3.6.3.1 Pre-Study Study Drug and Post Administration Monitoring of Subjects	3.6.3.1 Pre-Study Study Drug and Post-Study Drug Administration Clinical Monitoring of Subjects	Added drugs and listed equipment for management of acute allergic reactions	24
	3.6.3.1 Pre-Study Study Drug and Post-Study Drug Administration Clinical Monitoring of Subjects	Post SYN023 administration monitoring interval increased to 240 minutes	24
	3.6.3.2 New chapter Recognition of Anaphylaxis	Added wording requiring plasma histamine, plasma tryptase and urinary N-methyl-histamine when the diagnosis of anaphylaxis is considered.	25
	3.6.3.2 New chapter Recognition of Anaphylaxis	Wording added on recognition of anaphylaxis (Sampson)	28
	3.6.3.3 New chapter Treatment of Anaphylaxis	Added chapter on treatment of anaphylaxis (Sampson)	25

	3.6.3.4 New chapter Recognition and evaluation of Immune Complex Illness	Added chapter on recognition of immune complex induced illness	26
3.6.4 Window Periods …	3.6.4 Window Periods …	ECG added	28
4.2 RIG(HyperRab ST®)	4.2 RIG ((HyperRab ST®)	Wording added to permit supply by the sponsor	29
5.15 Subject Temperature Monitoring.	5.15 Subject Daily Temperature	Wording added to require temperature to be taken upon awakening.	42
6.1 Safety Pausing Rules	6.1 Safety Pausing Rules	The following wording was added to the chapter; The FDA must be notified if the Study is paused for safety reasons. The FDA must be notified if the Study is then resumed. CPK was exempted from pausing rules since elevations are anticipated with IM RIG injections	42
6.2 Safety Stopping Rules		CPK was exempted from stopping rules since elevations are anticipated with IM RIG injections. FDA wording added.	42
13 References	13 References	Added Karplod Reference	54
13 References	13 References	Added Sampson Reference for Anaphylaxis	54
13 References	13 References	Added Vodopija References	54

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APPENDIX A Detailed Description of Selected Study Visits

Screening Visit (Up to 4 weeks prior to start of study medication, Day -28 to -1)

- Obtain informed consent
- Verify eligibility by review of inclusion/exclusion criteria
- Record medical history
- Conduct physical examination (including height and weight and BMI calculation)
- Perform ECG
- Collect urine sample for:
  - βHCG (all females)
  - Urinalysis
  - Urine Toxicology
- Collect blood samples for:
  - Hepatitis B, Hepatitis C, HIV-1,2
  - PT and PTT
  - Serum chemistry: creatinine, ALT, AST, alkaline phosphatase and others if part of panel
  - Hematology: CBC including differential and platelets
  - Serum IgA

Baseline Visit (Study Day 0)

- Verify eligibility by review of inclusion/exclusion criteria
- Conduct focused physical examination including weight
- Insure that results of Serum βHCG are negative
- Record vital signs and oximetry
- Record interval history
- Record concurrent medications
- Collect urine sample for urinalysis
- Insure that blood samples collected for:
  - Serum chemistry: total bilirubin, BUN, CPK, troponin, creatinine, ALT, AST, alkaline phosphatase, sodium, potassium, chloride, bicarbonate calcium

  - Hematology: CBC including differential and platelets
  - Clotting studies: PTT and prothrombin INR
  - Anti-SYN023 antibodies
  - SYN023 antibody levels
  - Rabies Virus Inhibitory Serum Activity
- Administer Study Drug (RIG or SYN023) on Right side of body
- Within approximately 75 minutes administer RVa or RVi on Left side of body
- Distribute diary and thermometer and instruct subject in their use
- Assess patient for AEs and SAEs
- Perform vital signs & oximetry every 30 minutes during the 240 minutes of observation prior to discharge

APPENDIX B SAE Reporting Scheme

Synermore has designated Drug Safety Solutions to manage safety reporting for Protocol SYN-002.

Drug Safety Solutions, Inc.
Raleigh, NC 27613
www.drugsafetysolutionsusa.com

Contact information:

Kristen Eagle
Phone: +1 (704)488-6031
Fax: +1 (919) 844-6948
Email: keagle@drugsafety.biz

Backup:
Katherine Smith, MD
Phone: +1 (919) 264-5626
Fax: +1 (919) 844-6948
Email: ksmith@drugsafety.biz

SAEs should be reported to:
saereports@drugsafety.biz

APPENDIX C Sponsor's Representative

ERIC TSAO
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Synermore Biologics Co., Ltd
6F-6, No. 5, Aly. 22, Ln. 513, Ruiguang Rd.,
Neihu Dist., Taipei 11492, Taiwan
Tel: +886 2 2659 0988
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APPENDIX D Protocol Facility and Contact List

Role in Study	Name	Contact Information
Clinical Study Manager	Jorge Mejia-Galvis	inVentiv Health Clinical Research Services LLC 1951 NW 7th Avenue, Suite 450 Miami, FL 33136, USA Tel.: 1-305-547-5800
Responsible Physician	David Wyatt, M.D. Vice President, Medical Affairs Miami Principal Investigator	inVentiv Health Clinical Research Services LLC 1951 NW 7th Avenue, Suite 450 Miami, FL 33136, USA Tel.: 1-305-547-5800
Medical Monitor (Emergency Contact)	J. Bruce McClain, M.D.	11673 Garnet Road Lovettsville, VA 20180 (Mobile) 202-236-6975
Study Monitoring	MJ Research Inc.	1815 Edgewood St. Bruno (Quebec) J3V 4P1 Canada Tel.: 450-461-6245
InVentiv Clinical Research Facility	inVentiv Health Clinical Research Services LLC (« inVentiv »)	1951 NW 7th Avenue, Suite 450 Miami, FL 33136, USA Tel.: 1-305-547-5800
Biomedical Laboratory Facilities (clinical safety laboratory tests)	LabCorp	LabCorp 4200 N. 29th Avenue Hollywood, FL 33020-1017 Tel.: 1-800-877-7831

Clinical Pharmacology & Regulatory Affairs	Mario Tanguay, B. Pharm., Ph.D., Vice-President, Clinical Pharmacology	Clinical Pharmacology and Regulatory Affairs, inVentiv Health Clinique Inc. 2500, rue Einstein Québec (Québec), Canada, G1P 0A2 Tel.: 1-418-527-4000
Clinical Pharmacology & Regulatory Affairs	Stéphane Lamouche,Ph.D. Director, Clinical Pharmacology & Regulatory Affairs	inVentiv Health Clinique inc. 2500, rue Einstein Québec (Québec), Canada, G1P 0A2 Tel.: 1-418-527-4000
Clinical Pharmacology & Regulatory Affairs	Pierre-Olivier Tremblay, M.Sc. Director, Pharmacometrics	inVentiv Health Clinique inc. 2500, rue Einstein Québec (Québec), Canada, G1P 0A2 Tel.: 1-418-527-4000
Rabies Virus Neutralizing Activity (RVNA)	Susan Moore	Rabies Laboratory, Mosier Hall, Kansas State University, 1800 Denison Avenue, Manhattan KS 66506-5600
Bioanalytical Facility	Christopher Beaver, Ph.D. Senior Director, Bioanalysis	inVentiv Health Clinical Bioanalytical Facility 301D College Road East Princeton, NJ 08540 Tel: 609-951-0005

APPENDIX E Toxicity Table

2. *Note: From final US FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Drug Clinical Trials (September 2007); laboratory values are in conventional and SI units. The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.*

Local Site of Infusion Symptoms	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

3. * In addition to grading the local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
4. ** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Fever**	38.0 – 38.4°C 100.4 – 101.1°F	38.5 - 38.9°C 101.2 - 102.0°F	39.0 - 40°C 102.1 - 104°F	>40°C >104°F
Tachycardia – beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – 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

5. * Subject should be at rest for all vital sign measurements. ** Oral temperature; no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 grams/ 24 hours	4 - 5 stools or 400 - 800 grams/24 hours	6 or more watery stools or > 800 grams/24 hours or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic 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

Infusion reaction	Requires no intervention and transient in duration	Requires slowing of infusion or non-prescription drug treatment	Requires prescription drug reatment presence of respiratory symtoms	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)**
Sodium – hyponatremia mEq/L or mmol/L:	132 – 134	130 – 131	125 – 129	<125
Sodium – hypernatremia mEq/L or mmol/L:	144 – 145	146 – 147	148 – 150	>150
Potassium – hyperkalemia mEq/L or mmol/L:	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	>5.6
Potassium – hypokalemia mEq/L or mmol/L:	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	<3.1
Glucose – hypoglycemia mg/dL: mmol/L:	65 – 69 3.6 – 3.8	55 – 64 3.0 – 3.5	45 – 54 2.5 – 2.9	<45 <2.5
Glucose – hyperglycemia Fasting - mg/dL: mmol/L: Random – mg/dL: mmol/L:	100 – 110 5.5 – 6.0 110 - 125 6.1 – 6.8	111 – 125 6.1 – 6.8 126 - 200 6.9 – 11.0	>125 >6.8 >200 >11.0	Insulin requirement or hyperosmolar coma
Blood urea nitrogen (BUN) – mg/dL: mmol/L:	23 – 26 8.3 – 9.5	27 – 31 9.6 – 11.2	>31 >11.2	Requires dialysis
Creatinine – elevated mg/dL: umol/L:	1.5 – 1.7 121 – 145	1.8 – 2.0 146 – 170	2.1 – 2.5 171 – 208	>2.5 or requires dialysis >208 or requires dialysis
Calcium – hypocalcemia mg/dL: mmol/L:	8.0 – 8.4 2.00 – 2.10	7.5 – 7.9 1.87 – 1.99	7.0 – 7.4 1.75 – 1.86	<7.0 <1.75
Calcium – hypercalcemia mg/dL: mmol/L:	10.5 – 11.0 2.63 – 2.76	11.1 – 11.5 2.77 – 2.88	11.6 – 12.0 2.89 – 3.00	>12.0 >3.00
Magnesium – hypomagnesemia mg/dL: mmol/L:	1.3 – 1.5 0.52 – 0.62	1.1 – 1.2 0.43 – 0.51	0.9 – 1.0 0.37 – 0.42	<0.9 <0.37
Phosphorus – hypophosphatemia mg/dL: mmol/L:	2.3 – 2.5 0.73 – 0.80	2.0 – 2.2 0.63 – 0.72	1.6 – 1.9 0.51 – 0.62	<1.6 <0.51
CPK – elevated mg/dL or ukat/L:	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Albumin – hypoalbuminemia g/dL: g/L:	2.8 – 3.1 28 – 31	2.5 – 2.7 25 – 27	<2.5 <25	---- ----
Total protein – hypoproteinemia g/dL: g/L:	5.5 – 6.0 55 – 60	5.0 – 5.4 50 – 54	<5.0 <50	---- ----
Alkaline phosphatase (ALP) – increased	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver Function Tests (LFT): AST, ALT – increased	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin (with any increase in LFT) - increased	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin (with normal LFT) - increased	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 – x ULN	>3.0 x ULN

Cholesterol – increased mg/dL: mmol/L:	 201 - 210 6.0 – 6.3	 211 – 225 6.4 – 6.7	 >226 >6.7	 ---- ----
Pancreatic enzymes: amylase, lipase – increased	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.0 x ULN

6. ** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Very Severe (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
7. *** ULN (upper limit of normal) dependent on normal reference ranges per institutional parameters.

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Hemoglobin (Female) – g/dL: g/L:	 11.0 – 12.0 110 – 120	 9.5 – 10.9 95 – 109	 8.0 – 9.4 80 – 94	 <8.0 <80
Hemoglobin (Male) – g/dL: g/L:	 12.5 – 13.5 125 – 135	 10.5 – 12.4 105 - 124	 8.5 – 10.4 85 – 104	 <8.5 <85
WBC – increased cells/mm^3: cells x 10^9/L:	 10,800 – 15,000 10.8 – 15.0	 15,001 – 20,000 15.1 – 20.0	 20,001 – 25,000 20.1 – 25.0	 >25,000 >25.0
WBC – decreased cells/mm^3: cells x 10^9/L:	 2,500 – 3,500 2.5 – 3.5	 1,500 – 2,499 1.5 – 2.4	 1,000 – 1,499 1.0 – 1.4	 <1,000 <1.0
Lymphocytes – decreased cells/mm^3: cells x 10^9/L:	 750 – 1,000 0.8 – 1.0	 500 – 749 0.5 – 0.7	 250 – 499 0.3 – 0.4	 <250 <0.3
Neutrophils – decreased cells/mm^3: cells x 10^9/L:	 1,500 – 2,000 1.5 – 2.0	 1,000 – 1,499 1.0 – 1.4	 500 – 999 0.5 – 0.9	 <500 <0.5
Eosinophils – increased cells/mm^3: cells x 10^9/L:	 650 – 1,500 0.7 – 1.4	 1,501 – 5,000 1.5 – 5.0	 >5,000 >5.0	 Hypereosinophilic
Platelets – decreased cells/mm^3: cells x 10^9/L:	 125,000 – 140,000 125 – 140	 100,000 – 124,000 100 – 124	 25,000 – 99,000 25 – 99	 <25,000 <25
International normalized ratio (INR) – increased	>1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	>1.25 x ULN
Partial thromboplastin time (PTT) – increased	>1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	>1.5 x ULN
Fibrinogen – increased mg/dL: g/L:	 400 – 500 4.00 – 5.00	 501 – 600 5.01 – 6.00	 >600 >6.00	 ---- ----
Fibrinogen – decreased mg/dL: g/L:	 150 - 200 1.50 – 2.00	 125 – 149 1.25 – 1.49	 100 - 124 1.00 – 1.24	<1.0 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

8. ** "ULN" is the upper limit of the normal range.

Urine	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (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 (rbc/hpf)	1 – 10	11 – 50	>50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion